Advanced Organic Chemistry III

Contents

References

General

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Abbreviations of substituents

http://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf

1. Stereochemistry of Organic Compounds

(1) Structure and size of organic compounds

(a) Bond length

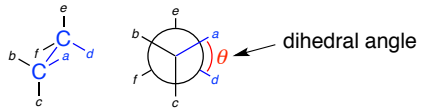
bond	length (Å)	bond	length (Å)	bond	length (Å)	bond	length (Å)
C–H	1.09	C–F	1.38	C–C	1.53	C=C	1.34
C–C	1.53	C–Cl	1.77	C–C=	1.50	C=C=	1.31
C–N	1.47	C–Br	1.94	C–C≡	1.46	=C=C=	1.28
C–O	1.43	C–I	2.14	=C–C=	1.48		
C–F	1.38			=C–C≡	1.43	C≡C	1.20
C=O	1.22			≡C–C≡	1.38	C–C (in C_6H_6)	1.39

- Bond length is defined as the distance between two nuclei.
- Distortion hardly affects bond length.

(b) Bond angle

- Bond angle is defined with the positions of three nuclei.
- Typically, the bond angles involved with sp-, sp^2-, and sp^3-hybridized carbons are 180°, 120°, and 109.5°, respectively.
- Distortion hardly restricts the bond angles. Therefore, the C–C–C bond angle in cyclopropane is allowed to be 60°. However, the strain does not highly distort the angle of two sp^3 orbitals. The C–C bond in cyclopropane is constituted with a banana shaped orbital.

(c) Dihedral angle



- Bond angle is defined with the positions of four nuclei.
- Shape of molecule can be defined with bond lengths, bond angles, and dihedral angles.
- In stable conformation, each dihedral angle should be 60°, 180°, or 120° (if the molecule have sp^2-hybridized atom). (see Conformation of organic molecules)

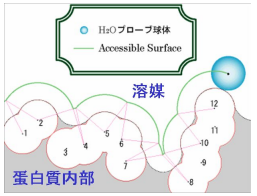
(d) Van der Waals radius

Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

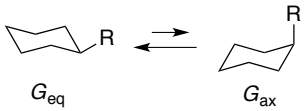
atom	H	C	N	O	F	P	S	Cl	Br	I
radii (Å)	1.20	1.70	1.55	1.52	1.47	1.80	1.80	1.75	1.85	1.98

CH_3 2.0 Å C_6H_6 (thickness) 1.7 Å

- Generally, van der Waals radius is useful for considering the bulkiness of substituent.
- However, van der Waals volume, which is calculated from the radii, does not contains the effect of bond rotation.
- Solvent accessible surface area is sometimes used for evaluating the accessibility of a reagent to a substrate.



(e) A-value



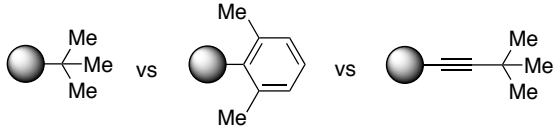
A value = $-\Delta G^0 = G_{ax} - G_{eq}$ (in kcal/mol)

R	A-value	R	A-value	R	A-value	R	A-value	R	A-value
H	0.00	C≡CH	0.41	F	0.25	OMe	0.55	CHO	0.56
Me	1.74	CH=CH$_2$	1.49	Cl	0.53	O(*t*-Bu)	0.75	COMe	1.02
Et	1.79	Ph	2.8	Br	0.48	OSiMe$_3$	0.74	CO$_2$H	1.4
i-Pr	2.21	SiH$_3$	1.45	I	0.47	NHMe	1.29	CO$_2$Me	1.2
Cy	2.2	SiMe$_3$	2.5	OH	0.60	NMe$_2$	1.53	CN	0.2
t-Bu	4.7	SnMe$_3$	1.0	NH$_2$	1.23	PMe$_2$	1.5	CF$_3$	2.4
		Sn(*i*-Pr)$_3$	1.10	NH$_3^+$	1.7	PPh$_2$	1.8		

- A-value is widely used for discussing the steric effect of substituent.
- In general, A-value correlates with the size of substituent. Furthermore, the value includes the effect of bond rotation. Therefore, the value reflects the steric environment around the atom bearing the substituent.
- A-value is affected by bond length (C–R) as well as by van der Waals radius.

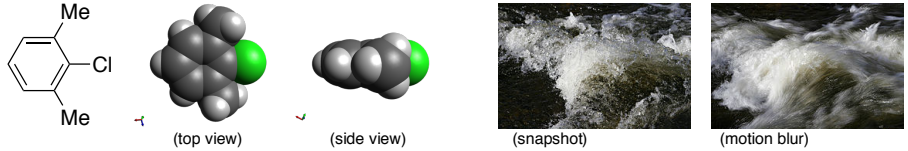
(f) Tips to consider steric effect of a substituent

i) Where is the most important for the related steric repulsion (near or far)?



- If you will consider the steric effect around the atom ●, *t*-Bu or 2,6-xylyl must be larger than -C≡C(*t*-Bu) group.
- If you would like to create a steric hindrance far from ●, -C≡C(*t*-Bu) should be larger than *t*-Bu and 2,6-xylyl.

ii) Snapshot or motion blur? (in the case of aryl group)



- Snapshot may be preferable when you consider the steric hindrance in dynamic phenomena.
- Motion blur may be suitable for thermodynamic phenomena.
- In snapshot steric effect, phenyl group can be regarded as a smaller substituent than methyl one.
- In motion blur steric effect, phenyl group can be regarded as a larger substituent than secondary alkyl ones.

