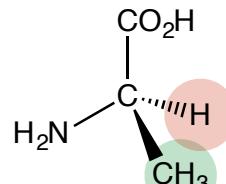
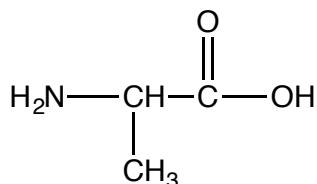
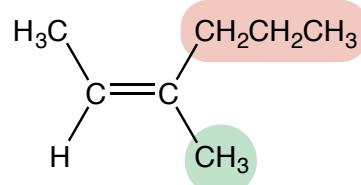
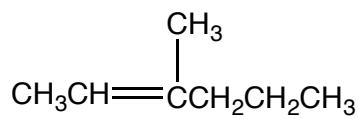
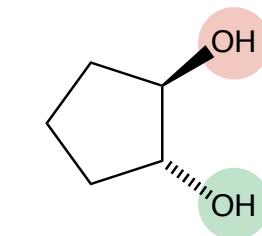
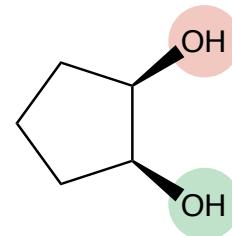
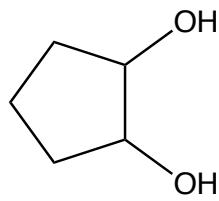


Chapter 5: Stereochemistry & Stereoisomers

Stereochemistry - Study of the 3-D structure of molecules

- constitutional isomers differ in bonding sequence
- stereoisomers have the same bonding sequence, but differ in the orientation of atoms in space

Ex:

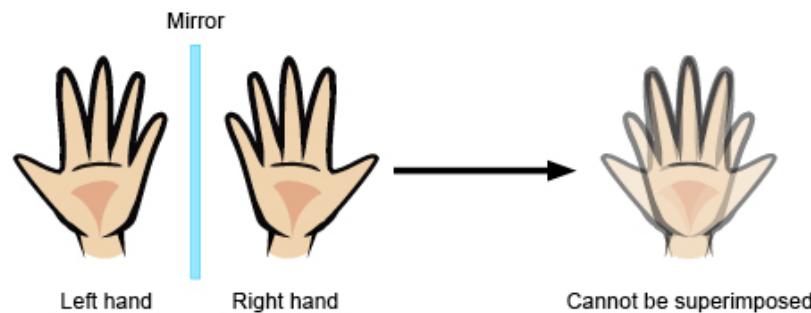


Chirality (5-2)

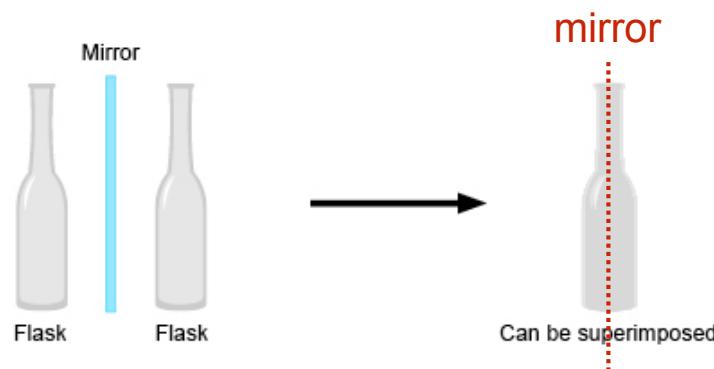
- a property of **objects** that have “handedness” (i.e., asymmetry)

Definitions:

1. **Chiral** - when an object is **non-superimposable** on its mirror image
2. **Achiral** - when an object is **superimposable** on its mirror image



→ chiral objects (asymmetric)
not identical
different 3-D structures

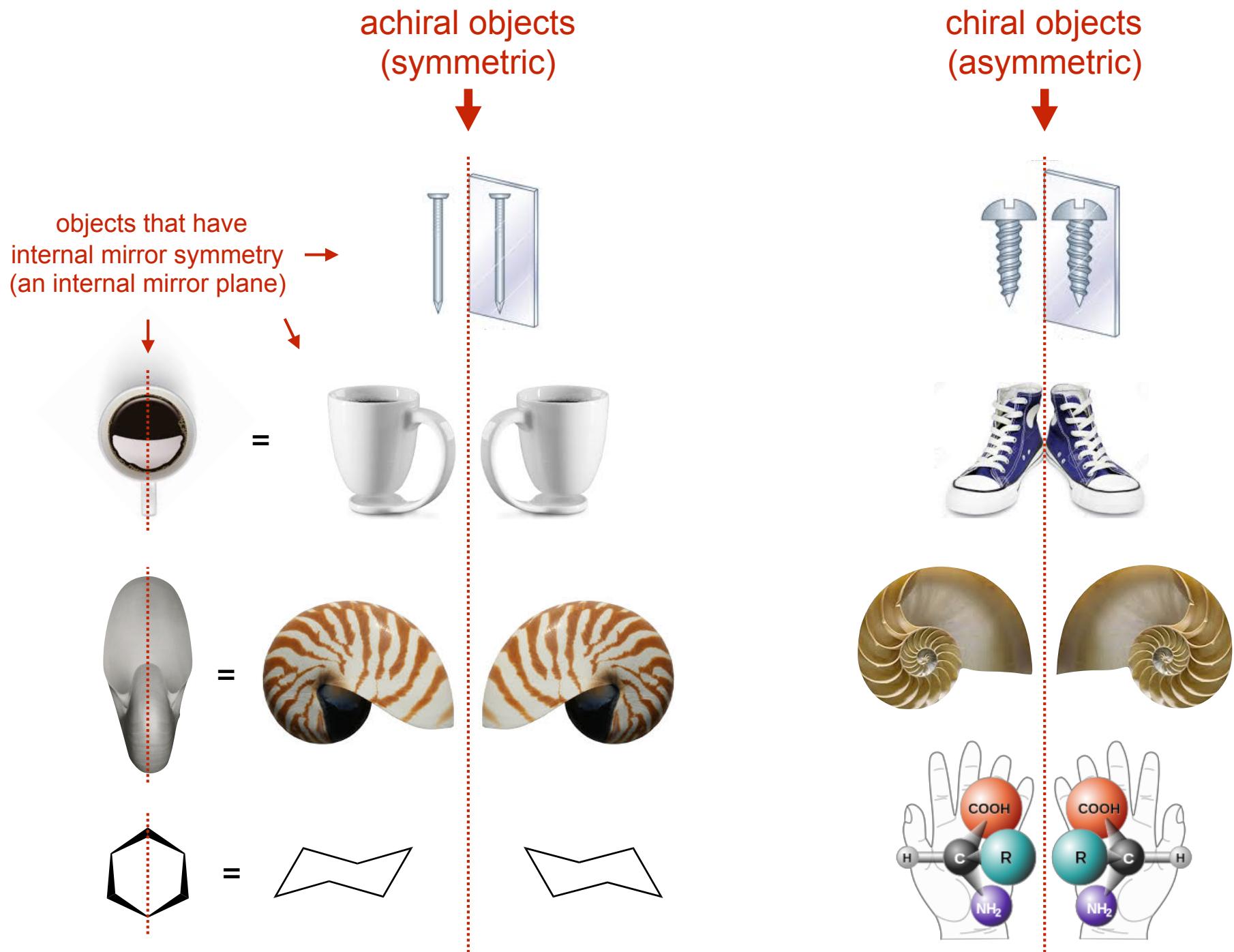


→ achiral objects (symmetric)
identical
same 3-D structure

Test for chirality - no internal mirror symmetry

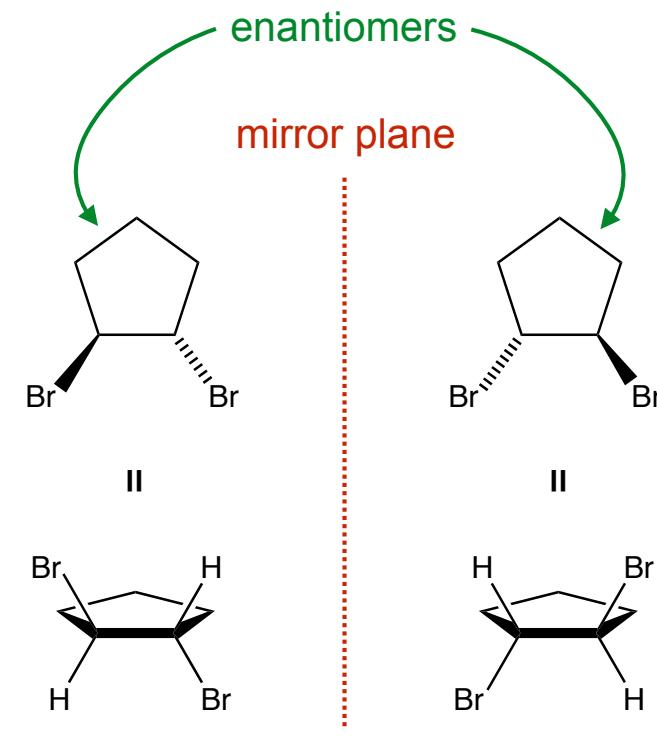
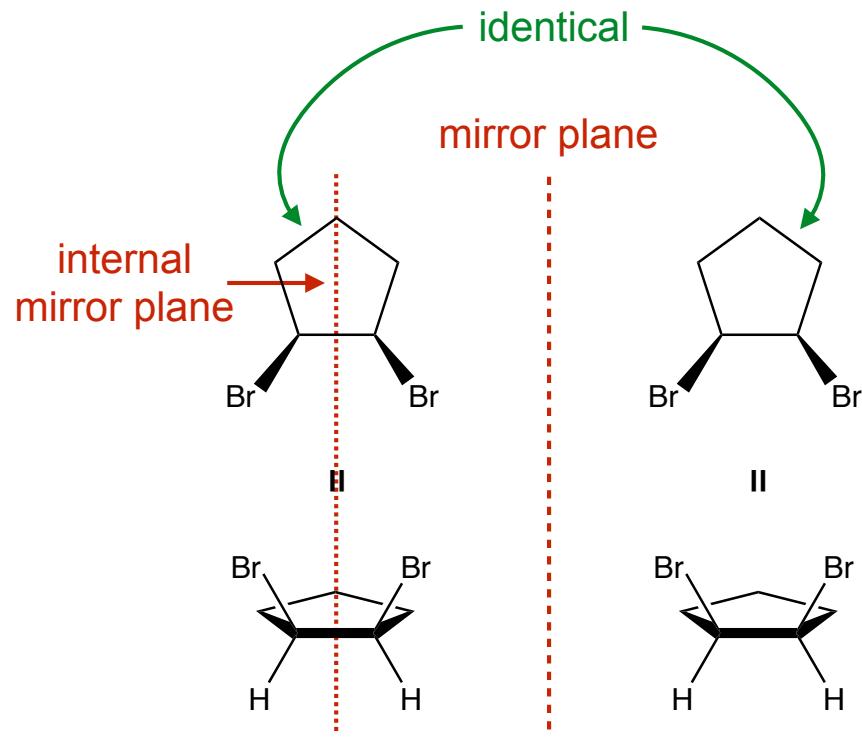
→ a plane of symmetry (mirror plane) destroys chirality

Examples of achiral and chiral objects



Ex: 1,2-dibromocyclopentane

Q: Are the stereoisomers of *cis*- and *trans*-1,2-dibromocyclopentane chiral or achiral?



achiral
mirror images are superimposable (identical)
internal mirror symmetry

chiral
mirror images are nonsuperimposable (unique)
no internal mirror symmetry (asymmetric)

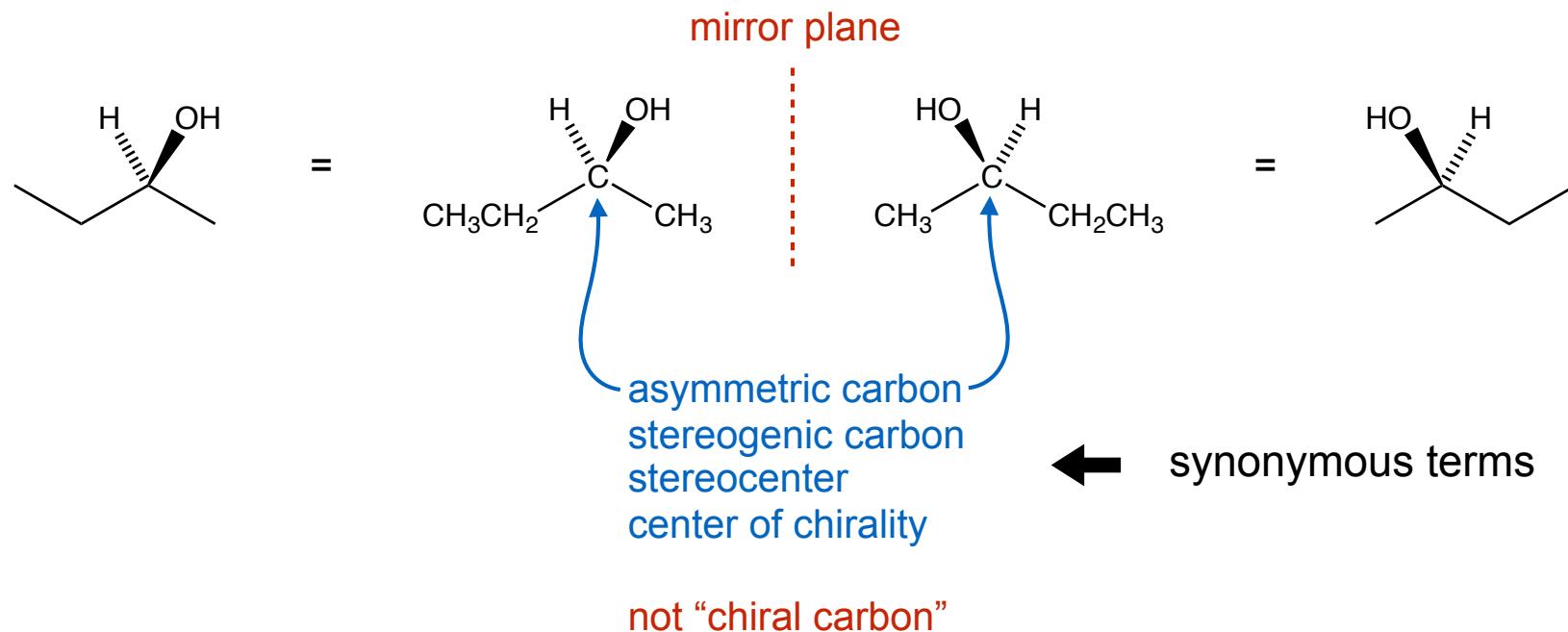
Definition:

- Enantiomers - stereoisomers that are mirror images that are nonsuperimposable

Q: How many unique stereoisomers are there in total?

Q: What is the origin of chirality in organic molecules?

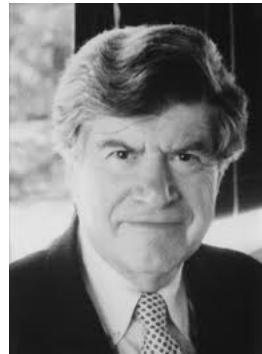
Ex: 2-butanol



Chirality is a property of the 3-D structure of an object

Chirality results from asymmetry

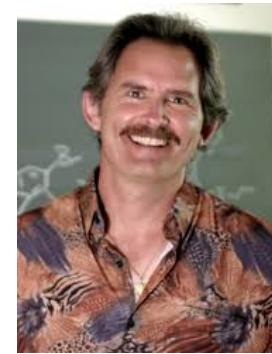
Chirality in a molecule results from the presence of an asymmetrically substituted carbon atom—that is, a carbon atom with substituents that all differ chemically and structurally



Stereoisomerism and Local Chirality

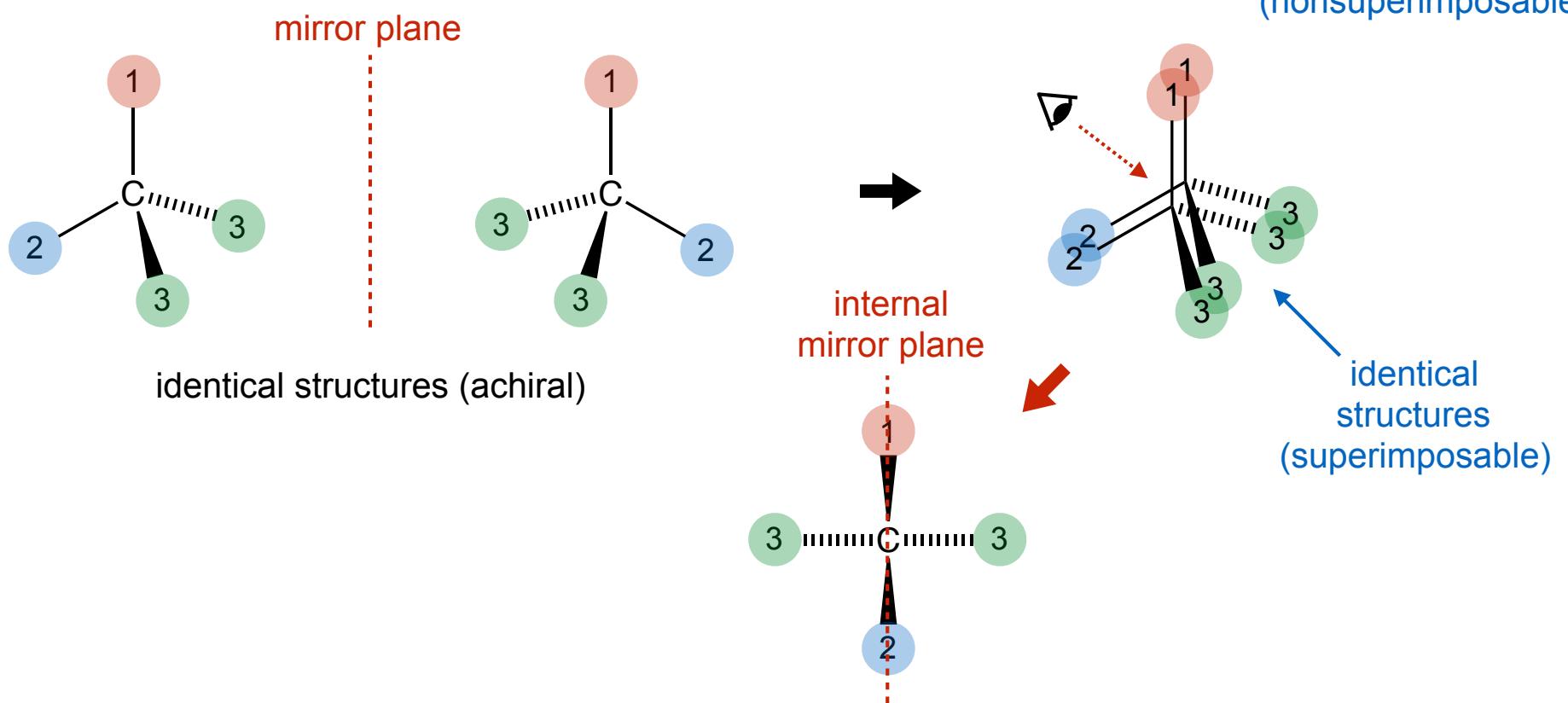
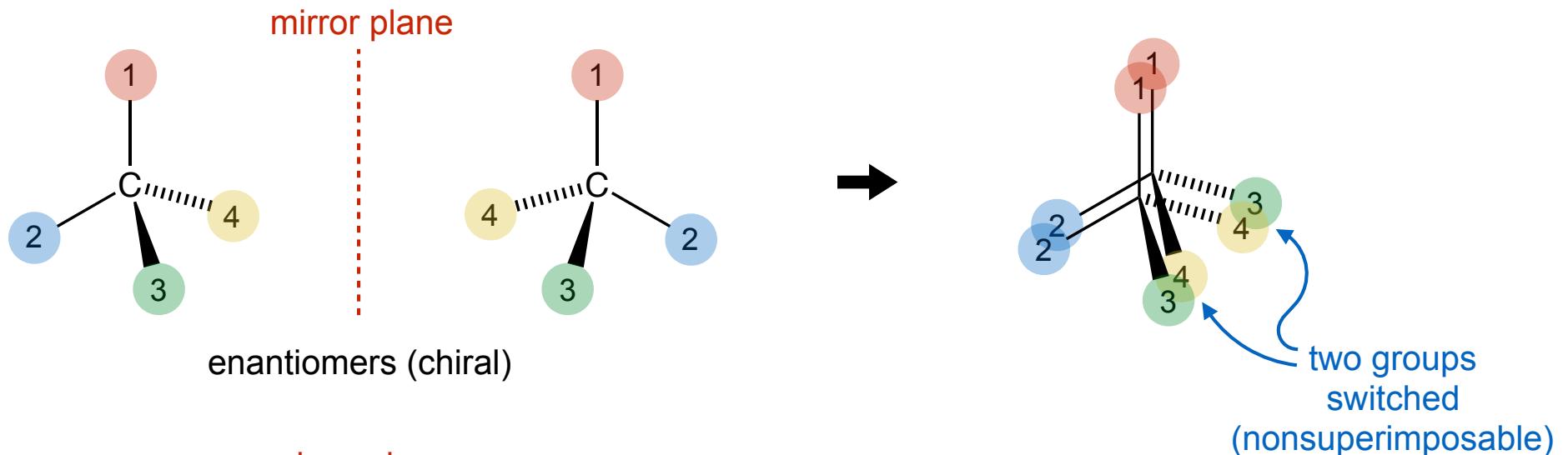
Kurt Mislow and Jay Siegel

J. Am. Chem. Soc., 1984, 106 (11), pp 3319–3328



The traditional linkage between stereoisomerism and local chirality that is expressed in terms such as “asymmetric carbon atom” or “element of chirality” represents a source of conceptual confusion in modern stereochemistry. Molecular segments must be viewed from two separate and distinct aspects: their character as **stereogenic** units and their local symmetry. The first is dependent on bonding connectivity (constitution) and is rooted in graph and permutation theory, whereas the second is independent of constitution and is rooted in the theory of symmetry groups. Although these two aspects are in principle distinct and serve different purposes, they happen to overlap in the case of the regular tetrahedral permutation center. It is for this reason that **the concepts of chirality and stereogenicity are most closely associated in organic stereochemistry where this center plays a dominant role**. The present analysis clarifies stereochemical concepts, sheds new light on the meaning of stereochemical terminology, and *ipso facto* disposes of a number of notations introduced into stereochemistry since van't Hoff's day. To complete our analysis of stereochemical theory, a new treatment of prochirality is proposed. A theoretical framework is constructed that assigns membership in one of three classes of prochirality to any chiral molecular model according to symmetry.

Asymmetric Carbon/Stereogenic Carbon - carbon atom bonded to four different atoms or groups



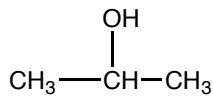
Criteria for a molecule to be chiral

1. Must have a stereocenter
2. Mirror images must be nonsuperimposable
3. Must have no internal mirror symmetry

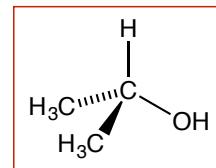
- Actual 3-D structure
- Why it's important to know about structures & conformation

Q: Any stereocenters? How many? Is the molecule chiral or achiral?

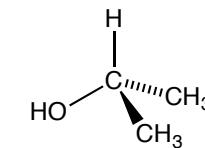
isopropanol



mirror

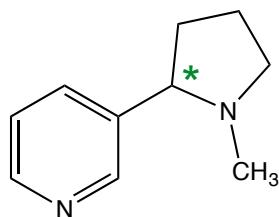


internal mirror plane



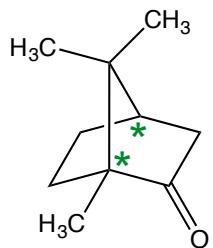
achiral

nicotine

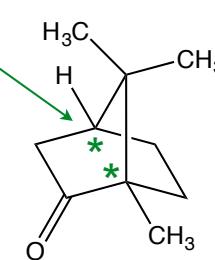
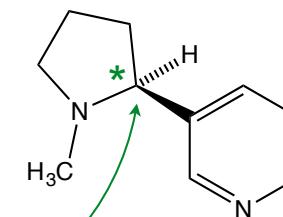
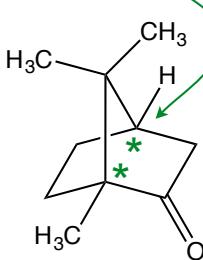
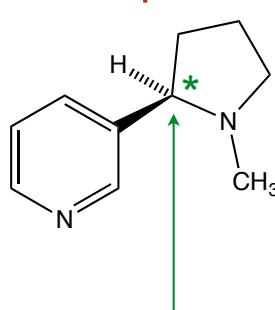


chiral
(enantiomers)

camphor

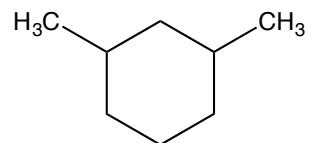


stereocenters (*)

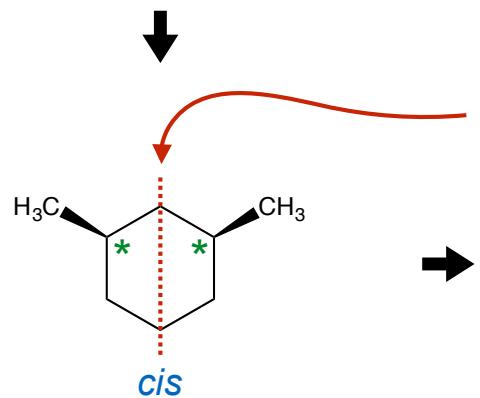


chiral
(enantiomers)

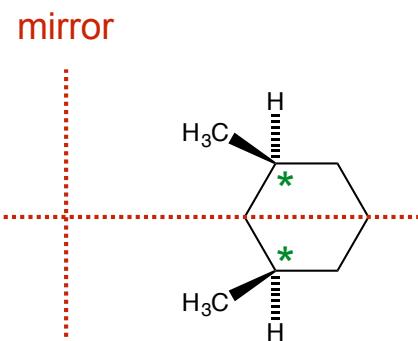
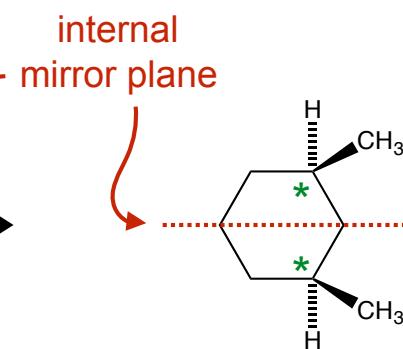
Q: Any stereocenters? How many? Is the molecule chiral or achiral?



