CHAPTER 1

# *Identifying and Classifying Stereoisomers*

Stereochemistry is a field of chemistry concerned with the spatial aspects of molecules.[1] Molecules that differ only in the spatial arrangement of atoms are stereoisomers. The molecular formula and atom connectivity of stereoisomers is identical.The two classes of stereoismers are enantiomers and diastereomers. Enantiomers are nonsuperposible mirror image molecules; all other stereoisomers are diastereomer. Indentifying symmetry elements in a molecule also reveals whether enantiomers of the molecule exist.These different spatial arrangement within stereoisomers are caused by the rigidity of chemical bonds, restricted rotation along chemical bonds, or by the interlocking of bond paths. This rigidity or rescricted rotation creates stereogenic units – centers, axes, or planes – in a molecule. This chapter focuses on identifying and classifying stereoisomers and also identifying stereogenic units within them.

Isomerism identifies a relationship between two molecules, so one must have two molecules in mind to discuss isomerism. One cannot have a single molecule and ask: is this a diastereomer? You need to compare it to another molecule for that question to make sense. A molecule may be a structural isomer to one molecule, a diastereomer to another, an enantiomer to a third. Isomerism is like kinship - a per-

1. Stereochemistry is not a synonym for configuration; thus, one should not refer to the 'stereochemistry of the product', but to the 'configuration of the product.' Nevertheless, you may often encounter this incorrect use.

son may be a father to one person, a husband to another, a brother to a third - all-ways keeping in mind two people to identify the kinship between them.

## *1.1 Stereoisomers differ only in three-dimensional shape, not in atom connectivity.*

Structural isomers are compounds with the same molecular formula, but different structure. A flow chart for the classification of structural isomers, Figure 1, divides them into constitutional isomers and stereoisomers. Constitutional isomers differ from each other in atom connectivity, for example, *n*-butane and isobutane. Most constitutional isomers do not interconvert because it would involve breaking covalent bonds. However, some constitutional isomers do interconvert and these are given the special name tautomers. For example, the keto and enol forms of acetone are constitutional isomer that are also called tautomers.

Stereoisomers have the same atom connectivity, but differ in the arrangement of the atoms in space. Stereoisomers differ only in their three-dimensional shapes.

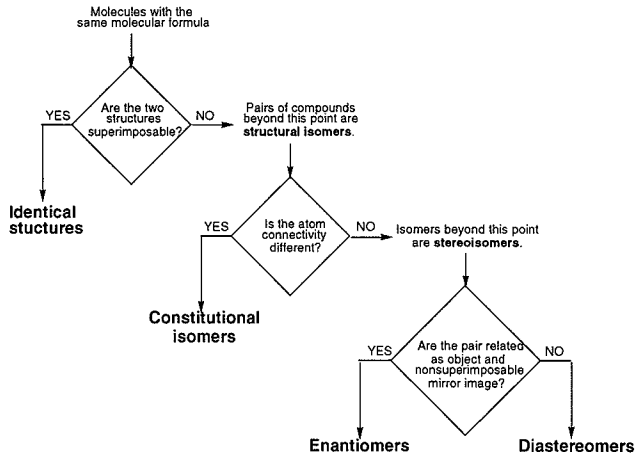
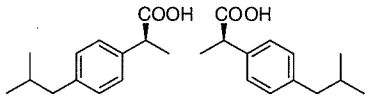
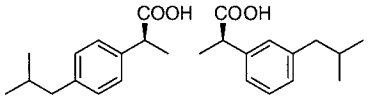



**FIGURE 1.** A flow chart for the classification of isomers. Stereoisomers differ from each other only in the arrangement of the atoms in space.

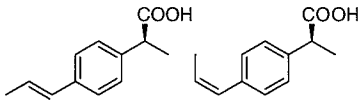
Stereoisomers are divided into enantiomers and diastereomers based on symmetry criteria. Enantiomers are related as object and nonsuperimposable mirror image. All other stereoisomers are diastereomers.




**enantiomers** - same connectivity, mirror images
(contained in ibuprofen, a common pain reliever)




**constitutional isomers** - different atom connectivity




**diastereomers** - same connectivity, not mirror images

Enantiomers have identical physical properties (except that they rotate the plane of plane-polarized light in opposite directions) and identical chemical reactivity with achiral reagents. Enantiomers have different chemical reactivity with other chiral molecules.

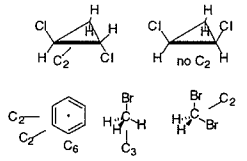
## *1.2 Chiral molecules cannot contain an improper rotation axis*

A foolproof method for identifying chiral molecules is to build models of the molecule and its mirror image. If the two models are not superimposable, then the molecule is chiral and can exist as a pair of enantiomers. Another, faster method for identifying chiral molecules relies on symmetry elements. A chiral molecule cannot contain any of the following symmetry elements: a mirror plane, an inversion center, or an improper rotation axis. All molecules that lack these symmetry elements are chiral.

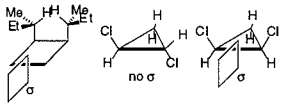
Symmetry refers to two parts that look the same. A molecule has symmetry if two parts of the molecule are the same. For example, benzene has symmetry because rotation by 60° gives an indistinguishable molecule. This rotation is called a symmetry operation and the rotation axis is a symmetry element. This rotation interchanged equivalent atoms (caution). As we will see shortly, the mirror plane and

inversion center are special types of improper rotations, so we can succintly state that chiral molecules lack an improper rotation axis. The only symmetry element that can be present in chiral molecules is a rotation axis. To identify chiral molecules using symmetry elements, we need to be able to identify four symmetry elements: a rotation axis, a mirror plane, an inversion center, and an improper rotation axis.

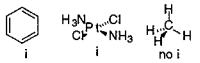
A rotation axis, $C_n$, is an axis about which a molecule can be rotated to produce an indistinguishable orientation. The subscript n indicates the number of equivalent positions about the axis. For example, *trans*-1,2-dichlorocyclopropane, possesses a rotation axis, $C_2$, because rotation by 180° about this axis gives an indistinguishable molecule. Benzene has seven rotation axes, three of which are labeled below.




A mirror plane, σ, is a plane that passes through the molecule and divides it into two halves that are mirror images. The symmetry operation associated with this symmetry element is reflection through the plane. Mirror planes are sometimes labeled $\sigma_h$ (horizontal), $\sigma_v$ (vertical), $\sigma_d$ (dihedral) to indicate their relationship to rotation axis. Planar molecules contain at least one mirror plane.

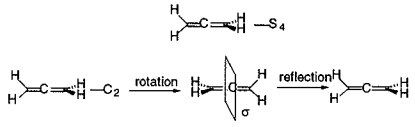



A center of symmetry or inversion center, *i*, is a point through which the molecule is inverted. Each atom in the molecule is moved in a straight line through this center and an equal distance on the other side of the center. A molecule possesses an inversion center if the structures before and after this inversion operation are indistinguishable.

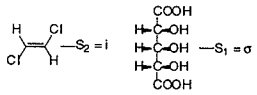



A rotation-reflection axis or improper rotation axis, $S_n$, is an axis about which the molecule is first rotated by 360°/n, then reflected in a plane perpendicular to the axis. For example, allene contains an $S_4$ axis of symmetry that passes through the

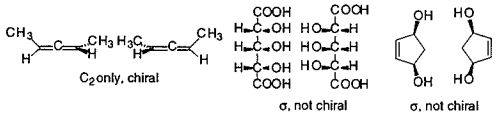
three carbon atoms. Rotation by 90° followed by reflection through a mirror plane that is perpendicular to the axis and passes through the central carbon gives an indistinguishable structure.




A center of inversion symmetry element is the same as an $S_2$ axis; similarly, a mirror plane symmetry element is the same as an $S_1$ axis.




To identify whether a molecule is chiral using symmetry elements, look for improper axes of rotation. All molecules that lack an improper axis of rotation are not superimposable on their mirror image and therefore are chiral molecules. For example, allene is not chiral because it has an $S_4$ axis, but 1,3-dimethylallene is chiral because it has only a $C_2$ axis. Similarly, 2,3,5-trihydroxyglutaric acid is not chiral because it possesses a mirror plane symmetry element.




Note that the short cut of looking for carbon atoms with four different substituents does not reliably identify chiral molecules. Many chiral molecules do not contain carbon atoms with four different substituents, for example, 1,3-dimethylallene above. Further, some molecules that do contain carbon atoms with four different substituents are achiral. For example, the central carbon of 2,3,5-trihydroxyglutaric acid above is joined to four different substituents. The two -CH(OH)COOH substituents are different because they have opposite configurations. Nevertheless, the molecule is not chiral. The only reliable methods to identify chiral molecules are either to compare molecular models or to establish the absence of an improper axis of rotation.

Symmetry elements also help explain the difference between the terms asymmetric and dissymmetric, Figure 2. Asymmetric means the absence of all symmetry elements. All asymmetric molecules are also chiral or dissymmetric. Chiral and dis-

symmetric are synonymous and mean not superimposable with its mirror image. Chemists usually use the word chiral when referring to molecules and dissymmetric when referring to other objects such as staircases. A dissymmetric or chiral molecule may contain a proper axis of rotation, for example, trans-1,2-cyclohexanediol, and therefore not be asymmetric. Bromochlorofluoromethane is both dissymmetric and asymmetric because it contains no symmetry elements. Chemists sometimes incorrectly use asymmetric as a synonym for chiral, as in asymmetric synthesis. More accurate expressions are stereoselective synthesis, enantiomerically pure compound synthesis or enantiopure compound synthesis.

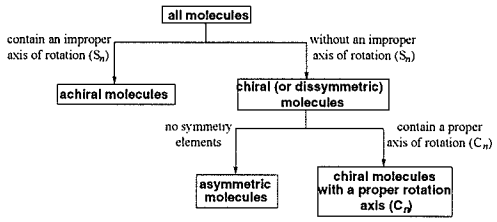


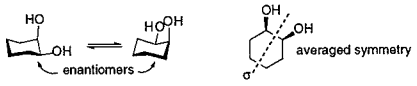

**FIGURE 2.** Flow chart showing that asymmetric is not synonymous with chiral (or dissymmetric). Some chiral molecules are not asymmetric.

## Averaged symmetry and residual stereoisomers

A molecule often has many possible conformations. To assign symmetry to the overall molecule, use the highest symmetry of any of the possible conformations. For example, *n*-butane exists as three rapidly interconverting species: an achiral anti-conformation, a chiral gauche$^+$ conformation and a chiral gauche$^-$ conformation. (These conformations will be discussed in detail in Chapter 7.) The overall symmetry of this mixture corresponds to the achiral trans conformation with a plane of symmetry. Thus, n-butane is an achiral molecule.

To remind others that one is ignoring inseparable conformational stereoisomers, some researchers use the expression 'residual stereoisomers.' This expression refers to the number of stereoisomers that can be distinguished by a given technique. For example, chlorocyclohexane consists of two residual diastereomers when viewed by IR (axial vs. equatorial orientation of the chlorine), but only a single residual species when viewed by NMR at room temperature. Unless otherwise specified, for this course we will use the term 'residual stereoisomers' to mean stereoisomers that could be isolated at room temperature. So chlorocyclohexane contain a single residual species (not an isomer because there is only one).

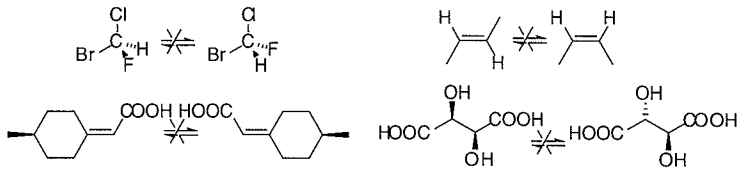
In *n*-butane example, the overall symmetry corresponded to the highest symmetry of the contributing structures. However, flexible molecules can simulate a *higher* symmetry than the contributing structures. For example, is *cis*-1,2-cyclohexanediol a chiral molecule? The two chair conformations are enantiomeric, but ring-flipping interconverts them. At room temperature there is only one residual species – the average of the two rings. The averaged symmetry of this species contains a mirror plane indicating that it is an achiral molecule. Thus, *cis*-1,2-cyclohexanediol is a chiral molecule because it exists as two rapidly interconverting enantiomers. However, there is only one residual achiral stereoisomer for most purposes.




## *1.3 Molecular origins of stereoisomerism: configuration, conformation or topology*

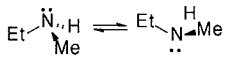
To further classify isomers, one can consider the origin of the stereoisomerism. Different spatial arrangements of atoms can be caused by configuration, conformation, or topology. The most common cause is the configuration of the atoms. Configuration refers to the arrangement in space due to the geometrical rigidity of bonds. For example, BrClFCH does not interconvert with its enantiomer because the C-H and C-X bonds are fixed in space. A deformation of these bonds (flattening) would interconvert the enantiomers, but this deformation does not occur. The bonds have geometrical rigidity, similar to that of molecular models. Similarly, trans-2-butene does not interconvert with *cis*-2-butene both because the carbon-carbon double bond does not rotate and because the carbon-carbon single bonds and carbon-hydrogen bonds do not deform. The most common types of configurational diastereomers are those having several stereocenters, but differing in the configuration at one or more of these stereocenter. The two tartaric acids below are a typical example. These types of configurational diastereomers are also called epimers. Epimers

are configurational diastereomers that differ in configuration at one or more stereocenters.

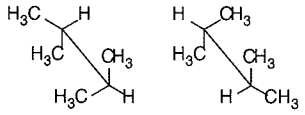



configurational enantiomers configurational diastereomers

On the other hand, the bonds at nitrogen in an amine deform by inversion at nitrogen, similar to the inversion of an umbrella in a strong wind. The H–N–C bond angle changes from approximately 109° to 120° in the flat transition state and then back to approximately 109°. For this reason NHMeEt interconverts with its enantiomer. (Although this is a change in configuration, most chemists group it together with changes in conformation below.)



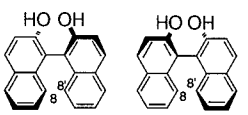

Conformation refers to rotations around single bonds. Conformational stereoisomers are those that can be interconverted by rotations around single bonds. Since rotations around single bonds are rapid, most conformational stereoisomers can not be separated. For example, the conformers of 2,3-dimethylbutane are enantiomeric, but can not be separated under normal laboratory conditions. Similarly, the enantiomers of *cis*-1,2-dichlorocyclohexane interconvert by ring-flipping of the cyclohexane ring.



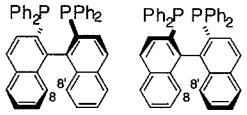

inseparable conformational enantiomers of 2,3-dimethyl butane

Some conformational stereoisomers can be separated because rotation about a single bond is restricted by other parts of the structure. For example, rotation about the aryl-aryl bond in 1,1'-bi-2-naphthol is hindered by the hydroxyl groups and by the hydrogens at the 8 and 8' positions. The two enantiomeric conformers of 1,1'-bi-2-naphthol can be separated and do not interconvert even at 100°C. Conformational stereoisomers that can be separated are called atropisomers. Enantiomers of BINAP

(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl), a useful chiral ligand for hydrogenation catalysts, are also atropisomers.



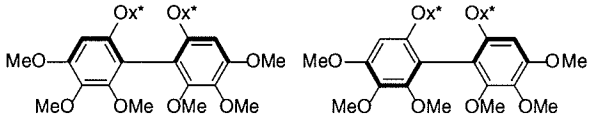

enantiomeric atropisomers
of 2,2'-dihydroxy-1,1'-binaphthyl



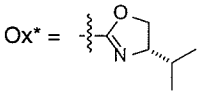

enantiomeric atropisomers of BINAP,
2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

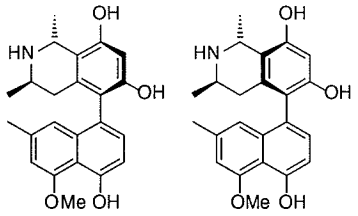
Examples of conformational diastereomers include *s-cis* and *s-trans* *N*-methyl acetamide, the oxazoline derivatives of biaryls[2] and the alkaloids korupensmime-A and -B, which show antimalarial activity.[3]


inseparable conformational diastereomers




diastereomeric atropisomers




korupensamine-A




korupensamine-B

2. Nelson, T. D.; Meyers, A. I. (1994), The asymmetric Ullmann reaction. III. Application of a first-order asymmetric transformation to the synthesis of C2-symmetric, chiral, non-racemic biaryls, Tetrahedron Lett. 35, 3259-3262.

3. Rao, A. V. R., Gurjar, M. K., Ramana, D. V., Chheda, A. K. (1996), Synthesis of optically active *O,O,O*-trimethylkorupensamines A and B, Heterocycles 43, 1-6.

In addition to rotations about single bonds, structures that can be interconverted by inversion at a three-coordinate center or by pseudorotation at phosphorus are often included in this category. Although these reactions are not simple rotations about a single bond, they are fast.

Topology refers to properties solely dependent on connectivity. Topology remains unchanged upon deformation in three-dimensional space. For example, a square and a circle have the same topology, which is different from the topology of a line. Most stereoisomers differ because of the molecular rigidity of bonds. However, some stereoisomers differ only in topology; that is, two structures can not be interconverted by a continuous deformation (flattening or stretching) in three-dimensional space. Bonds may not pass through one another during this deformation. Such stereoiosmers are not configurational or conformational stereoisomer, but topological stereoisomers.[4] For example, the binaphthol enantiomers above can be interconverted by flattening, but the knotted structures shown below cannot be converted into their enantiomers by flattening. Topological stereoisomers are cyclic molecules often containing knots or interlocking rings (catenanes). They can be either topological enantiomers or topological diastereomers.

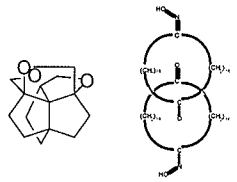


**FIGURE 3.** Examples of molecules that exists as topological enantiomers.[5] The chirality in these molecules is not due to the rigidity of chemical bonds, but due to the way that the bonds are connected. First, convince yourself that these molecules are indeed chiral. Next, observe that you cannot interconvert enantiomers by mentally flattening these molecules without crossing any bonds.

4. Walba, D. M. (1985), Topological stereochemistry, Tetrahedron 41, 3161-3212.
5. Benner, S. A.; Maggio, J. E.; Simmons, H. E., III (1981), title, J. Am. Chem. Soc. 103, 1581-1582; Wasserman, E. (1960), title, J. Am. Chem. Soc. 82, 4433-44xx.

Other examples of molecules that exist as topological enantiomers include a molecular Möbius strip,[6] knotted macrocycles,[7] and knotted DNA molecules.[8]

A flow chart for the classification of enantiomers according to the origin of the stereoisomerism is shown in Figure 4.[9] A similar flow chart could be used to classify diastereomers.

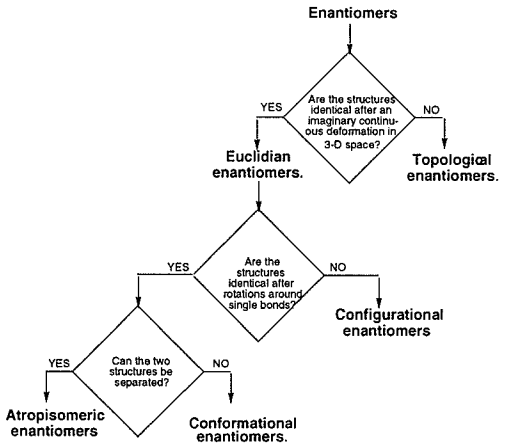
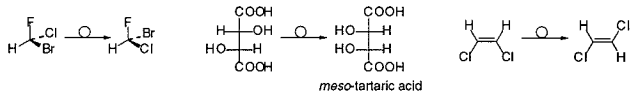



**FIGURE 4.** Flow chart for the classification of enantiomers. Stereoisomerism is caused by configuration of the atoms, conformation about single bonds, or by the topology of the molecule. Different types of enantiomers can be classified according to these causes. A similar flow chart can be used to classify diastereomers.

6. Walba, D.; Richards, R.; Haltiwanger, R. C. (1982), Total synthesis of the first molecular Möbius strip, *J. Am. Chem. Soc.* **104**, 3219-3221.
7. Dietrich-Buchecker, C.; Sauvage, J.-P. (1989), Cloverleaf-knot compounds, *Angew. Chem. Intl. Ed. Engl.* **28**, 189-192.
8. Wasserman, S. A.; Dungan, J. M.; Cozzarelli, N. R. (1985) Discovery of a predicted DNA knot substantiates a model for site-specific recombination. *Science* **229**, 171-174.
9.

## *1.4 Stereogenic units – centers, axes and planes*

Most chiral molecules contain a stereogenic center. The term stereogenic comes from stereoisomerism generated by permutation. A stereogenic center, or more simply a stereocenter, is an atom where permutation of two substituents gives a stereoisomer. For example, the three structures below contain stereocenters. Permutation of two substituents in CHFClBr yields the enantiomer, while permutation of two ligands in tartaric acid or cis-dichloroethene yields a diastereomer.



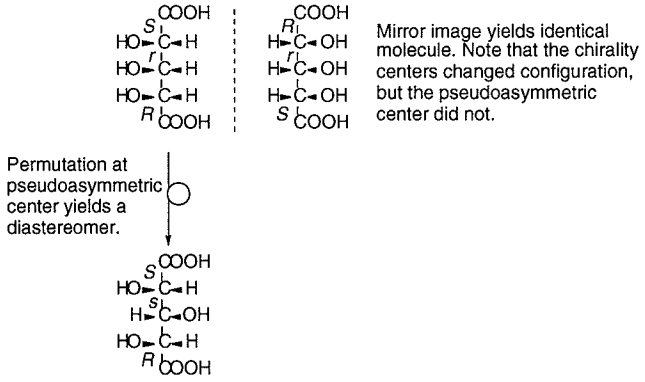

*meso*-tartaric acid

Most stereocenters are also chiral centers. A chiral center is an atom at which interchange of two ligands gives the enantiomeric configuration at that center. It must also be possible to assign a chirality descriptor (R or S) to the center. Chiral centers have either a tetrahedral arrangement of four substituents (e.g., Cabcd) or a trigonal pyramidal arrangement of three substituents (e.g., Nabc). Thus, both CFFClBr and meso-tartaric acid contain stereocenters that are also chiral centers, but the stereocenter in cis-dichloroethene is not a chiral center.