(g) Steric parameters other than A-value

1) Taft steric constant (E_s)

R. W. Taft, *J. Am. Chem. Soc.*, **74**, 2729 (1952); J.-E. Dubois, *Tetrahedron*, **34**, 3553 (1978).

- Taft steric constant was based on the average ratio of the rate constants between the acetate and carboxylate solvolyses or related esterifications under acidic conditions. As a premise, the acid-catalyzed hydrolysis is considered to be scarcely affected by the polar effect of the substituent.

$$R{-}CO_2R' + H_2O \xrightarrow[cat.\ H^+]{k} R{-}CO_2H + R'OH$$

k: rate constant for any R
k_0: rate constant for R = Me

$$E_s = \frac{\log(k/k_0)}{\delta}$$

δ: sensitivity factor to steric effect
E_s: steric constant

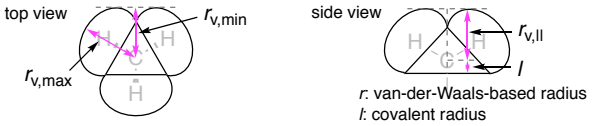
- Similarly, steric constant had been defined with the solvolyses and esterifications involving *o*-substituted benzoates.

2) Charton parameters (ν)

M. Charton, *J. Am. Chem. Soc.*, **91**, 615 (1969); *ibid.*, **97**, 1552 (1975); *J. Org. Chem.*, **41**, 2217 (1976).

- Charton parameter is the difference in van der Waals radus between a substituent and hydrogen atom. The radii of substituents are $r_{v,min}$ in the following figure.

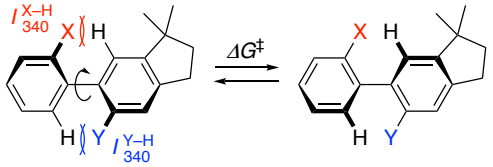
$\nu = r_{v,min} - r_H$



3) Interference value (I_{340}^{X-H})

S. Sternhell, *J. Am. Chem. Soc.*, **102**, 5618 (1980).

- Interference value is an index of the steric repulsion between the *o*-substituent and proton in biaryl compounds.



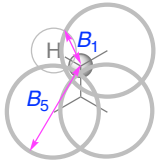
$\Delta G^{\ddagger} = I_{340}^{X-H} + I_{340}^{Y-H}$

- The rotational barrier ($\Delta G^{\ddagger}$) of 2,2'-disubstituted biaryl compounds can be predicted with sum of two interference values.

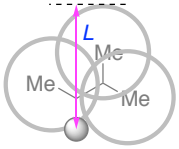
4) Sterimol parameters (B_1, B_5, L etc.)

A. Verloop, in "Drug Design Vol. III," ed. by E. J. Ariens, Academic Press, (1976) p. 133.

- Sterimol parameters describe the dimension of substituents and are based on space-filling model, which indicates the van der Waals surface of molecule. The parameter is orginally used in a computer program, STERIMOL.
- Parameters B indicate widths of the substituent and are based on the axis of the bond between the parent skeleton and substituent. B_1 and B_5 are the smallest and largest width, respectively.
- Parameter L indicates length of the substituent from the parent skeleton.



top view



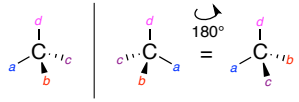
side view

: the atom bonding to the substituent
: van der Waals surface of H (r_{vdw} = 1.2 Å)
: van der Waals surface of CH_3 (r_{vdw} = 2.0 Å)

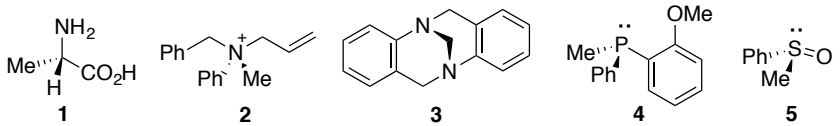
(2) Chiral Compounds and Enantiomers

- Chiral molecule cannot overlap with its mirror image. Therefore, chiral compounds have no symmetry plane (σ) or rotation-reflection axis (S_n).
- Achiral compounds are the compounds that are not chiral.
- "Chiral molecule" means the molecule possessing any chirality.
- "Chiral compound" means the mass of chiral molecules.
- "Racemic compound (racemate)" means the 1:1 mixture of both enantiomers (*R* and *S*). Each molecule constituting a racemic compound should be "chiral molecule".
- "Optically active compound" means the chiral compound other than racemate. A mixture of enantiomers is often categorized as optically active compounds, even if *R*:*S* is 51:49. However, the term often indicates pure enantiomer (enantiopure compound or optically pure compound).
- "Enantiomer" originally means the mirror image of a chiral molecule (*e.g.* (S)-2-octanol is the enantiomer of (*R*)-2-octanol.). The term often indicates the enantiopure compound, whose absolute configuration has been known.
- "Diastereomer" means any stereoisomers other than enantiomer.
- "Epimer" means stereoisomers bearing only one chiral center with the opposite absolute configuration. The configuration of other chiral centers in the epimer must be identical to the original compound.

(a) Central chirality

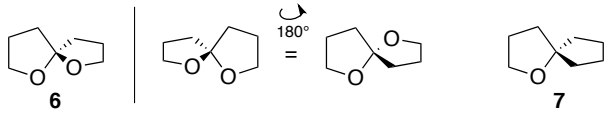


- The chirality caused by asymmetric atom is called "central chirality".
- Asymmetric atom is not limited to carbon (*e.g.* N, S, P, *etc.*). Lone pair can function as a substituent and is regarded as atomic number 0 in CIP rule (see **3**–**5**).



