

(3) Diastereomers

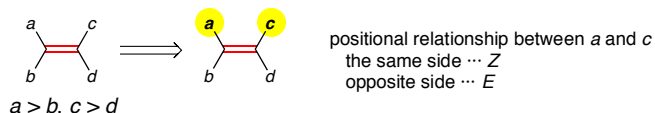
(a) Notations of diastereomeric stereochemistry

1) *E/Z* notation for alkenes

- As with *R/S* notation, *E/Z* notation unambiguously defines the geometrical configuration of alkenes. The notation is based on CIP rule.

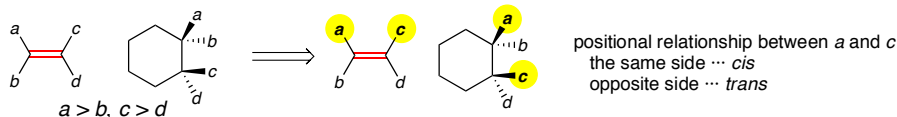
i) Determine the priority of the two substituents on each atom involved with the C–C double bond.

ii) Confirm the positional relationship of each substituent with higher priority.



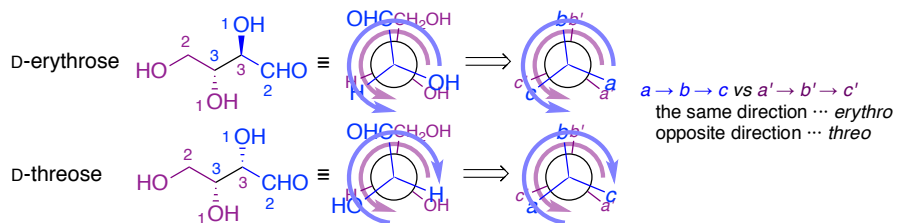
2) *cis/trans* notation

- Cis/Trans* notation is ambiguous, but often used for indicating the geometrical configuration of alkenes or the relative configuration of cyclic skeletons including two chiral centers.
- Priority of each substituent is determined with common sense, which causes the ambiguity (CIP priority or main chain in IUPAC nomenclature?).
- In the case of alkene geometry, *cis* and *trans* configurations correspond to *Z* and *E*, respectively.



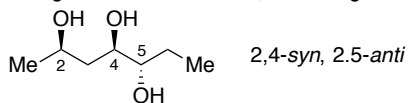
3) *erythro/threo* notation for relative configuration

- Erythro/threo* notation is ambiguous, but often used for indicating the relative configuration of acyclic vicinal chiral centers. *Erythro* and *threo* forms are strongly related to the stereochemistry of erythrose and threose.
- If the substituents on each chiral carbon are arranged in a similar manner, the configuration is *erythro*. Otherwise, the configuration is *threo*.



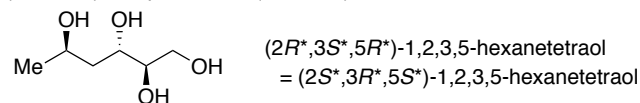
4) *syn/anti* notation for relative configuration

- Syn/anti* notation is less ambiguous than *erythro/threo* notation and applicable to various acyclic compounds.
- Draw the structure of the target compound with zig-zag projection. If two substituents are arranged on the same face, the configuration is *syn*. Otherwise, the configuration is *anti*.



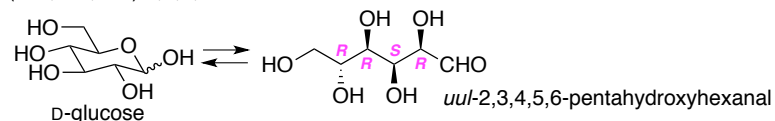
5) *R*/S** (or *RS/SR*) notation for relative configuration

- R/S* notation is applicable in relative configuration. This notation is unambiguous.
- Assign the absolute configurations of all chiral center in an enantiomer. Attach an asterisk to each *R* or *S* descriptor.
- (*2R**, *3S**) is equivalent to (*2S**, *3R**).



6) *l/u* notation for relative configuration

- Determine the absolute configurations (*R/S* or *P/M*) of all chiral centers, and then arrange them according to the numbering rule in IUPAC nomenclature.
- If the absolute configurations of two neighboring chiral centers are identical or similar each other, the relative configuration is *l* (like). Otherwise, *u* (unlike) must be used as the stereochemical descriptor. For example, *uu*-1,2,3,5-hexanetetraol is equivalent to (*2R**, *3S**, *5R**)-1,2,3,5-hexanetetraol.

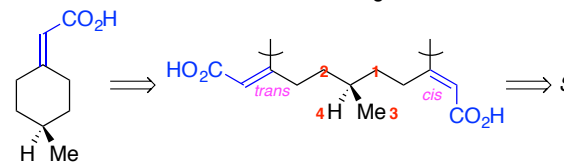


(b) Treatment of stereochemistry in CIP rule

In CIP rule

- Atomic number larger \rightarrow higher priority
- Isotope atomic mass: larger \rightarrow higher priority
- Alkene stereochemistry priority: *Z* > *E* (*cis* > *trans*)

In most cases, the priority of two geometrically isomeric groups can be determined by *Z/E* system. However, the system is useless to 4-substituted alkylidenecyclohexanes, although they can be regarded as axially chiral molecules. In this case, the alkene configuration is determined from the substituent bearing the chiral center.