1,3-dimethylcyclohexane

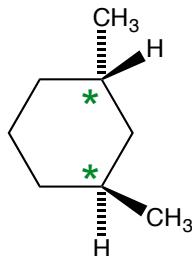
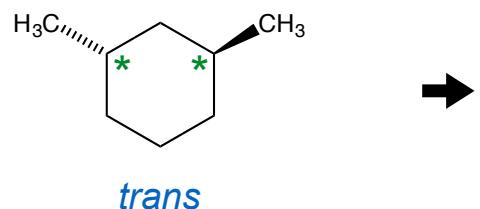


Overall the structure is symmetric (achiral) even though the molecule contains local stereocenters

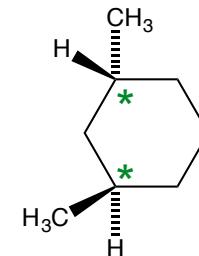


achiral

stereocenters (*)

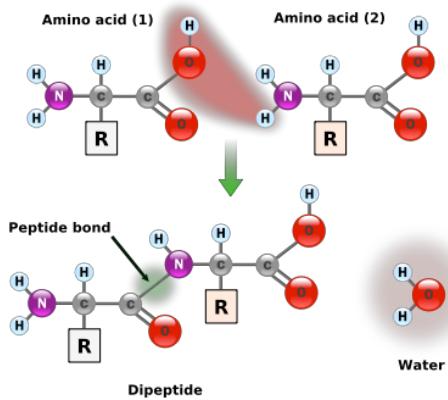
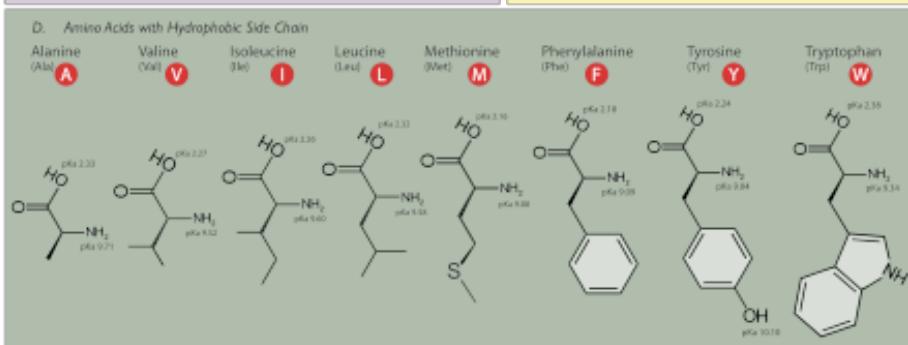
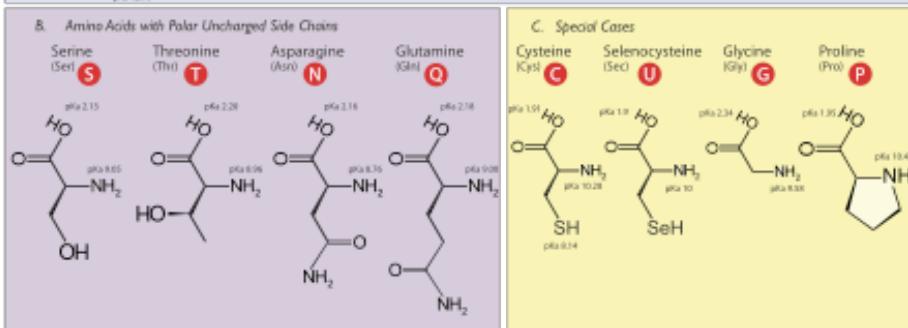
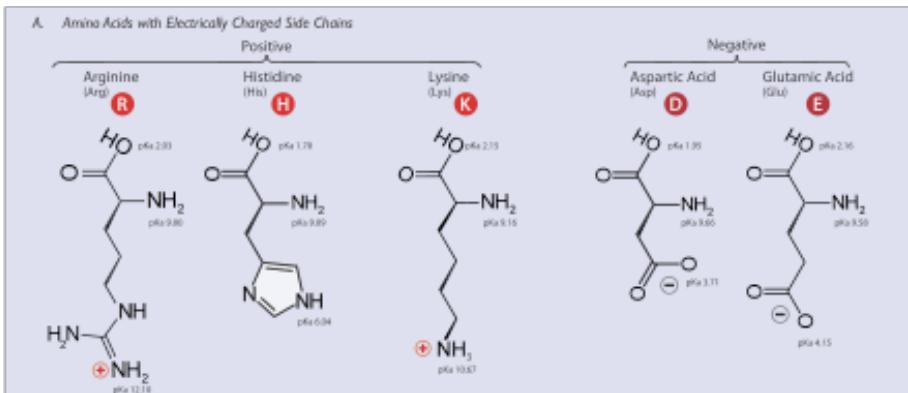


chiral
(enantiomers)



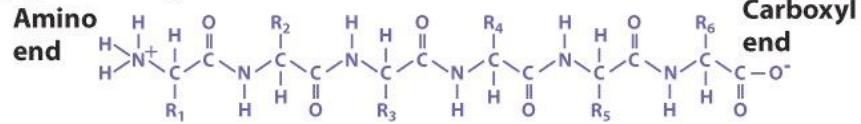
Q: Importance, prevalence, and impact of chirality in nature and technology?

Chirality & the Structure of Proteins

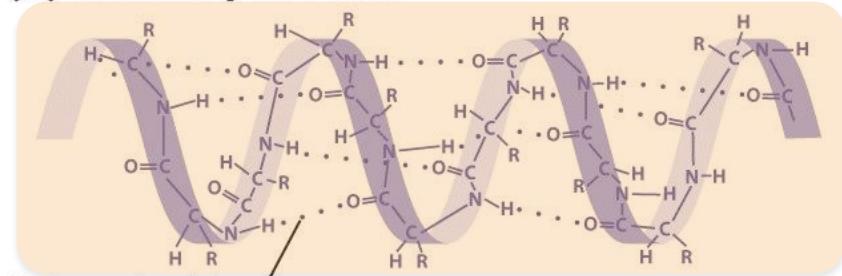


driver with one arm

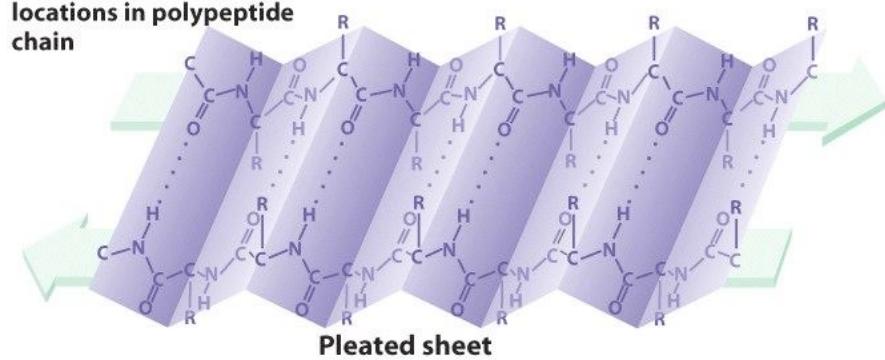
(a) Primary structure



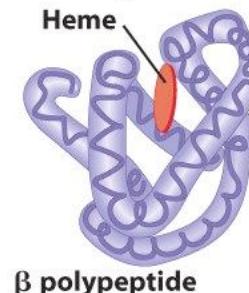
(b) Secondary structure



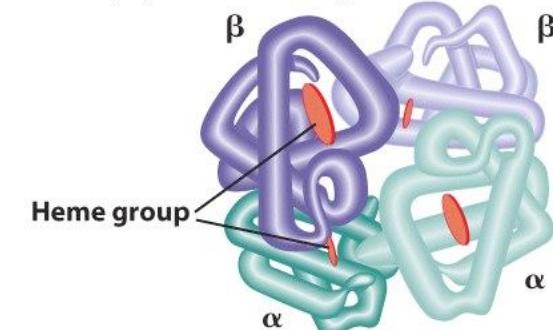
Hydrogen bonds between amino acids at different locations in polypeptide chain



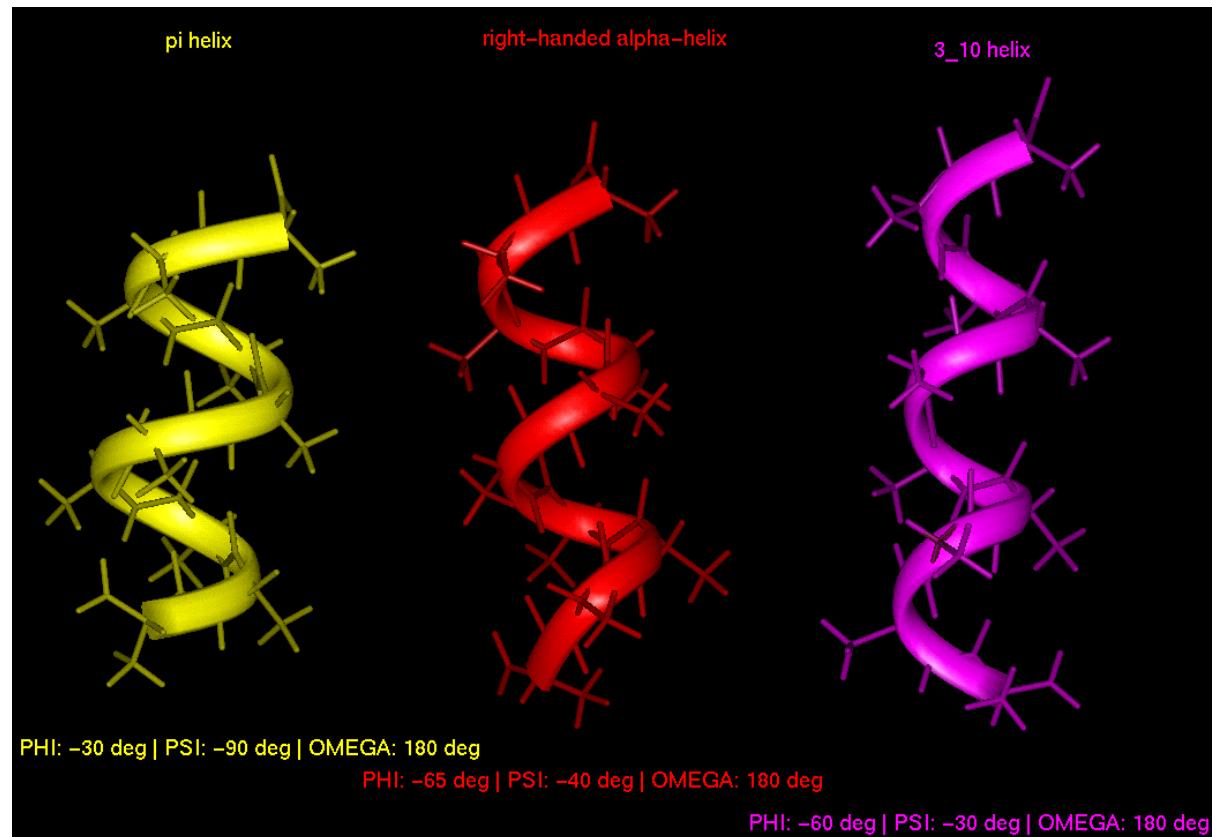
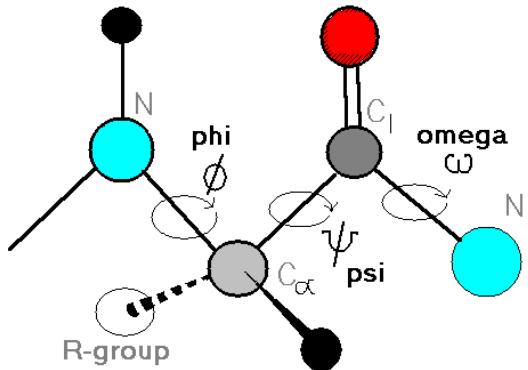
(c) Tertiary structure



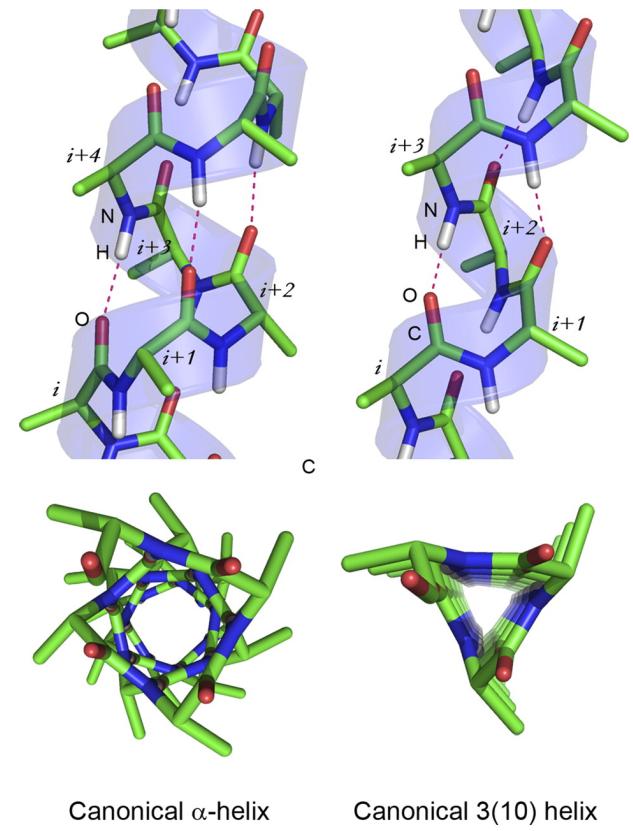
(d) Quaternary structure



α -Helices in Proteins

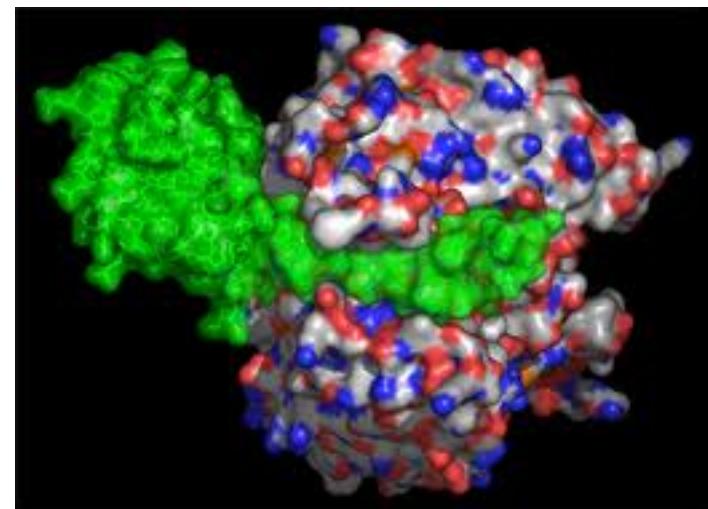
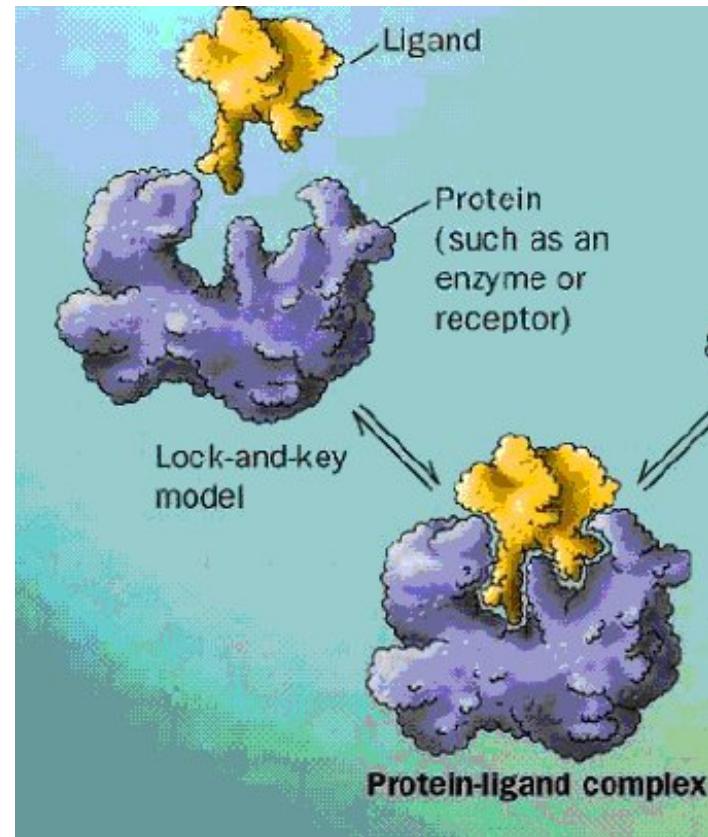
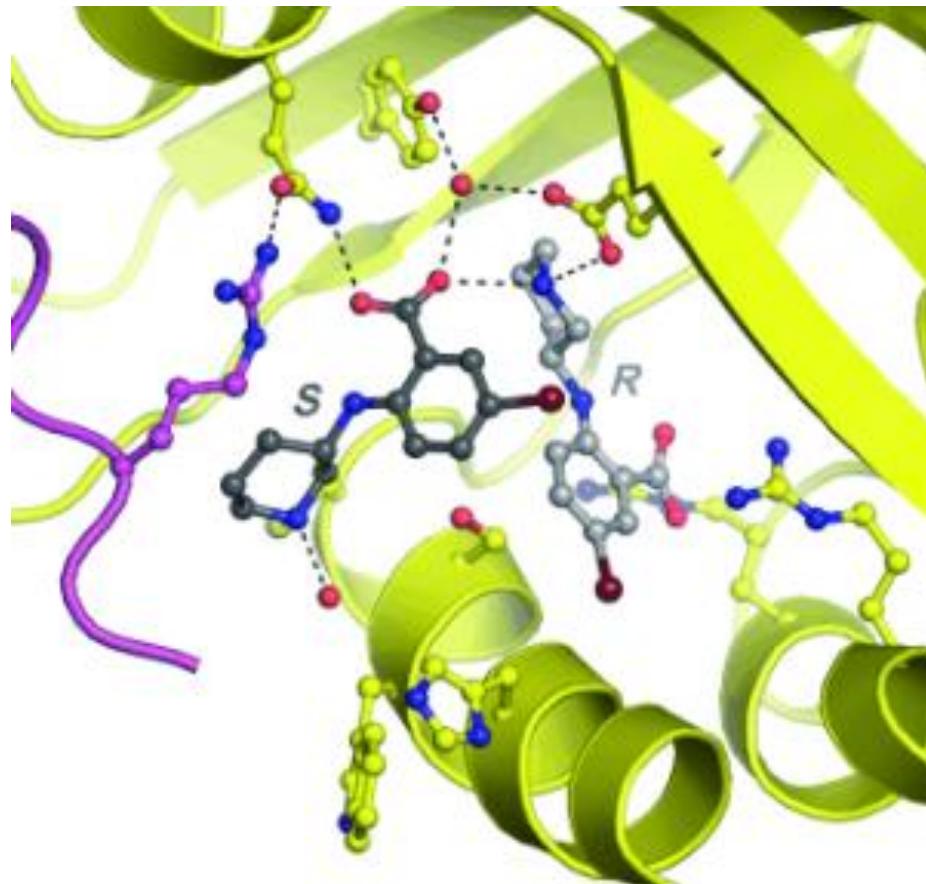
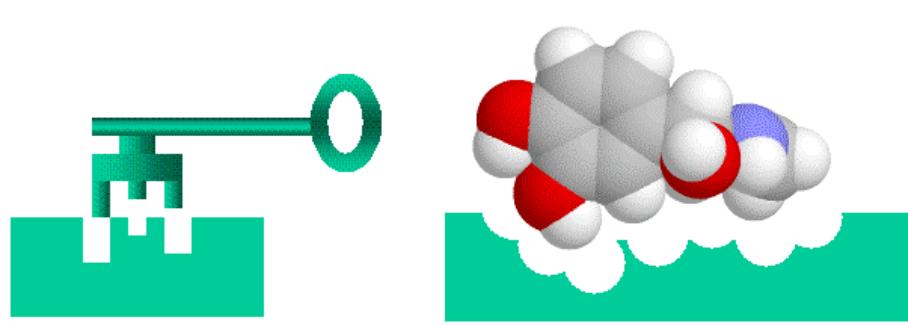


Canonical helical conformations.

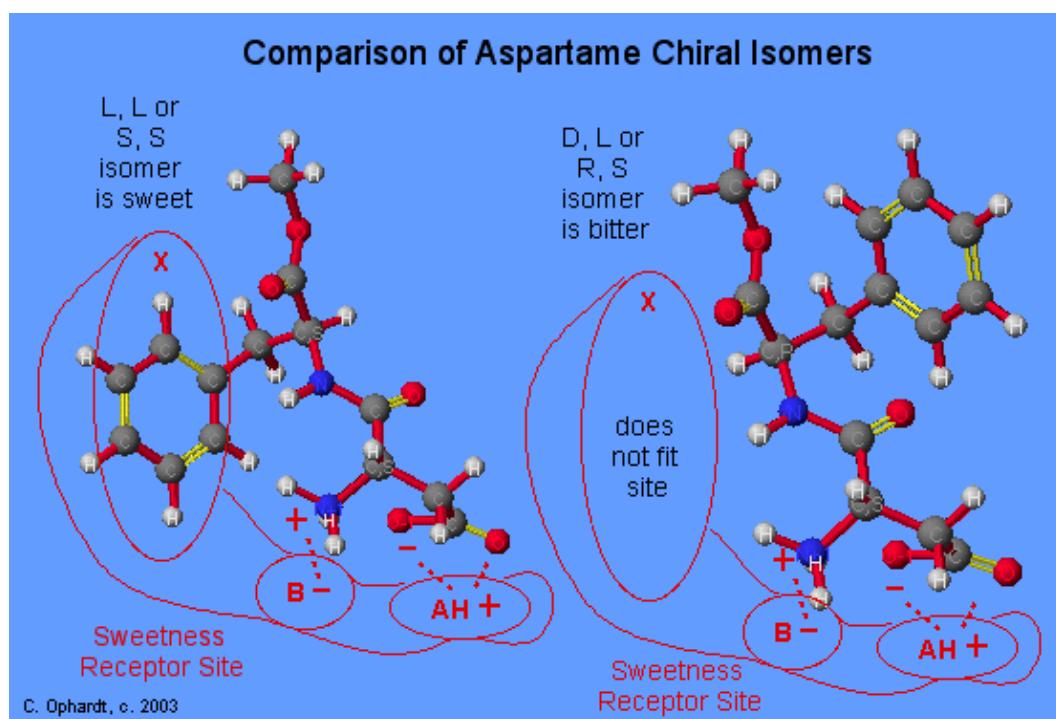
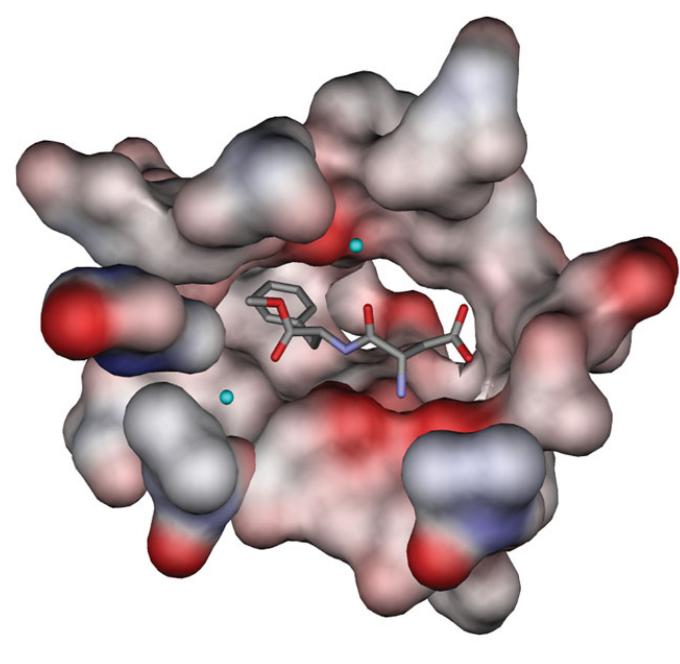
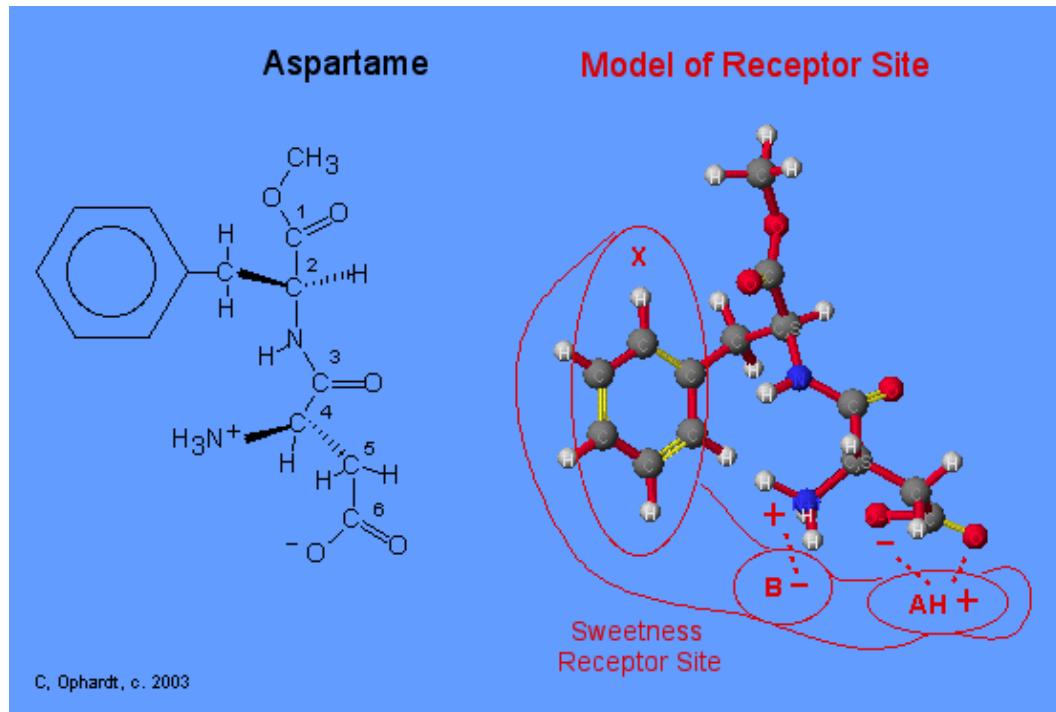
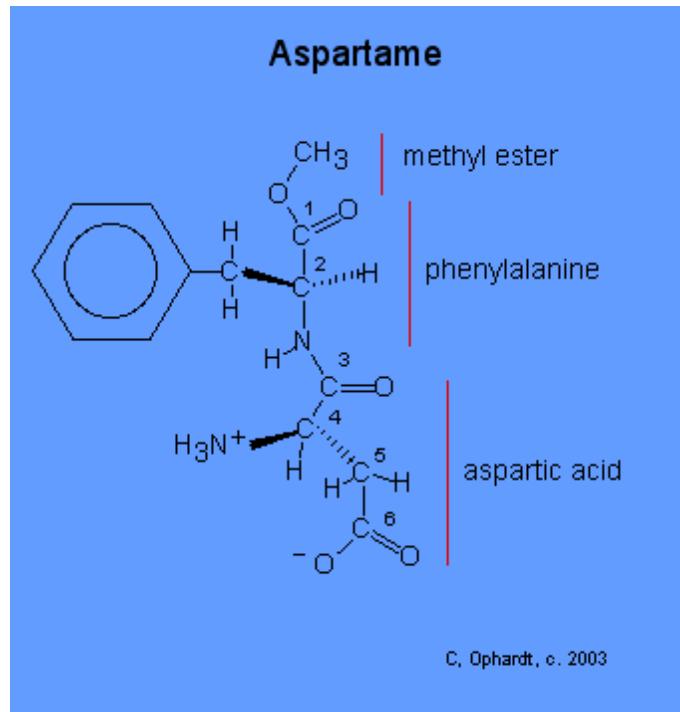