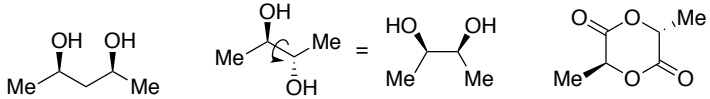
1 **2** **3** **4** **5**

- Spiro compound **6** is chiral, although they seem to have no asymmetric atom. However, compound **7** is achiral because its tetrahydrofuran ring is symmetry plane.



6 **7**

- The molecules possessing symmetry plane (see **8**, **9)** or rotation-reflection axis (see **10**) must be achiral, even if they have asymmetric atoms (*e.g.* meso compound).



8 **9** **10**

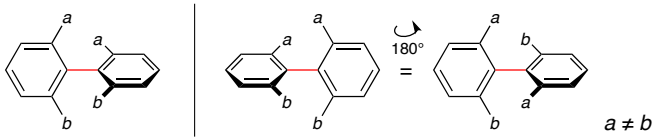
- Metal complexes are possible to be chiral when they are tetrahedral, trigonal bipyramidal, or octahedral.

(b) Axial chirality

• Axial chirality takes two forms: atropisomerism and isomerism in allenes.

Atropisomerism

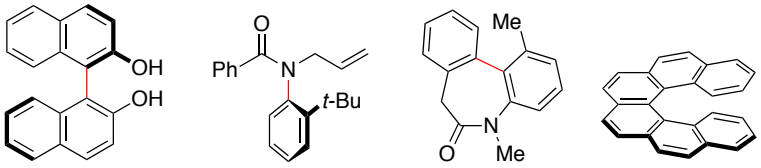
• Atropisomerism is caused by inhibition of free rotation of a single bond. The inhibition of free rotation is often observed in the biaryl compounds bearing four ortho-substituents or some sterically hindered carboxamides.



• A racemate of axially chiral compound can be resolved into each enantiomer when the rotation barrier is over 20 kcal/mol.

• Axial chirality will be stable at room temperature when the rotation barrier is over 30 kcal/mol.

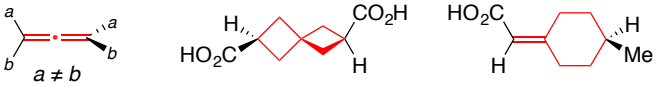
• Herical chirality is originated from the accumulation of axial chirality.



Isomerism in allenes

• Each terminal carbon in C=C=C is plane because it is sp²-hybridized. One of the planes is perpendicular to another because the internal carbon in C=C=C is linear and hybridized in sp manner to form two C–C double bonds. Therefore, substituted allenes are possible to be chiral as with biaryls.

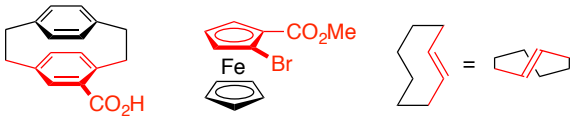
• The chirality is seen in some spiro bicyclic compounds and alkylidene cycloalkanes.



(c) Planar chirality

• Planar chirality appears when a planar molecule loses its symmetry plane by bridging with short tether or forming π-complex.

• The chirality is seen in some cyclophanes, metallocenes, and *trans*-cycloalkenes.

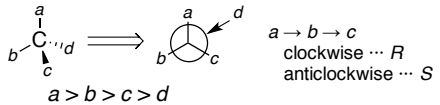


(d) Notations of absolute configuration

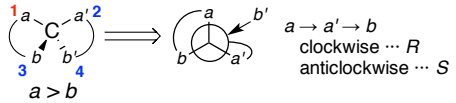
1) *R*/*S* notation

• According to CIP rule, determine the priority of each substituent involved with the chirality.

Central chirality



(in the case of spiro compounds)

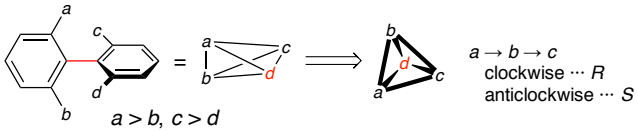


Axial chirality

i) Determine the priority of the two substituents on each atom involved with the chiral axis.

ii) The sequence of substituents becomes $a > b > c > d$ or $c > d > a > b$. Both sequences result in the same configuration.

iii) Put the substituent with the lowest priority (*d* or *b*) on the location far from you. Confirm the direction of $a \rightarrow b \rightarrow c$ (or $c \rightarrow d \rightarrow a$).



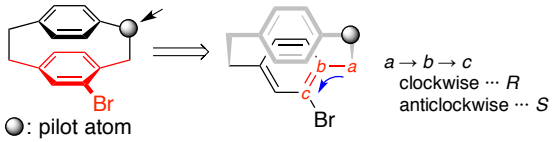
iv) To distinguish the axial chirality from others, prefix 'a' (or sufix '$_a$') is sometimes attached to the chiral descriptor *R* or *S* (*e.g.* (a*S*)-2,3-pentadiene or (S_a)-2,3-pentadiene)

Planar chirality (cyclophanes, *trans*-cycloalkenes *etc.*)

i) Determine 'pilot atom' from the bridging tether. The pilot atom is out of the plane and closest to the plane. There are two candidates in general. The pilot atom is the candidate binding to the in-plane atom with higher priority in CIP rule.

ii) Among the atoms in the chiral plane, the atom binding the pilot atom is assigned to '*a*'. The next atom is '*b*', and the third atom is '*c*'. If there are two candidates, the atom with higher priority is assigned to 'c' (or 'b').

iii) View the molecule from the pilot atom.