Note that an achiral molecule can contain chiral centers. *meso*-Tartaric acid above is achiral, but contains two chiral centers. The descriptor meso is used for an achiral member of a set of diastereomers that also includes a least one chiral member. The chiral centers in a meso compound are related by an improper axis of rotation, often a mirror plane as in the example above.

Besides a chiral center, another type of stereocenter – a pseudoasymmetric center – occurs in a few cases and causes much confusion. A pseudoasymmetric center is a stereocenter in a meso compound that looks at first glance like a chiral center, but is not. For example, the carbon atom in CabFF* is a pseudoasymmetric center. (F and F* are enantiomorphic substituents.). Switching substituents at a pseudoasymmetric center yields diastereomers. (It is permutation variant.) Pseudoasymmetric centers lie on a plane of symmetry and contain two enantiomorphic ligands, plus two other non-identical ligands. Configuration at a pseudoasymmetric center is

described by a lowercase italic r or s to distinguish it from a chiral center, which is described by and uppercase italic R or S.

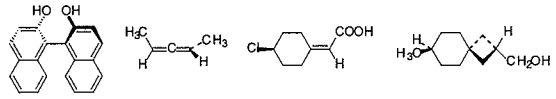



Mirror images of a meso compound are, of course, identical; so the configuration of the pseudoasymmetric center is also the same. (A pseudoasymmetric center is reflection invariant.) On the other hand, the configuration of a chirality center inverts in its mirror image. (It is reflection variant and permutation variant). In the example above, the (*R*)-stereocenter converts to an (*S*)-stereocenter so the configuration at that center indeed changes upon reflection. However, since both chiral centers change, they yield the same molecule after reflection.

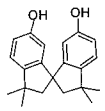
**TABLE 1. Comparison of chiral and pseudoasymmetric centers**

| **chiral center (R, S)** | **pseudoasymmetric center (r,s)** |
|---|---|
| permutation-variant | permutation-variant |
| reflection-variant | reflection-invariant |

Chiral molecules that do not contain a chiral center will contain either an axis of chirality or a plane of chirality. An axis of chirality is an axis containing a nonplanar arrangement of four substituents. The four substituents need not be different to make a chiral axis. It suffices to have two different substituents. For example, allenes of the type abC=C=Cab contain an axis of chirality. Several examples of molecules with axial chirality are shown below.

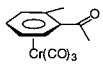


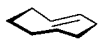
Note that spiro compounds, for example, the spirobiindanol below, do contain a chiral center and not an axis of chirality.




a spiro compound

In relatively rare cases, a chiral molecule will contain neither a chiral center, nor an axis of chirality. It then must contain a plane of chirality. The chiral plane is a plane that contains as many of the atoms as possible. (It cannot contain all the atoms – the molecule would not be chiral.) Chirality stems from the arrangement of the out of plane atoms with respect to plane. Some examples of molecules with a plane of chirality are shown below.

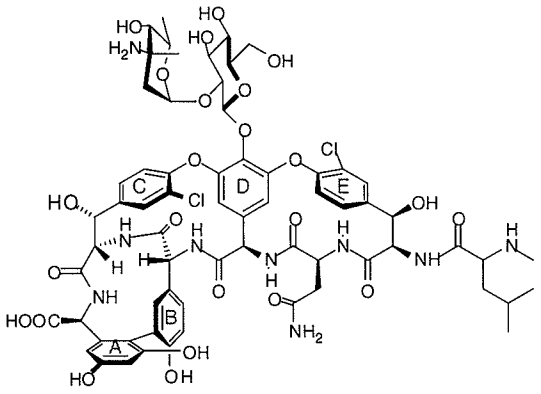


The maximum number of stereoisomers is $2^n$ where n is the number of structural units capable of stereochemical variation (stereocenters, axes, planes, double bonds). The number of stereoisomers is reduced when meso forms are possible. For example, tartaric acid contains two stereocenters so the maximum of stereoisomers is four. However, only three exist: (*R,R*)-, (*S,S*)-, and *meso*.

Vancomycin, an important glycopeptide antibiotic, contains several unusual stereogenic units. Rotation is hindered along the biaryl bond between rings A and B giving an axis of chirality. Rotation is also hindered for rings C and E along the axes defined by the *para*-CH(OH) and *O*-aryl substituents. This hindered rotation creates planes of chirality at both rings. Thus, even with pure enantiomers of all amino acids and sugars needed for the synthesis of vancomycin, a stereoselective assem-

bly of these fragments must control orientation of these aryl rings to avoid fomation of the seven other unwanted atropodiasteromers.[10]



There is no correlation between the molecular orgin of stereoisomerism and the stereogenic unit. A knotted molecule and a chiral metal-arene complex both contain a plane of chirality, but the molecular origin of chirality is different - topology in the first case, rigidity of chemical bonds in the second.

## General References

Eliel, E. L., Wilen, S. H. *Stereochemistry of Organic Compounds* Wiley: New York, 1994.

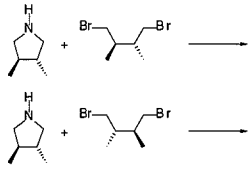
Mislow, K. *Introduction to Stereochemistry* Benjamin: New York; 1966.

Cotton, F. A. *Chemical Applications of Group Theory* 3rd ed.; Wiley: New York, 1990.

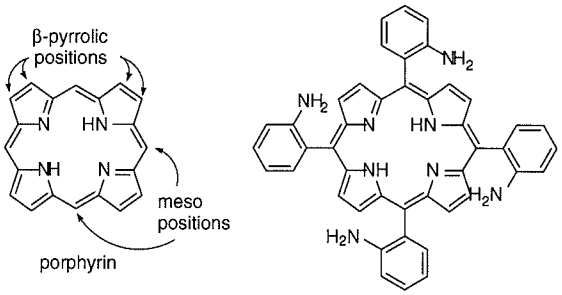
10. Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. (1998), Nonconventional stereochemical issues in the design and synthesis of the vancomycin antibiotics: challenges imposed by axial and nonplanar chiral elements in the heptapeptide aglycons, *Angew. Chem. Intl. Ed.*, **37**, 2704-2708.

## *Questions*

1. Enantiomers differ in their configuration. Is this statement true or false and give a brief explanation.
2. Give an example of an achiral molecule that contains a chiral center.
3. Are the quaternary ammonium salts formed in the following reactions chiral? Is the nitrogen atom at stereocenter?

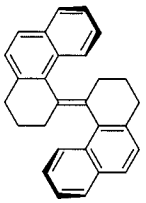


4. Conformational isomers are inseparable stereoisomers. Is this statement true or false and give a brief explanation.
5. Give an example where the total number of stereoisomers and the residual stereoisomers differ.
6. One of the stereoisomers of inositol (1,2,3,4,5,6-hexahydroxycyclohexane) is called *allo*-inositol. It exists in solution as a nonresolvable pair of enantiomers. Suggest a structure for this stereoisomer. [The prefix allo occurs in carbohydrate nomenclature and comes from the Greek *allos*, meaning other.]
7. James Collman's group at Stanford prepared a porphyrin substituted at the meso postions with *o*-aminophenyl groups, known at TAPP (*meso*-tetrakis(o-aminophenyl)porphine). This molecule exists as several atropisomers, which can be separated at room temperatures. Draw the structures of all possible atropisomers. [In this case, the prefix meso does not imply that it is a meso compound. Here meso (from the Greek *mesos* for middle) indicates the middle position]




TAPP
*meso*-tetrakis(*o*-aminophenyl)porphine

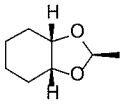
8. The (*E*)-isomer of the chiral olefin below contains two moieties of helicity - helicity between one naphthalene plane and the central double bond and another helicity between the other naphthalene plane and central double bond. The enantiomer shown is the (*M,M*) isomer. Make a model and draw a picture of the enantiomeric (*P,P*) isomer and of the achiral (*M,P*)-isomer. What symmetry element does the (*M,P*)-isomer contain?



9. (*E*)-Cyclooctene is a chiral molecule. Draw the two enantiomeric forms of the molecule.

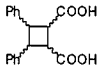
10. Which of the molecules below are chiral?


11. The cyclic compound below has the averaged symmetry that corresponds to the drawing below. Discuss whether this compound is chiral or not.

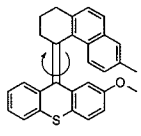



12. In addition to pseudoasymmetric center, one can also have a pseudoasymmetric axis. Suggest an example of a molecule containing a pseudoasymmetric axis.

13. Identify all the residual stereoisomers of truxillic acid, shown below. [Hint: consider the maximum possible.]



**14.** Stereoisomers of the compound below differ by the orientation about the double bond shown. How many stereoisomers are possible? Identify all the stereoisomers and their relationships with one another.



CHAPTER 2

# *Nomenclature for Configurations and Conformations*

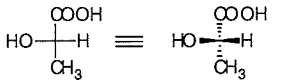
Nomenclature allows us to talk and write about stereoisomers with out drawing a three dimensional picture for each one.[1] Researchers have devised many different, sometimes inconsistent, ways of naming stereoisomers. No one system is clear and convenient for all applications; rather, different nomenclature systems work best in different situations. For example, researchers continue to use Fisher's nomenclature, developed over one hundred years ago, for sugars and amino acid because it shows similarities in a series of stereoisomers. On the other hand, researchers use the more systematic and general Cahn-Ingold-Prelog system for most other organic molecules.

1. Stereochemical descriptors of all types (e.g. R, R*, exo, trans, E) are italicized when they are part of the compound name, e.g. *exo*-norborneol. The italics denote letters that are ignored in the alphabetical ordering of compound names. However, stereochemical descriptors are not in italicized when they are used in the text as not part of a compound name, e.g. the exo diastereomer, the exo anomeric effect.

## *2.1 Fisher's nomenclature is useful for amino acids and carbohydrates.*

### Fisher projection

The Fisher projection is a two dimensional drawing that implies the three dimensional structure shown below. To convert a Fisher projection into a three dimensional structure, one can imagine the horizontal arms reaching out to hug you.




Fisher projection — implied 3-D representation

One can inadvertantly invert the configuration of a molecule while manipulating a Fisher projection. To avoid this, follow the rules in Table 1.

**TABLE 1.** Rules for manipulating Fisher projections without changing the absolute configuration.

| **OK** | **not OK** |
|---|---|
| turn by 180° | turn by 90° |
| permute groups in 3's | permute groups in pairs |
| two succesive permuation of groups in pairs | |

### Fisher nomenclature (D, L)

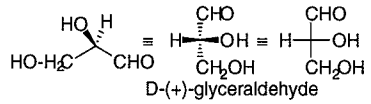
Fisher's nomenclature system is based on similarities to (+)-glyceraldehyde and is indicated by the symbols D and L.[2] Note that d and l do not refer to absolute configuration, but are an obsolete designation for the direction of rotation of plane-polarized light. (Current notation uses (+)- and (–)- to indicate the direction of rotation of plane-polarized light.) The rules for naming enantiomers under the Fisher system are as follows:

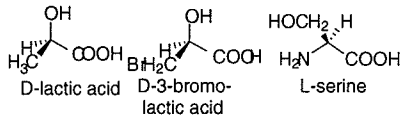
2.

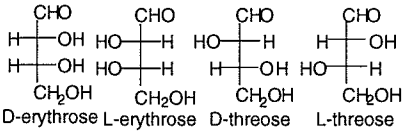
1. Place the number one carbon (most highly oxidized carbon) at the top in a Fisher projection with the main carbon chain extending vertically.
2. If the substituent X is on the right then the structure has the D configuration, if on the left then it has the L configuration.

For sugars the descriptor d or L refers to the configuration at the carbon closest to the primary hydroxyl (lowest stereocenter in a Fisher projection or the highest-numbered stereocenter). The name of the sugar specifies the configuration of the other centers.

The major advantage of this nomenclature is that it emphasizes similarities in a series. For example, the common amino acids all belong to the L-series and the common sugars all belong to the D-series. Another advantage is that the nomenclature is often related to experimental facts. The absolute configuration of many compounds was established by conversion to glyceraldehydes so this nomenclature reminds us these correlation experiments.

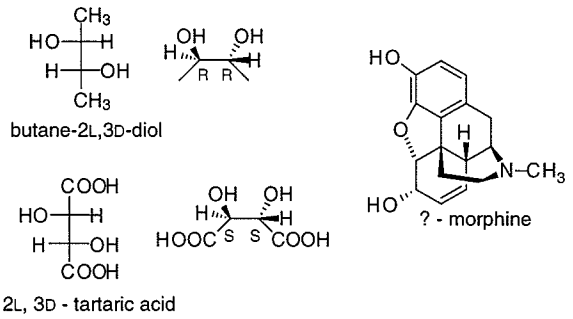



There are several serious disadvantages to the Fisher nomenclature system. First, because the nomeclature is based on a Fischer projection, not on the actual three-dimensional structure, similar configurations can have a different designations. For example, each stereocenter in (*R,R*)-2,3-butanediol has the same three dimensional arrangement of substituents, yet the Fisher nomenclature gives opposite designations to the two centers. There the same problem with (*S,S*)-tartaric acid. Additionally, it is impossible to use the Fisher nomenclature system for complex molecules, like morphine, where the relatedness to glyceraldehyde is hard to find. Neverther-

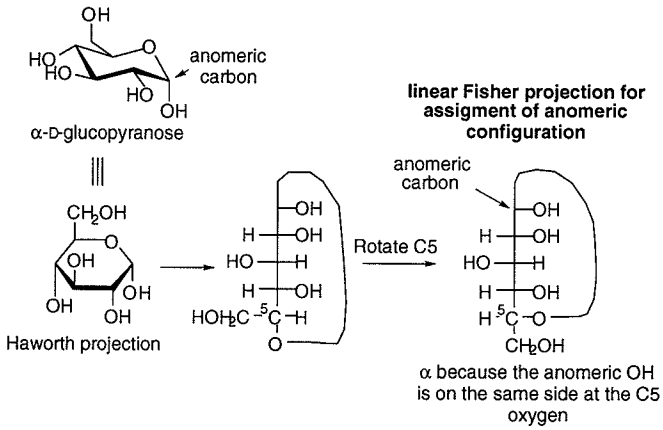
less, the Fisher nomenclature system remains useful in the carbohydrate field where it is widely used.




## Anomeric prefix in carbohydrates: $\alpha$ or $\beta$

Monosaccharides often cyclize to a hemiacetal. The size of the ring is indicated by the suffixes -furanose (five), -pyranose (six), or -septanose (seven). This cyclization also creates a new stereocenter at the hemiacetal carbon. The configuration of this carbon (the anomeric carbon, the two epimers are anomers) is defined relative to the same carbon that defines the Fisher D or L descriptor. The prefix α indicates that the hydroxyl at the anomeric carbon lies on the *same* side as the hydroxyl on the carbon that defines the Fisher descriptor (the lowest stereocenter in a Fisher projection or the highest-numbered stereocenter). The prefix β indicates that the hydroxyl at the anomeric carbon lies on the *opposite* side as the hydroxyl on the carbon that defines the Fisher descriptor. Note that this definition refers to the Fisher projection of the molecule, not the cyclic chain form, where the carbons are not all in a line. The correct anomeric designation may not be obvious from the cyclic form, so con-

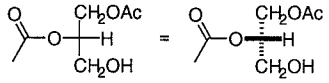
vert the structure to the linear Fisher projection to assign the anomeric descriptor correctly.




**EXERCISE.** Show that the $CH_2OH$ and anomeric OH lie on the opposite sides of the six-membered ring in both α-D-glucopyranose, and in α-L-glucopyranose. Note that in the three dimensional drawing, in one case the anomeric OH points 'down' while in the other case it points 'up'.

## Chiral lipids

A related nomenclature is used for chiral lipids is the *sn* (stereochemical numbering) system. In the Fischer projection the central hydroxyl group of glycerol is position to the left and the carbon atoms are number 1-3 starting from the top. For example, the enantiomer of *sn*-1,2-diacetylglycerol, below, is *sn*-2,3-diacetylglycerol.

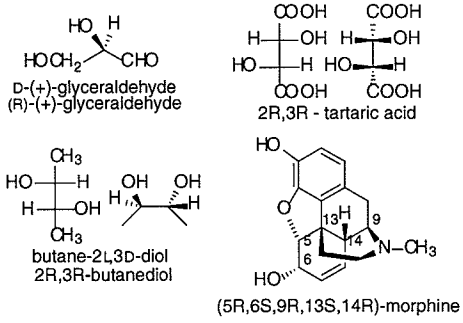


## 2.2 Cahn-Ingold-Prelog system for absolute configurations

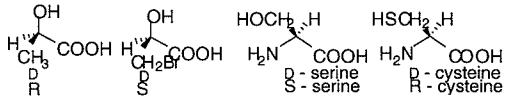
The Cahn-Ingold-Prelog (CIP) system for naming absolute configurations uses the actual three-dimensional arrangement of substituents combined with a ranking system for the substitents based on atomic number.[3] It does not use a reference compound. To apply this system, the four substituents are ranked by atomic number and the molecule is oriented with the lowest priority substituent furthest away from the viewer. A clockwise 1-2-3 sequence of the remaining substituents is called *R*; a counterclockwise *S*.

example

The advantage of this nomenclature system is that it is less equivocal because it is based on the actual 3-D structure of the molecule. It applies to a wide range of compounds and can be used for complex molecules that are difficult to draw in Fischer projection.




A disadvantage is that similar compounds can have different R, S designations. For example the amino acids L-serine and L-cysteine have similar three dimensional stuctures, but opposite designations in the CIP nomenclature system.



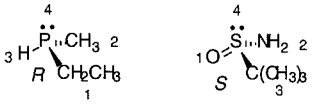

3. Cahn, R. S.; Ingold, C.; Prelog, V. Angew. Chem. Int. Ed. Engl. 1966, 5, 385.authorJ. Org. Chem. 1970, 35, 2849-67; Prelog, V.; Helmchen, G. Angew. Chem. Intl. Ed. Engl. 1982, 21, 567-583.

The detailed rules for ranking substituents, called sequence rules, are as follows.

- Atoms of higher atomic number precede atoms of lower atomic number. For isotopes, the isotope of higher mass number precedes the isotope with lower mass number.

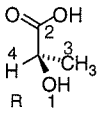
For example, bromine precedes chlorine, which precedes fluorine. Deuterium predates hydrogen.

- A missing substituent (usually a lone pair) on a tetravalent atom is treated as an imaginary atom of atomic number zero.



- When two or more atoms attached to the same chiral center are the same, one proceeds outwardly to the second sphere of atoms, then, if needed, to the third and so on.

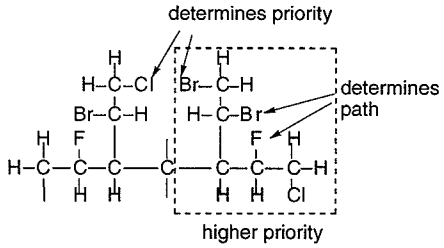
For example, the stereocenter below contains two carbons attached to it. To decide which of these will have higher priority one compares the atoms in the second sphere: H,H,H for the methyl and O, O, (O) for the carboxylic acid. Since an oxygen has higher priority than a hydrogen, the carboxylic acid carbon has higher priority that the methyl carbon.



- All ligands in a give sphere must be explored before proceeding to the next sphere.
- Once a precedence of one path of exploration over another has been established, that precedence carries over to the next sphere.

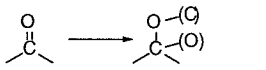
In the example below, the path of exploration follows the upward path because a bromine has higher priority than a fluorine. The priority of the two substituents is

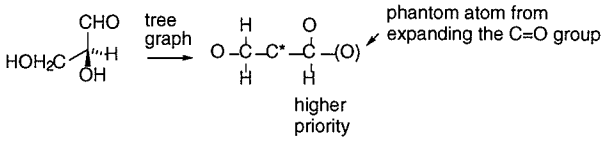
then decided by comparing the bromine and chlorine. Note that although an iodine exists on the path not chosen, it does not contribute to the ranking in this case.



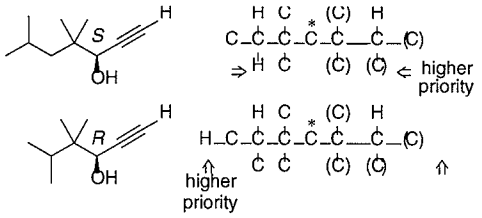

- Expand multiple bonds by adding phantom atoms. Phantom atoms are a duplicate of the atom at the other end of the multiple bond. Phantom atoms, indicated by parentheses, have no substituents.

For example, the carbonyl group expands as shown below. Such an expansion allows one to assign the configuration of glyceraldehye. The –CHO group has priority over the $-CH_2OH$ group as shown by the tree graph.

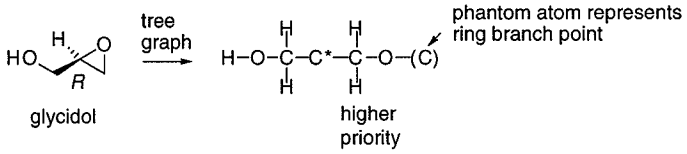





Two other examples are shown below. In the upper example, the ethynyl group, –C≡CH, has higher priority because the phantom carbon, added upon expansion of the triple bond, has priority over a hydrogen. In the lower example, the ethynyl group has lower priority because the a phantom carbon has no substituents. Comparing nothing to a hydrogen, gives priority to the hydrogen.