Vieira-Pires R S , and Morais-Cabral J H J Gen Physiol
2010;136:585-592

Enzyme-Substrate Recognition & Binding



Chirality & Taste/Smell



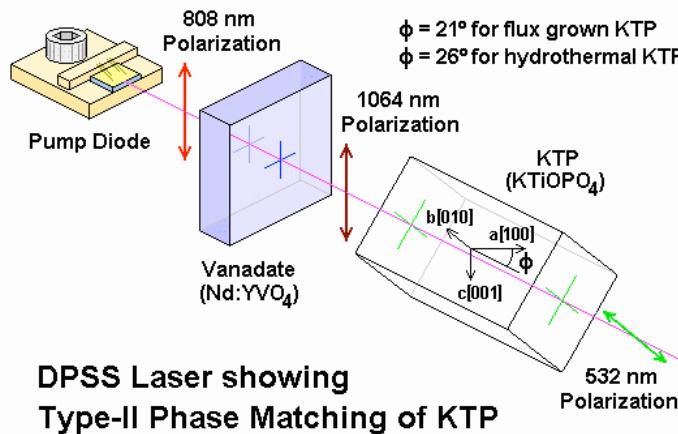
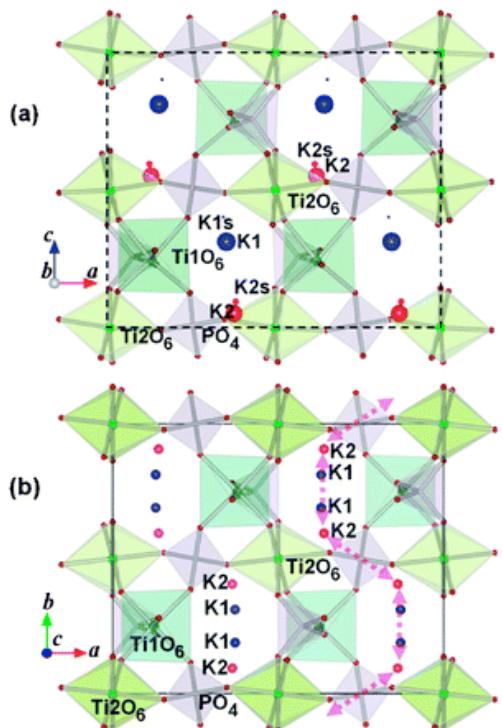
Impact of Chirality in Optical Materials

Potassium Titanyl Phosphate (KTP) - KTiOPO₄

Chiral compound that forms chiral crystals

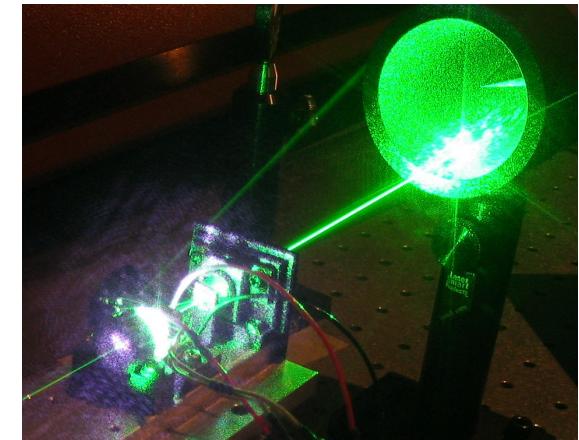
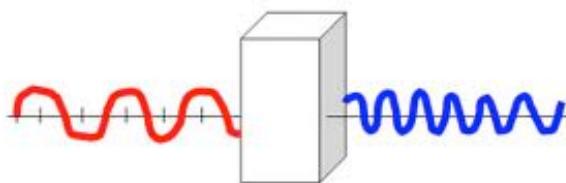


Chiral Crystal Structure of KTiOPO₄



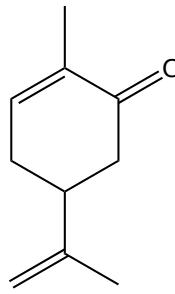
DPSS Laser showing
Type-II Phase Matching of KTP

Frequency of Light Doubles!

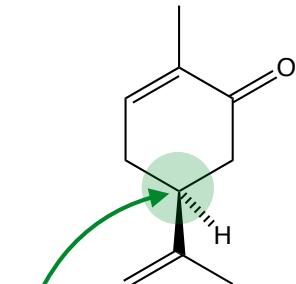


Demo:

1) carvone

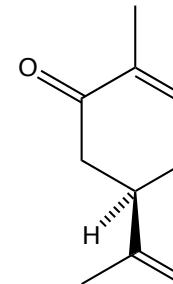


different spacial arrangement of 4
different substituents on carbon

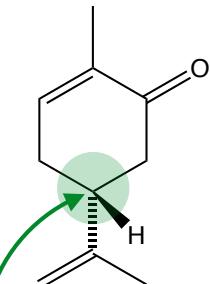


(S)-(+)-carvone
D-carvone
caraway seed

mirror plane

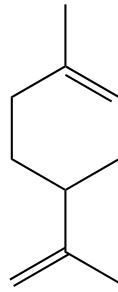


(R)-(−)-carvone
L-carvone
spearmint



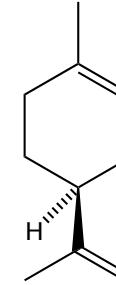
mirror plane

2) limonene



(R)-(+)-limonene
L-limonene
citrus, oranges

mirror plane



(S)-(−)-limonene
D-limonene
terpentine, hint of lemon



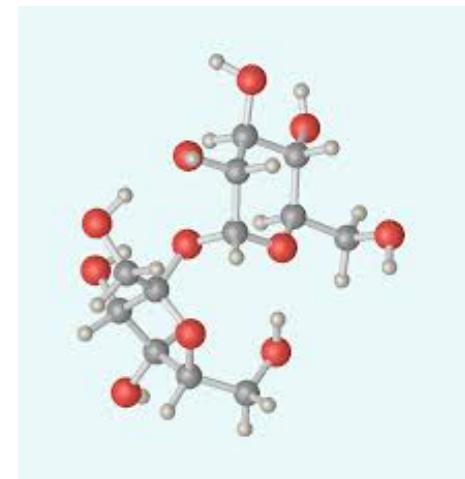
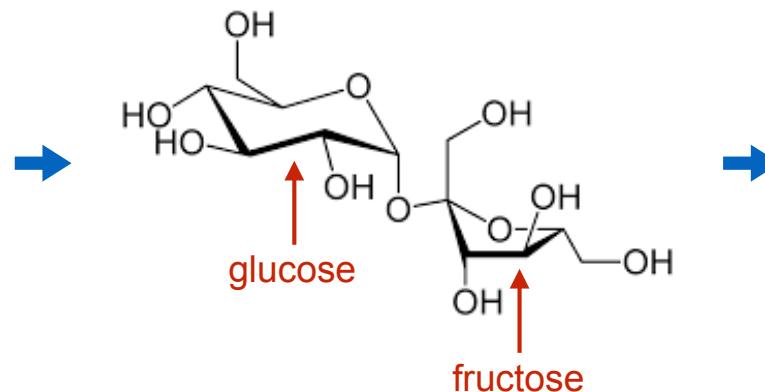
Q: How are the structures different?

Q: Why do the compounds smell different?

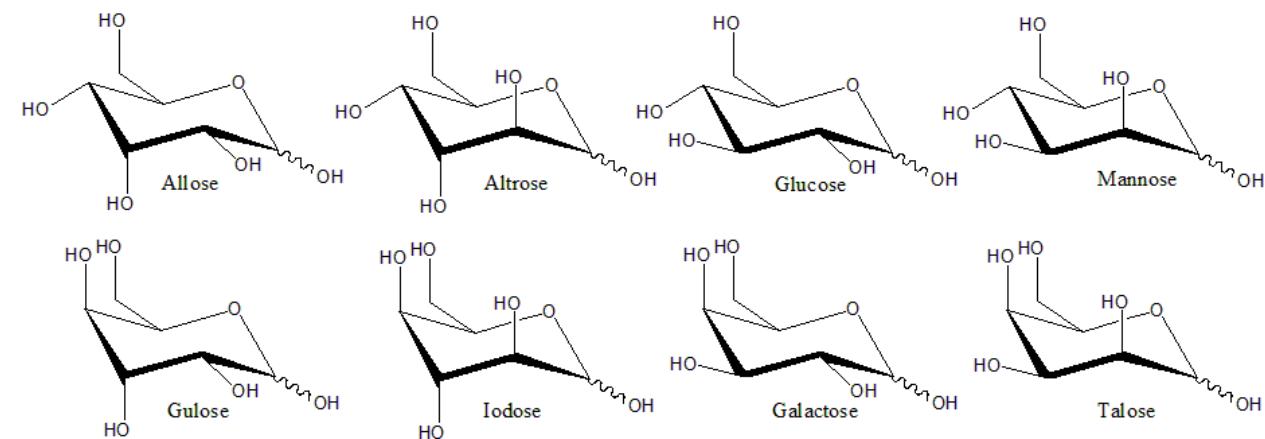
Q: What do (R)/(S), (+)/(-), and D/L mean?

Chirality & the Structure of Sugars

sucrose

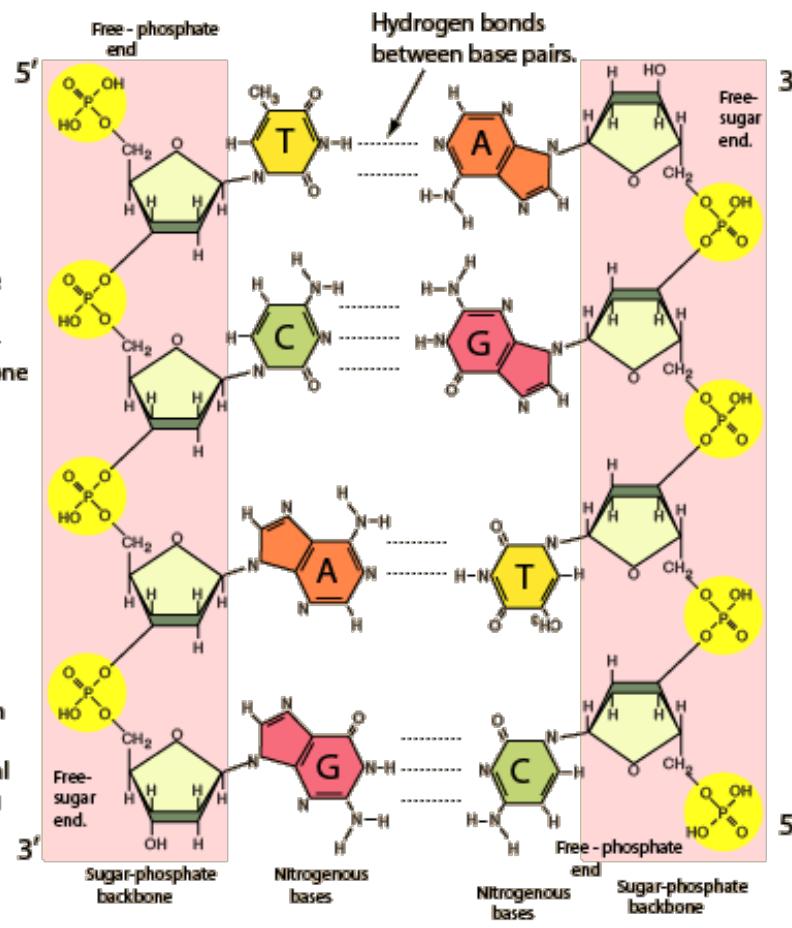
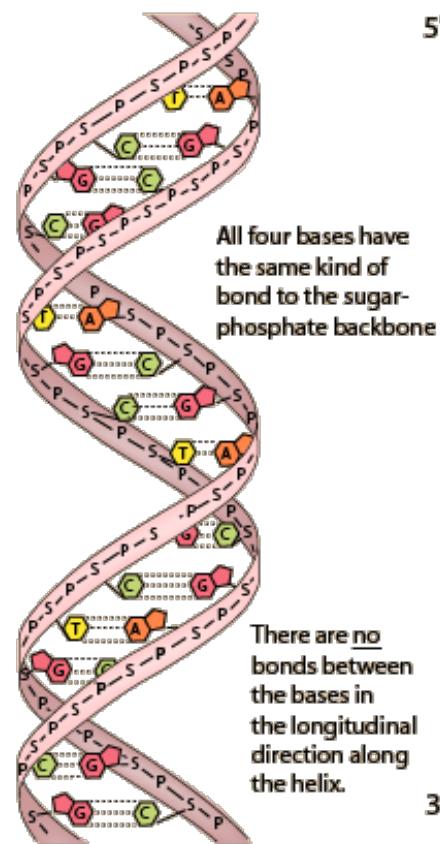
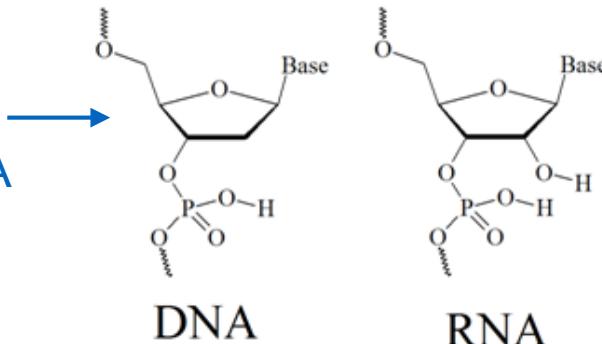


pyranose
sugars

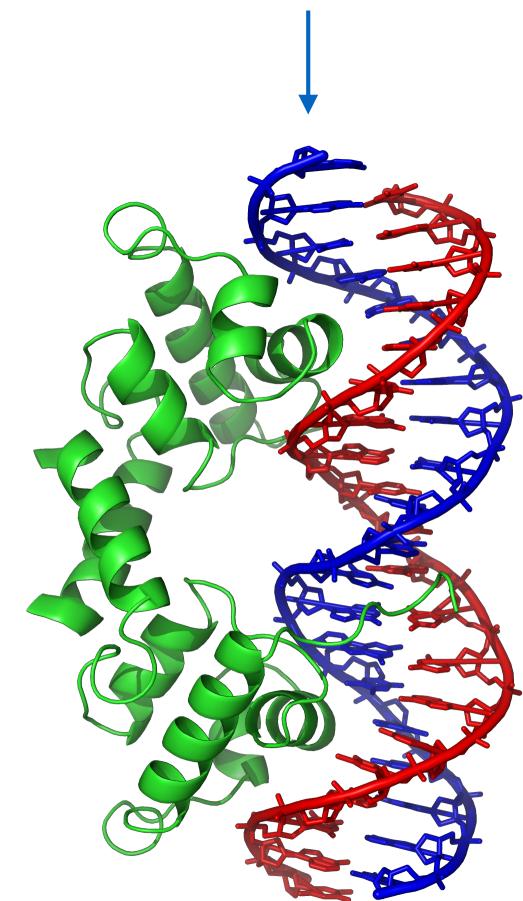


Comparison of DNA and RNA structures

chiral sugar-phosphate units forming the backbone of DNA & RNA



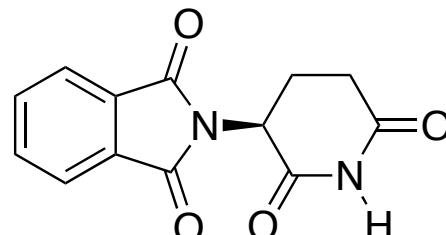
protein bound to the major groove of DNA



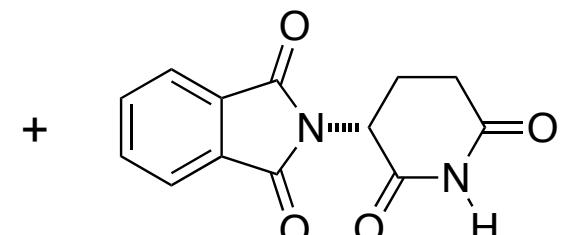
Pharmacological impact of chirality: Thalidomide



racemic
mixture



(S)-enantiomer



(R)-enantiomer

Thalidomide - Contergan®

Grünenthal (1950s)

- antinauseant
- sedative



teratogen!



inhibits morning sickness

Federal Food, Drug & Cosmetic Act (1938)

- allowed “experimental” use of drugs pending approval without demonstration of efficacy

Kefauver-Harris Drug Amendment (1962)

- requires proof of efficacy and safety of drugs before approval



synthesis or separation of single enantiomers of drugs

Importance today



\$133 billion
single-enantiomer drug sales in 2000

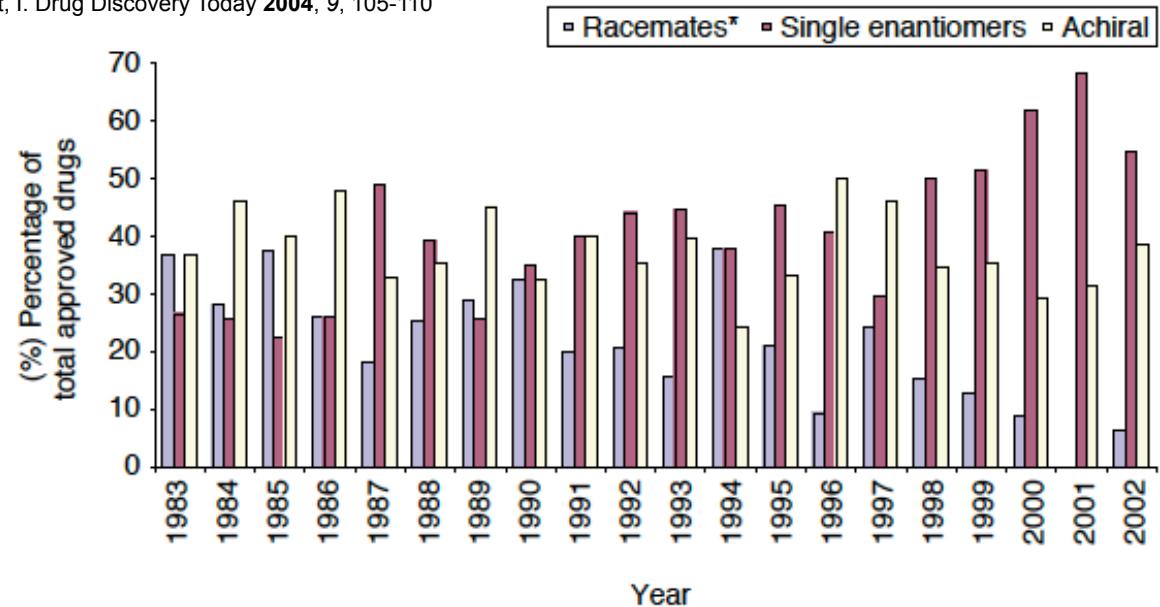
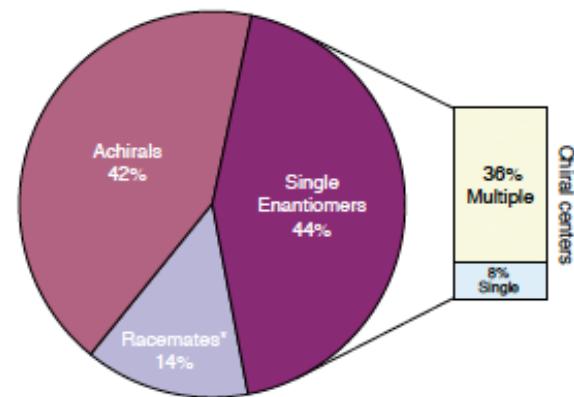
GLOBAL BRAND	2003 SALES (\$ BILLIONS)	ACTIVE INGREDIENT(S)	FORM OF ACTIVE INGREDIENT(S)	THERAPEUTIC EFFECT
Lipitor	\$10.3	Atorvastatin	Single enantiomer	Lipid-lowering agent
Zocor	6.1	Simvastatin	Single enantiomer	Lipid-lowering agent
Zyprexa	4.8	Olanzapine	Achiral	Psychotropic agent
Norvasc	4.5	Amlodipine	Racemate	Calcium channel blocker
Procrit	4.0	Epoetin a	Protein	Stimulant of blood cell production
Prevacid	4.0	Lansoprazole	Racemate	Inhibitor of gastric acid secretions
Nexium	3.8	Esomeprazole	Single enantiomer	Inhibitor of gastric acid secretions
Plavix	3.7	Clopidogrel	Single enantiomer	Inhibitor of platelet aggregation
Advair	3.7	Salmeterol	Racemate	β_2 -adrenergic bronchodilator
		Fluticasone	Single enantiomer	Anti-inflammatory agent
Zoloft	3.4	Sertraline	Single enantiomer	Selective serotonin reuptake inhibitor
TOTAL	\$48.3			

NOTE: Sales figures from IMS Health.

9/10 chiral

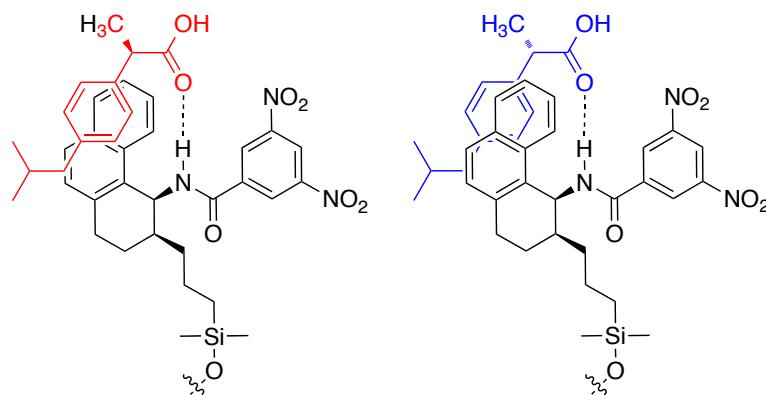
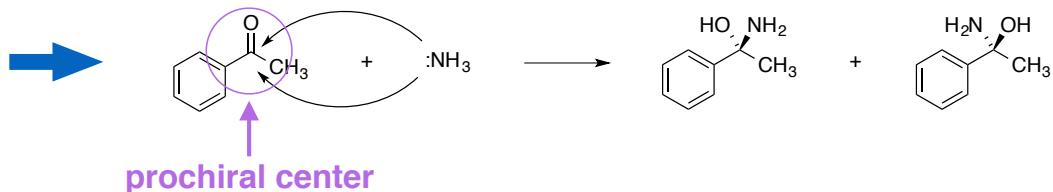
Distribution of world-wide approved drugs 1983-2002

Caner, H.; Groner, E.; Levy, L.; Agranat, I. Drug Discovery Today 2004, 9, 105-110

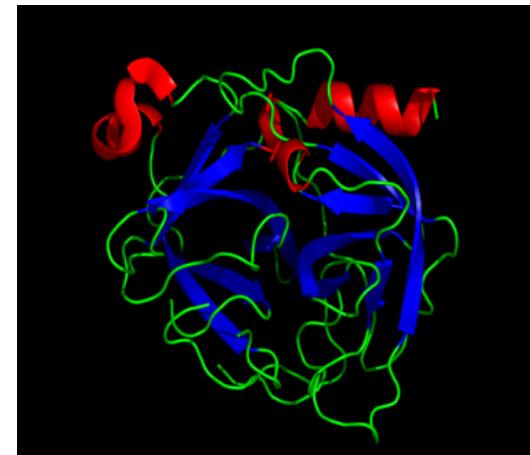


Methods to separate enantiomers

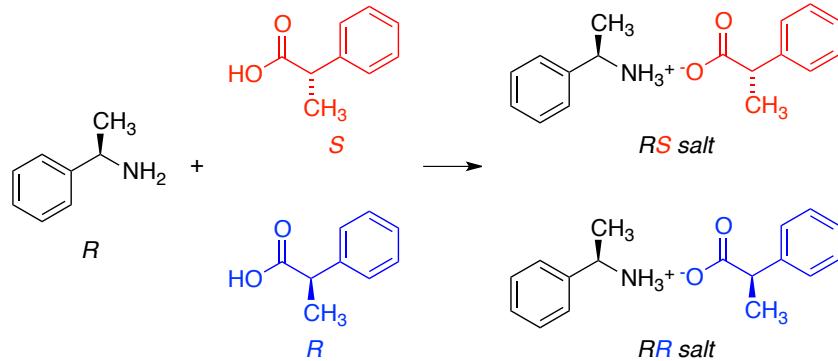
Reaction forms a 50:50 mixture
of two stereoisomers
(racemic mixture)



chiral chromatography



enzymatic resolution



diastereomeric crystallization



entrainment by seeding

Q: How can we indicate stereochemistry when naming compounds that are chiral?