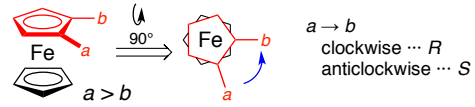
iv) To distinguish the planar chirality from others, prefix 'p' (or sufix '$_p$') is sometimes attached to the chiral descriptor *R* or *S* (*e.g.* (p*S*)-(*E*)-cyclooctene or (S_p)-(*E*)-cyclooctene)

Planar chirality (metallocenes)

- Three rules have been proposed to assign the stereochemical descriptor, *R* or *S*, for the planar chiral metallocenes. One is based on central chirality and proposed by Prelog, Cahn, and Schloegl (Rule 3). Others are based on planar chirality and proposed by Ugi and Schloegl, independently (Rule 1 and 2).
- Unfortunately, the rules 1 and 2 resulted in configuration different from each other. However, rules 2 and 3 reach the same result in most cases.

Rule 1

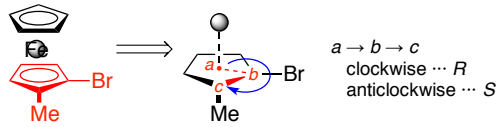
(i) View the substituted Cp ligand from the side opposite to the metal atom.
(ii) Confirm the direction of *a* → *b*.



I. Ugi *et al.*, *J. Am. Chem. Soc.* **92**, 5389 (1970).

Rule 2

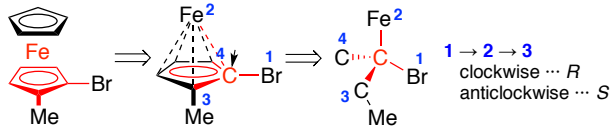
(i) Assign the metal atom to the pilot atom.
(ii) Regard the centroid of the substituted Cp ligand as atom 'a'.
(iii) The cyclopentadienyl atom bearing the substituent with the highest priority is 'b'.
(iv) The ortho-atom with higher priority is assigned to '*c*'.
(v) View the Cp ring from the pilot atom, and then confirm the direction of *a* → *b* → *c*.



K. Schloegl, *J. Organomet. Chem.* **300**, 219 (1986).

Rule 3

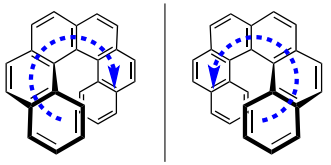
(i) Treat chirality of metallocene as central chirality of the cyclopentadienyl carbon with the highest priority.
(ii) Consider the metal atom to bond to the carbons in Cp ring.
(iii) The absolute configuration can be similarly assigned to *R* or *S* with the rule for central chirality.



K. Schloegl, *Forschr. Chem. Forsch.* **6**, 479 (1966).

2) *P*/*M* notation

- *P*/*M* notation is based on the chirality of helix (helicity).
- The descriptor *P* is used for right-handed helicity, and *M* is used for left-handed helicity (from before backward).

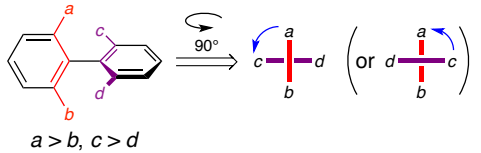


(*P*)-[6]helicene (*M*)-[6]helicene

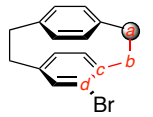
from before backward
clockwise ··· *P*
anticlockwise ··· *M*

- The notation can be applied to axial and planar chiralities.
- In the case of planar chirality, p*R* and p*S* configurations correspond to *P* and *M*, respectively.

For axial chirality



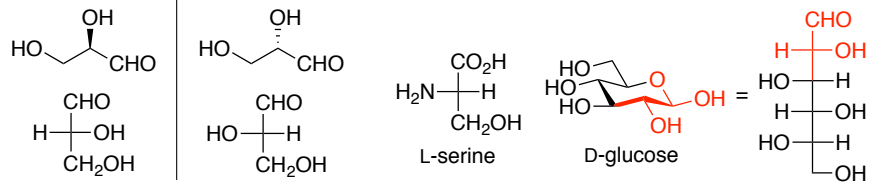
For planar chirality



- The *a*–*b*–*c*–*d* unit can be regarded as a helix.
- View the helix from *a*.
- Confirm the direction of the helix.

3) D/L notation

- D/L notation is sometimes used for the stereochemistries of carbohydrates and α-amino acids.
- Descriptors D and L strongly relate to the stereochemistries of (*R*)-(+)- and (*S*)-(–)-glyceraldehyde, respectively. D and L, must be smaller in size than other characters.



4) Notations based on the direction of optical rotation

- Descriptor (+) or (–) corresponds to the direction of optical rotation. (+) and (–) are used for dextrorotatory and levorotatory compounds, respectively.
- Descriptors *d* and *l* are equivalent to (+) and (–), respectively.
- *dl* notation is not related to D/L notation.

(e) Characteristic properties of chiral compounds

- Most properties of an enantiopure compounds are identical to those of its enantiomer. Exceptionally, the direction of optical rotation is different.
- However, an enantiopure compound is different in most properties from its racemate.

1) Crystals of racemate

- Three types of crystalline racemate are known, as follows: racemic conglomerate, racemic compound, and psudoracemate. Most racemates preferentially to form racemic compounds.