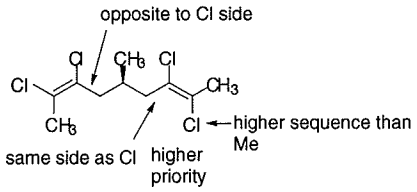
- Complement ring disconnection by phantom atoms.

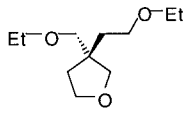



Note that acetylation of glycidol above reverses the stereochemical descriptor due to a change in the priority of the substituents. Such reversals in descriptor with similar compounds is a disadvantage of the CIP system.

- An olefinic ligand where the substituent of higher sequence is on the same side of the olefinic bond as the chiral center has precedence. An (*R*)- configuration precedes an (*S*)-configuration.

Note that the rule above does *not* mean that cis precedes trans or Z preceed E. Rather, the higher sequence substituent is on the same side as the chiral center. For example, in the olefin below, the substituent with the trans configuration has higher priority because the substiuent with higher sequence (Cl) is on the same side as the substituent bearing the chiral center.



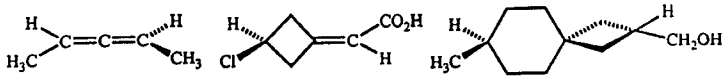
**EXERCISE.** Show that the compound above has the (*S*)-configuration.

## *2.3 Naming molecules with axial or planar chirality*

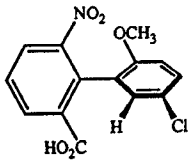
Researchers extended the CIP system to name axially- and planar-dissymmetric molecules.[4] These rules are summarized below.

1. Look for a stereocenter first. If no stereocenter exists, then look for an axis of chirality, then a plane of chirality.
2. For an axis, you must assign a priority to all the ligands at one end of the axis are ranked before ranking any ligands at the other end.
3. For a plane, first identify the plane of chirality. Next identify the preferred side of the plane (usually the side that contains the rest of the molecule) and a point P from which to view the plane. (P is an atom directly bonded to atoms in the plane.) Finally, trace a path from P in the plane using the sequence rule until either a right- (*R*) or left- (*S*) hand turn is formed.
4. Helical structrures are named M for left-handed helices, P for right-handed helices.

Examples of compounds with a chiral axis.




Allene Alkylidenecycloalkane Spirane

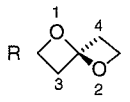



Biphenyl

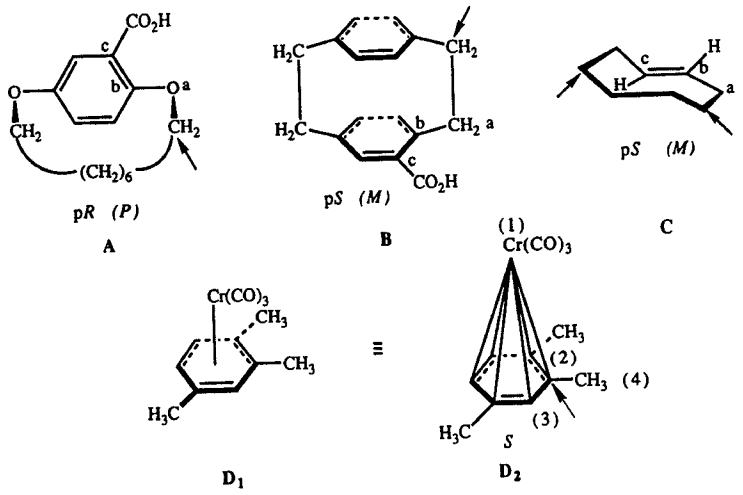
Note that spiro compounds contain a stereocenter not a stereogenic axis and therefore must be named according to the rules in the earlier section. For example, the spiro compound below has the R configuration. Starting arbitrarily with the ring on the left side, the oxygen has higher priority than the carbon of the methylene so the

4. Krow, G. (1969), The determination of absolute configuration of planar and axially dissymmetric molecules, *Top. Stereochem.* **5**, 31-68.

oxygen is assigned priority one. The oxygen in the right ring then get priority two. Then, the carbon of the methylene in the left ring gets priority three because it is in the same ring at the priority one oxygen. Finally, the remaining carbon gets priority four. Verify that one also arrives at the same configuration if one start the numbering in the right ring.




Examples with a chiral plane: paracyclophanes, trans-cyclooctene




Examples of helices (*P/M*)

Although the Cahn-Ingold-Prelog system was designed for chiral molecules, it has been also been adapted to name olefin configuration.

## *2.5 Klyne and Prelog devised a precise nomeclature for conformations.*[5]

The Klyne and Prelog nomenclature, based partly on the sequence rule, starts by defining the torsion angle A-X-Y-B (usually designated theta, θ, sometimes also tau, τ ).[2] Substituents A and B are selected by the following criteria:

- If all substituents are different, then apply the sequence rule.
- If two substituents are identical, chose the unique one independently of the sequence rule.
- If all substituents are identical, chose the one providing the smallest torsion angle.

When viewing A-X-Y-B along X-Y as shown in Figure 1, the torsion angle is the smaller of the two angles between the planes A-X-Y and X-Y-B. Conformations are named based on this angle. A positive angle corresponds to a clockwise rotation from A to B; a negative angle corresponds to a counterclockwise rotation.

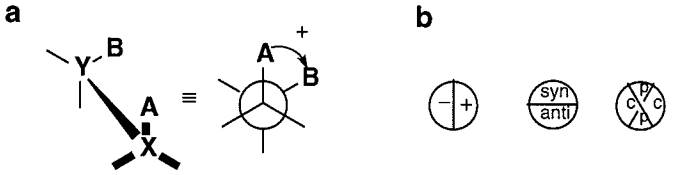



**FIGURE 1.** The Klyne and Prelog nomenclature for conformations. a. The torsion angle between the substituents A and B defines the conformation. b. The Klyne and Prelog nomenclature for conformations divides the circle into six regions according to the descriptors shown. c = clinal; p = periplanar. The conformation shown in a is the +synclinal conformation.

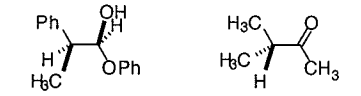
In addition to + and –, Klyne and Prelog use two addition descriptors, syn or anti, and clinal or periplanar, to divide the circle into eight regions, Figure 1. The resulting designations are listed in Table 2.

5. Klyne, K.; Prelog, V. Experientia 1960, 16, 521-523.

**TABLE 2.** Description of Steric Relationships across Single Bonds

| Torsion angle | Designation[a] | Other Names |
|---|---|---|
| $0^o \pm 30^o$ | ± synperiplanar ( ± sp) | eclipsed or syn |
| $+60^o \pm 30^o$ | + synclinal (+sc) | gauche ($g^+$) |
| $+120^o \pm 30^o$ | + anticlinal (+ ac) | skew |
| $180^o \pm 30^o$ | ± antiperiplanar (±ap) | anti or trans |
| $-120^o \pm 30^o$ | - anticlinal (-ac) | skew |
| $-60^o \pm 30^o$ | - synclinal (-sc) | gauche ($g^-$) |

Examples of confomations named using the Klyne and Prelog nomenclature are shown below.

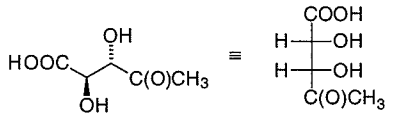



Note that this definition leaves some amiguity. For example, a torsion angle of 90° could be either synclinal or anticlinal.

## *2.6 Overview of several systems for naming relative stereochemistry*

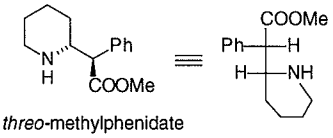
The terms threo and erythro are derived from threose and erythrose. Threose has the two hydroxyls on opposite sides in a Fisher projection, see page 21, while in erythrose they are on the same side. This nomenclature is easily applied to compounds where two groups are the same and the third is different. The threo diastereomer has its substituents on opposites sides when drawn in a Fisher projection; the erthro

diastereomer has them on the same side. For example, the relative configuration of the dihydroxy compound below is erythro.




erythro

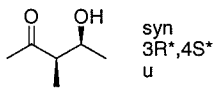
This nomenclature is also used for more complex molecules. For example, the methyphenidate isomer below is assigned as threo by redrawing it in the Fisher projection and noting that the phenyl and amino substituents lie on opposite sides. (Racemic threo-methylphenidate is prescribed as Ritalin for treatment of hyperactivity in children.)




*threo*-methylphenidate

This system is inconvenient today, since researchers favor zigzag drawings for organic molecules. Masamune introduced the terms syn and anti for use with products of the aldol addition[6] and this system is very common today. One draws the longest carbon chain in an extended zigzag. If two substituents are on the same side of the plane defined by the chain, then it is a syn diastereomer; if the subsituents are on opposite sides, then it is an anti diastereomer.

Chemical abstracts uses a system based on the Cahn-Ingold-Prelog system. After drawing one enantiomer, one assigns the configuration to the two stereocenters. The corresponding racemate can them be assigned either the R*,S* and R*,R* designation, where the '*' (pronounced 'star') indicates that the descriptors are used to describe relative, not absolute, configuration. A related notation is the u (unlike) and l (like) notation. R*,S* and S*,R* correspond to unlike, while R*,R* and S*,S* correspond to like.




syn
3R*,4S*
u

6. Masamune, S.; Kaiho, T.; Garvey, D. S. (1982), title, *J. Am. Chem. Soc.* **104**, 5521-xxxx.

Several other relative nomenclature systems also used.[7]

### General references

Eliel, E. L. "Stereochemistry of Carbon Compounds" McGraw-Hill, 1962, Chapter 5.

Cahn, R. S.; Ingold, C.; Prelog, V. "Specification of Molecular Chirality"*Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385.

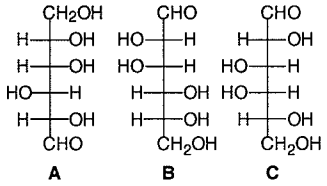
"IUPAC Tentative Rules for the Nomenclature of Organic Chemistry. Section E. Fundamental Stereochemistry" *J. Org. Chem.* **1970**, *35*, 2849-67

Krow, G. (1970), The determination of absolute configuration of planar and axially dissymmetric molecules, *Top. Stereochem.* **5**, 31-68.

Eliel & Wilen, Chapter 14.

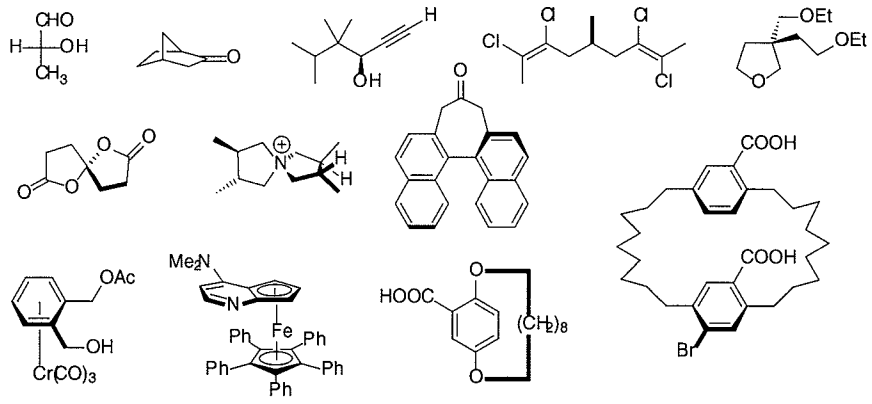
## *Questions*

1. Describe the relationship of the following structures to D-glucose. Draw a chair structure of the ß-anomer of compound C.

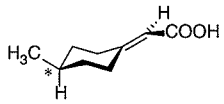



7. Brook, M. A. (1987) The nomenclature of relative stereochemistry, *J. Chem. Educ.* **64**, 218-220. There are a couple of errors in this article. The fourth structure in the table is incorrect and the syn and anti designation of the last compound in the table are reversed.

2. Name the absolute configuration using the R,S-nomenclature. Where appropriate, also give the P, M-nomenclature. For the quaternary ammonium salt in the second row, recall Question 3 on page 16.

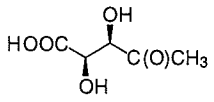


3. The compound below caused controversy in naming its absolute configuration. Before 1982, the accepted procedure was to name it according to the rules for axially chiral molecules (Me, H at one end of the axis; COOH, H at the other end). Show that it has the *S* configuration according to this convention. In 1982 Prelog and Helmchen suggested that it could be named as a center of chirality (marked by *) by carefully expanding the ring. One branch ends up on the same side of the olefin as the COOH, while the other ends up on the opposite side. This new nomenclature could be written $R_n$ or $S_n$ to distinguish it from the old. Expand the alkylidene compound and show that it has the $S_n$ confguration.



4. The same controversy concerns the diamine below. Show that treating this as an axially chiral molecule gives the (*R*)-configuration. However, it can also be treated as center of chirality (marked by *) by expanding the ring. Expansion creates a stereocenter at the amino-substituted methine. Expansion in one direction yields an (*R*)-stereocenter, expansion in the other yields an (*S*)-stereocenter. since R has priority over S, the center of chirality can be assigned using the same approach as for other spiro compounds. Show that the center of chirality approach yields the $R_n$ configuration for the compound below.

5. Name the relative configuration of the compound shown below using each of the following nomenclature systems: a) threo or erythro based on similarity to threose and erythrose, b) the Chemical Abstracts system (R*,S*), c) Seebach and Prelog's *l, u* system, and d) Masamune's syn/anti system. How do these descriptors change when the sample is racemic vs. enantiomerically-pure?




6. Draw a Newman projection of the ap conformation of 1-bromopropane and 1-bromo-2-chloropropane. Compare the relative orientations of the methyl group and bromine in the two structures.

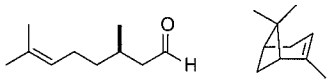
CHAPTER 3

# *Enantiopure Compound Synthesis and Prochiral Elements*

There are several routes to pure enantiomers: resolutions (separation of enantiomers), chiral pool (converting enantiopure natural compounds into your product), stereoselective synthesis (using an extisting stereogenic element to direct the formation of another one). No one method is always best. This chapter briefly mentions the chiral pool approach, but the main topic is an overview of strategies for stereoselective syntheses. In particular, we will learn to identify prochiral elements in a molecule. Selective reactions at these elements are the basis for stereoselective synthesis. Resolutions and stereoselective synthesis will be discussed in detail in later chapters.

## *Pure enantiomers from enantiopure natural products*

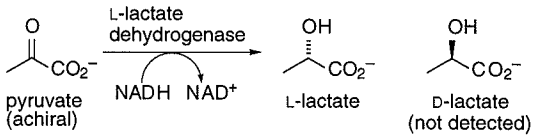
Most, but not all, natural products are enantiomerically pure. Citronellal from Java lemon grass shows only 75-80%ee.[1] North American pine trees yield (+)-α-pinene with ~90%ee, while European pine trees yield (-)-α-pinene with ~80%ee.




Another disadvantage of natural products is that usually only one enatiomer is readily available.

## *Stereoselective reactions can be enantioseletive or diastereoselective*

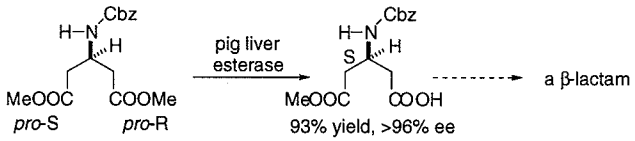
A stereoselective reaction is a reaction where the starting material could form two or more stereoisomers, but forms one preferentially. A stereoselective reaction converts an achiral unit in a molecule to a chiral unit in unequal amounts. For example, the L-lactate-dehydrogenase-catalyzed reduction of pyruvate yields L-lactate and no detectable D-lactate. Here the carbonyl carbon is the achiral unit which is converted a chiral unit by enantioselective addition of a hydride from NADH. This stereoselective reaction is an enantioselective reaction because it yields an excess of one enantiomer over the other.




Another example of an enantioselective reaction is the pig liver esterase catalayzed hydrolysis of the diester below. The starting diester is achiral since the carbon has

1. Valentine, D., Jr.; Chan, K. K.; Scott, C. G.; Johnson, K. K.; Toth, K.; Saucy, G. (1976), Direct dermination of R/S enantiomer ratios of citronellic acid and related substances by nuclear magnetic resonance spectroscopy and high pressure liquid chromatography, J. Org. Chem., 41, 62-5.

two identical groups attached. Howver, selective reaction at on of these groups yields a chiral monoester in high enantiomeric purity.[2]




An example of a diastereoselective reaction ...

A stereospecific reaction does *not* mean a highly stereoselective reaction.

## *Identifying enantiotopic, diastereotopic and equivalent elements.*

Molecules can contain groups, faces, axes, or planes that are enantiotopic or diastereotopic. A reaction that tranforms an enantiotopic group yields enantiomers; a reaction that transforms diastereotopic groups yields diastereomers.

Enantiotopic (sometimes less accurately called enantiomeric) groups or faces are indistinguishable by chemical reactivity or by NMR under achiral conditions. Reaction at either group (or addition to either face) gives enantiomers. Enantiotopic groups are interchanged only by an improper rotation ($S_n$, *i* or $\sigma$). The hydrogens in $CH_2BrCl$ are enantiotopic. Replacement of one H yields one enantiomer, replacement of the other H yields the other enantiomer. The ester groups in the diester example above are enantiotopic. Enantioselective hydrolysis of one group yielded a chiral molecule.

Diastereomeric groups are different from each other. They show different chemical reactivity and separate NMR resonances, but the chemical reactivity or chemical shift can be accidentally the same. Diastereomeric groups are not interchanged by symmetry operations.

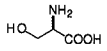
2. Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Y.-F.; Izawa, T. (1981), Synthesis of (*S*)- and (*R*)-4-[(methoxycarbonyl)methyl]-2-azetidinone by chemicoenzymatic approach, *J. Am. Chem. Soc.*, **103**, 2405-2406.

Molecules can also contain equivalent groups or faces. They have the same chemical reactivity and the groups have the same NMR chemical shift. Equivalent groups are interchanged by a proper rotation ($C_n$). Reaction at either group (or addition to either face) gives identical products. All the hydrogens in benzene are equivalent; the three methyl hydrogens in toluene are equivalent.

**TABLE 1. Characteristics of different types of groups and faces in molecules**

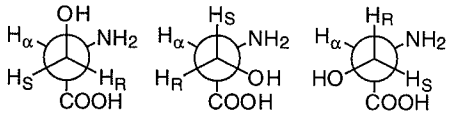
| Equivalent | Enantiotopic | Diasterotopic |
|---|---|---|
| exchanged by $C_n$ | exchanged only by $S_n$ (includes $\sigma$ and $i$) | not exchange by $C_n$ or $S_n$ |
| same NMR signal | same NMR signal | different NMR signal |
| same chemical reactivity with all reagents | same chemical reactivity with achiral reagents | different chemical reactivity |
| reaction at either group gives identical products | reaction at either group with achiral reagents gives enantiomers | reaction at either group gives diastereomers |

Methylene hydrogens in chiral molecules are often diastereotopic. For example, the methylene hydrogens in D-serine below are diastereotopic.

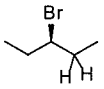



Some students find it difficult to believe so we will examine the serine example in more detail. The Newman projections below show the three staggered conformations of D-serine. First, since the three conformations likely have different energies, the hydrogens labelled $H_S$ and $H_R$ will encounter different environments on average. Second, even if the three conformations were equally populated, $H_R$ and $H_S$ still encounter different enviroments. For example, when $H_S$ is in the upward orientation (middle diagram) the hydroyl group lies between the amino and carboxyl groups, but when $H_R$ is in the upward orientation (right most diagram) the hydroyl group lies between the carboxyl group and $H_\alpha$. This difference in the orientation of the hydroxyl group make the two upward orientations of the $H_S$ and $H_R$ inequiva-

lent. Thus, the $H_S$ and $H_R$ encounter different enviroments on average and thus have different chemical reactivity.




Must a molecule be chiral to contain methylene groups with diastereotopic hydrogens? No, achiral molecules can also contain methylene groups with diastereotopic hydrogens if there is no proper or improper rotation that exchanges the two hydrogen. An achiral contains an improper axis of rotation. However, this axis may not exchange the two hydrogen in a methylene group so they are diastereotopic. For example, 3-bromopentane is achiral, but the two hydrogens shown are diastereotopic.

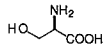



## *Prochiral or prostereogenic molecules and elements*

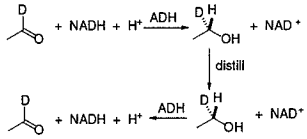
Prochiral molecules are achiral molecules that can easily become chiral. A simple replacement or addition can make them chiral. Prochiral molecules contain either ligands whose separate replacement yields stereoisomers (the ligands are the prochiral groups) or a double bond where separate addition to the two faces yields stereoisomers (the faces are prochiral faces). For example, $CH_2BrCl$ is a prochiral molecule because replacement of one of the two hydrogens would yield a chiral molecule. Replacement of the other hydrogen would yield the enantiomer of the same chiral molecule. Acetaldehyde is also prochiral because addition to opposite faces of the carbonyl yields enantiomers.

Although the term prochirality is still used today, many researchers favor the more general term prostereogenic. Consider the methylene group in D-serine shown below. Replacement of one of the hydrogen yields a stereocenter and creates a dias-

tereomer. However, since serine is already chiral, some object to calling this carbon a prochiral center. A more general expression is 'prostereogenic center'.