(R) and (S) Nomenclature of Asymmetric Carbon Atoms (5-3)

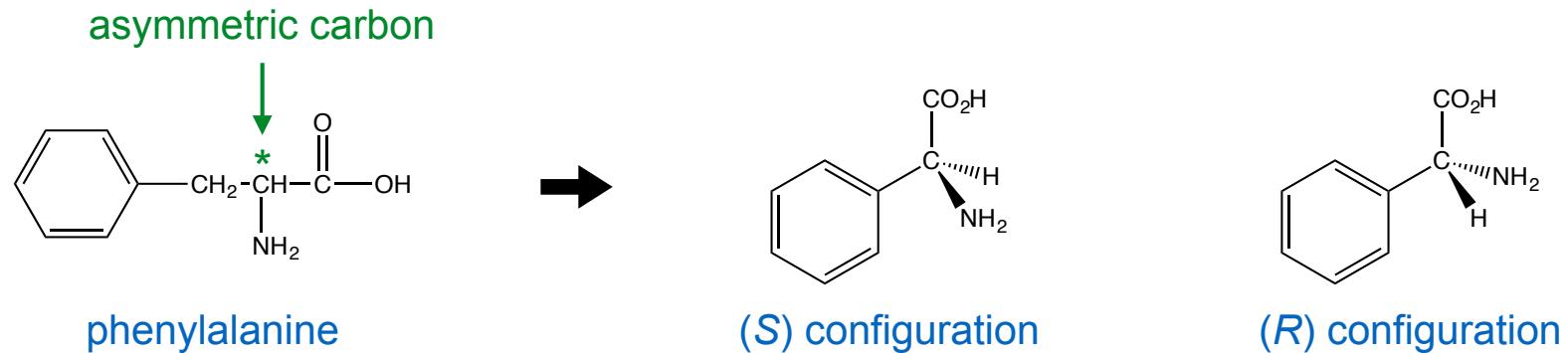
A method to indicate the spacial arrangement of four atoms/groups bonded to asymmetric carbon atoms

Used to distinguish between the two different mirror-image spacial arrangements

Called configurations

- Cahn-Ingold-Prelog (CIP) sequence rules
- (R) or (S) configuration

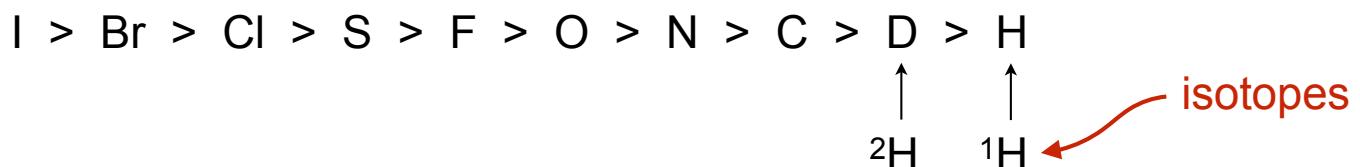
Ex:



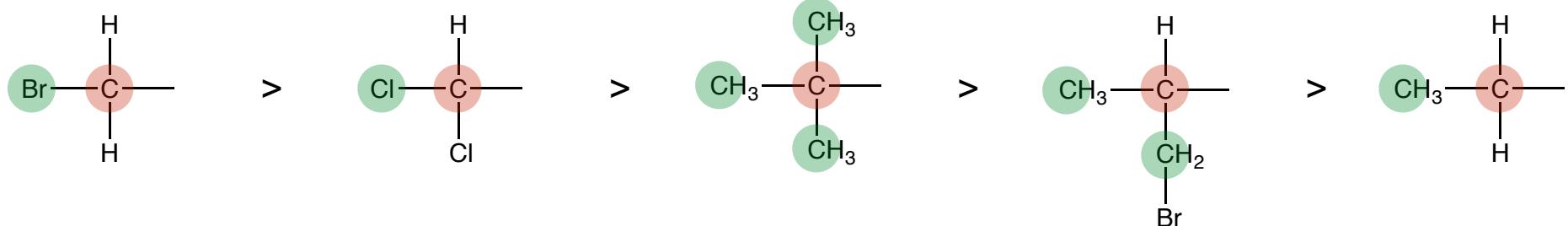
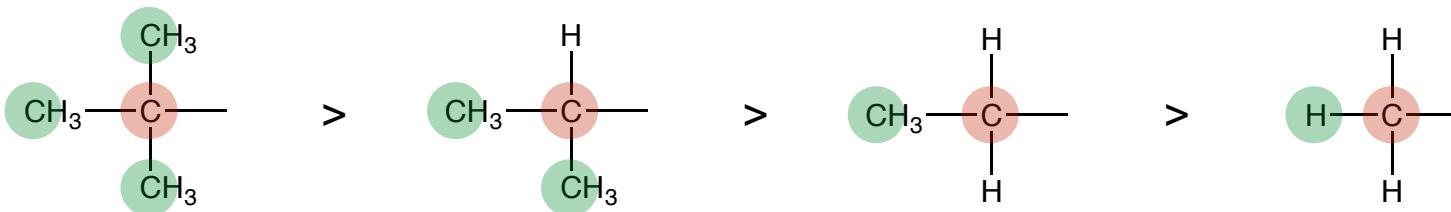
Q: How are (R) and (S) configuration determined?

CIP Priority Rules for Assigning (R)/(S) Configuration

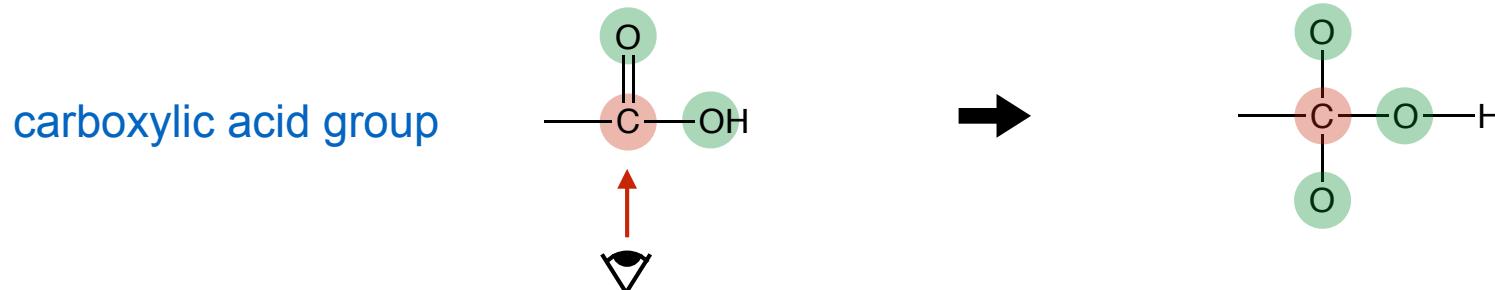
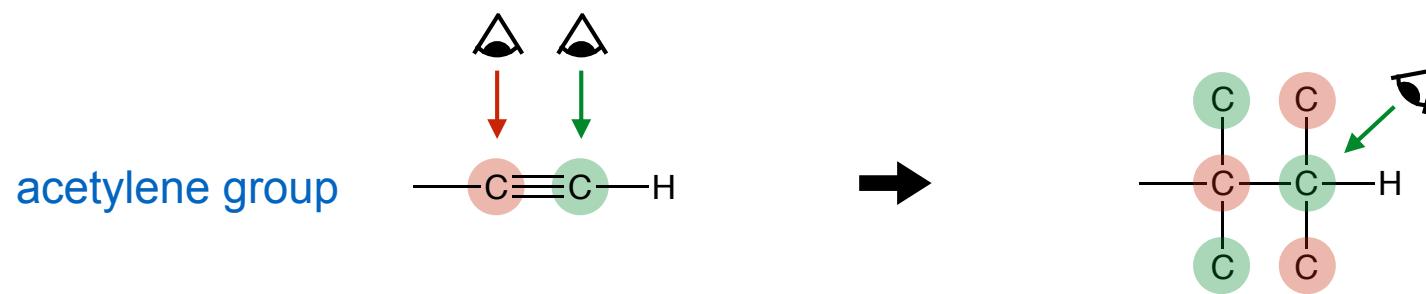
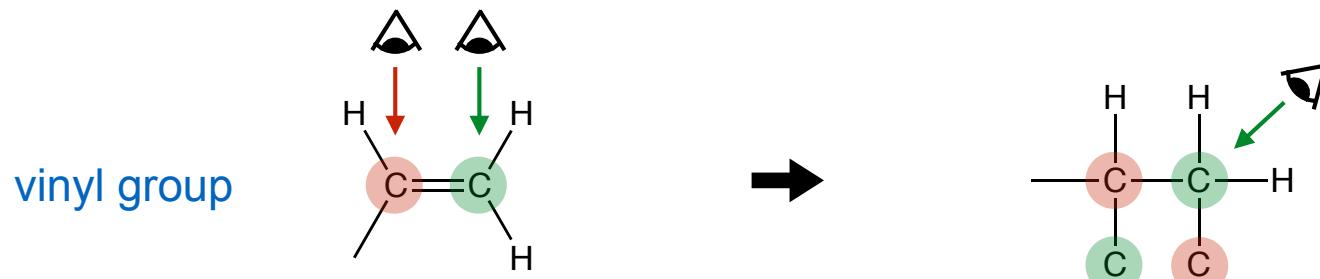
1. Rank atoms bonded to the asymmetric carbon in order of **decreasing atomic number**



2. If two atoms are identical, move to the next bonded atom(s) and so on until a difference is found applying rule #1. A greater number of the same atom is given higher rank.



3. Treat atoms with double or triple bonds as if singly-bonded to two or three separate atoms



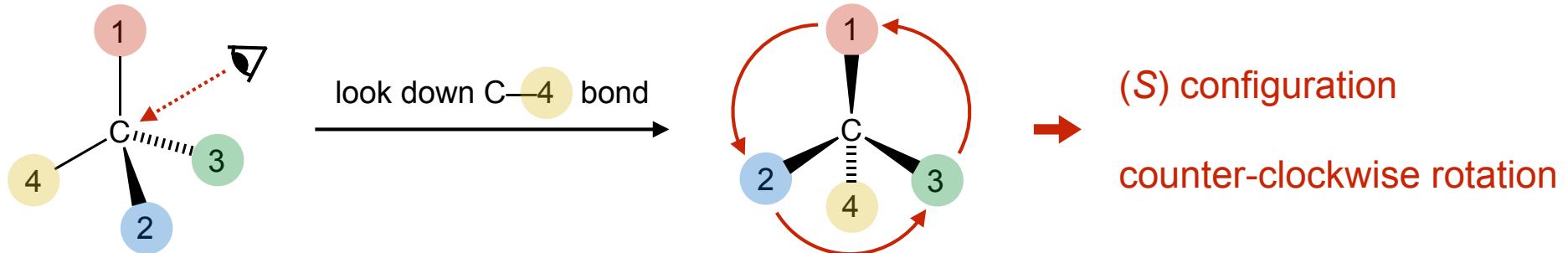
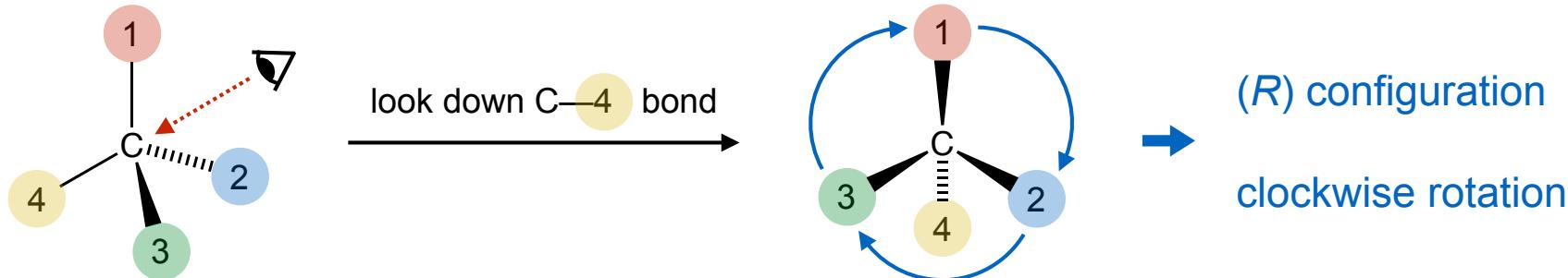
4. Having ranked the four bonded groups 1-4, look down the bond from the asymmetric carbon toward the lowest-priority group (i.e., #4) and determine if groups 1-3 are arranged clockwise (*R*) or counter-clockwise (*S*)

clockwise → (*R*) configuration

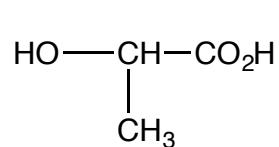
(*R*) = rectus (*upright* in latin)

counter-clockwise → (*S*) configuration

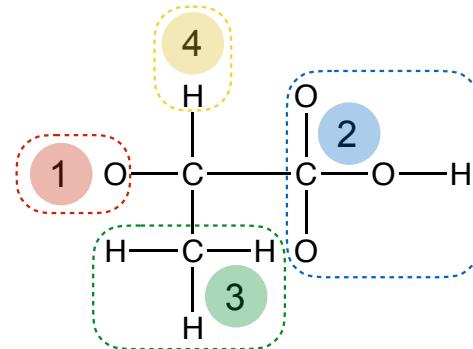
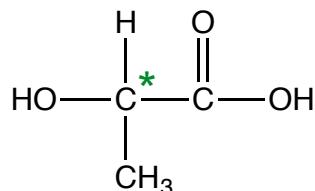
(*S*) = sinster (*left* in latin)



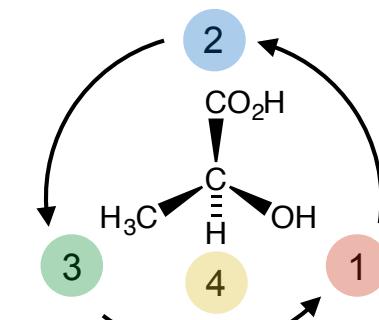
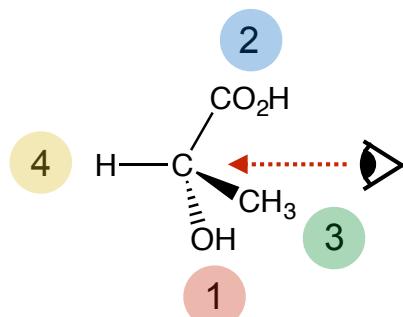
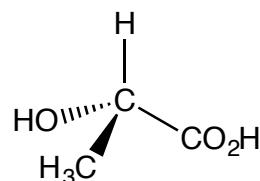
Ex: lactic acid



=

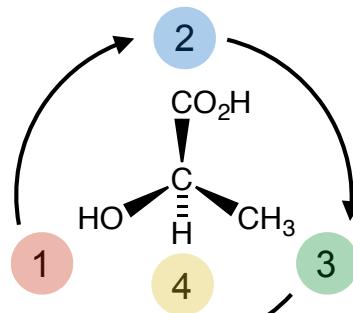
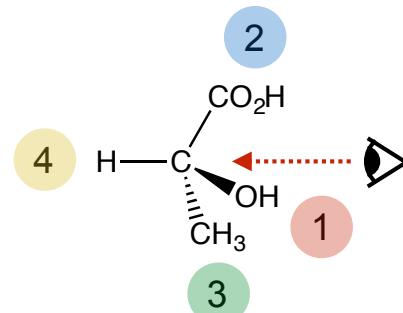
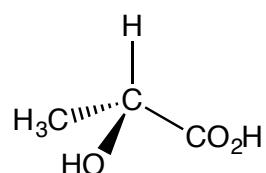


(+)-lactic acid



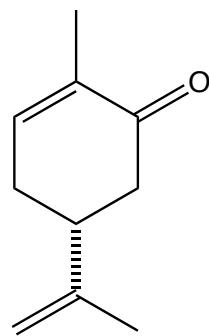
(S)-(+)-lactic acid

(-)-lactic acid

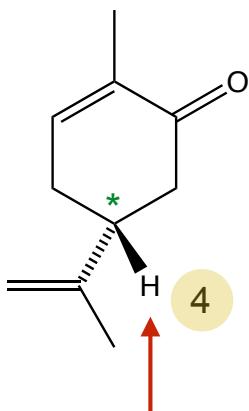


(R)-(-)-lactic acid

Ex: Configuration of (-)-Carvone?

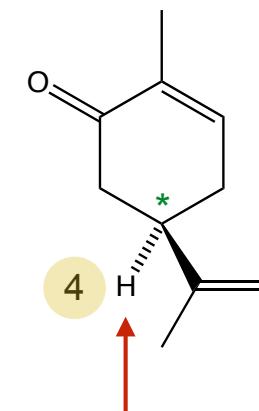


=



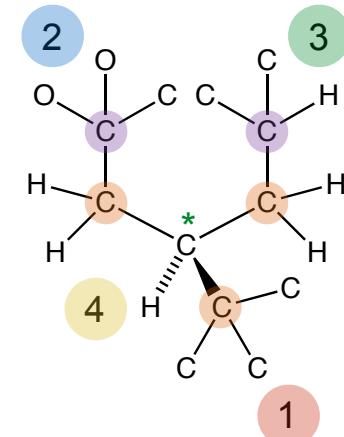
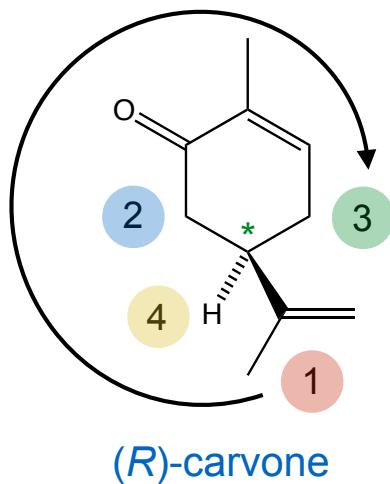
lowest priority
group is up

flip over
→

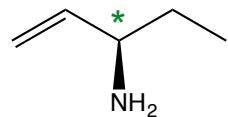


lowest priority
group is back

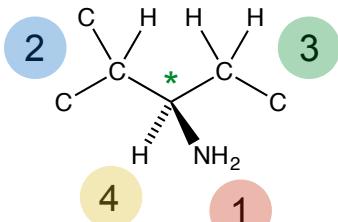
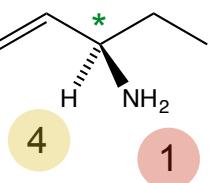
↓ prioritize
remaining groups



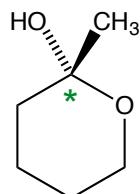
Ex: Assign (R)/(S) configuration



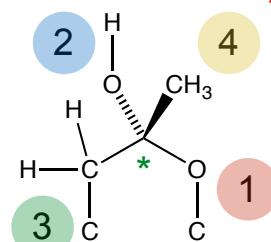
(R)



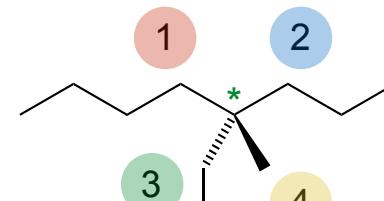
(R)



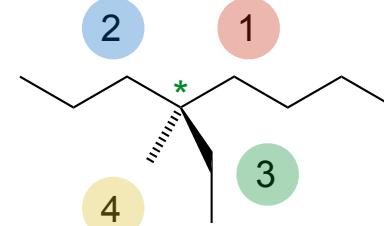
(R)



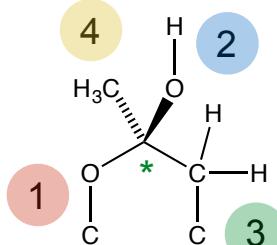
lowest priority
group is up



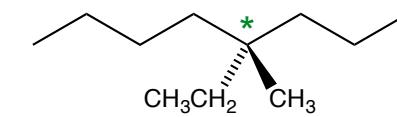
(S)



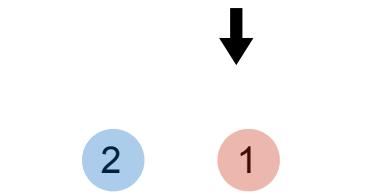
lowest priority
group is up



(R)



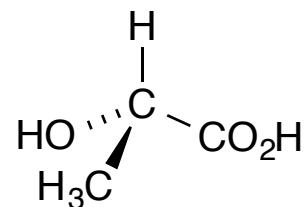
(S)



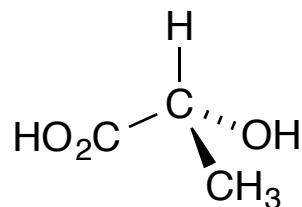
(S)

Optical Activity & Properties of Chiral Compounds (5-4)

Q: How do the properties of enantiomers compare?



(S)-(+)-lactic acid



(R)-(-)-lactic acid

m.p.	53 °C	53 °C
b.p.	122 °C	122 °C
pKa	3.9	3.9
[α]D	+2.6 °	-2.6 °

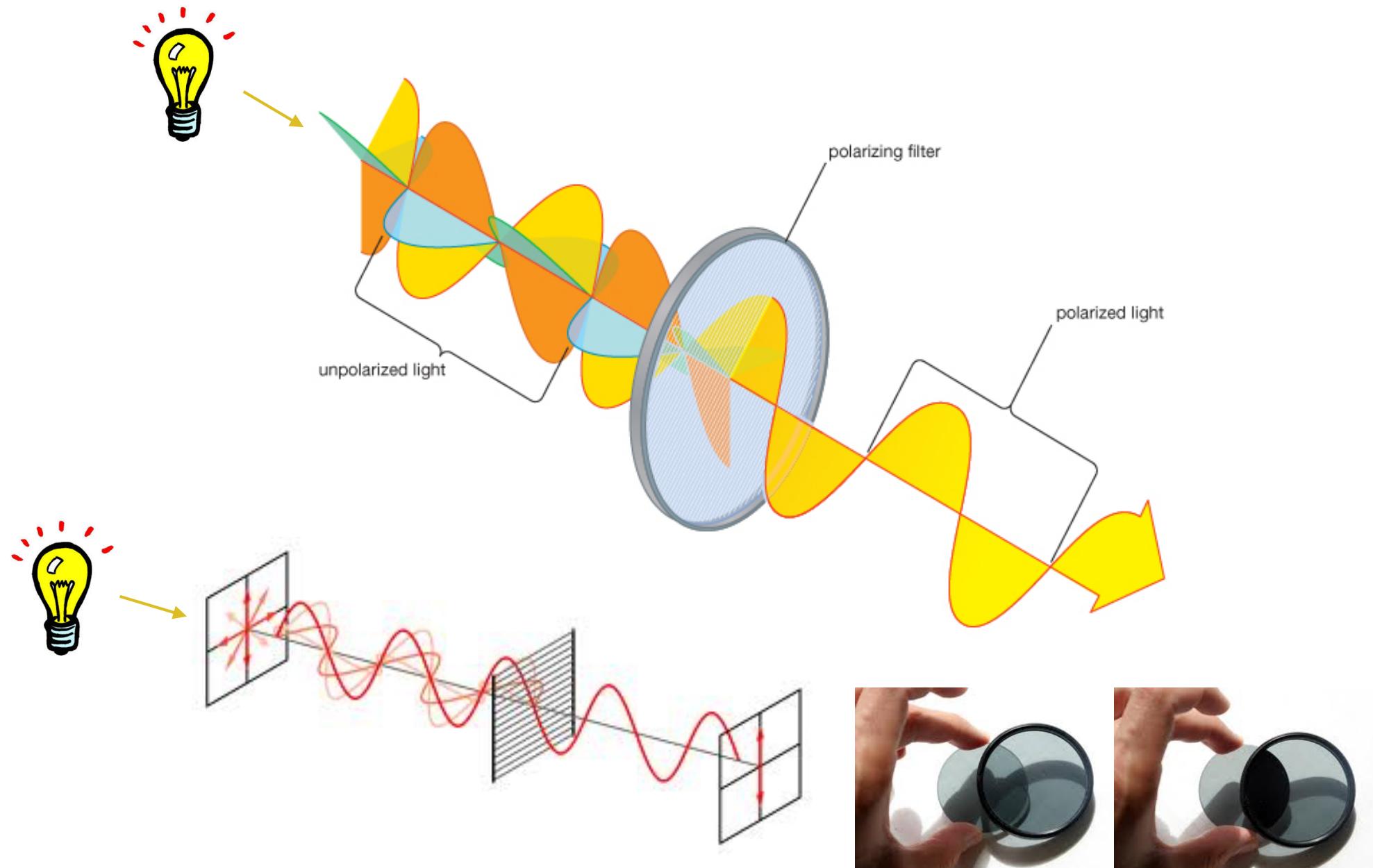
physical properties of
enantiomers are identical

optical rotation of
polarized light differs

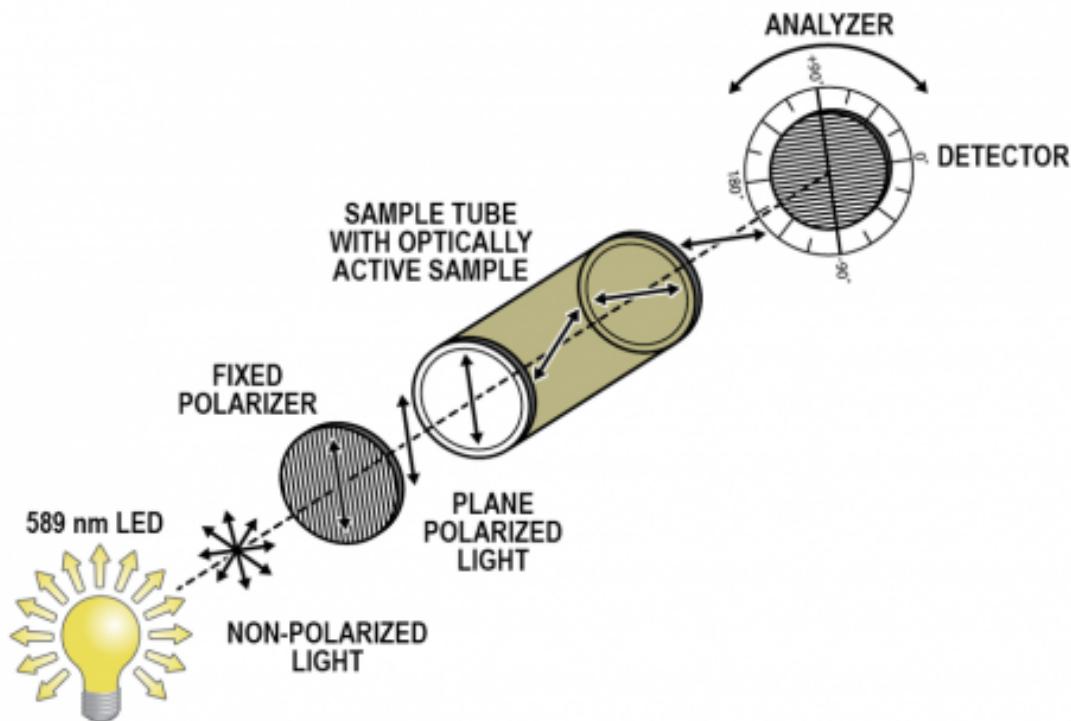
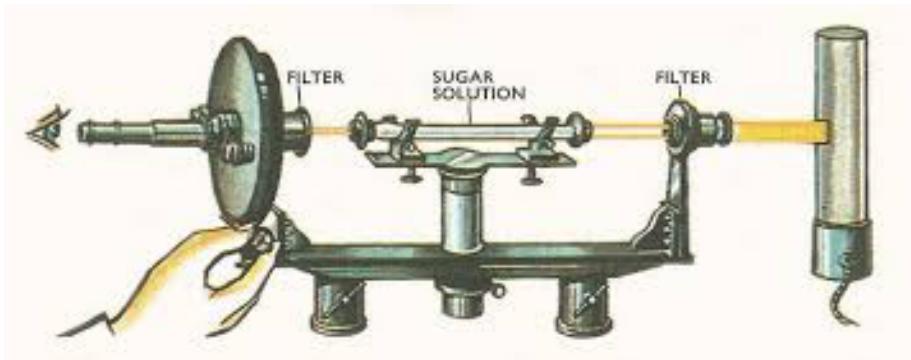
Q: What do (+) and (-) mean?