Racemic conglomerate

• Racemic conglomerate is a mechanical 1:1 mixture of *R* crystals and *S* crystals. Each crystal in the mixture is homochiral (constits of a sole enantiomer).
• Preferential formation of racemic conglomerate requires that the interaction between *R* and *R* (or *S* and *S*) is stronger than that between *R* and *S*.
• Racemic conglomate is much rarer than racemic compound.
• Chiral compounds, which preferentially form racemic conglomerate, can be resolved into each enantiomer through preferential crystallization without any other chiral source.

Racemic compound

• In racemic compound (true racemate), each crystal contains *R* and *S* molecules in 1:1 ratio. The both enantiomers form a racemic pair in a unit cell.
• Most chiral compounds prefer the formation of racemic compound to that of racemic conglomerate. In many cases, a chiral molecule has stronger affinity for its enantiomer than for itself.
• Nevertheless, homochiral crystals are preferentially obtained from the compound with relatively high enantiomeric excess

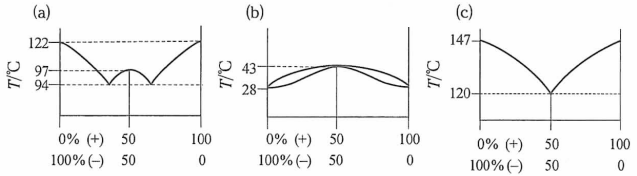
Psudoracemate

• In crystals of psudoracemate, both enantiomers coexist in an unordered manner.
• This type of chiral compound is very rare.

racemic conglomerate	racemic compound (true racemate)	psudoracemate
RRRRRR	*RSRSRS*	*RRSRSS*
SSSSSS	*SRSRSR*	*SRRSSR*

2) Melting point

• Melting point of chiral compound is affected by its enantiomeric excess. Each type of crystalline racemate exhibits characteristic behavior in solid-liquid phase transition.
• In racemic compound, racemate is generally higher in melting point than its enantiopure form.



Binary phase diagrams describing the melting behavior of a) 3-fluoromandelic acid (racemic compound); b) 2,3-diacetoxybutane (psudoracemate); c) 1.2-diphenylethane-1,2-diol (racemic conglomerate).

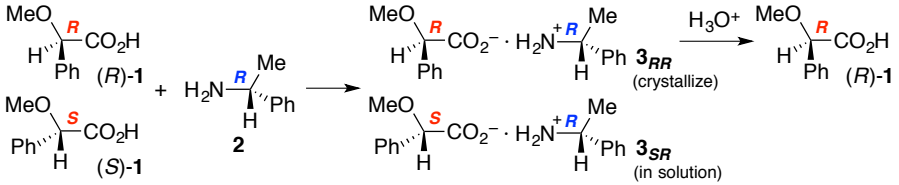
(f) Resolution of chiral compounds

1) Use of resolving agent

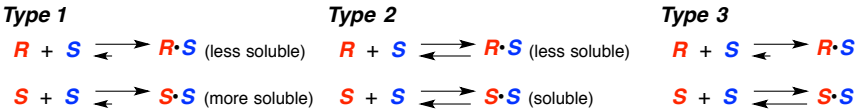
• Although an enantiomer is impossible to be separated from its racemate, an epimer is physically separable from the mixture of diastereomers.
• Therefore, formation of diastereomers with an optically active resolving agent is very useful for the optical resolution of racemates.

Crystallization of diastereomeric salts

• This method is useful for resolution of chiral carboxylic (phosphonic or sulfonic) acids, amines, and phosphine oxides.
• Acidic functional group (*e.g.* -CO_2H, -SO_3H) can readily form salts with basic functional groups (*e.g.* -NH_2). The acid–base pair is easier to crystallize from organic solvent than each compound, because the salt is generally less soluble.
• Treating racemic carboxylic acid **1** with stoichiometric enantiopure amine **2** gives the mixture of ammonium salt $\mathbf{3}_{RR}$ and $\mathbf{3}_{SR}$. If $\mathbf{3}_{RR}$ is less soluble than $\mathbf{3}_{SR}$, $\mathbf{3}_{RR}$ can selectively be obtained through crystallization. Purity of the crystals can be enhanced by recrystallization. Enantiopure (*R*)-**1** will be obtained by decomposing the pure $\mathbf{3}_{RR}$ in hand with acid.

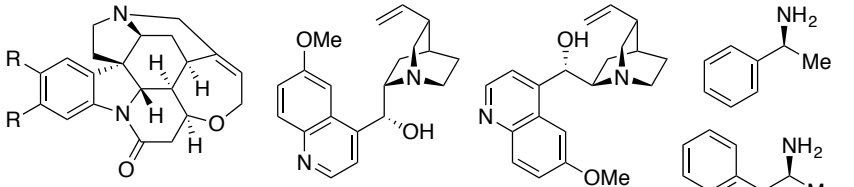


• Equimolar resolving agent (to racemate) is requires for the resolution controlled by type 1 thermodynamics. Halfmolar resolving agent may be enough for an efficient resolution, if it is controlled by type 2 or 3 thermodynamics.