Isotopic labeling can uncover the hidden stereochemistry of reactions at prostereogenic centers. For example, alcohol dehydrogenase removes only the *pro-R* hydrogen of ethanol.[3] Knowing the hidden stereochemistry of enzymatic reactions helps to establish biosynthetic pathways, shows relatedness in the evolution of enzymes, and aids drug design.[4]




Some groups become stereogenic after two reactions. These groups are called proprostereogentic (or proprochiral). For example, a methyl group ($-CH_3$) and a phosphoryl group ($-PO_3$) are proprostereogenic. Researchers used chiral methyl groups (CHDT) and chiral thiophosphates ($PS^{16}O^{17}O^{18}O$) to measure whether enzyme reactions of these groups occur with retention or inversion.[5]

Discuss prochiral center, prochiral axes, prochiral planes.

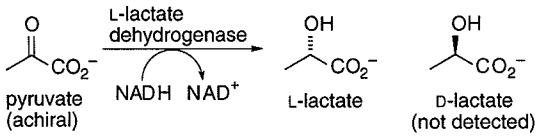
## *Izumi-Tai system for classification of stereoselective reactions*

The Izumi-Tai system classifies single step reactions according to the reactants.

3. Levy, H. R.; Talalay, P.; Vennesland, B. in Progress in Stereochemistry, vol. 3, de la Mare, P. B. D.; Klyne, W., Eds. Butterworths: London 1962, p. 299.
4. author (1975), title, *Acc. Chem Res.* **8**, 1-10.
5. Floss, H. G.; Tsai, M.-D.; Woodard, R. W. (1984), Stereochemistry of biological reactions at proprochiral centers, *Top. Stereochem.* **15**, 253-xxx.

### enantio-differentiating reactions

enantioface-differentiating reactions




enantiotopos-differentiating reactions (includes the meso trick)

enantiomer-differentiating reactions (kinetic resolution)

### diastereo-differentiating reactions

diastereoface-differentiating reaction

diastereotopos-differentiating reaction

diastereomer-differentiating reactions

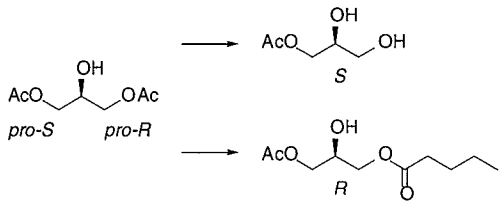
## *Naming prochiral groups and faces*[6]

The descriptors *pro-R* and *pro-S* distinguish ligands, while Re and Si distinguish faces.

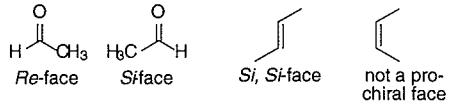
Name a prochiral group (pro-R, pro-S) by assuming the group being named has the higher priority. Select a group and arbitrarily assign it a higher priority than the other group. Don't disturb the priorities of the other ligands. If application of the sequence rule results in an asignment of R as the configuration of the prostereo-

6. Eliel, E. L. (1980), Stereochemical Non-Equivalence of Ligands and Faces (Heterotopicity)" *J. Chem. Educ.* **57**, 52-55; Hanson, K. R. (1966), Application of the Sequence Rule. I. Naming the Paired Ligands g,g at a Tetrahedral Atom Xggij. II. Naming the Two Faces of a Trigonal Atom Yghi." *J. Am. Chem. Soc.* **88**, 2731-2742.

genic center, then the selected group is pro-R. If the center was assigned S, then the selected group is pro-S.




The two faces of a trigonal atom can also be prochiral. Addition to prochiral faces yields enantiomers. Name a prochiral face (Re, Si) by ranking the three substituents at each end of the double bond.




The faces in *cis*-2-butene can be named as the Si,Re-face and the Re,Si-face, but some researchers feel that these faces on not prochiral. Symmetrical cis addition to either face (e.g., cis-dihydroxylation) yields a meso compound. Nonsymmetrical addition (e.g., addition of HX) can yield either enantiomer by the addition to either carbon of the same face. My opinion is that the individual faces of the carbon atoms in cis-2-butene are prochiral since the addition to either side yields enantiomeric configurations.

### General References

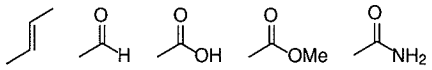
text 1

text 2

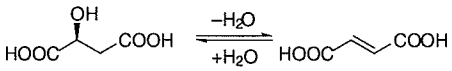
## *Questions*

1. Discuss the following statement: The ultimate source of all enantiomerically pure compounds is biological.

2. Name the prochiral faces shown below.

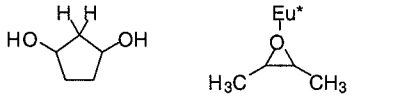


3. The enzyme fumarase catalyzes the reversible dehydration of (S)-malate to fumarate. Only the *pro-R* hydrogen reacts. Draw a structure showing which hydrogen is removed.



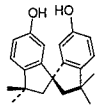
4. Identify equivalent, enantiotopic, and diastereotopic hydrogens in dioxolane.

5. Explain how to distinguish between the meso and chiral stereoisomers of compounds below using $^1$H-NMR.

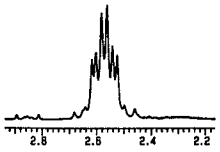


Eu* = chiral shift reagent

6. The compound below has four methyl groups. Predict whether the 1H-NMR spectrum for these methyl groups will be one singlet, two singlets or four singlets.

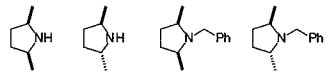


7. Mild oxidation di(*n*-octyl)sulfide yielded the sulfoxide. The $^1$H-NMR of the product showed the signal below for the methylenes next to the sulfur. Explain qualitatively why this signal is not a triplet.

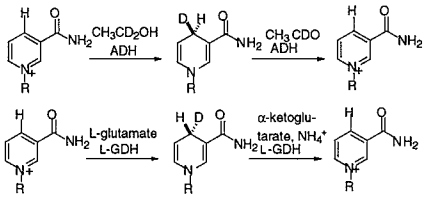



8. A researcher had a pure stereoisomer of 2,5-dimethylpyrrolidine shown below. However, she did not know whether it was the meso or racemic stereoisomer. Explain why a $^1$H-NMR would NOT distinguish the two. She treated her sample

with benzyl bromide to yield the *N*-benzyl derivative. The $^1$H-NMR resonance of the benzyl methylene unambiguously identified the starting stereoisomer. Explain.




9. Dehydrogenases catalyze reaction at only one of faces of the nicotinamide ring of $NAD^+$. Are these faces equivalent, enantiotopic or diastereotopic?




10. Like any classification system, the Izumi-Tai system is not perfect. For example, in some cases a reaction might be classified into more than one category. Which two categories could you classify the reaction below into?

CHAPTER 4

# *Separating Enantiomers: Resolutions*

Resolutions are separations of enantiomers. These separations usually involve a crystallization or chemical reaction where one enantiomer reacts faster than another (a kinetic resolution). This chapter examines these two types of resolutions. A less common method is resolution using chromatography. It is briefly mentioned in this chapter, but will be discussed in more detail in Chapter 6.

One major disadvantage of any resolution is the maximum yield of only 50% of one enantiomer. However, in a dynamic resolution the starting compound racemizes while the resolution continuously removes one enantiomer. A dynamic resolution can yield 100% of one enantiomer.

## *Separation by Direct Crystallization*

Enantiomers have identical properties in nonchiral environments, but can have different properties in a chiral environment. A well known example is the different rotation of plane-polarized light by enantiomers, which will be discussed in Chapter 5. In this case the light is the chiral environment. In other cases, the enantiomers themselves can create the chiral environment through intermolecular interactions. Pure enantiomer, which only interacts with like molecules (homochiral interactions), may have different physical properties from the corresponding racemate,

which interacts with both like and unlike molecules (homochiral and heterochiral interactions). The origin of these differences is differences in homochiral vs. heterochiral interactions. In a pure enantiomer, there can be only homochiral interactions, while in a racemate, there can be either homochiral or heterochiral interactions. When these interactions differ significantly, the pure enantiomer and the racemate will have different physical properties. Homochiral and heterochiral interactions are stronger in the solid state than in solution, so the differences in physical properties are largest in the solid state. For example, melting points for the pure enantiomer and its racemate are almost always different.

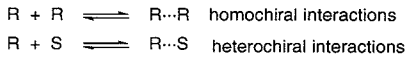



**FIGURE 1.** Interactions between enantiomers of like configuration are homochiral interactions, while interactions between enantiomers of opposite configuration are heterochiral interactions. Examples of interactions include van der Waals interactions, electrostatic interactions, hydrogen bonding, and π-complex formation. These interactions are usually weak in solution or the liquid state (~0.001 kcal/mol), but stronger in the solid state (~1 kcal/mol).

## Conglomerates, racemic compounds, and solid solutions.

Crystals of pure enantiomers usually differ significantly from crystals of racemate. Crystals of pure enantiomers contain only the pure enantiomer. However, racemates crystallize in one of three ways: as a conglomerate, as a racemic compound, or as a solid solution, Figure 2.

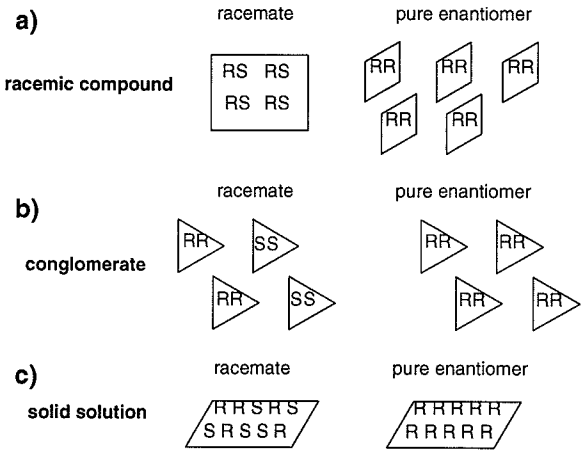


**FIGURE 2.** Schematic representation of the main types of crystalline racemates and crystalline pure enantiomers. a) For a racemic compound, the crystalline racemate contains both enantiomers in the unit cell because heterochiral interactions are stronger than homochiral interactions. Each single crystal of the racemate is racemic. Crystalline pure enantiomer has a crystal form different from the racemate because the unit cell contains only one enantiomer. b) For a conglomerate, the crystalline racemate contains only one enantiomer in the unit cell because homochiral interactions are stronger than heterochiral interactions. Each single crystal of the racemate is enantiomerically pure. Crystalline pure enantiomer has the same crystal form as the racemate. c) For a solid solution (or pseudoracemate), the crystalline racemate contains both enantiomers in the unit cell in a random distribution because homochiral and heterochiral interactions have similar energies. Each single crystal of the racemate is racemic. Crystalline pure enantiomer has the same crystal form as the racemate.

In a racemic compound both enantiomers coexist in each crystal because each enantiomer has a higher affinity for the opposite enantiomer, rather than one of its own kind. Heterochiral interactions are stronger than homochiral interactions. Racemic compounds are the most common of the three possibilities. Crystals of pure enantiomer and racemate differ because the unit cell of the racemate contains both enantiomers, while the unit cell of the pure enantiomer, of course, contains only one enantiomer.

In a conglomerate each enantiomer crystallizes in separate crystals because each enantiomer prefers to interact with like molecules, i.e., homochiral interactions are stronger than heterochiral interactions. Crystals of pure enantiomer and racemate both have the same structure since in both cases each unit cell contains only one enantiomer. Single crystals are enantiomerically-pure both in the enantiopure material and in the racemic material. Racemic conglomerates can be resolved by mechanical separation of crystals as Pasteur did for sodium ammonium tartrate, see below. Approximately 5-10% of all organic crystals are conglomerates; it is slightly more likely with ionic crystals than with uncharged compounds.

Note the difference between racemate and racemic compound. Racemate refers to any mixture where the enantiomers are in equal proportions. Racemic compound refers to the specific crystalline case where strong heterochiral interactions create crystals with equal amounts of both enantiomers in the unit cell.

In a solid solution (sometimes called a pseudoracemate), there is little difference in the affinity between molecules of like and opposite configuration, thus the arrangement of the two enantiomers is random.

## Pasteur's resolution of sodium ammonium tartrate

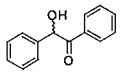
Since individual crystals of conglomerates are enantiomerically pure, several tricks can resolve the enantiomers by direct crystallization. For example, the first resolution of a racemate was a resolution of sodium ammonium tartrate by Pasteur in 1848. Sodium ammonium tartrate crystallizes as a conglomerate below 26°C and crystal form is such that the shapes of the crystalline enantiomers are mirror images of one another. Pasteur separated the dextrorotatory and levorotatory crystals with tweezers in 1848 and showed that they rotated plane polarized light in opposite directions. This was the first demonstration that the property of optical rotation was a property of molecules; before this researchers thought it was a property of crystals only.

To improve this tedious resolution, one can carry out the crystallization in a manner that each enantiomer crystallizes in a different *place*. Seed crystals of L and D are placed in opposite sides of the container. The instructions given by Jungfleisch to make giant 180-200 g crystals of sodium ammonium tartrate are translated below:[1]

> One operates in crystallizing dishes containing one to two liters of liquid whose ground edges permit an airtight enclosure to be maintained by covering the dishes with flat glass plates. The saturated solution is placed in the vessel while still warm. Upon condensation, the water vapor emitted by the warm solution wets the edges of the dish as well as the glass cover by capillary action thus yielding a hydraulic closure which allows the solution to cool completely while remaining supersaturated.... The solution having attained room temperature, one carefully wets the hands and places a small fragment of dextrorotatory sodium ammonium tartrate between the fingers; one washes the crystal by exposing it momentarily to the stream of a washbottle and allows it to fall in the right hand side of the crystallizing dish. One does the same with a crystal of levorotatory salt which is allowed to fall in the left side and then immediately replace the glass cover.... The introduction of crystalline dust must be carefully avoided which would otherwise rapidly lead to a mixed crystallization. The wetted crystals do not yield this phenomenon: they momentarily dilute the liquid layer which surrounds them, enlarge themselves slowly and attain their maximal size only after two to three days by which time the solution has ceased to be supersaturated. They remain perfectly isolated... and the dextrorotatory crystal has been enlarged only by dextrorotatory tartrate, while the levorotatory crystal is formed exclusively with levorotatory salt. It is easy to obtain well-formed and isolated crystals in this way each weighing 180 to 200 g.

1.

Another way to carry this type of resolution on a practical scale is "resolution by entrainment" where each enantiomer crystallizes at a different *time*. Small amounts of the two enantiomers crystallize alternately. This procedure was used industrially to resolve glutamic acid, 13,000 tons/year between 1963 and 1973.[2] Fermentation is used today to synthesize only the desired enantiomer. Detailed instructions for the resolution of hydrobenzoin are given below.




Racemic hydrobenzoin (11 g) is dissolved along with 0.37 g (-)-hydrobenzoin in 85 g of 95% ethanol and the solution is cooled to 15°C. Seeds of (-)-hydrobenzoin (10 mg) are added and the stirred solution is allowed to crystallize for 20 minutes. The weight of (-)-hydrobenzoin recovered after filtration (0.87 g) is roughly double that of the (-) enantiomer introduced in excess at the beginning of the experiment. Racemic hydrobenzoin is then added to the remaining solution in an amount equal to that of the (-) crystals collected. The solution is heated to complete dissolution of the solid and is then cooled to 15° and crystallized as above, after seeding with 10 mg (+) enantiomer, to yield a weight of (+)-hydrobenzoin nearly equal to that of the (-) isomer earlier collected. The same cycle of operations, namely, loading with racemic hydrobenzoin and collection of (+) and (-) crystals is carried out 15 times, yielding 65 g of (-) and 5.7 g of (+) enantiomer having ~97% optical purity.

## Identifying a conglomerate

To distinguish a conglomerate from a racemic compound, one searches for evidence of a new interaction in the racemate that is not present in the pure enantiomer. Typical tests are comparing x-ray diffraction patterns or ir spectra. This new interaction is evidence for a racemic compound, while the lack of interactions suggests a conglomerate.

The melting points of racemic samples and pure enantiomers differs for both conglomerates and racemic compounds. A racemic conglomerate behaves as a mixture of two materials (the two enantiomers). This mixture always melts at a lower temperature because of the entropy of mixing of these materials in the liquid phase. For example, norfenfluramine dichloroacetate crystallizes as a conglomerate. The race-

2. Monosodium glutamate (MSG), a flavor enhancer,. contains L-glutatamic acid.

mic conglomerate melts at 117°C, while the pure enantiomer melts at 139°C, Table 1.

**TABLE 1.** Some physical properties of crystalline pharmaceuticals

| compound | crystal type | mp, °C | solubility |
|---|---|---|---|
| norfenfliramine dichloroacetate | conglomerate | 117 | 24.9%[a] |
| norfenfluramine dichloroacetate | pure enantiomer | 139 | 14.5%[a] |
| ibuprofen | racemic compound | 71 | 0.94 mM[b] |
| ibuprofen | pure enantiomer | 46 | 1.79 mM[b] |

[a] in 95% ethanol at 22°C. [b] in aqueous HCl-KCl at 25°C

On the other hand, a racemic compound behaves as a mixture of three solids: one pure enantiomer, the other pure enantiomer and the racemic compound. The pure enantiomers each have identical melting points, but the racemic compound may melt at a higher or lower temperature than the pure enantiomers. The solid racemic compound and solid pure enantiomer are different substances.

Mixtures of solid pure enantiomer and solid racemic compound will also melt at lower temperatures due to the entropy of mixing. However, the minimum rarely occurs at a 50:50 mixture since they are different crystals and have different heats of fusion. The mixture whose constituents are in such proportions as to melt and solidify at one temperature is give the name eutectic, derived from the Greek words for true melt. Mixtures of two compounds usually have a broad melting point. A eutectic is a mixture of two compounds that has a sharp melting point.

Ibuprofen crystallizes as a racemic compound. The racemic compound melts at 71°C, while the pure enantiomer melts at 46°C. Solubility behavior parallels the melting points – the higher melting forms are also less soluble.Idealized binary phase diagrams for the three types of racemates are shown below. Adding crystals of pure enantiomer to the racemate will depress the melting point if the racemate is a racemic compound, but increase it if the racemate is a conglomerate.

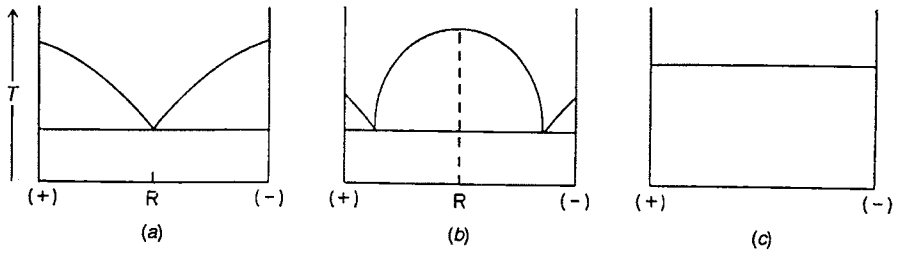
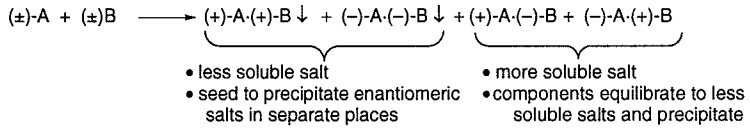



**Figure 6.3.** Binary phase diagrams describing the melting behavior of the common types of racemates. (*a*) Conglomerate, (*b*) racemic compound and (*c*) ideal solid solution (pseudoracemate).

**mutual resolution** – A resolution of a conglomerate by crystallization, where the conglomerate is a salt. Both components of the salt may be resolved simultaneously.




## Enhancing enantiomeric purity of enantiomerically enriched samples

The most common way to enhance the enantiomeric purity of an enantiomerically enriched sample is by recrystallization. This method always works for samples that crystallize as conglomerates and sometimes works for samples that crystalize as racemic compounds.

Samples where the racemate is a conglomerate. In this case, you can always increase the enantiomeric purity by recrystallization.

Samples where the racemate is a racemic compound. In this case, success depends on whether the enantiomeric purity is higher or lower than the eutectic compositions. If it is lower than the eutectic composition, you may be out of luck. Recrystallization will yield crystalline racemate. The enantiomeric purity of the solution can increase to the eutectic composition, but no more. (At that point the eutectic will crystallize.) If the enantiomeric purity of your sample is above the eutectic composition, the recrystallization can yield enantiomerically pure material. One way to remember – crystalline form will be 'uphill' of the composition.

As an example, consider a sample of ibuprofen with 70% ee S (85% S, 15% R). The eutectic is 84% ee (92 mol%), so recrystallization yielded a small crop of racemic crystals and a mother liquor with slightly enriched ee. On the other hand converting this sample to the sodium salt, where the eutectic composition is only 26% ee (63 mol%), permitted recrystallization from acetone to yield a crystalline crop of 98% ee. Also keep in mind that the melting point diagrams only approximate the solubility behavior.

Another way to increase enantiomeric purity is by "duplication", sometimes called the Horeau amplification principle.[3] This method relies on formation of dimers to make a mixture of meso and chiral diastereomers. The substrate (R with some S) dimerizes to form a meso (RS) and a chiral (RR + SS) dimer. These two diastereomers are separated and the chiral dimer is converted back to the substrate (R with less S than before). Removal of the meso dimer is the key to the purification. The meso dimer contains equal amounts of R and S. Since the starting sample contained more R than S, the proportion of R in the sample is now higher.

Assuming a random dimerization, the final enantiomeric purity, $ee_f$, can be calculated from the initial enantiomer purity, $ee_i$, using the equation below.

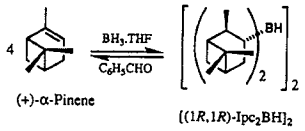
$$ee_f = \frac{2 \cdot ee_i}{1 + (ee_i)^2}$$

The amount of meso compound formed (and thus, the minimum amount lost during such a purification) is $1\text{-}ee_i$.