Q: What is $[\alpha]_D$?

Plane-Polarized Light



Measuring Optical Rotation with a Polarimeter



$$[\alpha]_D^{20} = \frac{\alpha_{observed}}{cl}$$



$[\alpha]$ = specific rotation

D = sodium D line (589 nm light)

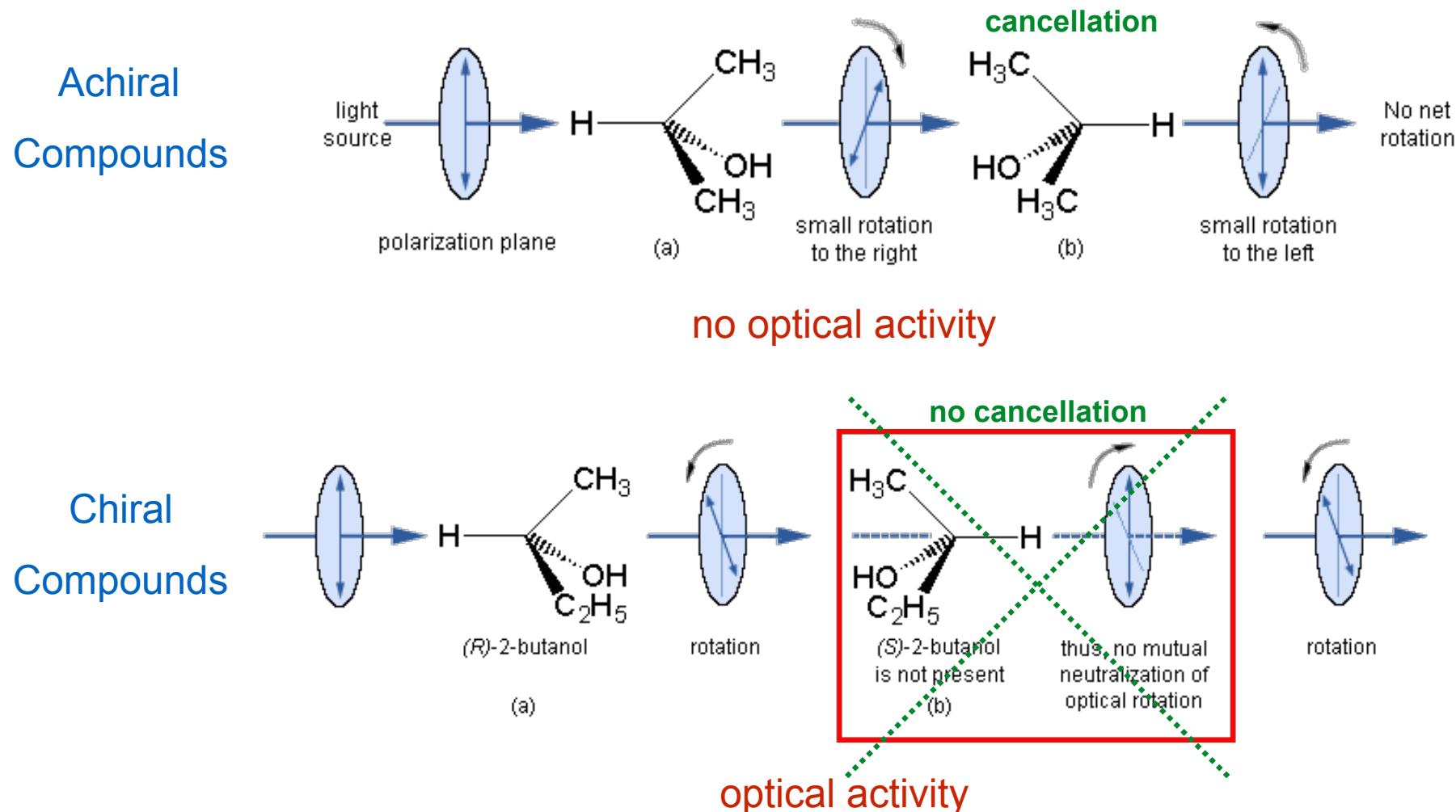
α = observed rotation in degrees

c = concentration in g/mL

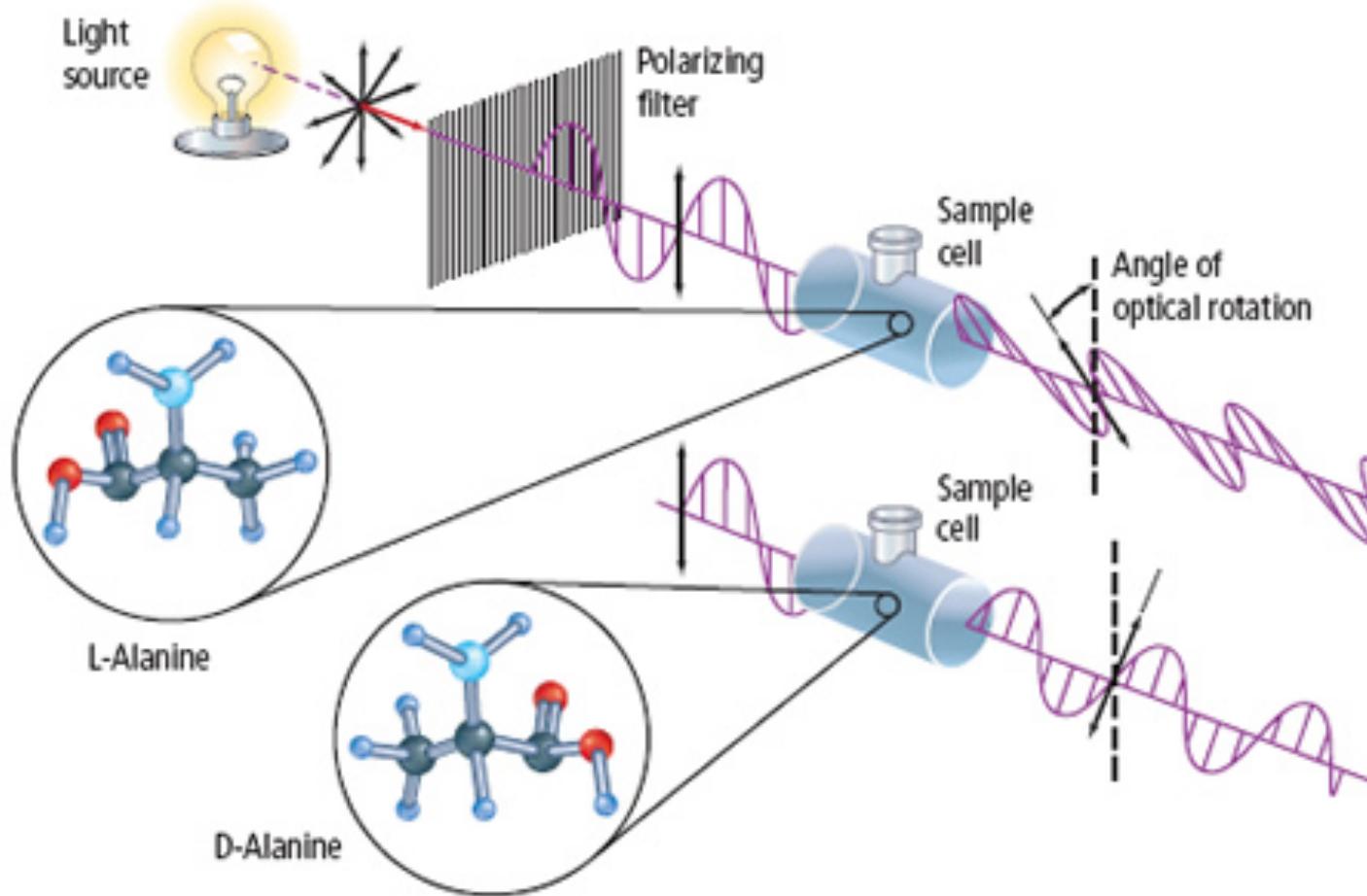
l = path length in decimeters (dm)

Optical Activity of Achiral vs Chiral Compounds

- Optical Activity - rotation of the plane of polarized light
- Optically Active Compound - compound that rotates polarized light

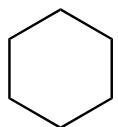


Optical Activity of Enantiomers



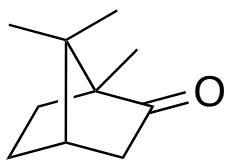
Enantiomers rotate the plane of polarized light **in opposite directions by exactly the same amount**

Optical Activity $[\alpha]$ of Some Compounds



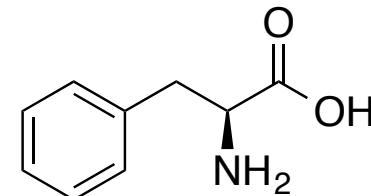
cyclohexane

$$[\alpha] = 0^\circ$$



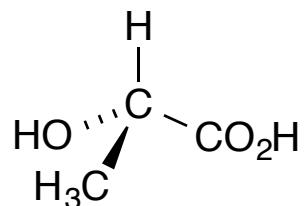
(+)-camphor

$$[\alpha] = 44.3^\circ$$



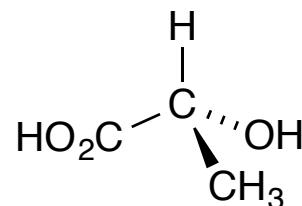
(S)-(-)-phenylalanine

$$[\alpha] = -33.7^\circ$$



(S)-(+)-lactic acid

$$[\alpha] = +2.6^\circ$$



(R)-(-)-lactic acid

$$[\alpha] = -2.6^\circ$$

Dextrorotatory - compounds that rotate plane-polarized light to the right (**clockwise**)

- designated as **(+)** or **d**

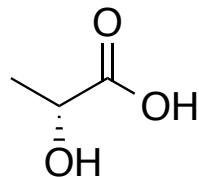
Levorotatory - compounds that rotate plane-polarized light to the left (**counter-clockwise**)

- designated as **(-)** or **l**

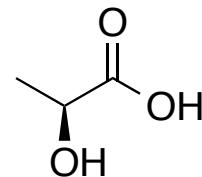
No relationship between **(+)/(-)** or **d/l** (empirical) with configuration **(R)/(S)** (naming)

Nomenclature for Chiral Compounds

(R)- and (S)- → Based on CIP rules for designating configuration

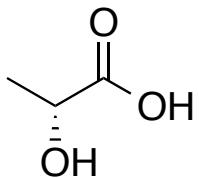


(R)-lactic acid



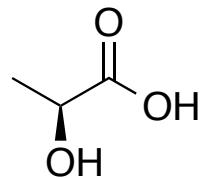
(S)-lactic acid

(+)- and (-), or d- and l- → Based on measured optical rotation



(-)-lactic acid

l-lactic acid



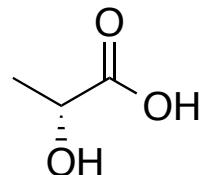
(+)-lactic acid

d-lactic acid

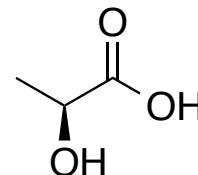
Note: Use of *d*- and *l*- is discouraged by IUPAC & is being phased out

D-/L- vs d-/l-

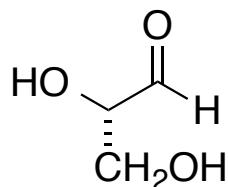
D- and L- → Based on similarity of configuration to glyceraldehyde, which happened to be a sample with a configuration that was dextrorotatory when tested (arbitrary designation)



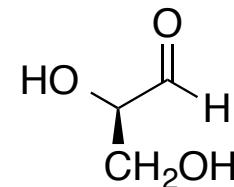
D-lactic acid



L-lactic acid



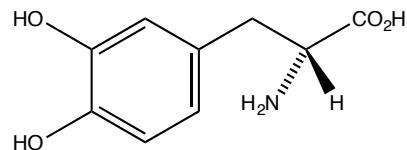
D-glyceraldehyde



L-glyceraldehyde

D-/L- should not be confused with *d-/l-*

Ex: dopamine

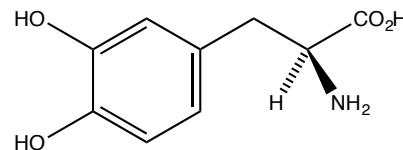


D-DOPA

(+)-DOPA

(*R*)-DOPA

no biological effect in humans



L-DOPA

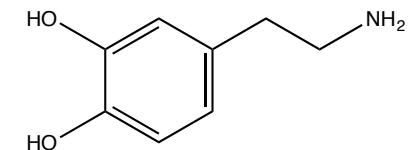
(-)-DOPA

(*S*)-DOPA

treatment of Parkinson's disease



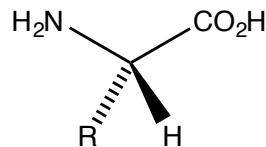
- CO_2



dopamine

(neurotransmitter)

Ex: amino acids



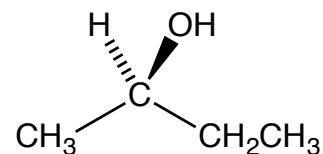
all natural amino acids are *L*-amino acids and (+)-amino acids

R = many different side chains

Racemic Mixtures (5-6)

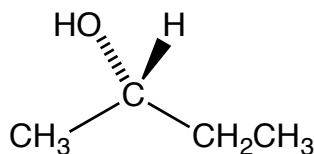
- Racemic Mixture - a mixture containing equimolar amounts (50:50) of enantiomers
- A racemic mixture is not optically active

Ex: 2-butanol



(*R*)-(-)-2-butanol

$$[\alpha] = -13.5^\circ$$



(*S*)-(+)-2-butanol

$$[\alpha] = +13.5^\circ$$



racemic mixture

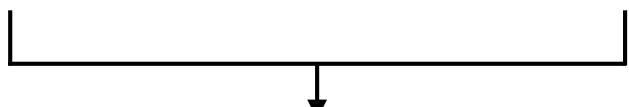
racemic pair

racemates

(+/-) pair

(d/l) pair

(D/L) pair



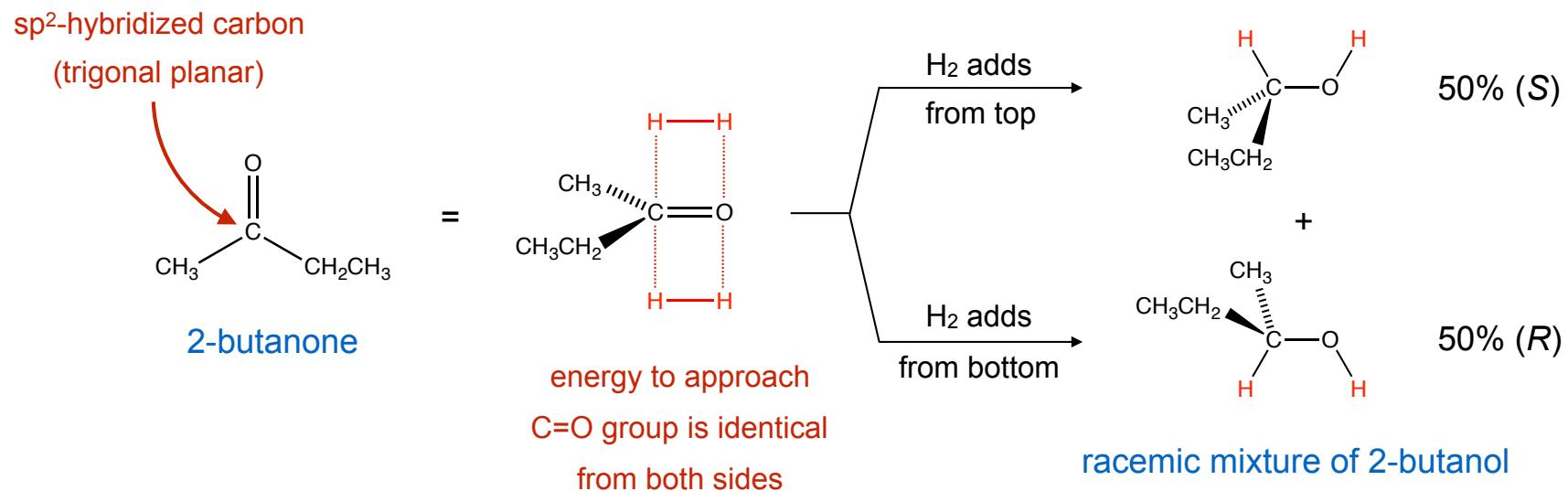
racemic mixture (50:50)

$$[\alpha] = 0^\circ$$

Q: Why no optical activity?

Q: Why do racemic mixtures form in reactions that produce stereocenters?

Ex: Formation of racemic 2-butanol via catalytic hydrogenation

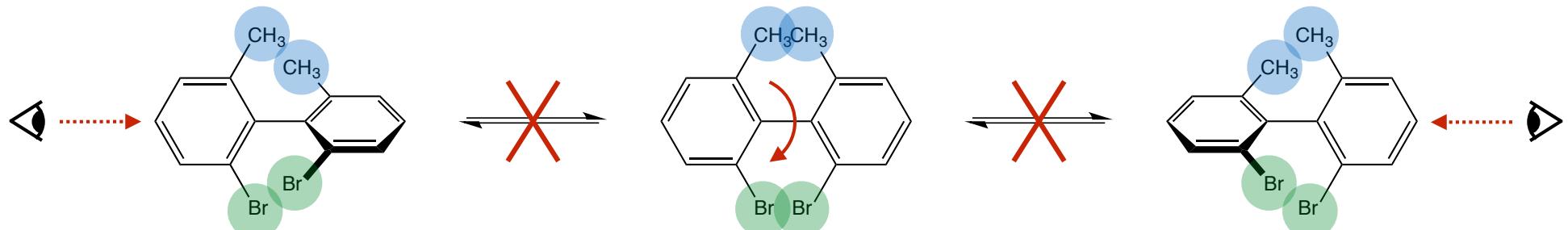


Note: A reaction using achiral (optically inactive) reagents or catalysts always will produce a racemic mixture if the product contains a stereocenter

Chiral Compounds without Asymmetric Atoms (5-9)

- Conformationally strained or locked compounds can be chiral despite not having an asymmetric atom

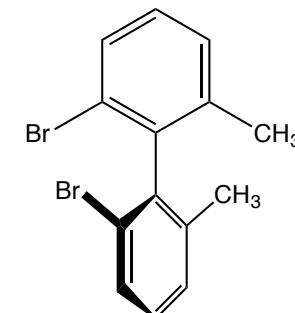
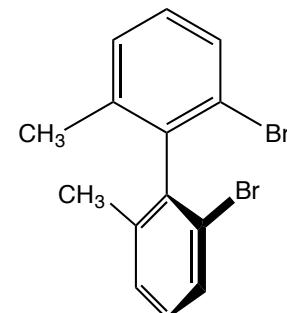
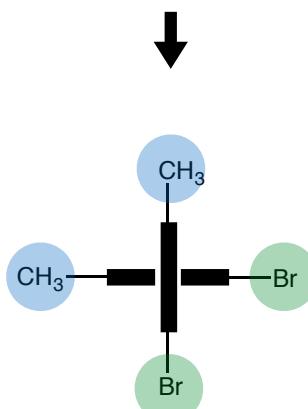
Ex: Substituted biphenyls



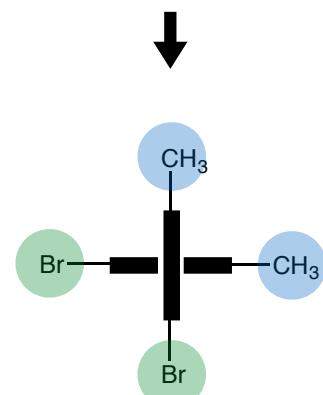
locked staggered conformation
chiral

too strained to rotate
about the central bond

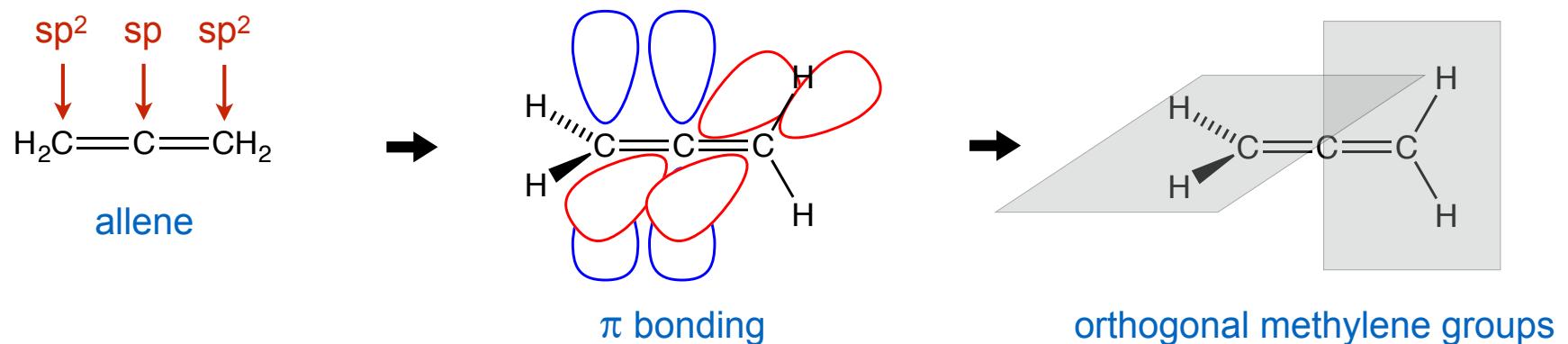
locked staggered conformation
chiral



nonsuperimposable mirror images
enantiomers

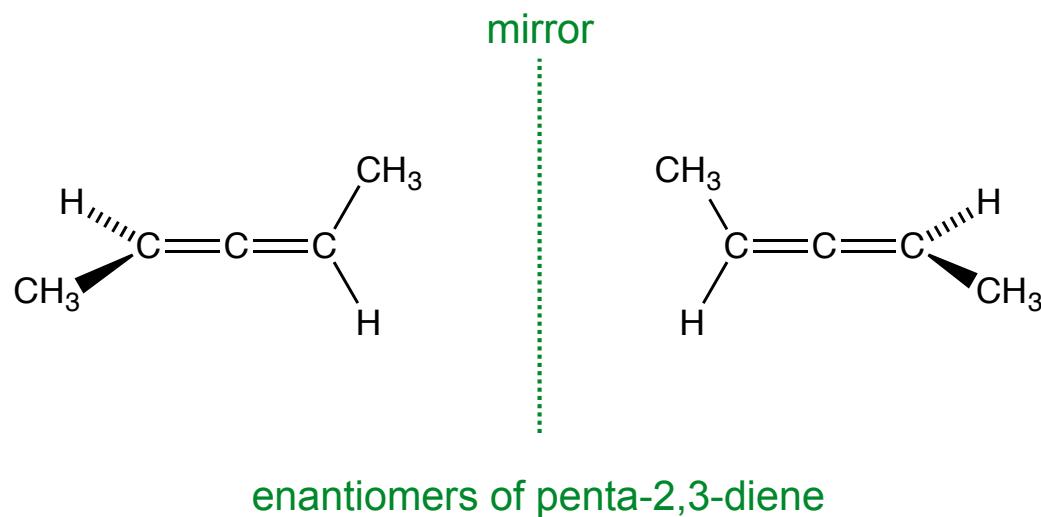


Ex: Substituted allenes



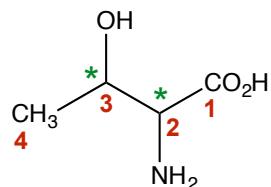
The carbon backbone and attached substituents are completely rigid!

Q: Consequence with respect to chirality when substituents are attached?