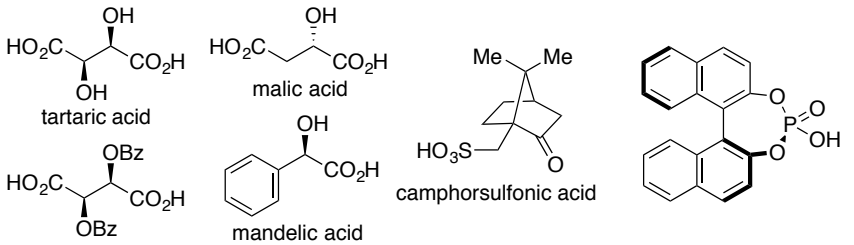


• Representative resolving agents

for acids



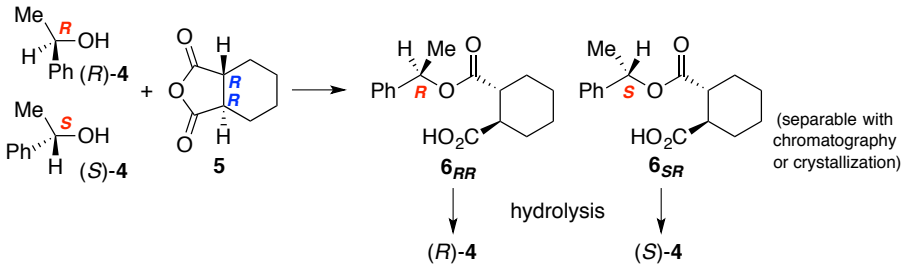
for bases



Crystallization or chromatographic separation after derivatization

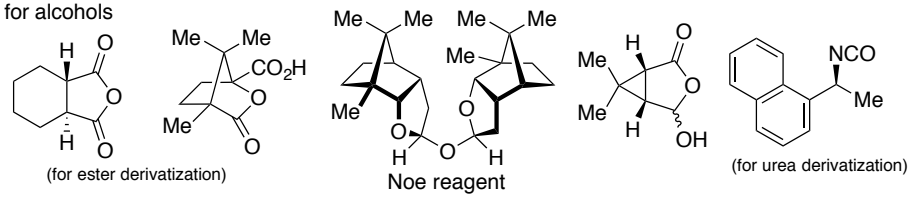
• This method is useful for the resolution of chiral alcohols and ketones. It is applicable for the resolution of chiral (secondary or primary) amines and acids.
• In the resolution of a racemic alcohol **4** (*e.g.* *R* and *S*), the racemate is esterified with an enantiopure acid anhydride **5** (*e.g.* *R*), which is the resolving agent. The esterification will give a

mixture of diastereomeric esters **6**$_{RR}$ and **6**$_{SR}$ (*RR* and *SR*). Both diastereomers can be separated by column chromatography or crystallization. Each pure diastereomer in hand can be transformed to (*R*)- or (*S*)-alcohol through hydrolysis.

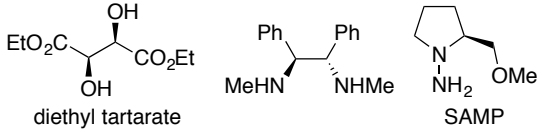


- A racemic chiral ketone or aldehyde can be resolved through the reaction with an enantiopure primary amine, which gives a mixture of diasteromeric imines.
- Representative resolving agents

for alcohols



for ketones and aldehydes

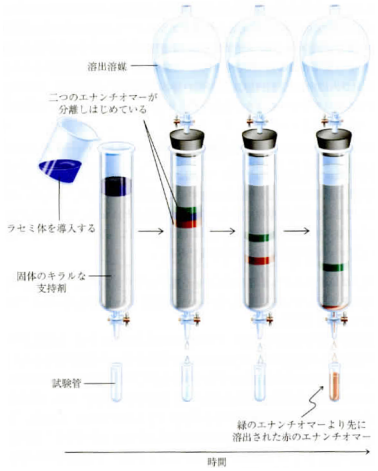


2) Chiral HPLC

- A racemate is resolved to each enantiomer through the column chromatography with a chiral stationary phase, which is typically composed of a chiral compound and silica gel.
- Information of each chiral column can be obtained from the following web sites.
  Daicel: http://www.daicelchiral.com
  Sumichiral: http://www.scas.co.jp/service/apparatus/hplc/sumichiral_introduction.html
  Astec: http://www.sigmaaldrich.com/japan/analytical-chromatography/hplc/chiral-astec.html

3) Preferential crystallization

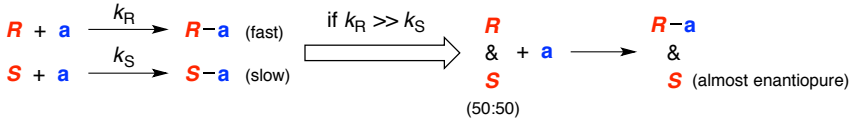
- Racemic conglomerate can be resolved through recrystallization without resolving agent, if you have its homochiral single crystal.



- To a saturated hot solution of the racemate, its homochiral crystal (*e.g. R*) is installed. The same enantiomer (*R*) will be crystallized in preference to the antipode (*S*). The resulting mother liquor will be *S*-enriched. The recrystallization of the mother liquor will preferentially form the crystals of *S*-compound.

4) Kinetic resolution

- In general, chiral reagents and catalysts exhibit different reaction rate for each enantiomer of substrates. If the reaction of the *R*-enantiomer is faster than that of *S*-isomer, the recovered substrate should be *S*-enriched. Therefore, the reaction of a racemate with a chiral reagent (or through asymmetric catalysis) is usable for the resolution.