A useful application of this principle is the enrichment of the enantiomeric purity of naturally occuring α-pinene. Hydroboration with an excess of natural α-pinene having 91% ee yielded an insoluble dimer: diisopinocampheylborane. Decomposition of the borane yielded a-pinene with 99.6%, exactly as predicted by the equation above. In this case the chiral and meso dimer equilibrate during the reaction, and only the chiral dimer precipitates. (Note that the true structure of the borane is a

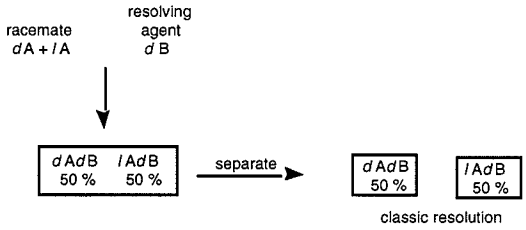
3. Rautenstrauch, V. (1994), The two expressions of the Horeau principle, $N^{th}$-order Horeau amplifications, and scales for the resulting very high enantiopurities, *Bull. Soc. Chim. Fr.*, **131**, 515-524; Horeau (1973), title, *Tetrahedron*, **29**, 1055-xxxx.

dimer containing four α-pinene groups in solution, but this does not affect the discussion above.)

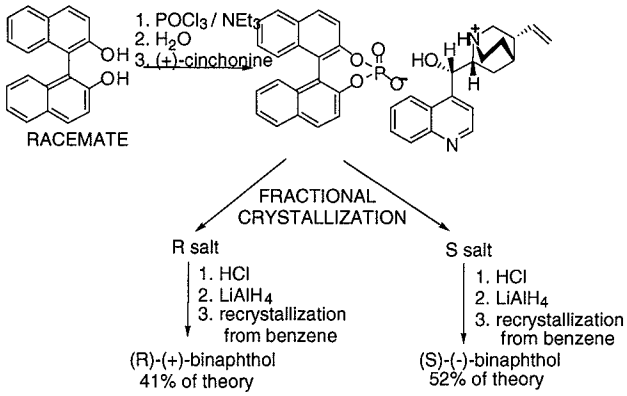



## *Classical resolution: crystallization of diastereomeric salts*

text




Example

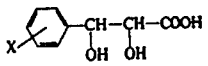



Refs: Jacques, Tet. Lett. 1971, 48, 4617-20; Cram, et al. J. Org. Chem. 1977, 42, 4173-84; Jacques, Truesdale Org. Syn. 1988, 67, 1-19.Resolutions of binaphthyl phosphate by crystallization with (R)-(-)-2-aminobutanol: Miyano, Synthesis, 1990, 222.

Typical trial and error procedure for finding the right salt:

1. Combine 0.1 to 1 mmol of racemate with an equivalent of resolving agent in ~1 mL of solvent. Ethanol and aqueous ethanol are often good choices. Set up several simultaneous crystallizations.
2. Collect, dry and weigh any crystals that form. Their mass should be less than half of the total weight of the two diastereomers. If too much has crystallized, then try again with more solvent.
3. Decompose any promising salts and determine ee.

**Table 2** Resolution trials for the phenylglyceric acids[a]




| | X | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Threo | H | l | 0 | | Oil | | 0 | | | 0 | Oil | | | 0 |
| | o-Cl | 0 | 0 | | | 0 | | l | | | l | d | | |
| | m-Cl | | | | | | | | | | | d | | |
| | p-Cl | l | | | | | | | | | | | | |
| Erythro | H | | | | | 0 | | | | | | | d | |
| | o-Cl | 0 | l | | | Oil | | | | | | | l | 0 |
| | m-Cl | | 0 | l | | Oil | | | 0 | | Oil | | 0 | |
| | p-Cl | | d | | Oil | l | 0 | | d | | | | d | |

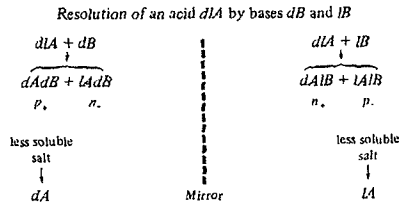
[a] Samples of acid (100 mg, ca. 5.0 mmol) are treated with 1 equivalent base in 1 mL ethanol. The crystals obtained are directly decomposed and the rotation of the acid measured. Key: 0 = no resolution; *d* or *l*, *d* or *l*, *d* or *l* = weak, fair, or good resolution. From ref. 13. 1 = (+) α-methylbenzylamine; 2 = (+)-*threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol; 3 = (+)-*threo*-1-*p*-nitrophenyl-2-dimethylamino-1,3-propanediol; 4 = (−)-ephedrine; 5 = (−)-deoxyephedrine; 6 = (−)-amphetamine; 7 = dehydroabietylamine; 8 = funtumine (3α-amino-5α-pregnan-20-one); 9 = quinine; 10 = cinchonine; 11 = cinchonidine; 12 = strychnine; 13 = brucine.

Unfortunately, we can not predict which salts are the best for resolution. Zingg et al. analyzed the crystal packing in several amine salts of mandelic acid, but could not predict which of the salts were less soluble.

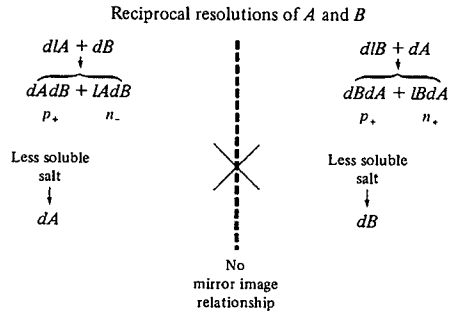
families of resolving agents.

## Marckwald principle and reciprocal resolutions

**Marckwald principle** – two enantiomers of a resolving agent give access in turn to both enantiomers of a substrate. Thus, if adding (*R*)-resolving agent to a racemic mixture of substrate precipitates the (*R*)-, (*R*)- salt, the adding (*S*)-resolving agent precipitates the (*S*)-(*S*)- salt. This principle, which seems obvious now, was proposed in 1896. The Marckwald principle always holds because the two cases are mirror images of one another.



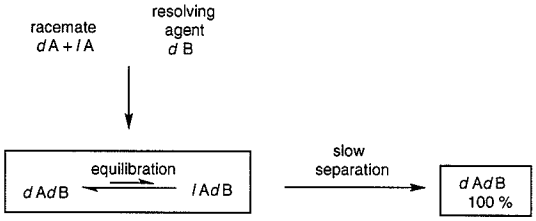

**reciprocal resolution principle** – switches the roles of resolving agent and substrate. Thus, if resolving agent A can resolve racemic B, then pure enantiomers of B should resolve racemic A. At first glance this seems as obvious as the Marckwald principle, but a closer look shows that the two cases are not mirror images of one another – the less soluble salts are the same, while the more soluble salts are mirror images. If the salts interact, they may do so differently and for this reason, reciprocal resolutions sometimes fail.




# *Asymmetric transformations coupled to crystallizations*

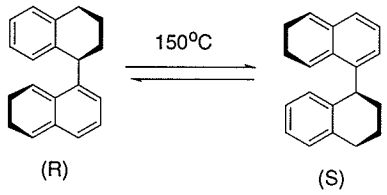
One big disadvantage of resolutions is that the maximum yield is only 50%. However, if the starting compound continuously racemizes during a resolution, then one can get up to 100% yield. This resolution with in situ racemization is called dynamic resolution or asymmetric transformation of the second kind. The requirements for a dynamic resolution are: first, the starting compound must racemize faster than the subsequent separation step, second, the product must not racemize

and third, as in any asymmetric synthesis, the separation step must be highly stereoselective.




## Racemization during direct crystallization of a conglomerate.

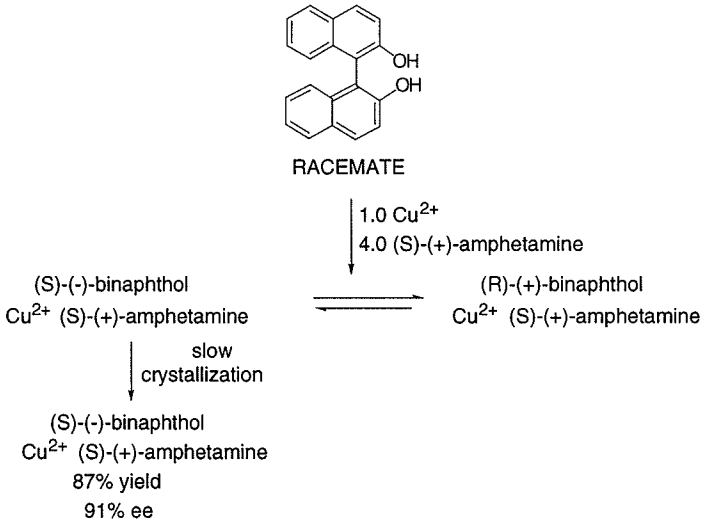
The binaphthyl below racemizes upon heating. Crystallization at high temperatures yields a non-racemic mixture. Once crystals of one enantiomer form, then more of the same one continues to crystallize.



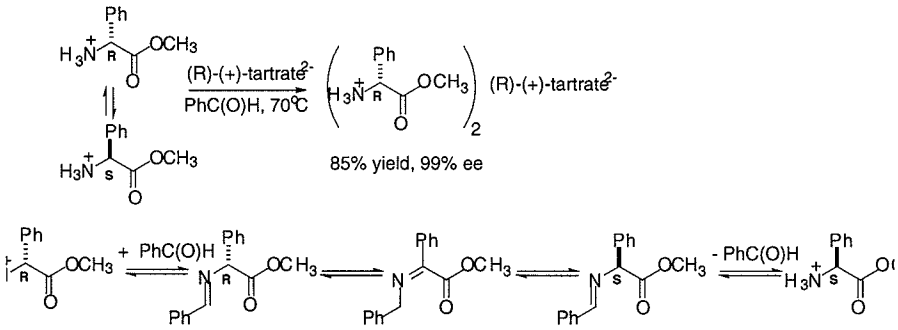

(R) (S)

## Racemization during crystallization of diastereomers.

Crystallization drives equilibrium to the less soluble diastereomer of a binaphthyl-Cu-amphetamine complex.




Racemization of amino acids combined with a crystallization.



## *Kinetic resolutions*

Kinetic resolutions involve an irreversible reaction where one enantiomer reacts faster. The enantiomeric purity of both the starting material and product change as the reaction proceeds. The starting material accumulates the slow-reacting enantiomer whose enantiomeric purity increases as the reaction removes the fast-reacting enantiomer. The product accummulates the fast reacting enantiomer whose enantiomeric purity decreases as the reaction proceeds. The enantiomeric purity decereases because the catalyst makes more and more 'mistakes' as the amount of fast-reacting enantiomer in the starting material decreases. Note that you can always get the remaining starting material in high enantiomeric purity if you are willing to accept a low yield, but the maximum enantiomeric purity of the starting material is always lower.

### Quantitative analysis of kinetic resolutions

Since the enantiomeric purity of the product and starting material varies as the reaction proceeds, comparing enantiomeric purities for two kinetic resolutions is meaningful only at the same extent of conversion. To more conveniently compare kinetic resolutions, Charles Sih's group developed equations to calculate their inherent enantioselectivity. The selectivity of a kinetic resolution, called s or E, is the ratio of the rates of the fast reacting over the slow reacting enantiomers. For enzymatic reactions, the selectivity is the ratio of the specificity constants, $k_{cat}/K_M$.

$$s \text{ or } E = \frac{rate_{fast}}{rate_{slow}}$$

$$s \text{ or } E = \frac{(k_{cat}/K_M)_{fast}}{(k_{cat}/K_M)_{slow}}$$

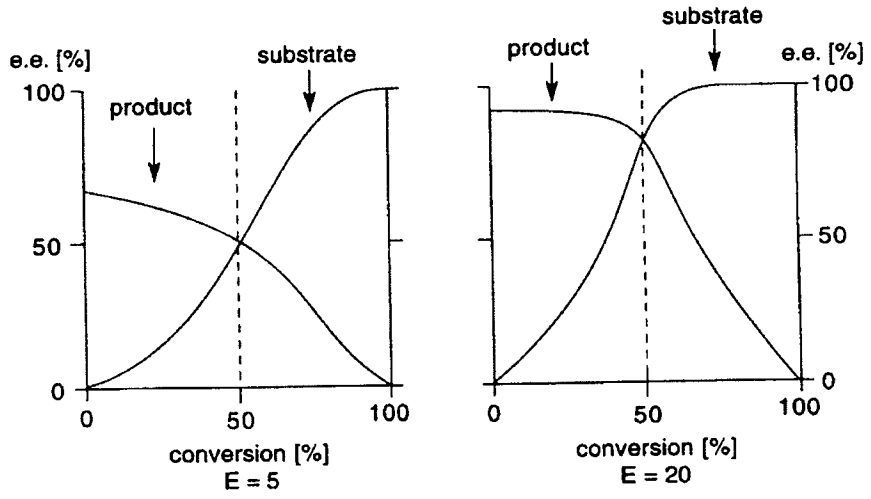
A non-selective reaction has an E of 1, while resolutions with E's above 20 are useful for synthesis. To calculate E, one measures two of the three variables: enantiomeric purity of the starting material (ees), enantiomeric purity of the product (eep), and extent of conversion (c) and uses one of the three equations below. Often enan-

tiomeric purities are more accurately measured than conversion; in these cases, the third equation is more accurate.

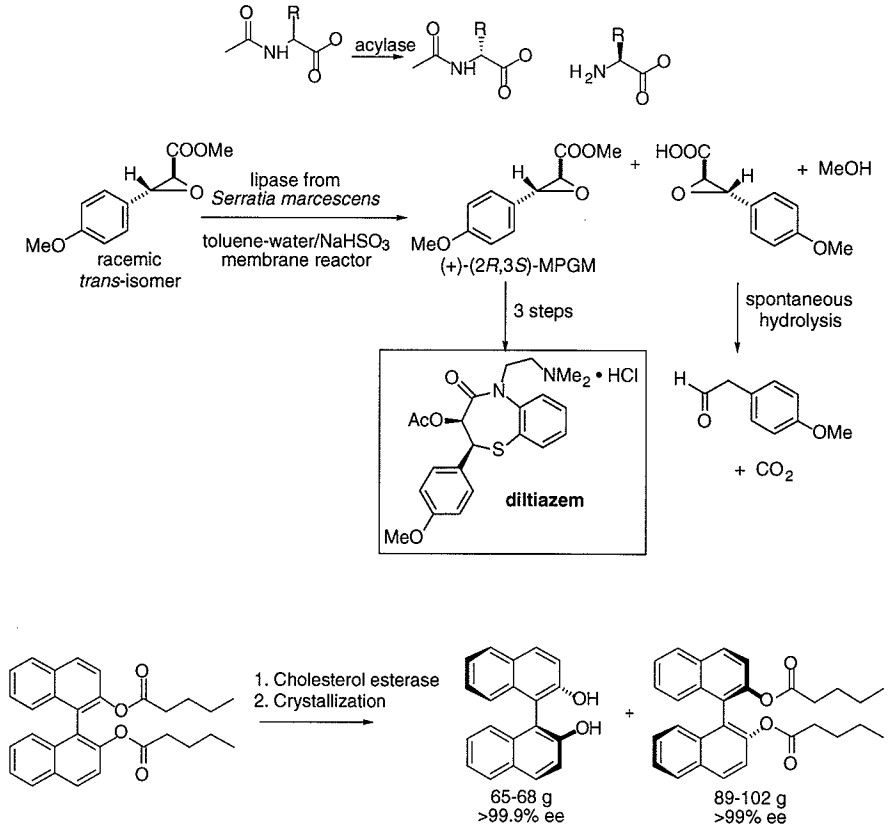
$$E = \frac{\ln\left[1-c\left(1+ee_p\right)\right]}{\ln\left[1-c\left(1-ee_p\right)\right]};\quad E = \frac{\ln\left[(1-c)(1-ee_s)\right]}{\ln\left[(1-c)(1+ee_s)\right]};\quad E = \frac{\ln\left[\dfrac{1-ee_s}{1+(ee_s/ee_p)}\right]}{\ln\left[\dfrac{1+ee_s}{1+(ee_s/ee_p)}\right]}$$

High E values (>100) are less accurately measured than low or moderate E values because the enantiomeric ratio is a logarithmic function of the enantiomeric purity. When E >100, small changes in the measured enantiomeric purities give large changes in the enantiomeric ratio. Thus, the survey below avoids reporting E values above 100. In practice, we found that even E values near 50 were sometimes difficult to measure more precisely than ±10. A simple program to calculate enantiomeric ratio using the above equations is freely available at http://www-orgc.tu-graz.ac.at. In spite of the fact that these equations include assumptions such as an irreversible reaction, one substrate and product, and no product inhibition, they are reliable in the vast majority of cases, especially for screening studies.

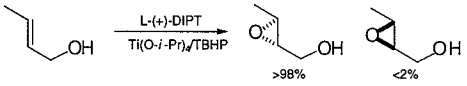
**Figure 2.4.** Dependence of optical purities (e.e.s/e.e.p) on the conversion

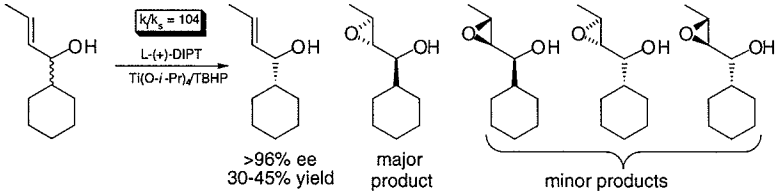


Example of an efficient enzymatic resolutions of amino acids, binaphthol, and a precursor to diltiazem, a drug for heart disease.

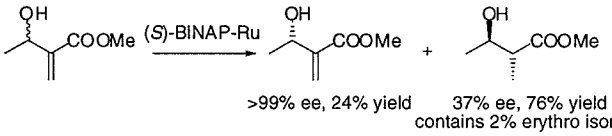


The Sharpless-Katsuki epoxidation can efficiently resolve enantiomers because the rela-tive rate of epoxidation depends on the chirality of a nearby stereocenter.



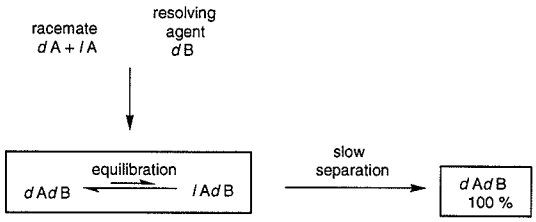

Enantioselective hydrogenation by Ru-BINAP-catalyzed hydrogenation also resolves allylic alcohols.



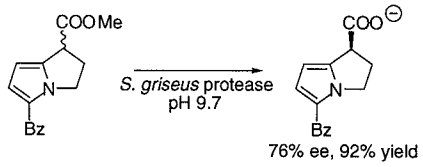

The researcher must stop a kinetic resolution at the optimum time. The optimum time will depend on the enantioselectivity of the kinetic resolution and whether the researcher in interested in the product, the remaining starting material or both. With a very high enantioselectivity (E>100), the optimum stopping point is 50% conversion. Both the starting material and product have high enantiomeric purity at this point. With a moderate enantioselectivity (E ~ 30), the optimum stopping point is below 50% conversion when the goal is the high yield and enantiomeric purity of the product. For example, eep = 89% at 40% conversion with E = 30. Then the goal is high yield and enantiomeric purity of the starting material, then the optimum stopping point is just beyond 50% conversion. For example, ees = 99.7% at 60% conversion with E = 30. The previous example highlights an important point about kinetic resolutions: with a moderate or low enantioselectivity, it is still possible to recover unreacted starting material with high enantiomeric purity. The E equations above cannot be solved explicitly for c, so calculating the optimum stopping con-version requires either an interative approach or an estimate from the graphs in Fig-ure x.

## *Dynamic kinetic resolutions*

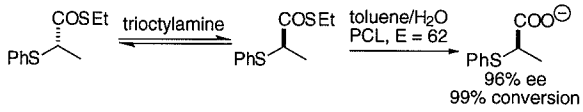
As in an asymmetric synthesis the enantiomeric purity of the product in a dynamic kinetic resolution remains constant as the reaction proceeds and is given by ee = (E-1)/(E+1), where E is the enantiomeric ratio. For example, an enantioselectivity of 50 yields product with 96% ee. Rearrangement of this equation gives E = (1 + ee)/(1-ee), useful to calculate the enantioselectivity from the enantiomeric purity of the product.




The first examples of dynamic kinetic resolutions used substrates that can easily be ra-cemized. For example, Fülling and Sih resolved an ester with a moderately acidic hydrogen at the a-position. The starting ester racemized via an enolate, but the product acid did not racemize because it was already charged.

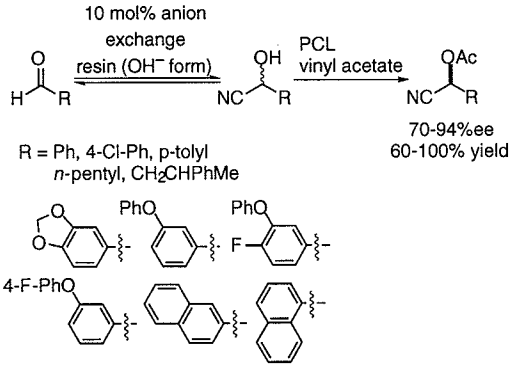



Similarly Tan et al. resolved 2-(thiophenyl)propanoic acid by PCL-catalyzed hydrolysis of the thioester in the presence of trioctylamine. Noyori resolved a b-ketoester with a stereo-center at the a-position.