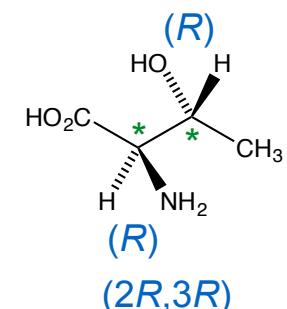
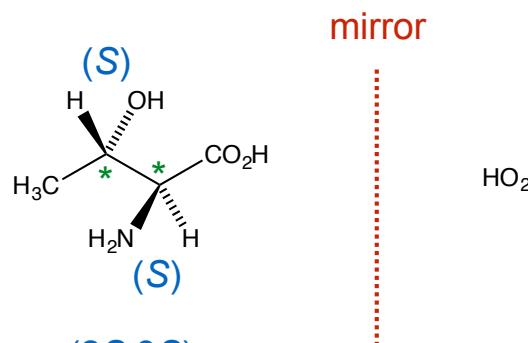
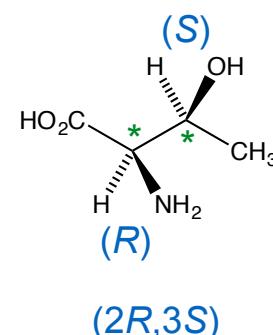
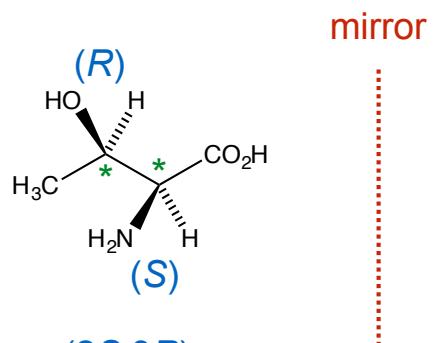
Diastereomers (5-11)

Ex: threonine (2-amino-3-hydroxybutanoic acid)



Two stereo centers (*) → C2 and C3 both can be (*R*) or (*S*)

Q: How many possible stereoisomers?



enantiomers

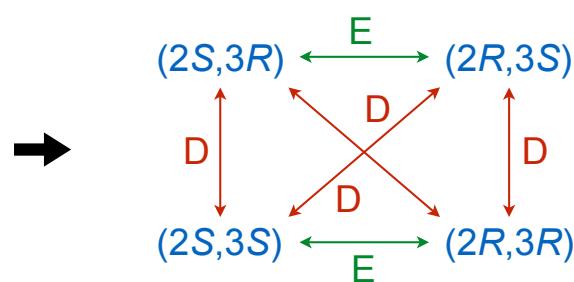
enantiomers

Note: Enantiomers have opposite (*R/S*) configuration at every stereocenter. Why?

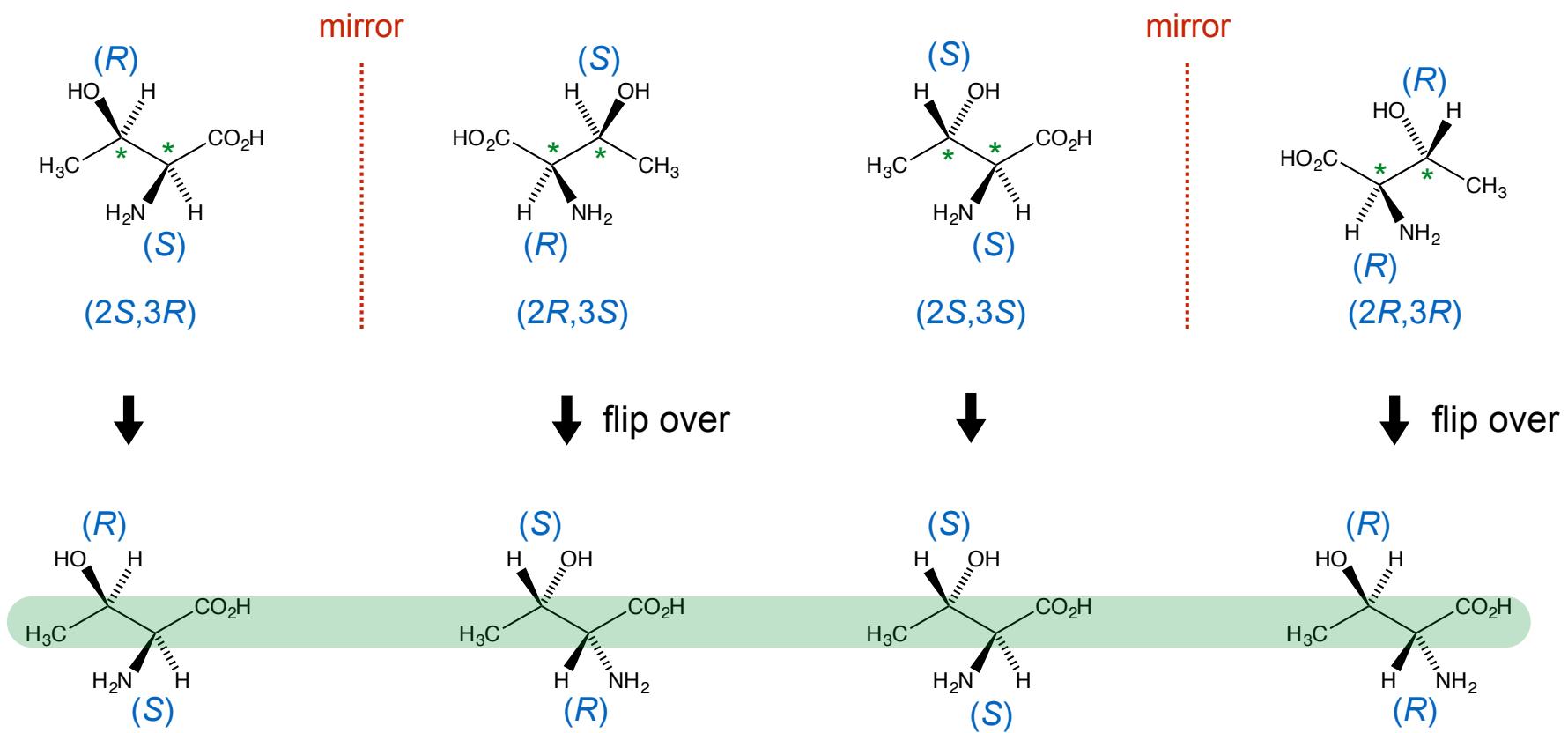
Q: Stereochemical relationship of (*2S,3R*) or (*2R,3S*) with (*2S,3S*) or (*2R,3R*)?

Definitions:

- Enantiomers - stereoisomers that are mirror images
- Diastereomers - stereoisomers that are not mirror images

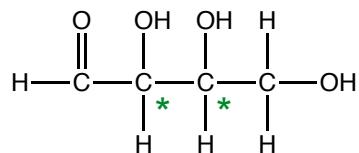


Now compare the structures with the carbon backbones all drawn in the same orientation



It's sometimes easier to see and compare differences between stereoisomers this way

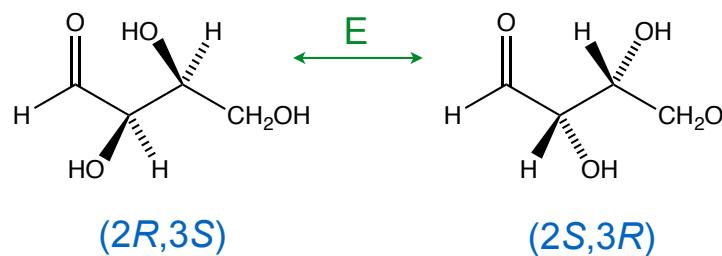
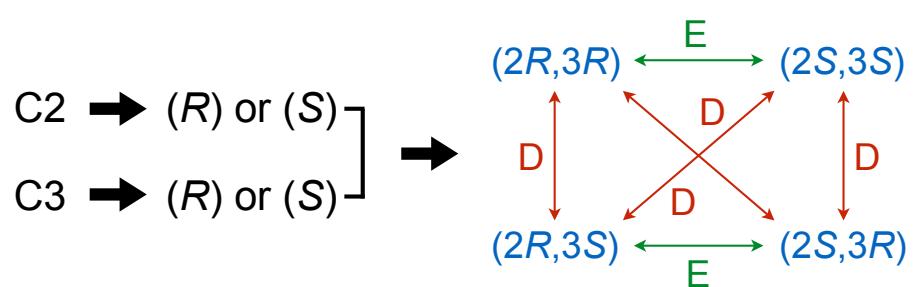
Ex: 2,3,4-trihydroxybutanal



Q: How many stereocenters? Stereoisomers? Enantiomers? Diastereomers?

$$\text{Number of stereocenters (n)} = 2$$

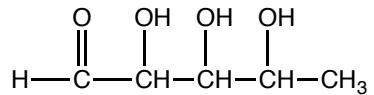
$$\text{Number of possible stereoisomers} = 2^n = 2^2 = 4$$



Property

[α]	+29°	-29°	-22°	+22°
m.p.	solid (130°C)	solid (130°C)	liquid at RT	liquid at RT
solubility in EtOH	slight	slight	very	very

Ex:



Q: How many possible stereoisomers?

Number of stereocenters (n) = 3

Number of possible stereoisomers = $2^n = 2^3 = 8$ possible stereoisomers

Q: What are they? Configurations?

(RRR) \longleftrightarrow (SSS)

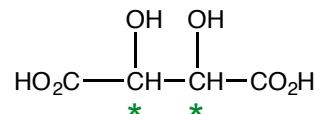
(RRS) \longleftrightarrow (SSR)

(RSR) \longleftrightarrow (SRS)

(SRR) \longleftrightarrow (RSS)

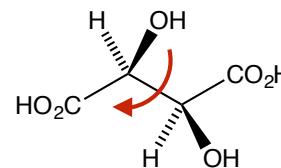
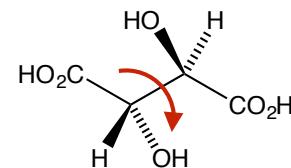
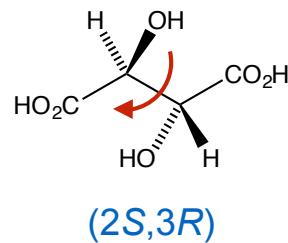
Meso Compounds

Ex: tartaric acid

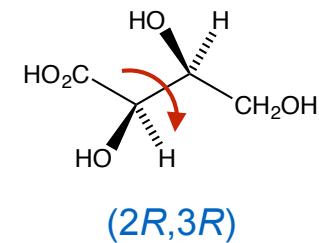


$2^2 = 4$ possible stereoisomers

mirror

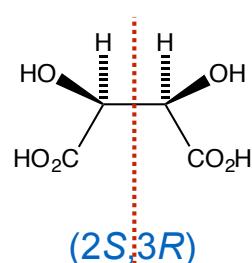


mirror

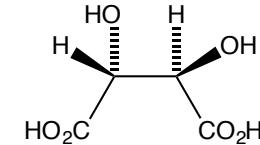
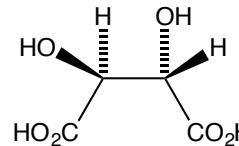
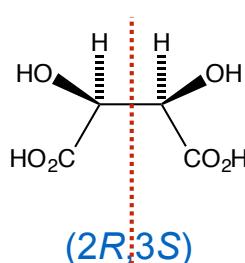


Q: How many different stereoisomers with unique structures?

mirror



mirror



same compound!

meso compound

(achiral, no optical activity)

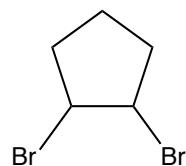
enantiomers

(chiral, optically active)

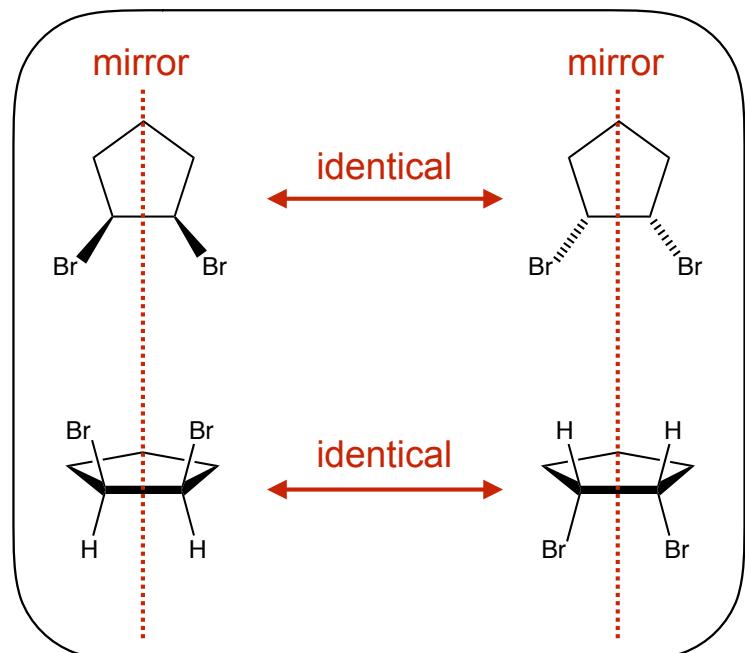
Definition:

- Meso Compound - compound that contains two or more stereo centers that is achiral (has an internal mirror plane of symmetry)

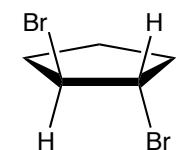
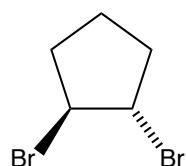
Ex: 1,2-dibromocyclopentane



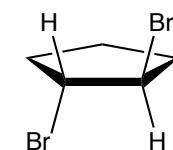
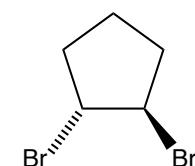
$2^2 = 4$ possible stereoisomers



cis-1,2-dibromocyclopentane
a meso compound



(1*S*,2*S*)-1,2-dibromocyclopentane



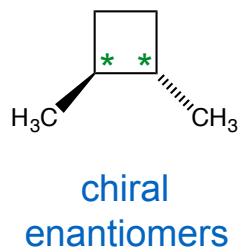
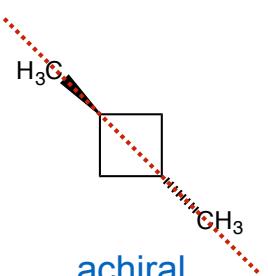
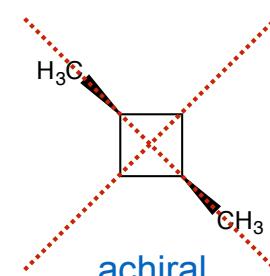
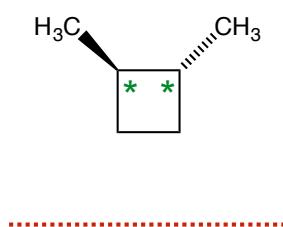
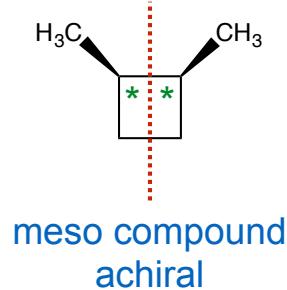
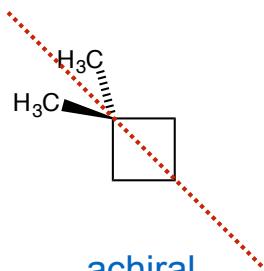
(1*R*,2*S*)-1,2-dibromocyclopentane

Ex: Stereoisomers of dimethylcyclobutane

Q: How many different stereoisomers with unique structures?

Q: Do they have stereocenters?

Q: Are they chiral or achiral?

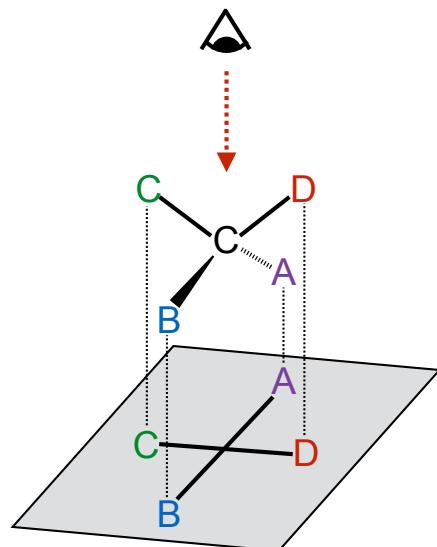


Fischer Projections (5-10)

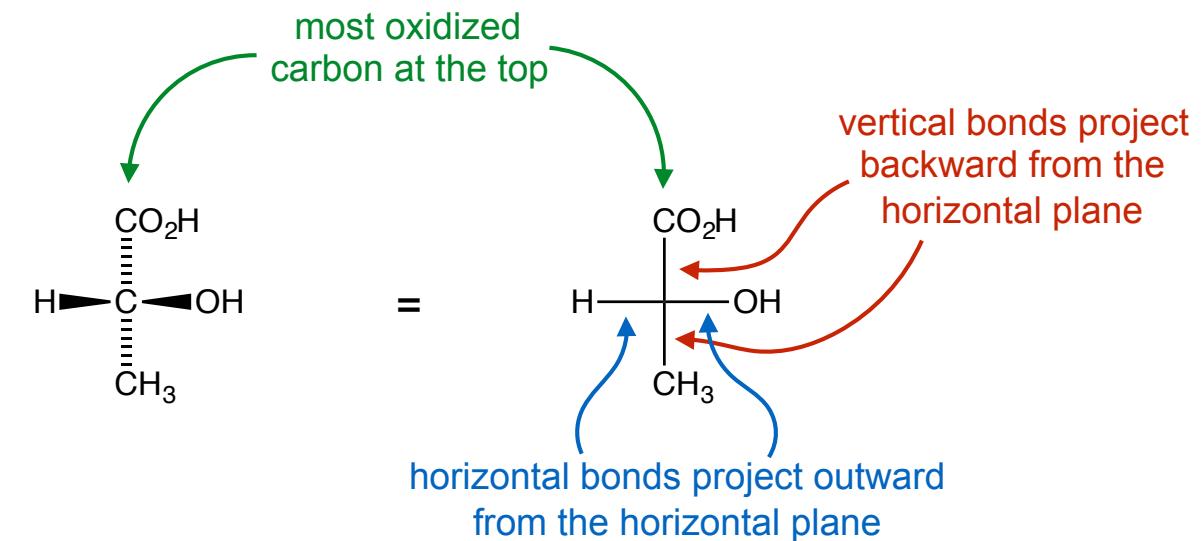
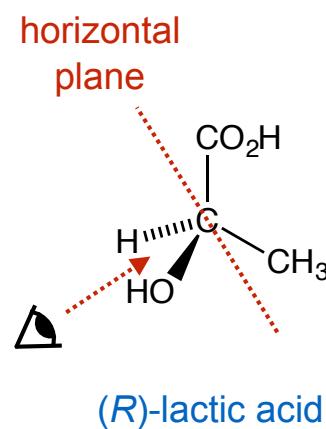
- Method to draw asymmetric carbon atoms without using dashed lines and wedges
- Developed by Emil Fischer to represent the structures of sugars



Emil Fischer 1891

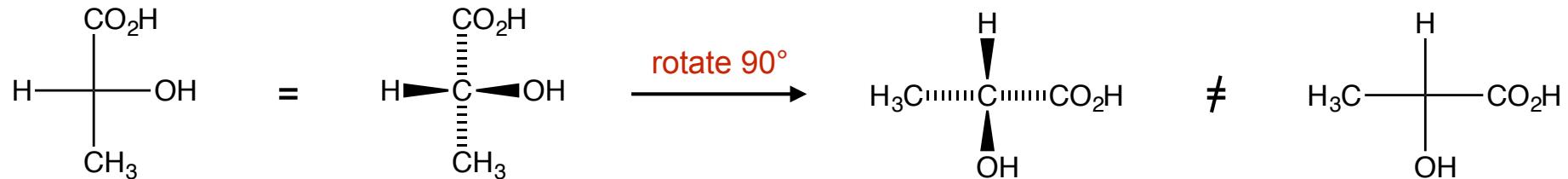


→ projection of a stereocenter onto a horizontal 2-D plane



Rotation of Fischer Projections

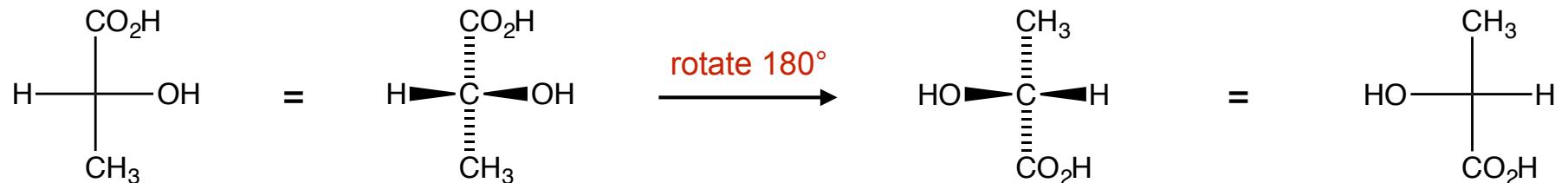
- rotating or reorienting Fischer projections can lead to structures with incorrect configuration



(R)-lactic acid

incorrect orientation of
horizontal and vertical bonds

(S)-lactic acid



(R)-lactic acid

correct orientation of horizontal
and vertical bonds

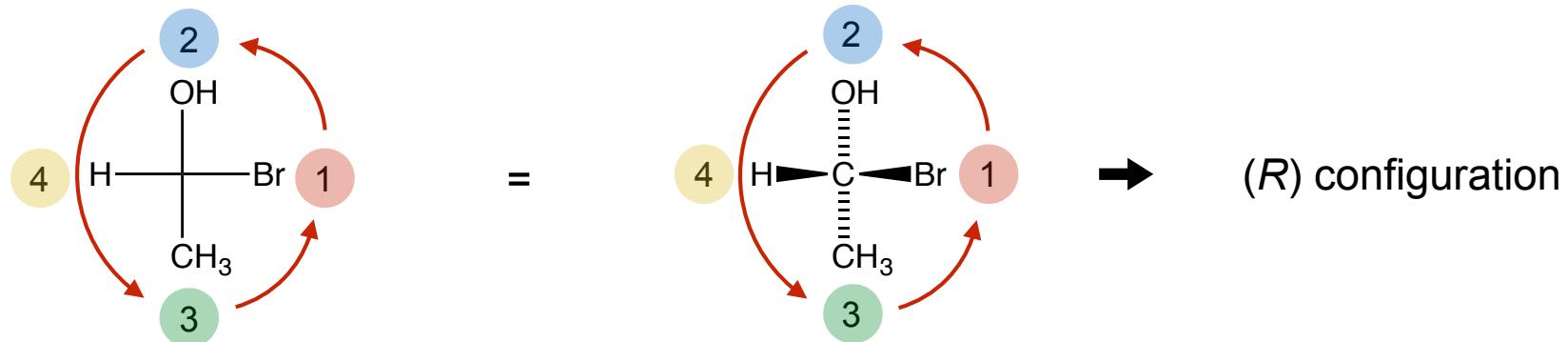
(R)-lactic acid

90° rotations are forbidden → changes configuration

180° rotations are allowed → preserves configuration

Assigning (R) and (S) Configuration to Fischer Projections

- Apply CIP rules and determine if the lowest priority substituent points up or down



Lowest priority group points up

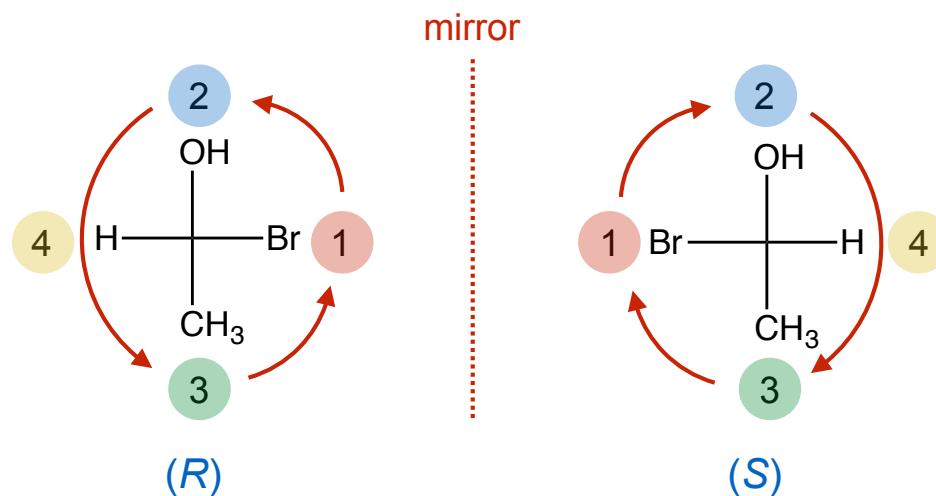


Invert counter-clockwise rotation (S) to clockwise rotation (R)

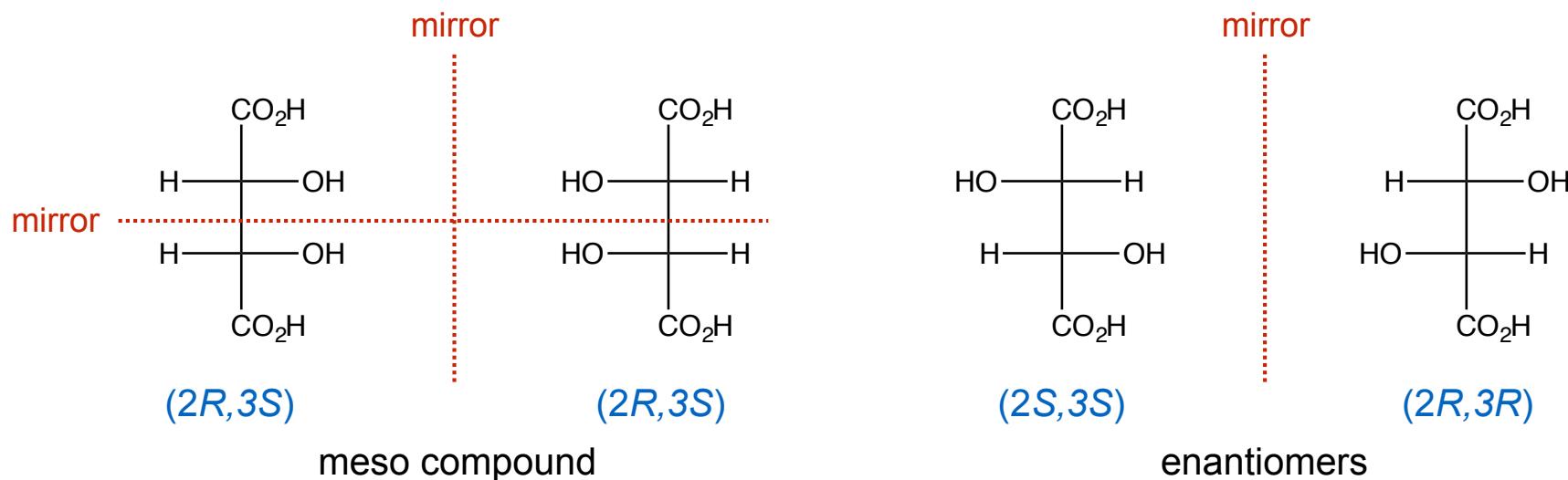
Mirror Images of Fischer Projections

- Drawing the mirror image of a Fischer projection inverts configuration at every stereocenter and generates the enantiomer