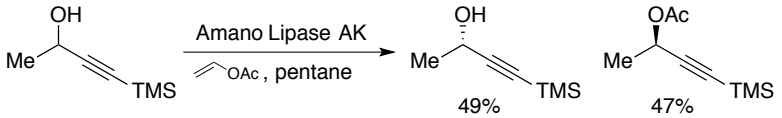


- The efficiency of kinetic resolution (s) is expressed by the ratio of the reaction rate of each enantiomer (k_R/k_S).

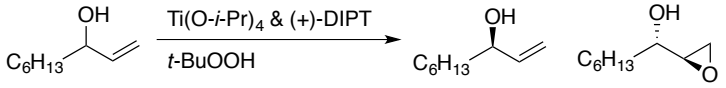
$s = k_R/k_S = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)] = \ln[1-C(1+ee')]/\ln[1-C(1-ee')]$

C: conversion
ee = enatiomeric excess of unreacted substrate
ee' = enatiomeric excess of product

- Examples



Marshall, J. A. *Org. Synth.* **2005**, *82*, 43.

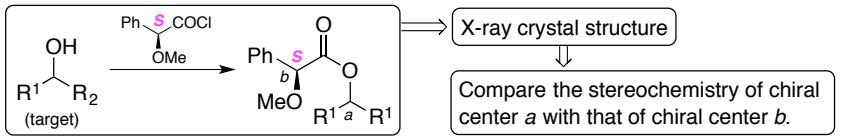


Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(g) Method for determining absolute configuration

1) Chemical transformation

a) The target molecule is reacted with a known optically active compound. If the product, which must have two chiral centers, is crystalline solid, it is subjected to X-ray crystal structure analysis. The absolute configuration of the target is found through the resulting structure, because the absolute configuration of one of its chiral centers is known.



b) The target molecule is transformed to a known optically active compound. Possibility for racemization must be considered during the transformation. The specific rotation of the resulting product is compared with the reported $[\alpha]_D$. Comparison of the retention times in the

chiral HPLC analyses is also useful for the assignment of absolute configuration.

target ⟶ other compound (Its $[\alpha]_D$ has been reported.) ⟹ Measure its optical rotation and caluculate $[\alpha]_D$. ⇩ Compare it with the $[\alpha]_D$ reported in the literature.

c) The authentic sample of the target molecule is synthesized from a known optically active compound. The specific rotation or the chiral HPLC retention time of the authentic sample allow us to assign the absolute configuration.

other compound (Its $[\alpha]_D$ has been reported.) ⟶ authentic sample ⟹ Measure its { optical rotation. / retention time in chiral HPLC. } ⇩ Compare the value with that of the target.

2) Crystallography (Bijvoet method)

- Commonly, X-ray single crystal analysis gives no information about the absolute configuration of the chiral compound. However, the configuration can be determined with the crystallography, when the compound has one heavy-weight atom.
- The heavy-weight atom induces anomalous X-ray scattering, which caused that intensity $F(h\ k\ l)$ is not equal to that of $F(-h-k-l)$ in a chiral crystal.
- Flack parameter (x) is widely used for estimating the absolute configuration of crystal structure.

$$I(h\ k\ l) = (1-x)|F(h\ k\ l)|^2 + x|F(-h-k-l)|^2$$

x: Flack parameter
I: the square of the scaled observed structure factor
F: the calculated structure factor

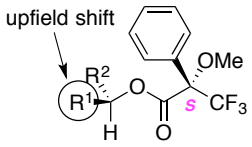
If x is near 0, the crystal structure has the correct absolute configuration. If the crystal structure has the inverted configuration, x is near 1.

- Bijvoet method is applicable for chiral compounds bearing no heavy-weight atom. In this case, a protective group containing a heavy-weight atom (*e.g. p*-bromobenzoyl) is installed to the target molecule.

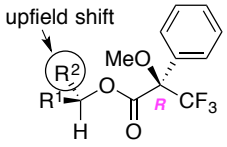
3) Advanced Mosher method and its related methods see: Riguera, R. *Chem. Rev.* **2004**, *104*, 17.

Advanced Mosher method

- Advanced Mosher method is empirical, but very useful for determining the absolute configuration of an unknown chiral secondary alcohol. This method is applicable for the chiral secondary alkyl primary amines.



(*S*)-MTPA ester



(*R*)-MTPA ester

$\Delta\delta = \delta_S - \delta_R$
If $\Delta\delta > 0$, the proton belongs to R^2.
If $\Delta\delta < 0$, the proton belongs to R^1.

(original) Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(alcohol) Kusumi, T.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(amine) Kusumi, T.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939.

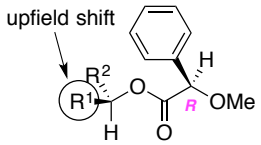
- Prepare two samples of the secondary alcohol. Each Sample is esterified with (*R*)- or (*S*)-MTPA to prepare (*R*)- and (*S*)-MTPA esters (MTPA is 3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid).

For each proton in the secondary alcohol moiety, calculate the difference between the ^{1}H NMR chemical shifts of (*S*)- and (*R*)-MTPA esters ($\Delta\delta = \delta_S - \delta_R$) as shown in above figure.

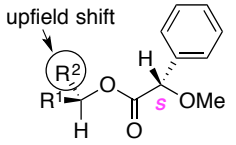
- In MTPA esters, their CF_3 groups are located at the pseudo eclipse of the proton attaching to the chiral carbon of the secondary alcohol. The aromatic ring in MTPA induces upfield shift of the resonances of the protons in the secondary alcohol moiety. Therefore, if $\Delta\delta$ is negative, the proton should be located over the aromatic ring of (*S*)-MTPA.