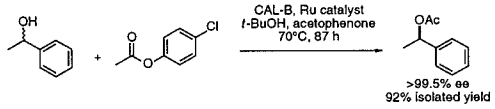



Inagaki et al. racemized cyanohydrins by the reversible base-catalyzed addition of HCN to aldehydes. Enantioselective acetylation of the (S)-cyanohydrin catalyzed by PCL yielded the acetate in good to moderate yields and enantiomeric purity. In general, PCL showed higher enantioselectivity toward cyanohydrins derived from

aromatic aldehydes than from aliphatic al-dehydes. PCL did not catalyze acylation of the HCN donor, acetone cyanohydrin, a tertiary al-cohol, presumably because it is too hindered.




A potentially more general reaction is the racemization of simple secondary alcohols by temporary oxidation followed by reduction using hydrogen transfer catalysts Similarly, Reetz and Schimossek catalyzed the racemization of amines with palladium during a resolution.




## *Resolutions using chromatography*

Liquid chromatography with a chiral stationary phase can separate enantiomers. Researchers often use this separation mthod to measure the enantiomeric purity of samples as will be discussed in Chapter 6. However, by using a large column, one can also use this as a preparative method. For example, a semi-preparative column 25 cm long and 1 cm in diameter can resolve several hundred milligrams of compound in a single injection. Larged columns can resolve grams, but it is rarely practical to scale up beyond a several gram scale. New methods such as radial flow chromatography allow scale-up to a kilogram scale for industry.

## General References

Jacques, J., Collet, A, Wilen, S. H. *Enantiomers, Racemates, and Resolutions* Wiley: New York, 1981.

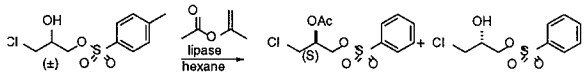
a kinetic resolutions reference

## *Questions*

1. Draw phase diagram for conglomerates, racemic compounds, and solid solutions (pseudoracemates). Describe what happens when you measure a melting point for a sample with 90% ee in each of these three cases.
2. In the case of a conglomerate, the melting point of a racemate is always lower than the melting point of the enantiomerically-pure sample. Explain. Is it also true in the case of a racemic compound?
3. Suggest three different experimental tests to determine if a molecule crystallizes as a conglomerate, a racemate, or a solid solution (pseudoracemate).
4. Can you separate the enantiomers in a racemic sample by chromatography on an achiral column (without a chiral solvent)? Can you separate the enantiomers in a nonracemic sample by chromatography on an achiral column (without a chiral solvent)?
5. Elementary textbooks stress the fact that enantiomers have identical physical properties, save the sign of optical rotation, but this is somewhat misleading because the racemate does not have identical physical properties as the pure enantiomer. What, in your opinion, should the elementary textbooks say instead?
6. In some resolutions involving diastereomeric salts, a 1: 0.5 ratio of substrate to resolving agent instead of a 1: 1 ratio is better for two reasons. First, it saves resolving agent. Second, it can save solvent. The solubility of salts increase as the pH of the solution increases or decreases from the pH of the pure salt solution. It saves resolving agent and .[4]
7. Derive the equation for the enantiomeric purity enhancement in the Horeau duplication.

4. Leclercq, M.; Jacques, J. (1979), title. *Nouv. J. Chim. 3*, 629-6xx.; Jacques, J., Collet, A, Wilen, S. H. *Enantiomers, Racemates, and Resolutions* Wiley: New York, 1981, p 307-317.

8. Chen and Liu used a lipase from Pseudomonas fluorescens to catalyze the following reaction. At 47% conversion, the enantiomeric purity of the product acetate was 83% ee and the enantiomeric purity of the remaining starting material was 75% ee. (Chen, C.-S.; Liu, Y.-C. Tetrahedron Lett. 1989, 30, 7165-7168.)

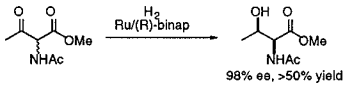



a) Calculate the enantioselectivity (E) of this reaction.

b) Draw an approximate graph showing how the ee of the starting material and product vary with the percent conversion.

c) If you needed 1.0 g of either enantiomer in >95% ee, how much racemate do you need to start with and when would you stop your resolution/

9. Explain qualitatively what happens in the reaction below. (Noyori, R.; et. al. J. Am. Chem. Soc. 1989, 111, 9134-5.)



CHAPTER 5

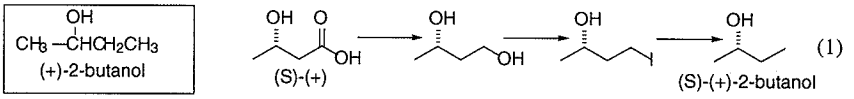
# *Determining Absolute Configuration*

The absolute configuration of a stereocenter, usually denoted by the descriptor R or S, is its true three-dimensional structure. For many organic molecules, the absolute configuration is already known. For these molecules, one identifies the absolute configuration of an unknown sample by comparing it to known properties of the molecule. For example, one might measure the rotation of plane-polarized light or the relative retention time on a gas chromatography column with chiral stationary phase. This chapter focuses on methods to determine absolute configurations of new molecules, whose absolute configuration has not yet been established. One can use relative methods or absolute methods. Relative methods compare stereocenters with unknown configurations to stereocenters with known configurations. Absolute methods establish the true three dimensional structure of the unknown independently by physical measurements.

## *Relative methods*

### Chemical correlations[1]

Chemical correlations compare the unknown to a known compound to find out if the two have the same or different configuration. Chemical correlations are a common and reliable method to establish absolute configuration. To make the comparison, you must either convert the unknown compound into a compound with known absolute configuration or alternately, synthesize the unknown starting from a compound with a known absolute configuration. For example, you could establish the absolute configuration of (+)-2-butanol by synthesis of (*S*)-2-butanol from (*S*)-3-hydroxybutyrate, a naturally occurring material, eq 1.




(1)

Comparing some property of the unknown and synthetic sample would establish whether the two samples had the same or enantiomeric configurations. For example, if the rotation of both samples is (+), the the unknown must have the same configuration as the synthetic sample, that is, (S). Since the absolute configuration (+)-2-butanol and many other molecules are already known,[2] one would not have to do such a correlation today; you could just look it up.

Today most determinations of absolute configuration involve more complex materials, especially natural products. For these materials the unknown is cleaved into fragments and the configuration of each fragment is determined. For example, to determine the absolute configuration of (-)-botryococcene, a terpene-derived hydro-

1. Kagan, H. B., Ed. *Determination of Configurations by Chemical Methods* Thieme: Stuttgart 1977. Chapter 1: Chemical Correlations; QD75.2 D4
2. Klyne, W.; Buckingham, J. Atlas of Stereochemistry: Absolute Configurations of Organic *Molecules* Oxford: Oxford, 1978; Kagan, H. B., Ed. *Absolute Configuration of 6000 Selected Compounds with One Asymmetric Carbon* Thieme: Stuttgart; 1977.QD481.K64

carbon with six stereocenters isolated from green algae, White *et al.* cleaved it into four fragments, Scheme I.[3]

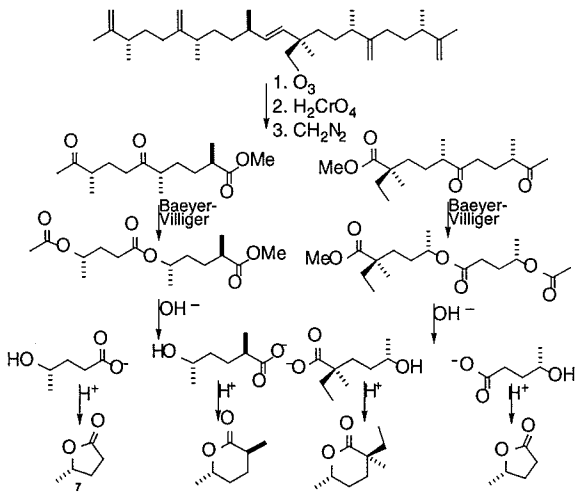
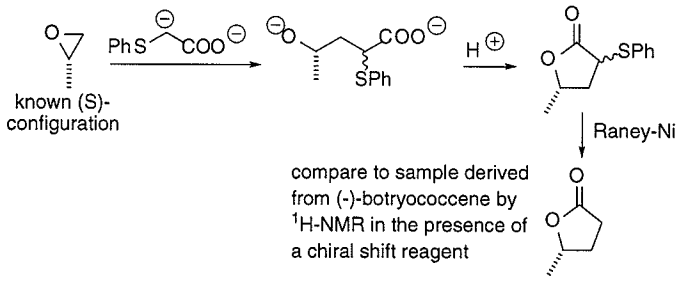



**FIGURE 1.** To establish the absolute configuration of a complex natural product, researchers cleaved it into four smaller fragments.

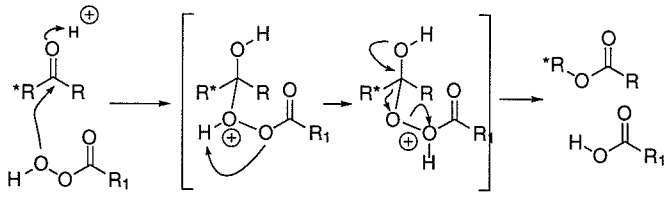
The first cleavage, ozonolysis of the double bonds, cleaved the molecule in two. The next two steps, Baeyer-Villiger oxidation followed by hydrolysis of the resulting esters, cleaved each of those fragments in two, yielding four fragments. They identified the absolute configuration of each fragment by comparing the fragments

3. White, J. D.; Somers, T. C.; Reddy, G. N. *J. Am. Chem. Soc.* **1986**, *108*, 5352-5353.

derived from the natural product to authentic samples prepared from (*S*)-propylene oxide. For example, the synthesis of one lactone is shown below.




The Baeyer-Villiger oxidation reaction used in the second cleavage step deserves some additional comment since it disturbed the stereocenters under investigation. This reaction replaced one of the carbons at the stereocenter with an oxygen. Did this replacement occur with retention, as shown, or with inversion?. Previous mechanistic studies showed that the Baeyer-Villiger oxidation proceeds with retention of configuration, so the researchers reasonably assumed that this reaction also proceeded with retention.



Chemical correlations that avoid all reactions that disturb the stereocenters under investigation are more reliable than those that do disturb these stereocenters. However, the stereochemical course of many organic reactions has been established so they can be used reliaby in chemical correlations.[4]

## Chirooptic methods

Why chiral molecules rotate the plane of plane-polarized light

4. Reference 1 lists the stereochemical course of many common organic reactions.

Polarized light is chiral so enantiomers interact with polarized light differently. This interaction can be either a change in the speed of light, which causes rotation of the plane of polarization, or an absorption of light.

Plane-polarized light can be viewed as the sum a two circularly polarized waves, Figure 2a. The two circularly polarized waves are in phase in part a of the diagram below. If one of these circularly polarized waves travels slower than the other due to a strongre interaction with chiral molecules, then the sum will still be a plane-polarized wave, but the plane of polarization will have rotated, Figure 2b and c. Thus, rotation of plane-polarized light occurs because one of the circularly polarized waves travels more slowly than the other.

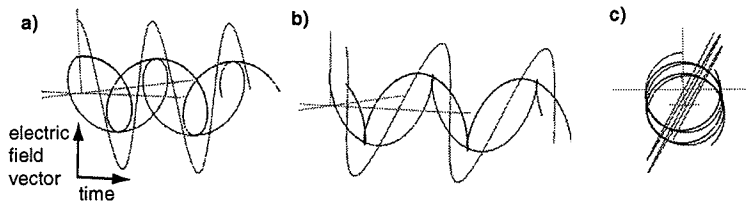



**FIGURE 2.** A plane-polarized light wave (purple) is the sum of a right-circularly polarized wave (blue) and a left-circularly polarized wave (red). In panel a) both circularly polarized waves are in phase. In panel b) the blue wave has slowed by a set amount. Panel c) is a different view of panel b).

A sample containing an excess of one enantiomer will rotate plane-polarized light. The electric component in one of the circularly polarized waves induces a larger larger dipole than the other and therefore travels at a different speed.[5]

It was previously impossible to accurately calculate the degree to which a molecule will rotate the plane of plane-polarized light. That is, knowing whether a molecule rotates light in the (+) or (–) direction did reveal whether it was (R) or (S). However, but recent advances in theoretical methods do make it possible to establish absolute configuration from the rotation of plane-polarized light.[6]

5. An exagerated picture of the interaction of the electric field vector with CHFClBr is shown in Applequist, J. (1987), title, *American Scientist*, Jan-Feb p59-xx.

## Brewster's rules[7]

Chemists also use empirical rules to predict rotations. These assignments are reliable when the unknown is similar to the reference compounds used to create the empirical rules. The rules may not hold when the unknown is very different, so these assignments are less reliable.

Brewster's rule is an empirical estimate of polarizabilities of atoms and a set of rules to use these polarizabilities to predict the sign of rotation at 589 nm. The substituents should be either atoms or small groups with conical symmetry. Brewster's rules work best for saturated hydrocarbons, olefins, alcohols, amines, and halides. The precedure is as follows.

1. Rank the polarizabilities of the atoms attached to the stereocenter. The polarizability sequence is I>Br>SH>Cl>CN>Ph>COOH>Me>$NH_2$>OH>H>F
2. If the atoms having the three highest polarizabilities are arranged so that they decrease clockwise, then a (+) rotation is predicted. A counterclockwise arrangement predicts a (-) rotation.
3. If two or more of the atoms attached to the stereocenter are the same then a larger portion of the molecule must be considered. Different conformations must also be considered.

For example, the 2-phenylpropanoic acid is predicted to have a negative rotation in agreement with the observed rotation of -72.


The certainty of an absolute configuration established by Brewster's rule is much lower than one established by chemical correlation because there are occasional exceptions to Brewster's rule. Brewster's rule is rarely used today because the absolute configurations of most compounds for which it applies have been determined by other methods. This rule also does not consider conformational flexibility. Brewster developed methods to treat conformational flexibility, but it will not be discussed here.

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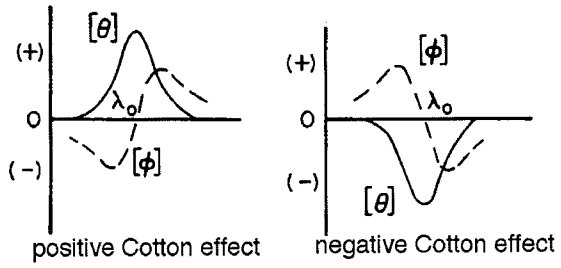
6. Kondru, R. K., Wipf, P.; Beratan, D. N. (1998), Atomic contributions to the optical rotation angle as a quantitative probe of molecular chirality, *Science* **282**, 2247-2250.
7. . Eliel, E. L. *Stereochemistry of Carbon Compounds* McGraw-Hill: New York, 1962; Chapter 14.

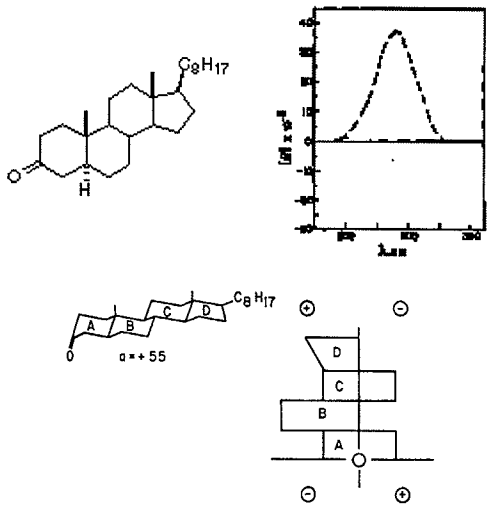
## Octant rule for cyclohexanones[8]

At wavelengths where molecules absorb light, they do more than rotate plane polarized light. This more complex behavior, called a Cotton effect, is caused by the unequal absorption of right and left circularly polarized light. A circular dichroism spectrum (CD) shows the difference in absorption of left and right circularly polarized light as a function of wavelength ($\Delta\varepsilon = \varepsilon_L - \varepsilon_R$, where $\varepsilon$ is the molar absorption coefficient). For historical reasons, the difference is sometimes given as molar ellipticity $[\theta]$, which is linearly proportional to $\Delta\varepsilon$. Unequal absorption of right and left circularly polarized light also causes the optical rotation to change sign as one scans through an absorption band. (A plot of optical rotation, $[\phi]$, as a function of wavelength is an optical rotary dispersion curve or ORD.)




8. Lambert, J. B. *et al. Introduction to Organic Spectroscopy* Macmillan: New York 1987, chapter 10. PSEAL: QD272 S6 I54

For example, cholestan-3-one shows a positive Cotton effect near 280 nm, where the carbonyl absorbs light due to an n $\rightarrow \pi^*$ transition.




The octant rule is an empirical rule that predicts the sign of the n $\rightarrow \pi^*$ Cotton effect for a carbonyl chromophore based on the contributions of the perturbing groups in the eight sectors (octants) around the carbonyl. The octant rule is most often used for cyclohexanones. To apply the octant rule, one orients the carbonyl in three dimensions as shown below, and compares the substituents in each of the octants. Substituents lying in the dividing planes make no appreciable contribution to the Cotton effect. Thus, substituents at the 4-position have no effect and equatorial substituents at the 2- and 6-positions have no effect. Most molecules do not have substituents in the front four octants, so these are usually ignored. For example, cholestan-3-one has most of the substituents in a (+)-octant; thus, the octant rule predicts a positive Cotton effect in agreement with experiment. Halogen substituents will override the effect of an alkyl group because a halogen is more polarizable. Note that conformational changes can change the octant orientation of the substituents. For example, the octant rule predicts a positive Cotton effect for the Me-equatorial conformation of (*R*)-3-methylcyclohexanone, but a negative Cotton

effect for the Me-axial conformation.This empirical rule enjoys some theoretical

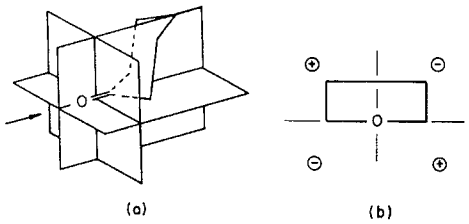



FIGURE 10-5 (a) Octant rule for saturated cyclohexanones. (b) Signs of the four rear octants viewed along the carbonyl bond axis from oxygen to carbon. (The front octants have opposite signs.)

**FIGURE 3.**

justification. The division of space into octants follows the nodal surfaces for the orbitals involved in the transition (oxygen lone pair and $\pi^*$ for the C–O bond). A non-symmetrical arrangement of substituents in these octants promotes the unequal absorption of right and left circularly polarized light.

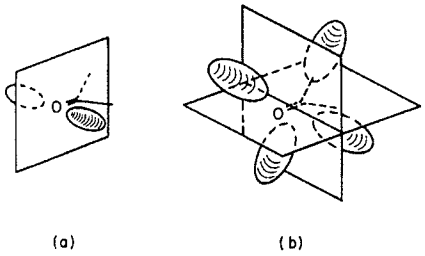
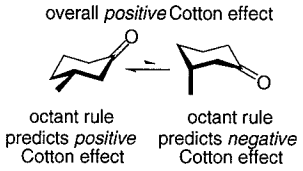


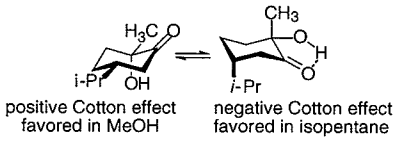

FIGURE 10-4 Nodal surfaces for a saturated ketone, R—CO—R'. (a) The nodal plane of the n orbital. It bisects the R—C—R' angle and is perpendicular to the plane of the ketone. (b) The nodal surfaces of the $\pi^*$ orbital. The plane of the carbonyl group is a nodal plane and there is another nodal surface, not necessarily a plane, perpendicular to the C-O axis and intersecting it between the carbon and oxygen atoms.

**FIGURE 4.** Theoretical justification fo the octant rule.

To assign the absolute configuration of a molecule using the octant rule, one measures the Cotton effect and uses the octant rule to chose which enantiomer should have that sign of a Cotton effect. Keep in mind alternate chair forms. For example, a sample of 3-methylcyclohexanone showing a positive Cotton effect must have the 3R configuration. 3-Methylcyclohexanone exists in two chair forms: one with the methyl axial, the other with the methyl equatorial. The octant rule predicts opposite signs for the Cotton effect for the two chair forms. The chair form with the equatorial methyl orientation predominates and determines the overall sign.



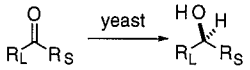

In a few cases, the sign of the Cotton effect reverses in different solvents. A switch of the favored chair form is the most likely explanation. For example, the menthone below shows a positive Cotton effect in methanol, but a negative Cotton effect in isopentane. The chair form with an equatorial *i*-propyl group minimize steric interaction, while the chair form with an axial *i*-propyl permits an intramolecular hydrogen bond.




## Asymmetric syntheses

### ENZYMIC METHODS

The absolute configurations of unknowns can be determined reliably if the unknowns are structurally similar to model compounds which have been already been tested with the same system. For example, reduction of ketones by yeast usually gives the enantiomer shown in eq 3, where $R_L$ represents a large substituent and $R_S$ represents a small substituent.

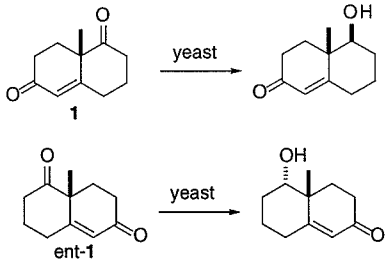



(3)

This reduction can be used in a straightforward fashion to establish the absolute configuration of alcohols. It can also be use to establish the absolute configuration of other stereocenters.[9] For example, to establish the configuration of **1**, it was reduced with yeast and the orientation of the methyl and hydroxyl in the product

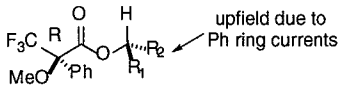
9. Review: Fiaud, J. C. in *Determination of Configurations by Chemical Methods* Kagan, H. B., Ed.; Thieme: Stuttgart 1977; pp 96-126.

was identified as syn; thus the configuration of **1** was (S) as shown. Yeast reduction of the enantiomer of 1 should give the anti product.