Ex: 1-bromoethanol

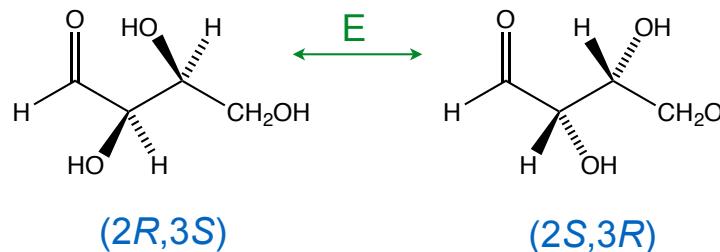
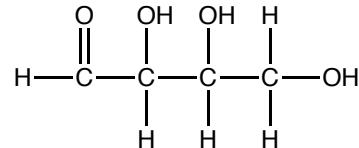


Ex: tartaric acid



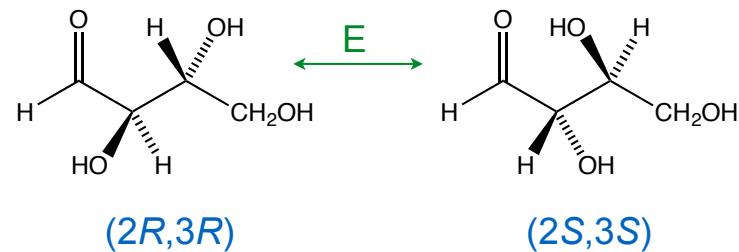
Physical Properties of Enantiomers vs. Diastereomers (5-15)

Ex: 2,3,4-trihydroxybutanal



(2R,3S)

(2S,3R)



(2R,3R)

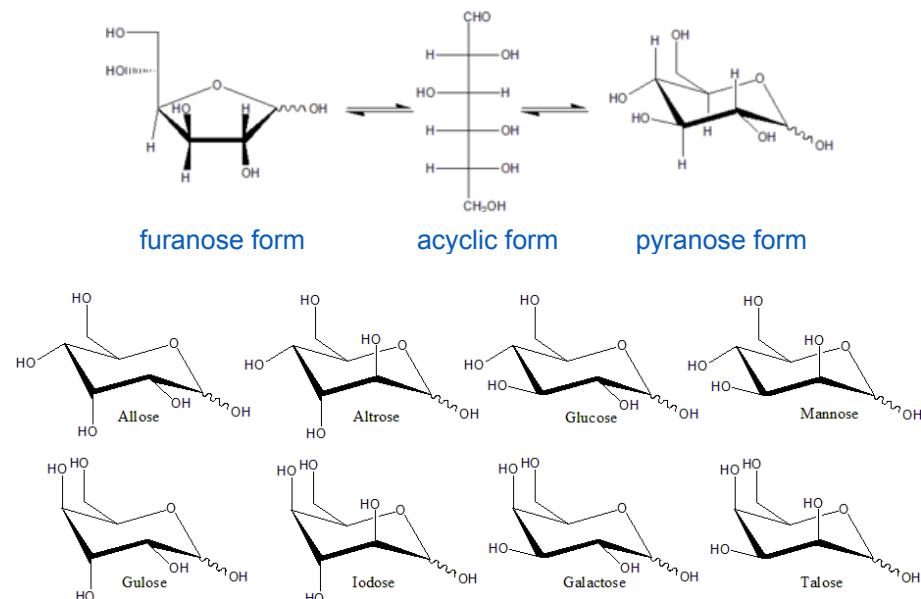
Property

[α]	+29°	-29°	-22°	+22°
m.p.	solid (130°C)	solid (130°C)	liquid at RT	liquid at RT
solubility in EtOH	slight	slight	very	very

The physical properties of enantiomers are **identical**

The physical properties of diastereomers are **different**

Properties of Diastereomers of Pyranose Sugars



U. S. DEPARTMENT OF COMMERCE

NATIONAL BUREAU OF STANDARDS

RESEARCH PAPER RP990

Part of Journal of Research of the National Bureau of Standards, Volume 18, May 1937

CONFIGURATION OF THE PYRANOSES IN RELATION TO THEIR PROPERTIES AND NOMENCLATURE¹

By Horace S. Isbell

TABLE 1.—Optical rotations¹ of

Sugar	$[\alpha]^{20}_D$
α -d-Glucose	+112.2
β -d-Glucose	+18.7
α -d-Mannose	+29.3
β -d-Mannose	-17.0
α -d-Galactose	+150.7
β -d-Galactose	+52.8
α -d-Talose	+68.0
β -d-Talose	+13.3
α -d-Gulose $\text{CaCl}_2 \cdot \text{H}_2\text{O}$	+37.1
β -d-Allose	-0.2
β -d-Altrose	+28.7

Melting Point

The melting point of sugars are important from the viewpoint of glassy candies

Name	Formula	Molecular Weight	Melting Point
D-Fructose	C ₆ H ₁₂ O ₆	180.16	105C
D-Galactose	C ₆ H ₁₂ O ₆	180.16	10.3 118 - 120
D-Glucose	C ₆ H ₁₂ O ₆	180.16	118-120 anh. 146C
Lactose	C ₁₂ H ₂₂ O ₁₁ .H ₂ O	360.31	-40C
Lyxose	C ₆ H ₁₀ O ₅	150.13	106-107
Maltose	C ₁₂ H ₂₂ O ₁₁ .H ₂ O	360.31	102.5C
D-Mannose	CH ₂ OH(CHOH) ₄ -CHO	180.16	132C
Raffinose	CH ₁₈ H ₂₂ O ₁₆ *5H ₂ O	594.52	118-Anhydrous
Rhamnose	C ₆ H ₁₂ O ₆ *H ₂ O	182.17	126
Sucrose	C ₁₂ H ₂₂ O ₁₁	342.30	179C 186
D-xylene	C ₆ H ₁₀ O ₆	159.13	153C

Handbook of Chemistry and Physics. 41st Edition 1959-1960. Chemical Rubber Publishing Co.

Name	Formula	Molecular Weight	Solubility in grams per 100 ml of Water
D-Fructose	C ₆ H ₁₂ O ₆	180.16	very soluble
D-Galactose	C ₆ H ₁₂ O ₆	180.16	10.3 68.3
D-Glucose	C ₆ H ₁₂ O ₆	180.16	83
Lactose	C ₁₂ H ₂₂ O ₁₁ .H ₂ O	360.31	8
Lyxose	C ₆ H ₁₀ O ₅	150.13	very soluble
Maltose	C ₁₂ H ₂₂ O ₁₁ .H ₂ O	360.31	108
D-Mannose	CH ₂ OH(CHOH) ₄ -CHO	180.16	248
Raffinose	CH ₁₈ H ₂₂ O ₁₆ *5H ₂ O	594.52	14
Sucrose	C ₁₂ H ₂₂ O ₁₁	342.30	179 487
D-xylene	C ₆ H ₁₀ O ₆	159.13	117

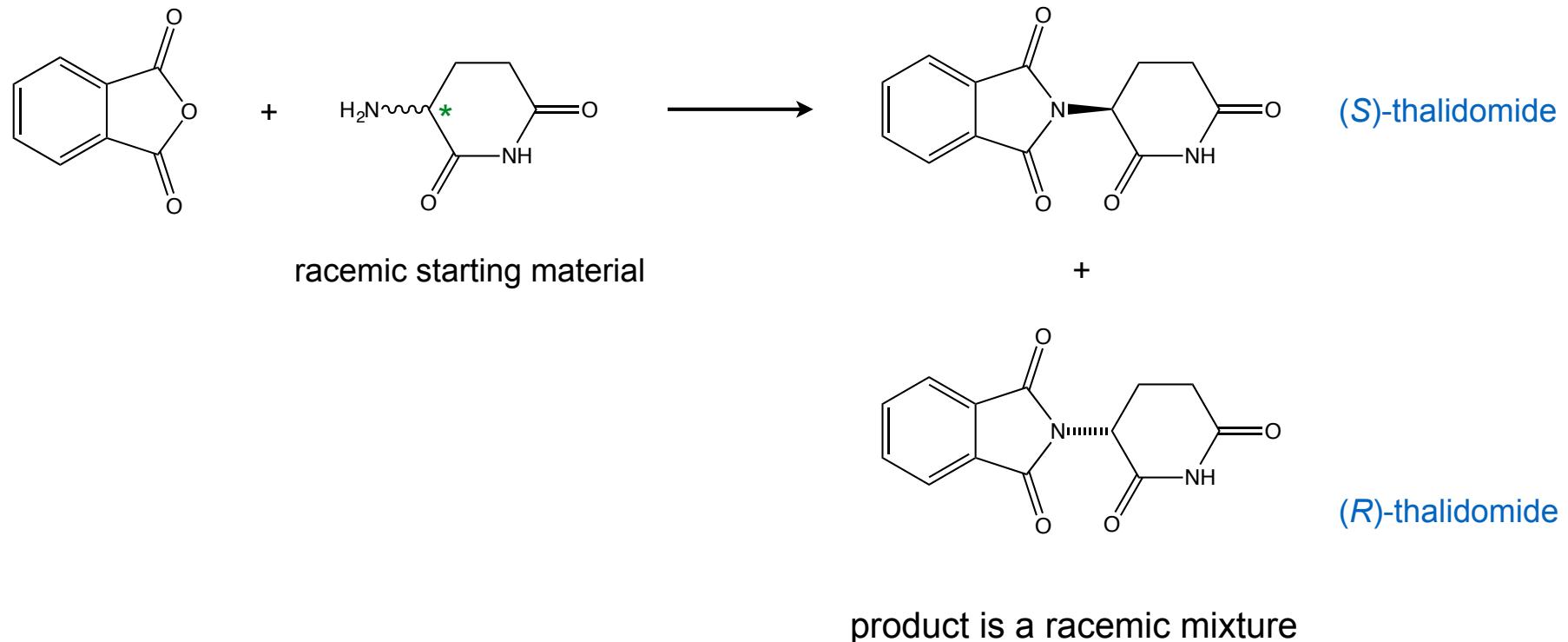
Handbook of Chemistry and Physics. 41st Edition 1959-1960. Chemical Rubber Publishing Co.

Resolution (Separation) of Enantiomers (5-16)

Q: Is it possible to obtain pure samples of a given stereoisomer from a racemic mixture given that enantiomers have identical physical properties?

Q: What techniques can be used to separate enantiomers?

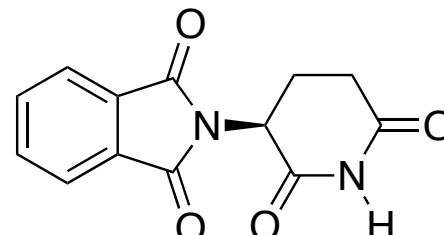
Ex: Synthesis of thalidomide



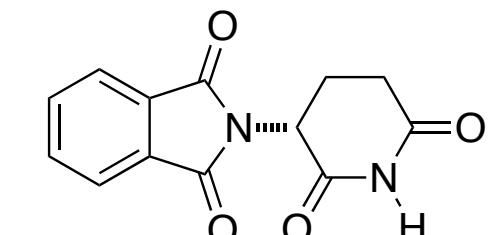
Pharmacological impact of chirality: Thalidomide



racemic
mixture



(S)-enantiomer



(R)-enantiomer

Thalidomide - Contergan®

Grünenthal (1950s)

- antinauseant
- sedative



teratogen!



inhibits morning sickness

Federal Food, Drug & Cosmetic Act (1938)

- allowed “experimental” use of drugs pending approval without demonstration of efficacy

Kefauver-Harris Drug Amendment (1962)

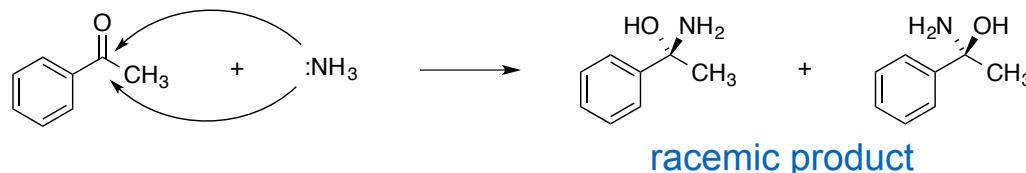
- requires proof of efficacy and safety of drugs before approval



synthesis or separation of single enantiomers of drugs

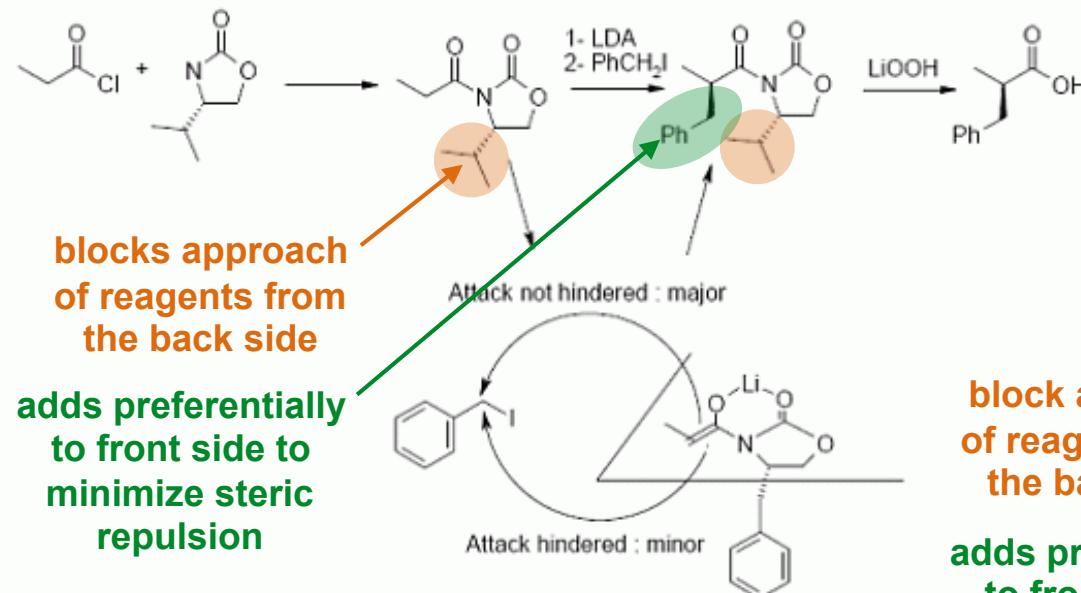
Resolution (separation) of enantiomers

Synthesis leading to racemic product

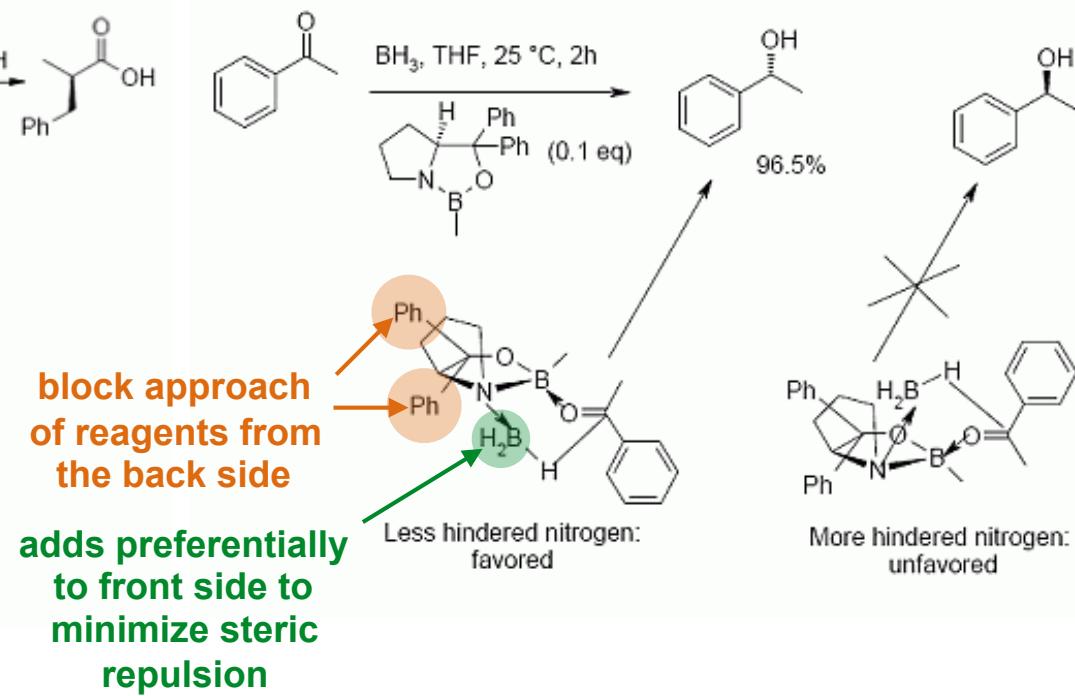


Enantiomers can be separated (resolved) using chiral auxiliaries or catalysts during synthesis to energetically favor formation of one stereoisomer

Asymmetric synthesis using a chiral auxiliary

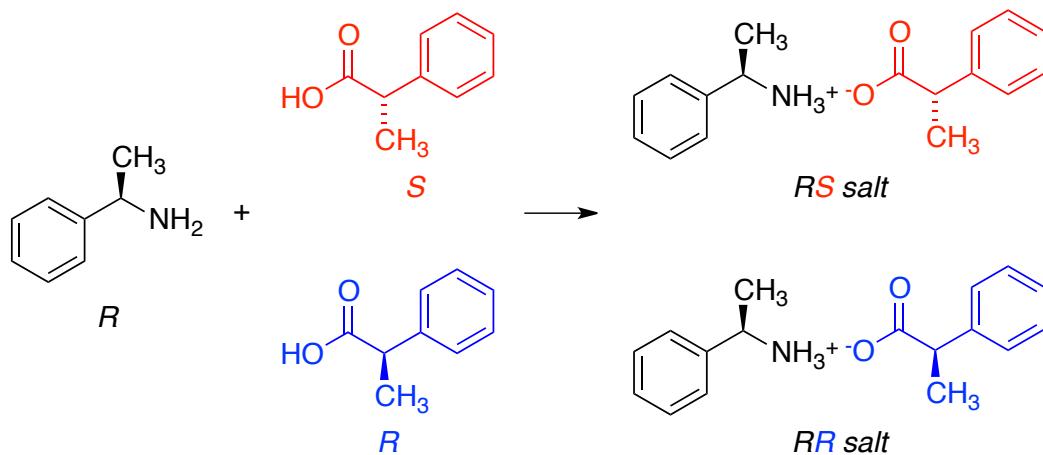


Asymmetric synthesis using a chiral catalyst



Resolution (separation) of enantiomers

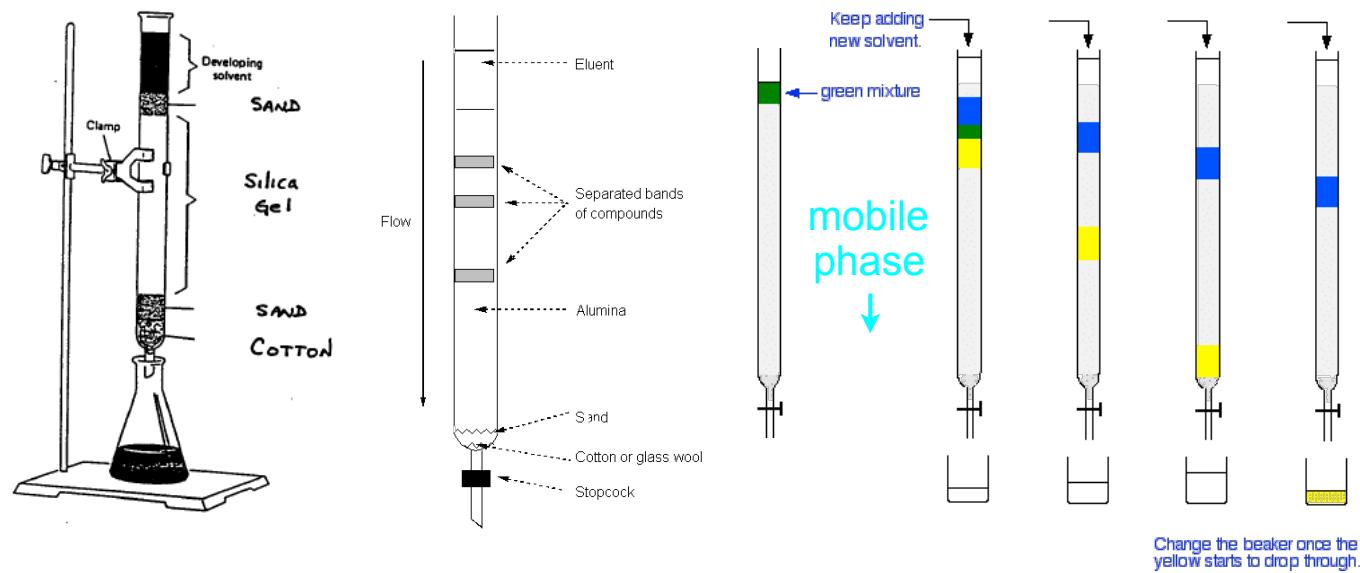
Enantiomers can be separated (resolved) using chiral reagents to make diastereomers



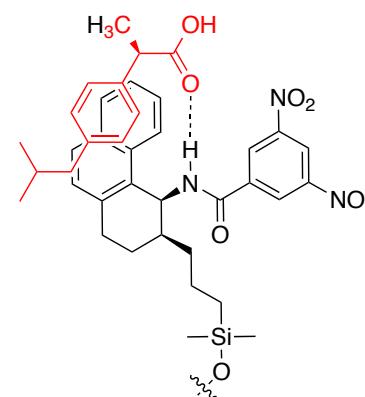
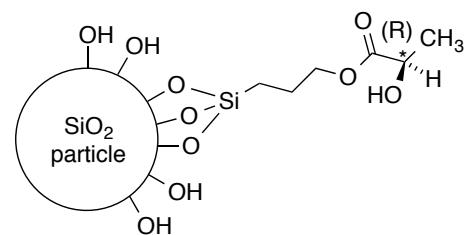
diastereomeric salts exhibiting different solubilities that
allow separation via crystallization

Resolution (separation) of enantiomers

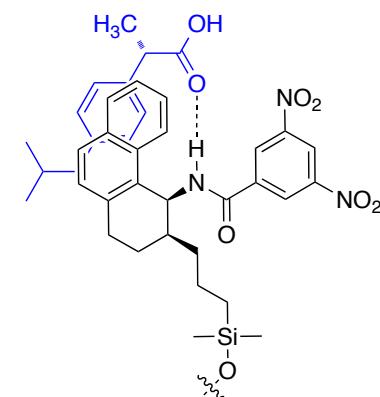
Enantiomers can be separated (resolved) using chiral reagents to create diastereomeric interactions at surfaces



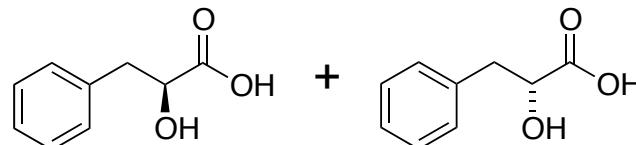
**stronger binding
(moves slower)**



**weaker binding
(moves faster)**



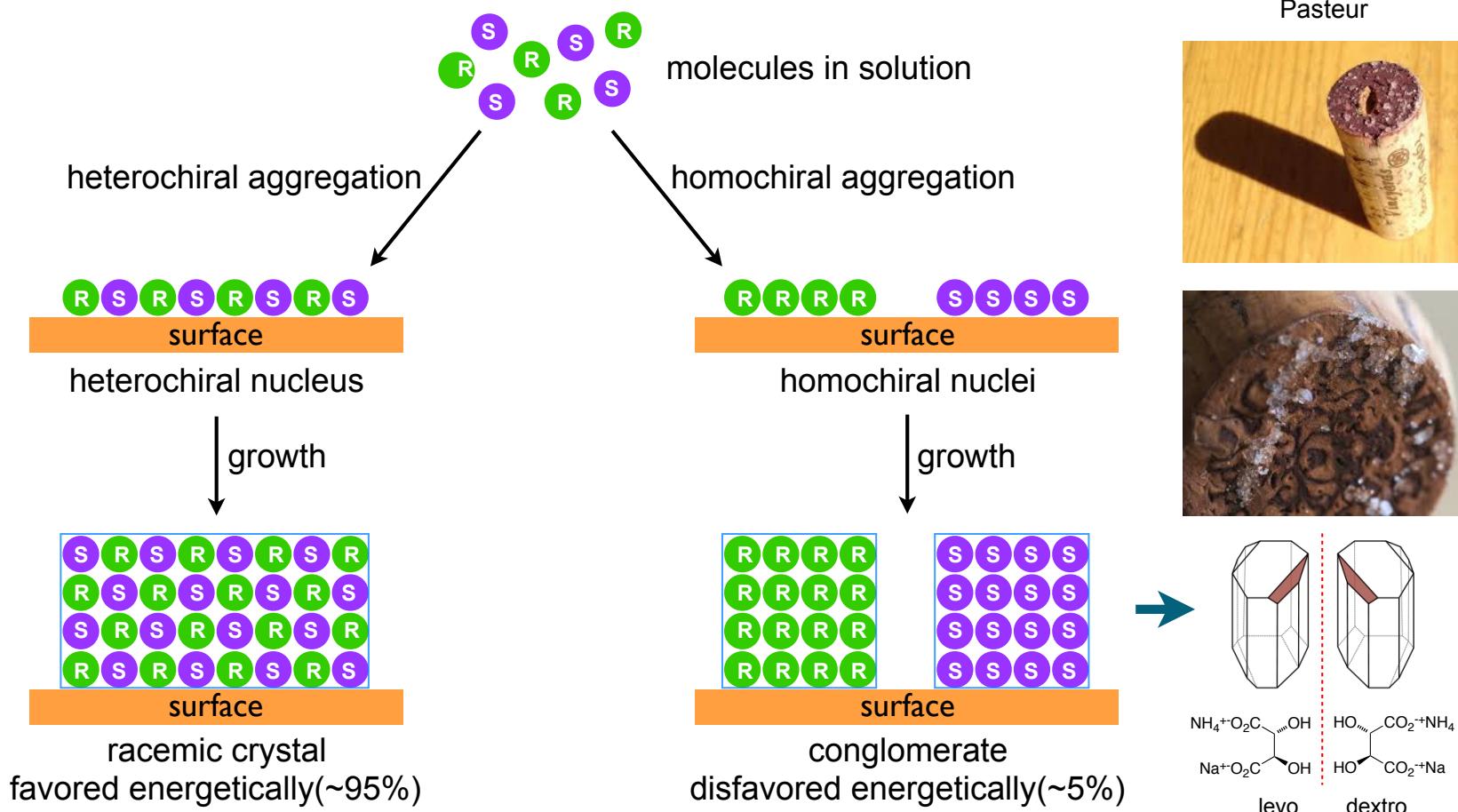
How do mixtures of enantiomers (racemates) crystallize?



racemic 3PLA

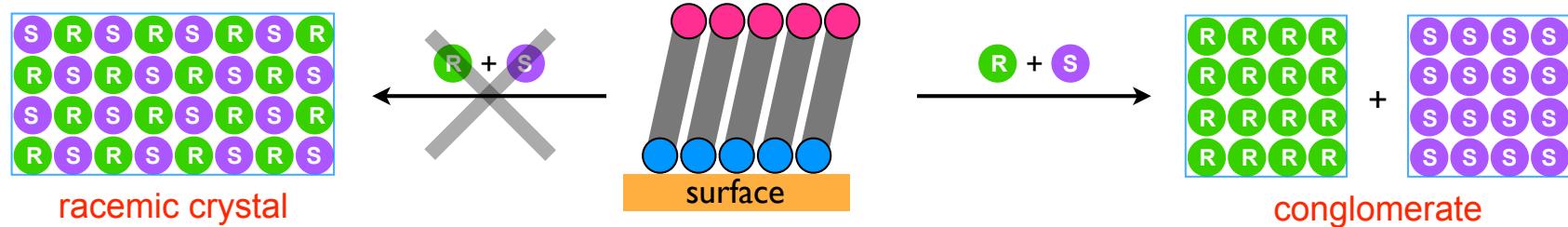


Pasteur

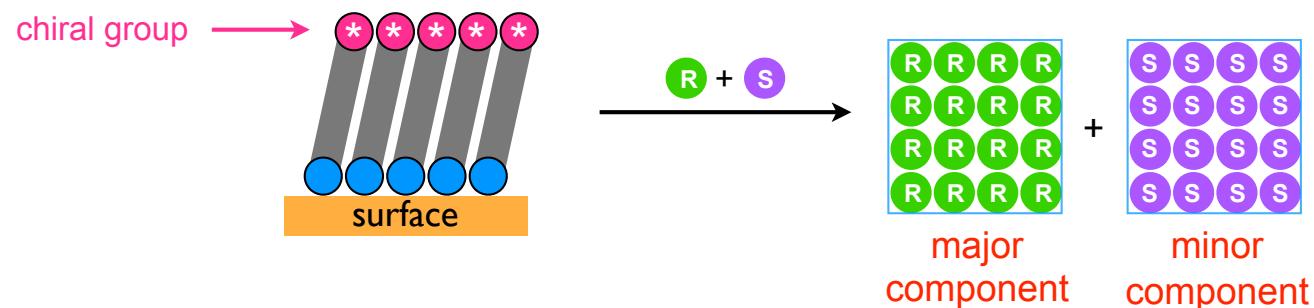


Can a Chiral Surface Be Used as a Template to Bias Crystallization of One Enantiomer?