Trost method

- Trost method uses *O*-methylmandelic acid instead of MTPA. The procedure is very similar to advanced Mosher method.
- *O*-Methylmandelic acid is easier to react with secondary alcohols than MTPA, but may be racemized during the esterification.
- In the *O*-methylmandelates, their OMe groups are located at the pseudo eclipse of the proton attaching to the chiral carbon of the secondary alcohol.



(*R*)-*O*-methylmandelate



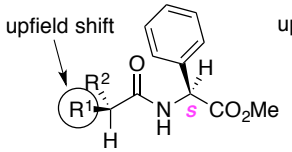
(*S*)-*O*-methylmandelate

$\Delta\delta = \delta_S - \delta_R$
If $\Delta\delta > 0$, the proton belongs to R^1.
If $\Delta\delta < 0$, the proton belongs to R^2.

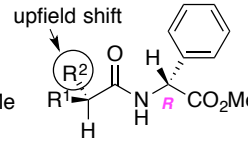
Trost, B. M. *J. Org. Chem.* **1986**, *51*, 2370.

PGME method

- PGME (phenylglycine methyl ester) method is useful for determining the absolute configuration of the chiral α-carbon of carboxylic acid.
- In the PGME amides, their CO_2Me groups are located at the pseudo eclipse of the α-proton of the chiral carboxylic acid.



(*S*)-PGME amide



(*R*)-PGME amide

$\Delta\delta = \delta_S - \delta_R$
If $\Delta\delta > 0$, the proton belongs to R^2.
If $\Delta\delta < 0$, the proton belongs to R^1.

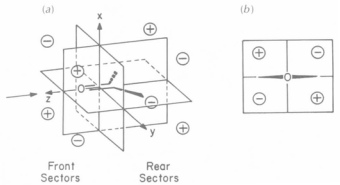
Kusumi, T. *Tetrahedron Lett.* **1995**, *36*, 1853; *J. Org. Chem.* **2000**, *65*, 397.

4) Circular dichroism (CD) spectrum

- Circular dichroism is active for only optically active compounds.
- Positive Cotton effect means that an enantiomer gives a positive peak in its CD spectrum.

Octant rule

- This method is empirical and useful for determining the absolute configuration of cyclic ketones.
- First, consider the most stable conformation for the target molecule. Geometry optimization with MO or MM may be useful for the consideration.
- Space around the carbonyl group is divided into eight sectors as shown in figure (a).
- In octant rule, the atoms in the + sectors induces a



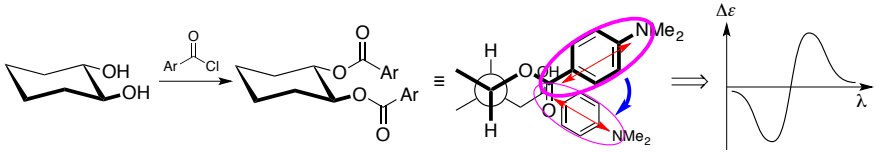
Octant rule for standard ketones. (a) Signs of the sectors in a left-handed Cartesian coordinate system; (b) projection of the rear sectors ($z < 0$).

positive Cotton effect. The atoms in the – sectors induces a negative Cotton effect.

- The Cotton effect can be predicted as above. Compare the prediction with the observed CD spectrum ($n \rightarrow \pi^*$ (C=O), ca. 300 nm).

Exciton chirality method

- This method is theoretical and useful for determining the absolute configuration of cycloalkanediol or diamine. Two equivalent chromophores (*e.g.* *p*-$Me_2NC_6H_4CO_2$-) in a molecule are required for the assignment.
- The two chromophores cause the split of their CD peak. One is negative and the other is positive.
- When the longer wavelength band of the split peak describes a positive Cotton effect and the shorter one describes a negative Cotton effect, the two chromophores arranged in a right-handed helix.



(h) Method for analyzing enantiomeric excess

- Percentage of enantiomeric excess (% ee) is commonly used for representing the ratio of enantiomers. (% ee (*R*-enriched) = ([*R*] – [*S*])/([*R*] + [*S*]) × 100)

1) Specific rotation

- Specific rotation is usable for measuring enantiomeric excess, if specific rotation of enantiopure compound has been reported.

  % ee = $[a]_D$ (sample)/$[a]_D$ (100% ee) × 100

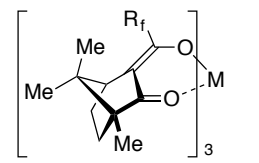
- However, the specific rotation is significantly affected by inpurity, solvent, and temperature. Sometimes, concentration of the sample affects the specific rotation.

2) Chiral HPLC and GC

- Chiral HPLC or GC analysis is commonly used for measuring enantiomeric excess.
- Chiral HPLC is effective for relatively polar compounds (alcohol, ketone, ester, amide *etc.*) with a UV active moiety (π-bond).
- Chiral GC is usable for less polar compounds (hydrocarbon, ether *etc.*) as well as above compounds. UV active moiety is not required, but the sample must be volatile.

3) Chiral shift reagent

- Prepare NMR sample of the target compound in $CDCl_3$ or C_6D_6 and measure ^{1}H NMR. Add a small amount of a shift reagent to the NMR sample, and then measure ^{1}H NMR again. Repeat the process several times until a proton signal completely splits. The enantiomeric excess of the sample is calculated from the ratio of the integrals of each split peak.
- Representative chiral shift reagents



$M(tfc)_3$ or $M(hfc)_3$

$R_f = CF_3$ (tfc) or C_3F_7 (hfc)

M = Yb or Eu