## Mosher's esters, amides and related derivatives.

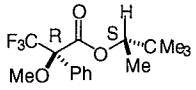
The $^1$H-NMR of Mosher's esters of secondary alcohols can establish their absolute configuration.[10] Mosher found that linking secondary alcohols to α-methoxy-α-(trifluoromethyl)-phenylacetic acid (Mosher's acid) caused unequal shifts in the $^1$H-NMR resonances of the two alkyl groups in the secondary alcohol. For esters of (R)-Mosher acid, the alkyl group marked $R_2$ is shifted more upfield than the alkyl group marked $R_1$. Mosher rationalized these different shifts by assuming that the ester adopts the conformation shown below. The upfield shift of the $R_2$ resonances was attributed to the effects of the phenyl.



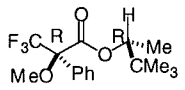

To determine absolute configuration of 3,3-dimethyl-2-butanol using Mosher's esters, the $^1$H-NMR spectrum of the (*R*)-Mosher's ester of the unknown is compared to the spectrum of the (*R*)-Mosher ester from the racemate. The (*R*)-Mosher ester from the racemate will contain two resonances for the tert-butyl group. The model predicts that the *tert*-butyl resonance for the ester derived from (*S*)-alcohol

10. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519; simple microscale preparation of Mosher's acid chloride: Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165-7166.

will lie upfield of the resonance for the ester from the (*R*)-alcohol. The *tert*-butyl resonances in the unknown should match one of these.



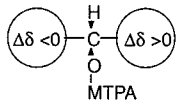
δ 0.85



δ 0.95

For complex molecules, the ester may also adopt other conformations. To make a reliable assignment, Ohtani *et al.*[11] suggested that all the protons in molecule be considered. If all the protons on one substituent show a consistent upfield shift and the all the protons on the other show a downfield shift, then the absolute configuration can be assigned with confidence.

In the example above, both enantiomers were available for the assignment. For most natural products, only one enantiomer is available. In these cases, one makes both Mosher's esters and compare the relative shifts: $\Delta\delta = \delta R - \delta S$. The diagram below translates these shifts into a 3-D structure.



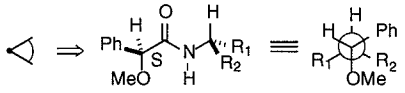

Kusumi *et al.* recently extended this method to a-chiral primary amines.[12] A similar model predicts the relative chemical shifts.

*O*-Methylmandelic acid, a chiral acid similar to Moshers acid, but less expensive, has also been used to measure establish absolute configuration of both secondary

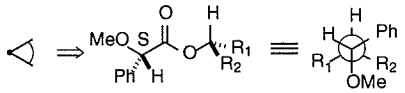
11. Ohtanic, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. (1991), title, *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.

12. Kusumi, T.; Fufushima, T.; Ohtani, I.; Kakisawa, H. (1991), Tetrahedron Lett. 1991, 32, 2939-xxx. also check #2

alcohols and α-chiral primary amines. To account for the relative chemical shifts, researchers proposed different conformations for the esters and the amides.




Amines: phenyl group shields $R_2$.




Secondary alcohols: phenyl group shields $R_1$.

**FIGURE 5.** Rules to account for the relative chemical shifts shifts of esters and amides of *O*-methylmandelic acid. The orientation of the stereocenter in the acid differs for the ester and amide.

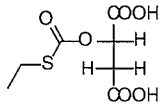
## The method of quasi-racemates[13]

Racemic compounds crystallize can crystallize three ways. First, a racemic compound (most common) occurs when the two enantiomers coexist in the unit cell. This behavior is favored when each enantiomer has a higher affinity for the opposite enantiomer, rather than one of its own kind. Racemic compounds have properties that differ from the pure enantiomers, e.g. melting point, infrared spectrum, and solubility. Second a conglomerate where each enantiomer crystallizes in separate crystals because each enantiomer prefers to interact with like molecules. Enantiomers of a conglomerate can be resolved by mechanical separation of crystals as Pasteur did for sodium ammonium tartrate. While the x-ray diffraction pattern and ir spectrum are the same for a conglomerate and enantiomerically pure material, the melting point of the racemate is lower (Racemate is 'impure'.) Lastly, a solid solution where the arrangement of the two enantiomers is random because there is little difference in the affinity between molecules of like and opposite configuration. The phase diagrams for each of the three classes is shown below.

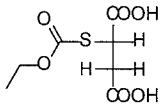
The method of quasi-racemates applies only to racemic compounds. Quasi-racemates are compounds formed from equal amounts of two optically active compounds of very similar structure, but 'opposite' configuration. Quasi-racemates behave like true racemates when they melt.

13. Eliel, E. L. *Stereochemistry of Carbon Compounds* McGraw-Hill, 1962; Chapters 5.

For example, Fredga determined the absolute configuration of the thiosuccinic acid derivative, shown below, by co-crystallizing first one, then the other enantiomer with the malic acid derivative shown. One mixture showed melting behavior characteristic of a racemate. This enantiomer of thiosuccinic acid was assigned the 'opposite' configuration of malic acid.



malic acid derivative
known absolute configuration



thiosuccinic acid derivative
unknown absolute configuration

## *Absolute Methods*

Absolute methods do not rely on reference compounds. Before the development of absolute methods, all absolute configurations were based on comparisons. Fisher simply assumed in the 1800's that the configuration of (+)-glyceraldehyde was (*R*) assigned other absolute configurations by comparison to glyceraldehyde. In 1951, Bijvoet (bay-voot) discovered the first absolute method and found that Fisher's guess was correct.[14]

### Bijvoet's x-ray method[15]

This method requires a crystal of the unknown that contains a heavy atom so that the *absorption* of x-rays as well as the usual diffraction can be measured. Simple x-ray diffraction cannot distinguish between enantiomers because both a structure and its inverse give identical diffraction patterns. Bijvoet determined the x-ray crystal structure of a mixed rubidium and sodium salt of (+)-tartrate. When he took into account the absorption of x-rays by the rubidium, then the (*R*,*R*)-configuration for tartrate fit the data better than the (*S*,*S*)-configuration.

14. Bijvoet, J. M.; Peerdeman, A. F.; van Bommel, A. J. *Nature (London)* **1951**, *168*, 271-2xx; Bijvoet, J. M. *Endeavour* **1955**, *14*, 71-77.

15. Dunitz, J. D. *X-Ray Analysis and the Structure of Organic Molecules* Cornell University: Ithaca, 1979; Stout, G. H.; Jensen, L. H. *X-Ray Structure Determination* Wiley: New York, 1989; Jones, P. G. Meyer-Base, K. *Acta Cryst.* **1987**, *A43*, 79-80.

Of course, x-ray crystallography can determine the relative configuration without including the heavy atom. If you add a stereocenter of known absolute configuration to the unknown by making a salt or other derivative, then the unknown configuration can be established by comparison to the known structure.

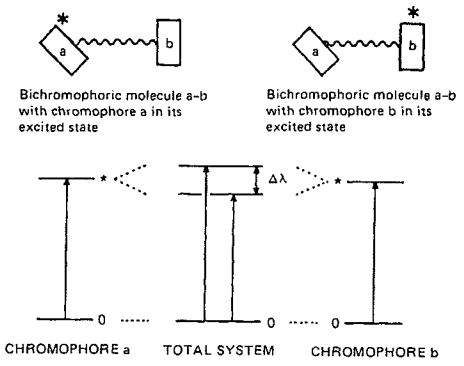
## The CD exiton method[16]

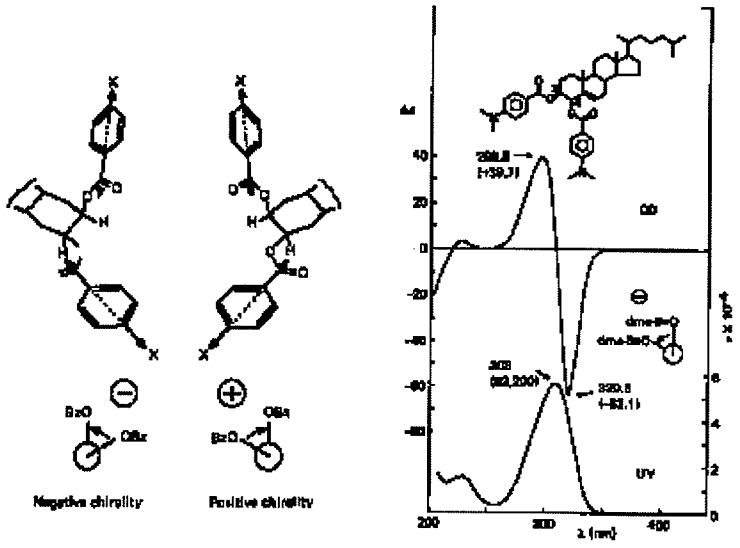
When two chromophores lie near one another, they interact with one another. This interaction slightly lowers the energy of one transition, but raises the energy of the other. For the Cotton effect, the two transitions will also have opposite sign. Theory unambiguously predicts the sign of the lower energy transition based on the three-dimensional orientation of the chromophores. If the requirements below are met, then the exiton chirality rule predicts a positive transition at lower energy for a positive absolute chirality.

- Absorptions with large absorption coefficients and well separated from other absorptions.
- No conjugation between chromophores and a known direction of the electric transition moment in the chromophore.
- Known conformation of the molecule

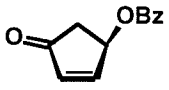
16.. Harada, N.; Nakanishi, K. "The Exiton Chirality Method and Its Application to Configurational and Conformational Studies of Natural Products" *Acc. Chem. Res.* **1972**, *5*, 257-63; Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exiton Coupling in Organic Stereochemistry* University Science Books: New York 1983. also: Lambert, J. B. et al. *Introduction to Organic Spectroscopy* Macmillan: New York 1987, chapter 10. PSEAL: QD272 S6 I54

If the above are true, then a positive absolute chirality will show a positive transition at lower energy in the CD and negative absolute chirality will show a negative transition at lower energy.



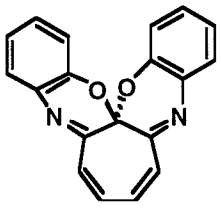




Other examples: enone: Tanaka, et al. *Tetrahedron*, **1976**, *32*, 1714-8.




(+) - CD @ 227 nm, therefore R

Spiro Compound: Harada, et al. *J. Am. Chem. Soc.* **1987**, *109*, 1061-5.



(-) - CD @ 398 nm, therefore S

Extensions to triols: Wiesler, W. T.; Nakanishi, K. "A Simple Spectroscopic Method for Assigning Relative and Absolute Configuration in Acyclic 1, 2, 3-Triols" J. Am. Chem. Soc. 1989, 111, 3446-7.

Extension to tetraols: J. Am. Chem. Soc. 1987, 109, 5586-5592.

## General References

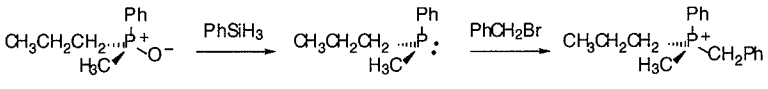

Lambert, J. B. *Introduction to Organic Spectroscopy* Macmillan: New York 1987, chapter 10. PSEAL: QD272 S6 I54

Harada, N.; Nakanishi, K. "The Exiton Chirality Method and Its Application to Configurational and Conformational Studies of Natural Products" *Acc. Chem. Res.* **1972**, *5*, 257-63.

Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy: Exiton Coupling in Organic Stereochemistry* University Science Books: New York 1983.


## Questions

1. Each reaction in the sequence shown is reported to proceed with retention of configuration; yet the starting material has the *R* configuration, and the product has the *S* configuration. Explain this apparent contradiction.



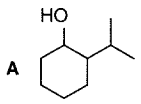

don't assume SN2

2. Treatment of the (R)-enantiomer of 2-bromopropanoic acid with excess ammonia followed by neutralization gives one of the enantiomers of alanine. On the other hand, treatment of the (S)-enantiomer of 2-bromopropanoic acid with excess NaOH gives after neutralization one of the enantiomers of lactic acid. The same enantiomer is produced by treatment of D-glyceraldehyde with bromine in water followed by reduction of the primary alcohol. From the informa-

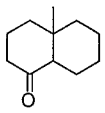
tion above deduce and briefly explain whether the absolute configuration of the alanine enantiomer produced in the first reaction is D or L.

3. Explain how you would determine the absolute configuration of *cis*-2-methyl cyclohexanol using (a) the octant rule and (b) Prelog's rule for yeast reductions. State what experiments you would do and what results you would expect to observe for the (1R,2S)-configuration.

4. The $^1$H-NMR spectrum of the Mosher's ester of *trans* **A** prepared using enantiomerically pure (*R*)-Mosher acid showed unequal amounts of the two diastereomers. The diastereomer with the *i*-propyl signals more upfield was in excess. Draw the absolute configuration of the enantiomer of **A** that was in excess.

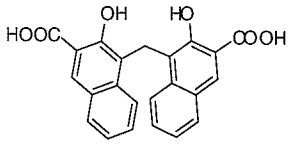



5. An isomer of the compound below has a weakly positive (+) Cotton effect. On treatment with base, another isomer is obtained with Δε -0.8. Draw the configurations and conformations of the two isomers and explain the transformation by drawing the intermediate between the two. Indicate (R, S) the absolute configuration. (Hint: in a later chapter we will show that the cis isomer is less stable than the trans isomer.)




6. The absolute configuration of succinic anhydride *trans*-2,3-diol was determined by measuring the CD Cotton effects of its dibenzoate ester: Δε240 +27.5, Δε223 -5.7. The UV spectrum showed a peak at 233 nm (ε 29,500). Draw the structure indicating the absolute configuration.

7. The compound below bound in the chiral cavity of γ-cyclodextrin shows a strong, bisignate Cotton effect in its CD spectrum: $\Delta\varepsilon_{256}$ +268, $\Delta\varepsilon_{238}$ -187. Draw the structure of the compound bound to γ-cyclodextrin and name its absolute configuration.



8. If you really had a sample of menthol in the lab with unknown configuration, what would you do to establish its absolute configuration?
9. Describe two ways that researchers can use X-ray crystallography to establish the absolute configuration of a molecule.

CHAPTER 6

# *Measuring Enantiomeric Purity*

Before the 1970's optical rotation was the most common method to measure enantiomeric purity of a sample. Unfortunately, optical rotation is not very accurate. Better modern methods include formation of diastereomeric derivatives, chiral stationary phases on columns for gas chromatography or high performance liquid chromatography, and chiral shift reagents for NMR. Several other less common methods are also discussed.

## *Enantiomeric excess may not equal the optical purity*

Enantiomeric purity is usually expressed not as the fraction of the major enantiomer, but as the fractional *excess* of one enantiomer, called enantiomeric excess. For example, one reports the purity of a sample containing 99 mol% of the S-enantiomer as 98% ee S.

$$enantiomeric\ \ excess\ \ (ee) = \frac{amount_{major} - amount_{minor}}{amount_{major} + amount_{minor}}$$

This measure comes from the older use of optical rotation to measure enantiomeric purity. The ratio of the measured rotation of the sample and the rotation for the pure

enantiomer is the optical purity. Of course, the measurement conditions must be the same. Since the minor enantiomer cancels the rotatory power of an equivalent amount of the major enantiomer, the value of the optical purity should be the same as the value of enantiomeric excess.

$$optical\ \ purity = \frac{rotation\ \ of\ \ sample}{rotation\ \ of\ \ pure\ \ material}$$

In the absence of intermolecular interaction, the optical purity indeed matches the enantiomeric purity. However, optical purity and enantiomeric purity may differ due to diastereomeric associations because the optical rotations of a homochiral and a heterochiral complex may differ. For this reason, the rotation of the sample may not vary linearly with the enantiomeric purity; thus, the optical purity may not match the enantiomeric purity. For example, a sample of 2-ethyl-2-methylbutandioic acid in dichloromethane with 50% ee shows a lower than expected optical rotation; the optical purity is only 35%. This diacid associates in solution and apparently, a heterochiral complex has a lower rotation than the homochiral complex. At infinite dilution, diastereomeric associations are absent and the optical purity equals the enantiomeric purity. The non equivalence of optical purity and enantiomeric excess is called the Horeau effect after the researcher who first pointed out this phenomena.[1]

## *Optical Rotation, an Outdated Method to Measure Enantiomeric Purity*

As explained in the previous paragraph, enantiomeric purity of a sample may not match the optical purity. Nevertheless, optical rotation is of historical importance for stereochemistry and we will cover the basic concepts.

### Specific Rotation

In UV-vis spectroscopy, the absorbance of a solution depends on the extinction coefficient of the material, $\varepsilon$, the path length, $b$, and the concentration, $c$. An analogous equation exists for optical rotation. The observed rotation, $\alpha$, depends on the

1. Horeau, A. (1969), Interactions between enantiomers in solution; effect on the rotatory power. Optical purity and enantiomeric purity, *Tetrahedron Lett.*, 3121-3124.

specific rotation, [α], the path length, and the concentration, c. Thus, the specific rotation measures the degree to which a substance rotates plane-polarized light.

$$A = \varepsilon bc$$
$$\alpha = [\alpha]lc$$

The traditional units in the two equations differ. In UV-vis spectroscopy, absorbance is unitless, ε has the units L / mol·cm, pathlength *b* has the units cm, and concentration has the units mol / L. For optical rotation, the observed rotation has the units degrees, specific rotation has the units degree·mL / g·dm (or deg $cm^2$ / 10g), pathlength has the units dm, and concentration has the units g/ mL. Researchers started measuring specific rotations long before the molecular structures were known.[2] For this reason, the specific rotation is calculated per unit weight of substance, not per mole of substance.

The specific rotation for a sample is calculated from the observed rotation after rearranging the equation above and reported as shown.

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{c \cdot l}$$
$$[\alpha]_{D}^{25} = 33 \ (c \ \ 2.5, \text{ ethanol})$$

Although it is tempting to add degrees as the unit for specific rotation, recall that the correct unit is degree·mL / g·dm. These units are understood and are usually omitted. Since the specific rotation changes with wavelength, temperature, solvent and concentration, researchers also note these parameters when reporting specific rotations. The D indicates the sodium D line, 589 nm. Confusingly, the units for concentration for this listing are usually g/100 mL, but g/mL in other cases.

For neat liquids one can either report the observed rotation or correct for the density of the sample and report a specific rotation. Recall that the specific rotation is calculated per unit weight.

$$[\alpha]_{\lambda}^{T} = \frac{a}{d \cdot l} \text{ for neat liquids}$$

For example, one can report the observed rotation of (-)-carvone noting the pathlength as shown below. Alternatively, one can calculate the specific rotation using

2. Biot, J. B. (1817), title, *Mem. Acad. Sci. Toulouse*, **2**, 41-xx.

the density of carvone ($d = 0.96$) and the equation above. Note again the correct use of the units.

$$\alpha_D^{20}\ 59°\ \text{(neat, l = 1 dm)}$$
$$[\alpha]_D^{20} = 61\ \text{(neat)}$$

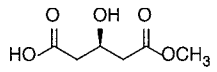
Since specific rotations are calculated per unit weight, not per mole, compounds with similar chiral groups, but different molecular weights, will have different specific rotations. Add example. Another useful measure is the molar rotation, [M] or [ϕ], which accounts for differences in molecular weight. The symbols are as above, except the concentration is expressed as moles per 100 mL.

$$[M]_\lambda^T = [\phi]_\lambda^T = \frac{\alpha}{c \cdot l} = [\alpha]_\lambda^T \times \frac{mol.\ wt.}{100}$$

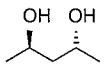
## Difficulties of measuring enantiomeric purity by optical rotations

As noted above, optical rotations are not a reliable measure of enantiomeric purity because optical purity may not equal enantiomeric purity. This problem is most common in molecules that form strong intermolecular interactions such as hydrogen bonds. The specific rotation changes if the conformation of the molecule changes or if it associates with another molecule. Some examples of large variations in specific rotation with temperature, concentration and solvent are given below.


$[\alpha]_{334}^{55}$ = +195 (hexane)
$[\alpha]_{334}^{15}$ = +94 (hexane)




$[\alpha]_D$ = -6.1 (*c* 0.64, $CHCl_3$)
$[\alpha]_D$ = -1.0 (*c* 12.1, $CHCl_3$)
*J. Org. Chem.* **1984**, *49*, 3657.




$[\alpha]_D$ = -22 (*c* 3.0, PhCN)
$[\alpha]_D$ = -11 (*c* 3.0, pyridine)
$[\alpha]_D$ = +1 (*c* 3.0, DMSO)
*J. Chem. Soc., Perkin Trans. 2,* **1991**, 197.

The specific rotation of the allylic alcohol varies strongly with temperature and the specific rotation of the acid varies strongly with concentration. In these cases, multimeric complexes (favored at lower temperature or higher concentrations) have a different rotary strength from the monomeric complex. The specific rotation of the diol above varies with solvent and even reverses sign. Formation of diol-solvent complexes is a likely explanation.

Concentration of an achiral impurity may also affect the specific rotation. (add heathcock example)

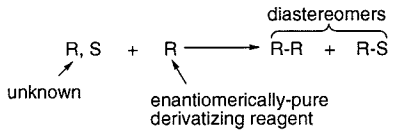
Different salts may have a different rotation. For example, D-lactic acid has a negative specific rotation, but the zinc salt of D-lactic acid has a positive rotation. Optical rotation depends on the polarizability of the groups surrounding the stereocenter. See "Brewster's rules" on page 76. Replacing a proton with a zinc ion is a big change in polarizability.

To report reliable optical rotations, it is best to check a couple of solvents and to measure the rotation at several wavelengths. The rotations at shorter wavelengths are more intense and thus more reliable.