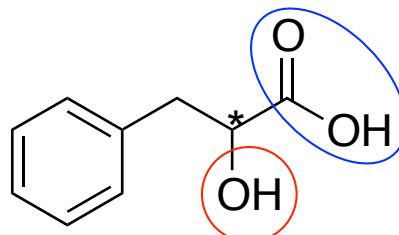
Determine if chiral surfaces act as templates that promote nucleation of conglomerates over racemic crystals



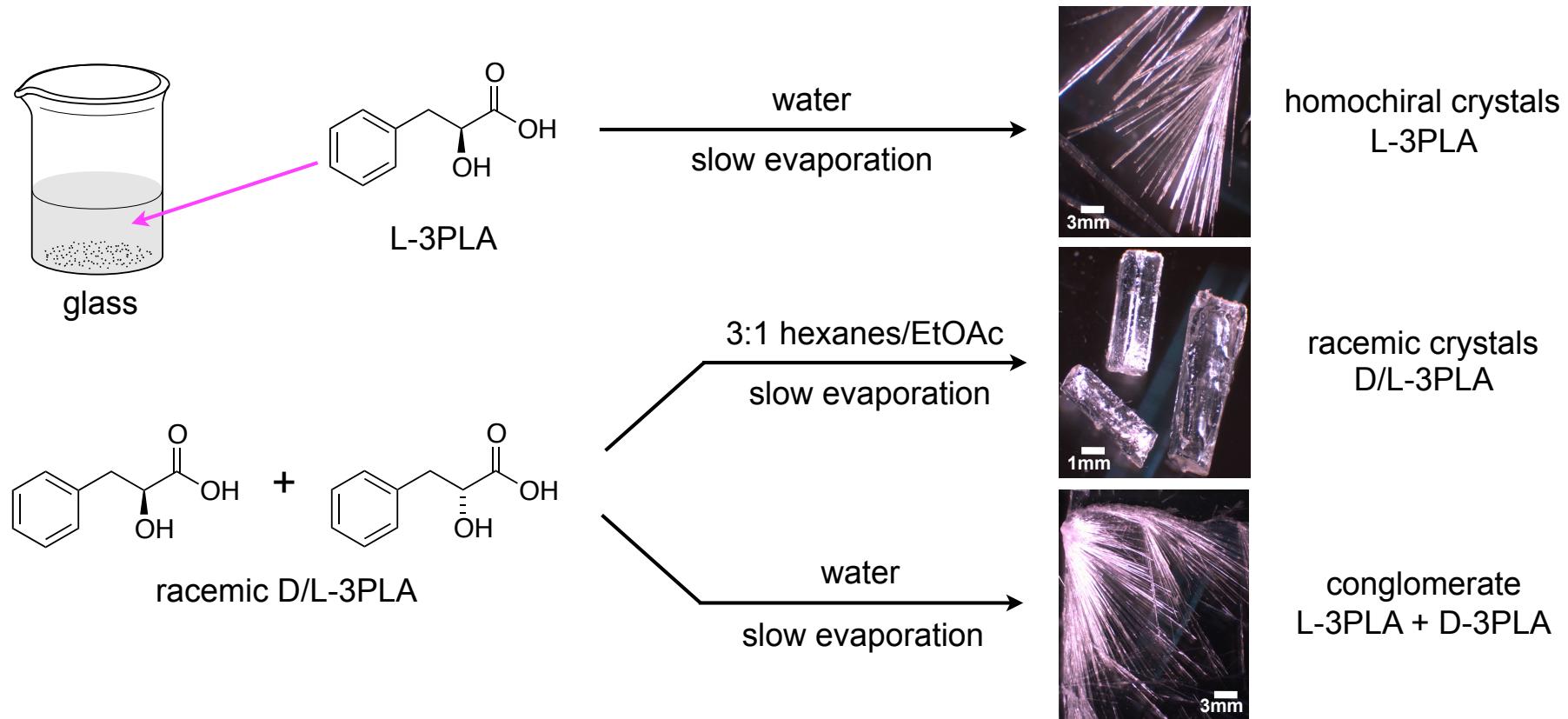
Determine if crystallization of racemic compounds on chiral templates leads to selective nucleation of one enantiomer over the other



Racemic drug investigated



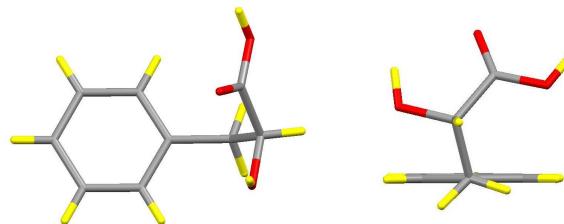
D/L-3-phenyllactic acid



Crystal structures of 3PLA

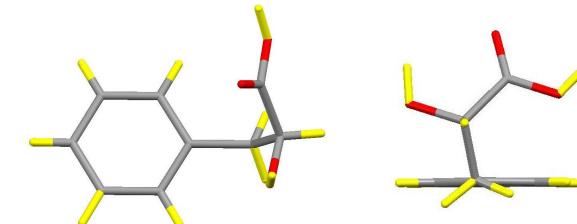
homochiral L-3PLA
(observed more frequently)

molecular
structures

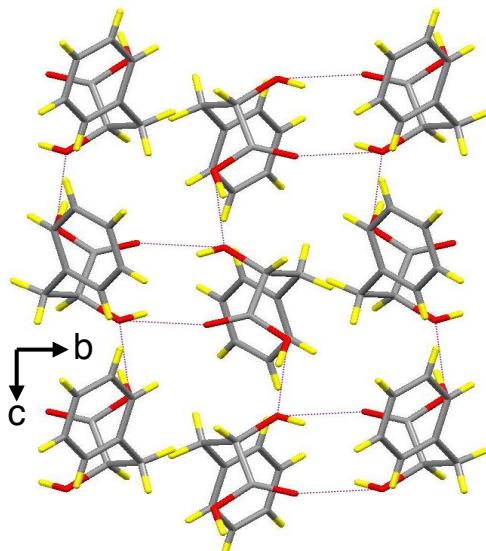


identical
conformation

racemic D/L-3PLA

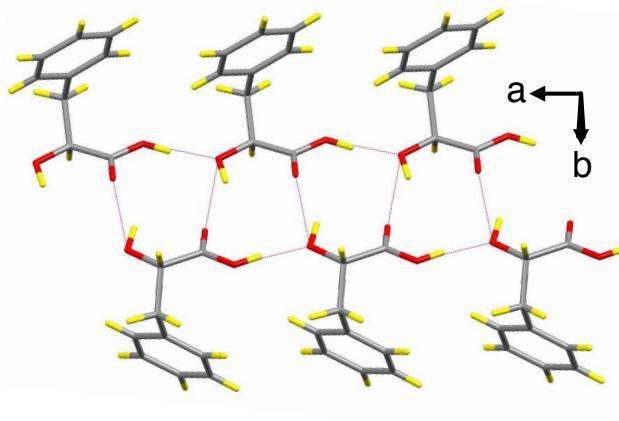


crystal
packing



homochiral sheets

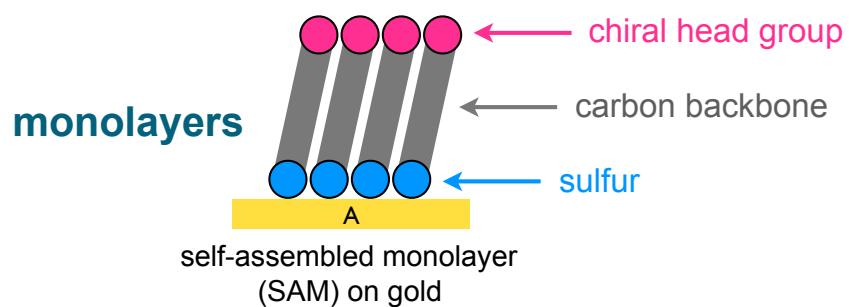
orthorhombic
 $P2_12_12_1$
 $V = 824.30(8) \text{ \AA}^3$
 $p_{calc} = 1.339 \text{ g/cm}^3$



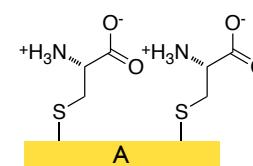
heterochiral ribbons

monoclinic
 $P2_1/c$
 $V = 794.96(11) \text{ \AA}^3$
 $p_{calc} = 1.388 \text{ g/cm}^3$

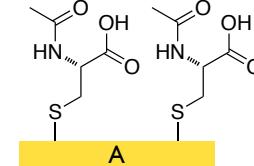
Strategies for making surfaces chiral



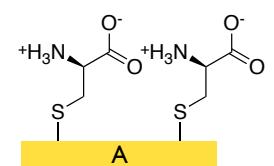
chiral amino acids & their derivatives



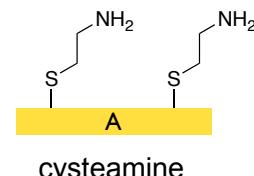
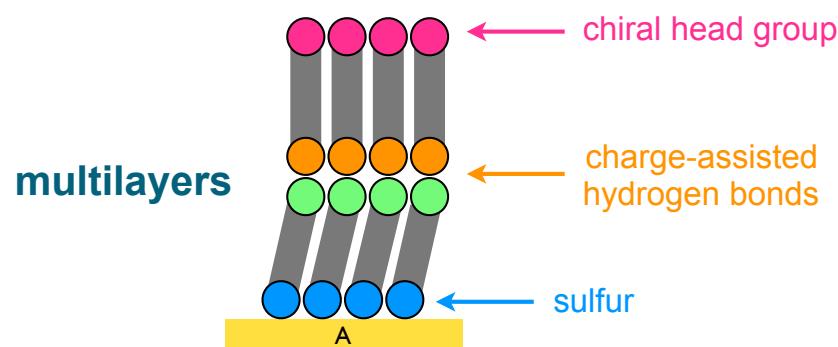
L-cysteine



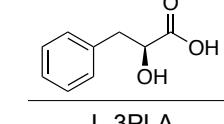
N-acetyl-L-cysteine



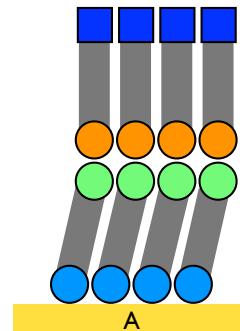
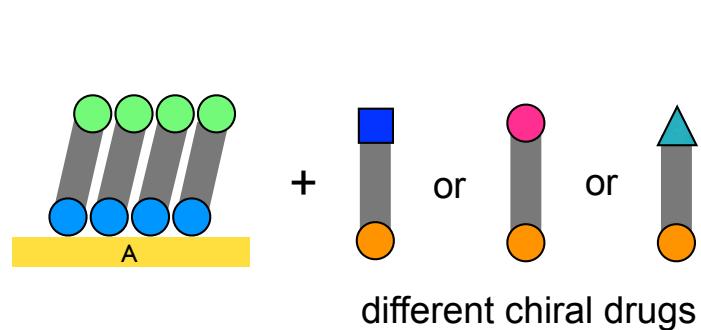
D-cysteine



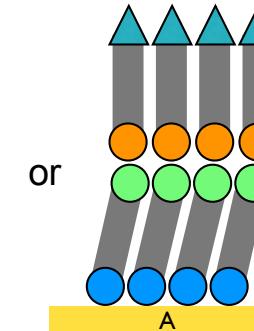
cysteamine



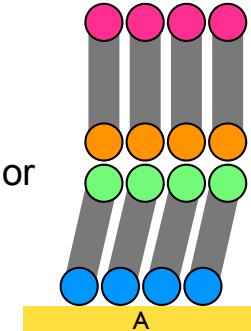
L-3-phenyllactic acid/cysteamine



or

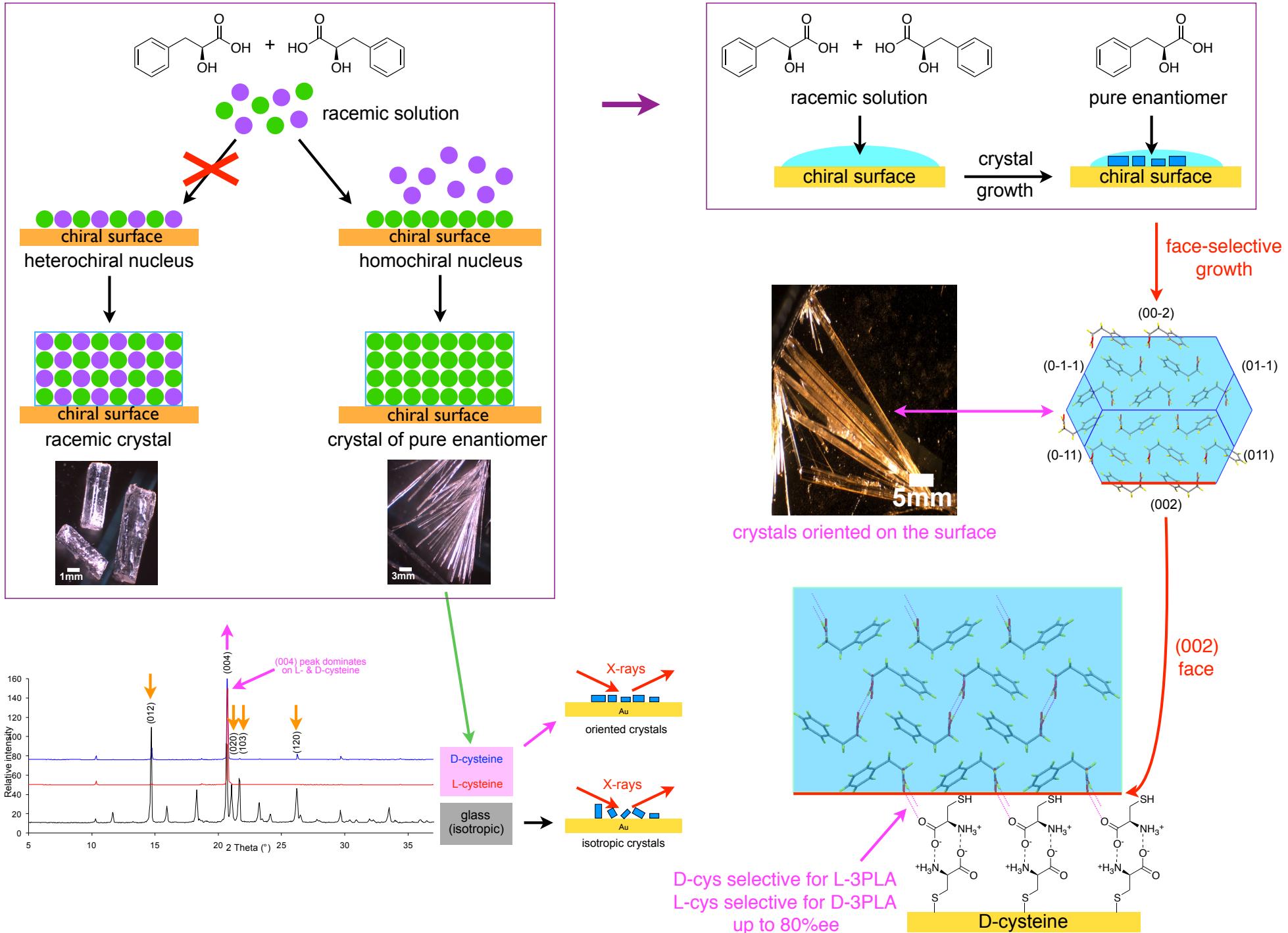


or

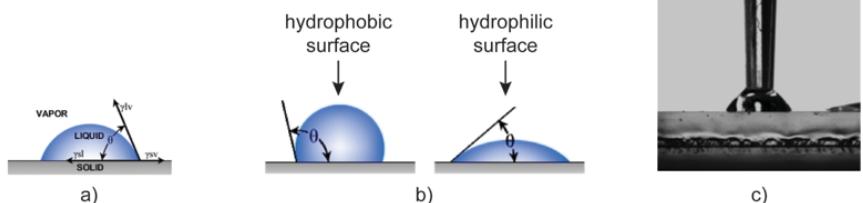
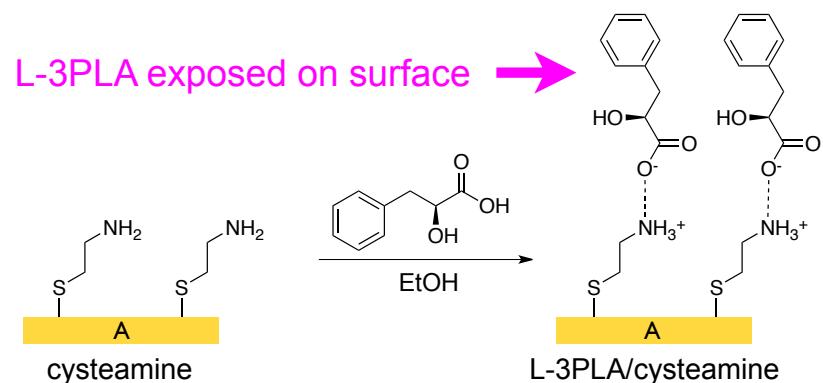


library of chiral surfaces based on drugs

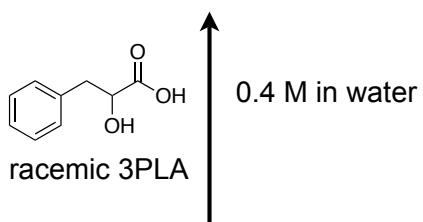
Enantioseparation of racemic drugs via crystallization on chiral templates



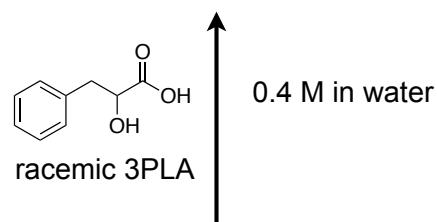
Crystallization of racemic 3PLA on surfaces functionalized with L-3PLA



SAM	contact angle (°)	thickness (nm)	type of film
bare gold	21.1 ± 1.8	-	-
cysteamine	52.1 ± 2.8	0.7 ± 0.2	monolayer
3-PLA/cysteamine	45.0 ± 2.8	1.9 ± 0.5	bilayer



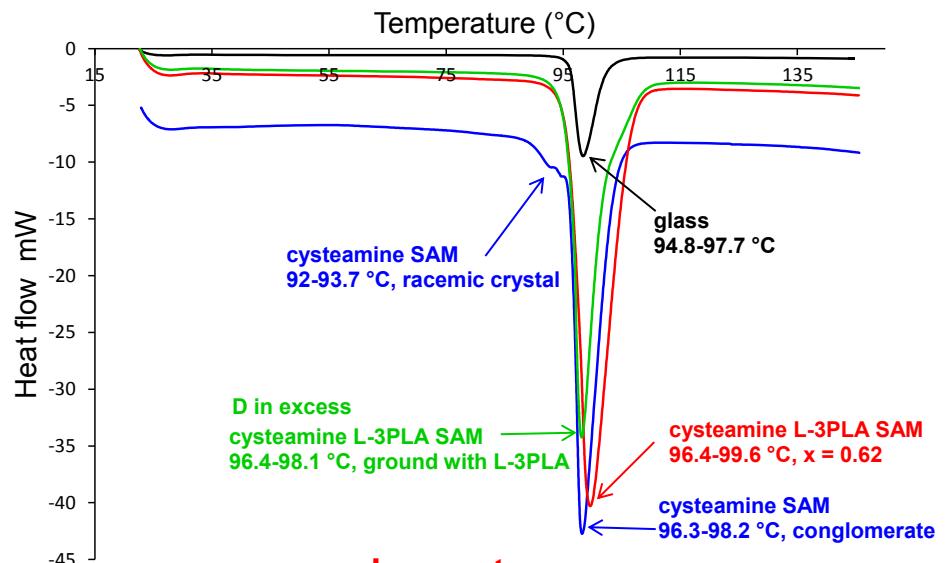
cysteamine SAM



L-PLA/cysteamine SAM

conglomerate

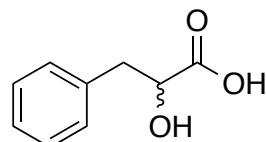
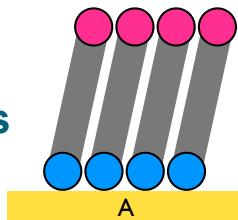
D-3PLA in excess



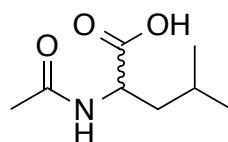
- conglomerate
- evidence of racemic crystal
- 16-24% enrichment of D-3PLA
- D-3PLA grows selectively on L-3PLA/cysteamine

Racemic drugs investigated

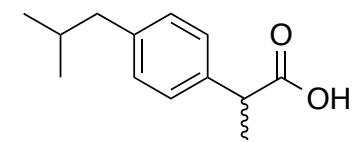
monolayers



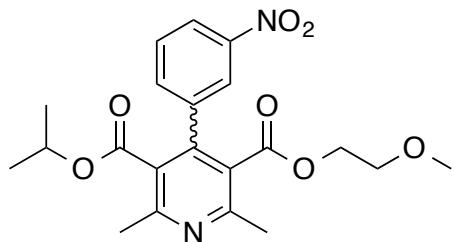
3-phenyllactic acid
(antibiotic)
60-80% ee



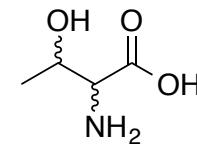
N-acetylleucine
(muscle tissue promoter)
80-90% ee



ibuprofen
(analgesic)
racemic

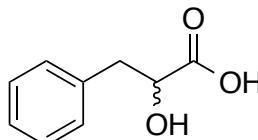
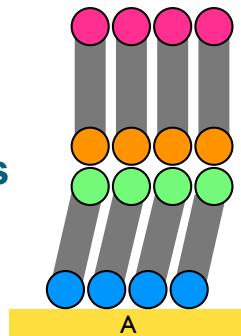


nimodipene
(Ca channel blocker)
conglomerate & racemic



threonine
(collagen formation)
60-85% ee

multilayers



3-phenyllactic acid

15-75% ee depending on chiral template

Achiral SAMs give conglomerates with no enantiomeric excess (ee).

Chiral SAMs preferentially nucleate one enantiomer in up to 90% excess.

The major enantiomer can be selected by switching the chirality of the SAM.

Chiral discrimination occurs on faces that maximize strong hydrogen-bonding interactions.

Drug templates give variable ee values that increase with drugs that expose hydrogen-bonding groups at the surface.