Dewey and Gladysz discussed similar cautions regarding measuring the optical rotation of organometallic compounds.[3]

## *Diastereomeric derivatives*

A good way to measure enantiomeric purity is to form diastereomeric derivatives. An enantiomerically pure reagent reacts with the unknown and forms two diastereomers. Standard analytical methods, e.g. NMR, HPLC or GC, then reveal the relative amounts of the diastereomers and hence the enantiomeric purity of the original material.




The requirements for this method include

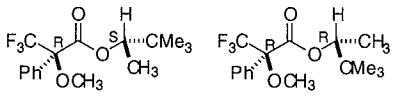
- Both reagent and unknown are stable to racemization under the conditions used.
- Sample reacts completely. Incomplete reaction may favor one enantiomer. An excess of derivatizing agent is usually used.
- Purification must avoid methods that could fractionate diastereomers, e.g. crystallization.

3. Further suggestions for reliable measurements: Dewey, M. A.: Gladyz, J. (1993), Optical rotation measurements of organometallic compounds: caveats and recommended procedures, *Organometallics*, **12**, 2390-2392.

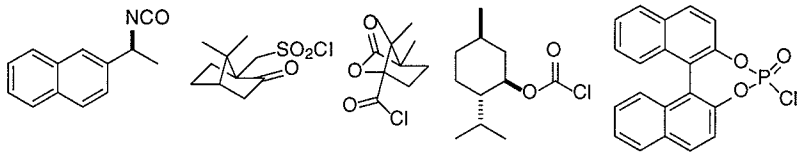
- Some method to distinguish diastereomers is required.

The accuracy of this method is limited by enantiomeric purity of the chiral reagent and by ability to measure amounts of the two derivatives, usually 5-99% ee. If the chiral reagent is impure, the measured enantiomeric purity will be lower than the true enantiomeric purity.

One example of a chiral derivatizing agent to measure enantiomeric purity of alcohols and amines is Mosher's acid (α-methoxy-α-trifluoromethyl phenylacetic acid, MTPA).[4] The sample is treated with an excess of the acid chloride and the amounts of the resulting esters or amides are determined by $^{1}H$- or $^{19}F$-NMR. In the previous chapter, the section "Mosher's esters, amides and related derivatives." on page 81 showed some example spectra.

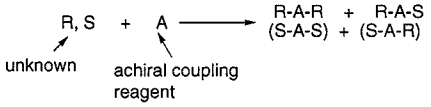


Other common derivatizing reagents are shown below.[5]



4. Dale, J. A.; Dull, D. L.; Mosher, H. S. (1969) α-Methoxy-α-trifluoromethyl phenylacetic acid, a versatile reagent for the determination of enantiomeric composition of alcohols and amines, *J. Org. Chem.* **34**, 2543-2549; A better method for the preparation of the acid chloride: Guivisdalsky, P. N.; Bittman, R. (1989) Regiospecific opening of glycidyl derivatives mediated by boron trifluoride. Asymmetric synthesis of ether-linked phospholipids, *J. Org. Chem.* **54**, 4637-4642.
5. α-naphthyl-1-ethylisocyanate: Pirkle, W. H., Robertson, M. R.; Hyun, M. H. (1984), title, *J. Org. Chem. 49*, 2433-xxxs; Camphorsulfonic acid chloride: Hoyer, G.-A.; Rosenberg, D.; Rufer, C.; Seeger, A. (1972), Bestimmung der optishen Reinheit und absoluten Konfiguration von enantiomeren Aralkylaminen, *Tetrahedron Lett.* 985-988; Camphanic acid chloride: *J. Chem. Soc. Chem. Commun.* **1973**, 274; Menthylchloroformate: *Israel J. Chem.* **1976/77**, *15*, 78; Binaphthylphosphate: Kato, N. (1990), Direct chirality determination of secondary carbinol by chirality recognition ability of C2 symmetry 1,1'-binapthyl-2,2'-diyl phosphoryl chloride, *J. Am. Chem. Soc.* **112**, 254-257.

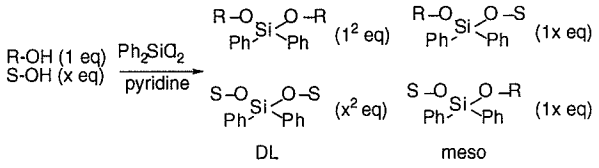
An *achiral* derivatizing agent that couples two molecules of the unknown can also be used. Assuming the coupling occurs in a statistical ratio, the ratio of the racemic




and meso diastereomers is given by: racemate/meso = $(1 + x^2)/2x$, where the quantity of the major enantiomer is 1 and the quantity of the minor enantiomer x. After solving this equation for x, the enantiomeric excess is given by: ee = (1-x)/(1+x). The requirements for this method include the following.

- No racemization under the conditions used.
- Sample reacts completely.
- Coupling must occur in a statistical ratio, i.e. no "chiral self-recognition"
- Some method to distinguish diastereomers is required.

An example of a determination of the enantiomeric purity of an alcohol using diphenyldichlorosilane as the coupling agent is shown below.[6]




For example, if one observes a 9.00: 1 ratio of the DL and the meso forms, then x = 0.0554 and the starting enantiomeric purity was 89.5% ee. Another useful reagent in $PCl_3$.[7] Only two of the three chlorides are displaced so the same equations apply.

This method is very similar to the Horeau duplication strategy to enhance enantiomeric purity, discussed on page 55.

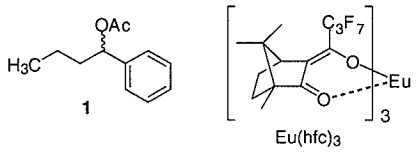
6. Wang, X. (1991) Determination of enantiomeric purity of alchols using achiral diphenyldichlorosilane, *Tetrahedron. Lett.* **32**, 3651-4.
7. Feringa, B. L.; Smaardijk, A.; Wynberg, H. (1985), Simple phosphorus-31 NMR method for the determination of enantiomeric purity of alcohols not requiring any chiral auxiliary compounds, *J. Am. Chem. Soc.* **107**, 4798-4799; Welch (1991), title, *Tetrahedron: Asymmetry*, 2, 1127-11xx.

## *Labile diastereomeric complexes*

### Chiral NMR shift reagents

NMR shift reagent complex to the analyte thereby cause different chemical shifts in at least some of the nuclei. The most useful shift reagents are complexes of lanthanide ions with organic ligands to make them soluble in organic solvents. Lanthanide ions are best because they cause the least signal broadening. Complexation of the analyte to the shift reagent changes its chemical shift according to the distance from the lanthanide ion and the orientation relative to the axis of symmetry ($\Delta\delta = k(1-3\cos^2\theta) / r^3$). Two analytes will have different shifts either because they form complexes with different geometries or, since complexation is a rapid equilibrium, because the complex to a different extent. In most samples, probabaly both effects contribute.

Chiral lanthanide shift reagents are lanthanide ions with enantiopure ligands that complex to your sample.



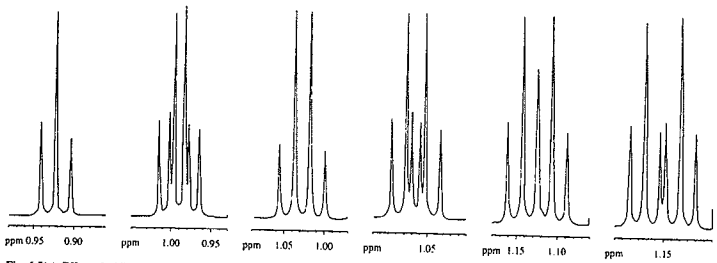




Fig. 6.5(a) Effect of adding chiral shift reagent Eu(hfc)$_3$ to a solution of (±)-1.

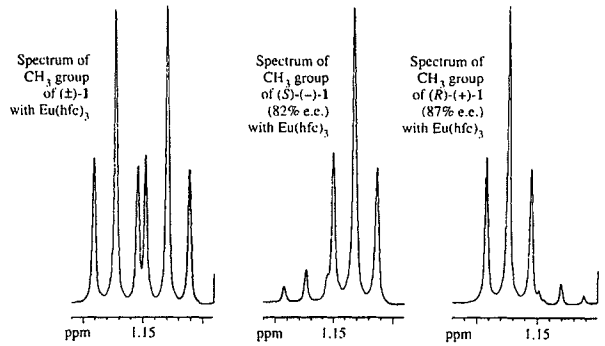
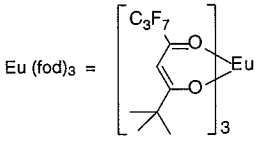



**Fig. 6.5(b)** Effect of adding $Eu(hfc)_3$ to solutions containing (±)-**1** and samples of **1** enriched with the (+)- or (−)-enantiomer.

Lanthanide shift reagents are *less* useful at high fields because the lines are very broad. Line-broadening is proportional to the square of the field, while the separation between the peaks is linearly proportional to the field.[8] Thus, enantiomeric purity using chiral lanthanide shift reagents is best measured on a moderate field NMR machine.

Lanthanide shift reagents do not have to be enantiomerically-pure to give the correct enantiomeric purity. The complexes are in rapid equilibrium in solution. Impure reagents will give smaller shifts, but will still give the correct enantiomeric purity.

Achiral shift reagents, such as $Eu(fod)_3$ are useful for analysis of diastereomers. When the differences between the two diastereomers are subtle, an NMR shift reagent can increase the difference in chemical shift.




8. Sanders, Hunter *Modern NMR Spectroscopy* Oxford, 1987, p 41

Chiral solvating agents such as $CF_3CH(OH)Ar$ form H-bonded complexes with amino acid esters.[9] Shifts are smaller than with lanthanide reagents:

add picture

## Chiral stationary phases in GC

The most common chiral stationary phases for gas chromatography are those based on cyclodextrins.[10] Cyclodextrins are cyclic glucose oligomers produced during starch degradation by *Bacillus macerans*. The most common cyclodextrins contain six (α-cyclodextrin), seven (β-cyclcodextrin) or eight glucose units (γ-cyclodextrin). The cyclic structure is slightly cone shaped. The secondary hydroxyl groups at the 2- and 3-position of glucose face the larger opening, while the primary hydroxyl groups at the 6-position face the smaller opening. The inside cavity is hydrophobic because it is lined with methine groups and the glycosidic links. Enantiomer recog-

9. Pirkle, W. H.; Hoover, D. J. (1982), NMR chiral solvating agents, *Top. Stereochem.* **13** 263-331.
10. Schuring, V. (1994), Enantiomer separation by gas chromatography on chiral stationary phases, *J. Chromatogr., A* **666**, 111-129.

ition involves both binding to the hydrophobic cavity and hydrogen bonding with the secondary hydroxyl groups.

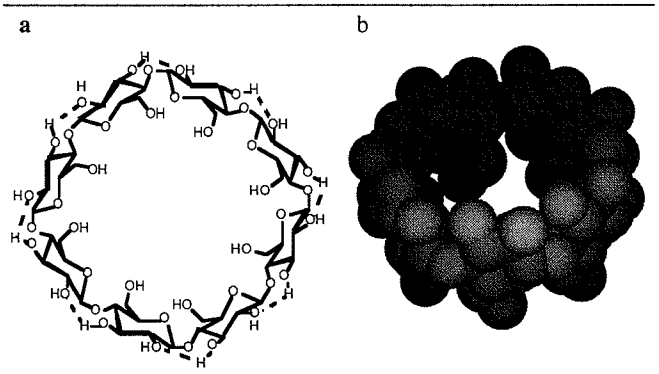
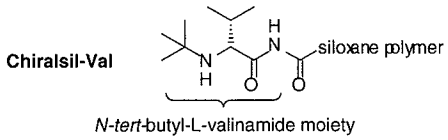



**FIGURE 1.** Structure of β-cyclodextrin. a) Line drawing shows the seven β 1→4 linked glucose units. b) Space-filling representation showing the donut-like shape. For clarity the hydrogen atoms are not shown. The primary hydroxyl groups all point down in this picture, while the secondary hydroxyl groups at the 2- and 3-positions all point up. The central cavity is hydrophobic. The top opening (lined with the 2- and 3-hydroxyl groups) is slightly larger than the bottom opening.

To create a stationary phase for gas chromatography from the solid, crystalline cyclodextrins, researchers derivatized the hydroxyl groups to make liquid cyclodextrins. For example, a ChiralDex G-TA column contains γ-cyclodextrin with added trifluoroacetyl groups.

A more stable and higher resolution material is Chirasil-Dex CB which contains permethylated β-cyclodextrin covalently bonded to a dimethylpolysiloxane. The methylation creates an ether link, which more stable than the ester link in the G-TA column. In addition, the bond to the polymer prevents the cyclodextrin from migrating to different locations in the surface film. This homogenity increases the resolution of the column.

Another chiral stationary phase for GC is Chirasil-Val, which contains a valine derivative covalently linked to a siloxane polymer.[11]




## Chiral stationary phases in HPLC

A number of diferenct approaches in liquid chromatography.[12] Cyclodextrins continue to be useful.[13]

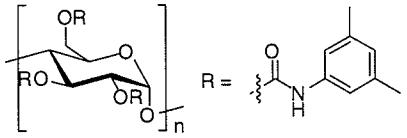
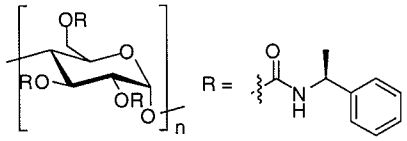
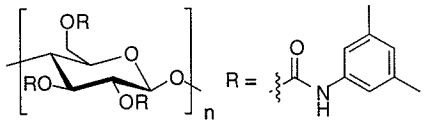
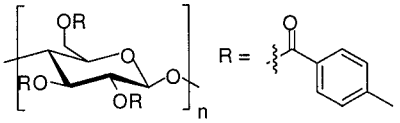
**TABLE 1.** Types of chiral stationary phases for HPLC.

| type of CSP | mobile phase | preparative scale feasible | |
|---|---|---|---|
| chiral polymer | polar or nonpolar | yes | wide scope, a bulky group at stereocenter desirable |
| protein | aqueous only | unlikely | usually need ionizable group, e.g., $NR_3$, COOH |
| ligand exchange | aqueous only | yes | multidentate analytes only, e.g., α-amino acids, α-hydroxy acids, Schiff bases |
| chiral crown ether | polar | yes | chiral amines, amino acids, bulky substituents at stereocenter |
| cyclodextrin | polar or nonpolar | yes | polar or aromatic substitution at stereocenter desirable |
| donor-acceptor | polar or nonpolar | yes | hydrogen-bond donor or acceptor, π-donor or π-acceptor |

11. Frank, H.; Nicholson, G. C.; Bayer, E. (1978), Chiral polysiloxanes for the resolution of optical antipodes, *Angew. Chem. Intl. Ed. Engl.* **17**, 363-365.
12. Pirkle, W. H.; Pochapsky, T. C. (1989), Considerations of chiral recognition relevant to the liquid chromatographic separation of enantiomers, *Chem. Rev.*, **89**, 347-62.

One of the most useful columns are the ChiralPak and ChiralCel series of columns invented by Y. Okamoto at Nagoya University. The columns contain either amylose derivatives (ChiralPak series) or cellulose derivatives (ChiralCel series) coated onto silica gel, Table 2.

**TABLE 2.** Examples of chiral polymers used as stationary phases for HPLC

| column | structure | guidelines |
|---|---|---|
| **ChiralPak AD** | | |
| amylose tris(3,5-dimethylphenyl carbamate) |  | |
| **ChiralPak AS** | | |
| amylose tris((S)-α-methylbenzyl carbamate) |  | |
| **ChiralCel OD** | | |
| cellulose tris(3,5-dimethylphenyl carbamate) |  | |
| **ChiralCel OJ** | | |
| cellulose tris(4-methylbenzoate) |  | |

13. Armstrong, D. W.; Ward, T. J.; Armstrong, R. D.; Beesley, T. E. (1986), Separation of drug stereoisomers by the formation of β-cyclodextrin inclusion complexes, *Science*, **232**, 1132-5.

A example of a protein column is human serum albumin attached to silica gel.
Human serum albumin

An example of a ligand exchange

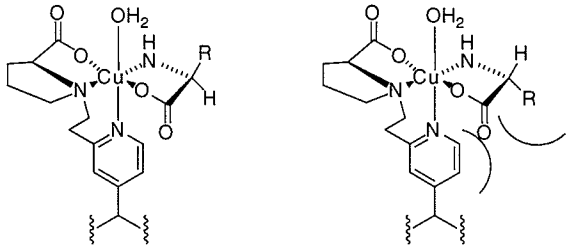
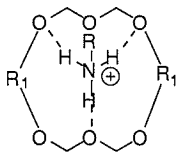


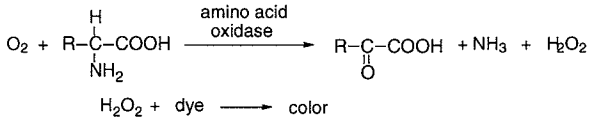

**FIGURE 2.** Schematic of interactions during ligand exchange chromatography. The column contains an immobilized ligand with a pyridine portion and an L-proline portion. A complex forms between this immobilized ligand, copper ion dissolved in the mobile phase, and the a-amino acid analyte. The complex on the right is less stable and that enantiomer elutes faster.

An example of a chiral crown ether column.



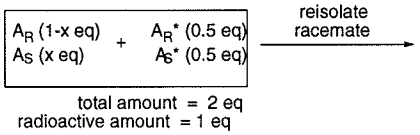
## *Other methods to measure enantiomeric purity*

Enzymic methods exploit the high enantioselectivity of enzymes.[14] Used for analogs of many natural products. Example below shows how amino acid oxidases could be used to measure the enantiomeric purity of amino acids. Both L-and D-amino acid oxidase are available.




Calorimetric methods exploit differences in the melting points of racemate and enantiomerically pure crystals. Use DCS (differential scanning calorimetry) to accurately measure melting. Accurate up to 99.9%ee.[15]

Isotopic dilution is another method.




### General References

Jacques, J.; Collet, A.; Wilen, S. H. "Enantiomers, Racemates, and Resolutions" Wiley: New York 1981, p. 405-22.

Morrison, J. D., Ed. "Asymmetric Syntheses, Volume 1, Analytical Methods" QD 481 A78

Raban, M.; Mislow, K. "Modern Methods for Determination of Optical Purity" *Top. Stereochem.* **1967**, *2*, 199-230.

Parker, D. "NMR Determination of Enantiomeric Purity" *Chem. Rev.* **1991**, *91*, 1441.

14. Bergmeyer *Methods of Enzymatic Analysis* 3rd ed, 1984.
15. Jacques, J.; Collet, A.; Wilen, S. H. "Enantiomers, Racemates, and Resolutions" Wiley: New York 1981, section 2.7

## *Questions*

1. A solution of 5 mg of a pure compound in 1 mL of methanol showed a rotation of 1° when measured in a cell with a pathlength of 10 cm. What is the $[\alpha]_D$?
2. Draw the $^1$H-NMR for the methyl resonance of the Mosher's ester derived from reaction of a large excess of enantiomerically-pure (*R*)-Mosher's acid chloride with (*R*)-1-phenylethanol at 90% ee. How would this change if the Mosher's acid chloride had only 95% ee?
3. If the chemist in the problem above had used a chiral lanthanide NMR shift reagent to determine the enantiomeric purity of the alcohol, then she would have measured the correct ee, even if the shift reagent was impure. Explain how the NMR spectrum differs when the shift reagent is enantiomerically pure and when it is contaminated with the other enantiomer. (For help see Rothchild, *J. Chem. Ed.* **1989**, *66*, 814)
4. A student injected a sample of racemic *trans*-1,2-diacetoxycyclohexane dissolved in diethyl ether onto a Chiraldex G-TA gas chromatograpy column (γ-cyclodextrin derivatized with trifluoroacetyl groups) at 125°C. The diethyl ether eluted at 2 min and two peaks of equal area eluted at 18 and 22 min. Calculate the difference in free energy of interaction for the two enantiomers with the column.
5. a) Choose a chiral derivatizing agent suitable to measure the enantiomeric purity of a sample of menthol by NMR. What checks do you need to ensure that your measurement is accurate?

   b) Suggest a way to measure the enantiomeric purity of this sample by 'duplication'. If the ee of you sample is 90%, what would you observe in the NMR by the duplication method? (Assume s = 1; how would you check to be sure this is valid?)
6. a) How do chiral solvating agents cause a difference in the chemical shift of two enantiomers? An enantiomerically impure chiral solvating agent still give the correct ee. What changes in the NMR when an enantiopure chiral solvating agent is replaced by an enantiomerically impure solvating agent?

   b) Choose a chiral solvating agent to determine the enantiomeric purity of a sample of menthol. What checks are needed to ensure that a measurement of ee using chiral solvating agents is correct?
7. Could you use a chiral lanthanide shift reagent to determine the enantiomeric purity of a sample of menthol?
8. Suggest a chiral stationary phase that may be suitable to measure the enantiomeric purity of menthol by chromatography.

9. Explain, qualitatively, how you could use a sample of racemic, $^{13}C$-labeled menthol to measure the ee of a sample of menthol. Note that menthol crystallizes as a racemic compound.

10. Donor acceptorPirkle published an x-ray crystal structure of a complex of an N-aryl amino acid with an *N*-(3,5-dinitrobenzoyl)-amino acid (*J. Am. Chem. Soc.* 1989, *111*, 9222) A similar complex may be involved during the separation of enantiomeric amino acids derivative, A, on a HPLC column with a chiral stationary phase, B. Draw a picture of (R)-A complexed to B and another picture of (S)-A complexed to B. Using the three-point interaction model, identify the three interactions that are responsible for enantiorecognition. Explain which complex is more stable and rationalize why it is more stable.(Note that the real situation is probably more complex: *J. Chromatogr.* 1989, *469*, 67.)