④ Diastereomeric groups

⑤ Enantiomeric groups

(c) How to determine stereochemistry of diastereomer

1) Crystallography

- If the sample is crystalline solid, its X-ray crystal structure analysis is the most reliable.

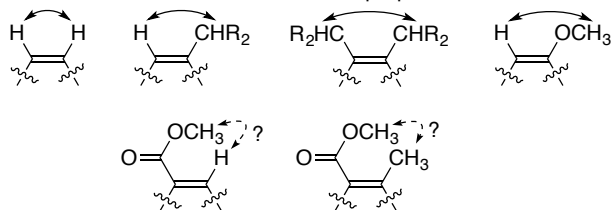
2) NMR

i) 1,2-Disubstituted alkene

nOe (nuclear Overhauser effect) difference spectrum

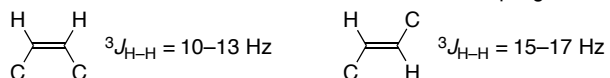
- Positive nOe will be observed between two substituents, which are located in the *cis* position each other.

- NOESY should be avoid to use for the purpose.



Vicinal H–H coupling ($^3J_{H-H}$)

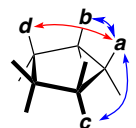
- In general, the coupling constant between the two alkenyl the alkenyl protons is 10–13 Hz when the protons are arranged with *cis* configuration. In the *trans* isomer, the coupling constant is 15–17 Hz.
- The above rule is useful only when a carbon atom attaches to each alkenyl carbon. Heteroatom substituents causes decrease in the coupling constant.



ii) Saturated four- and five-membered ring

NOESY or nOe difference spectrum

- Use only transannular nOe. Sometimes, nOe is observed between vicinal hydrogens with *trans* configurations, because these protons couple with each other.



- The nOe between **a** and **d** (red) is reliable for determining the relative configuration.
- The nOe between **a** and **b** (blue) should be avoid to use for the purpose, because an nOe is sometimes observed between **a** and **c**.

iii) Saturated six-membered ring

Chemical shift

- In general, an axial proton appears in higher field (*ca.* 0.5 ppm) than its corresponding equatorial proton.

Vicinal H–H coupling

- Karplus equation: $^3J_{H-H} = A \cos^2 \theta + B \cos \theta + C$ (θ : dihedral angle)
(*e.g.* $A = 9.4$, $B = -1.4$, $C = 0.4$ (for hydrocarbons))
- $^3J_{H_{ax}-H_{ax}}$ is 8–14 Hz, because dihedral angle θ for $H_{ax}-C-C-H_{ax}$ is 180° . $^3J_{H_{ax}-H_{eq}}$ and $^3J_{H_{eq}-H_{eq}}$ is 2–4 Hz, because the related dihedral angles are 60° .
- Higher magnetic field NMR spectrometer should be used for assigning the relative configuration of cyclohexane derivative. Assign as many peaks as possible by using not only 1D-NMR but also H–H cosy, HMBC. HSQC *etc.*
- Assign the stereochemistry by using each coupling constant in a similar way to solving a puzzle.

iv) Acyclic compound

see: Bifulco, G.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744.

General methods

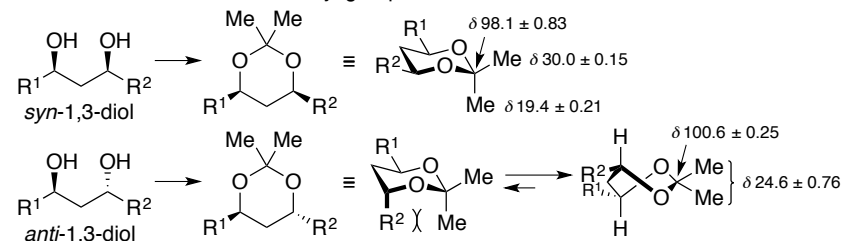
- JBCA (J-based configuration analysis) see, Murata, M. *J. Org. Chem.* **1999**, *64*, 866.
- UDB (Universal NMR Database) see, Kishi, Y. *Org. Lett.* **1999**, *1*, 2177 and 2188.
- Use of quantum mechanical calculation

1,2- or 1,3-diols (diamine)

- Protect the diol with acetone (or 2,2-dimethoxy propane, phosgene *etc.*) to give the corresponding acetonide. Analyze the resulting cyclic acetal with NOESY, nOe difference spectrum, H–H coupling constraints *etc.*

1,3-diols

- Acetonides of *syn*-1,3-diols have chair conformation, while those of *anti*-1,3-diols prefer twist boat conformation. Therefore, the relative configuration of 1,3-diols can be elucidated with the ^{13}C NMR resonances of the methyl groups of their acetonides.



(4) Conformation of organic compounds

(a) Acyclic saturated compounds

1) Ethane

- The staggered conformer ($\theta = 60^\circ$ or 180°) is more stable than the eclipsed one ($\theta = 0^\circ$ or 120°) ($\Delta E^\ddagger = 2.9$ kcal/mol).
- The eclipsed conformer is a transition state and not energy minimum.
- The $\sigma_{C-H} - \sigma^*_{C-H}$ interaction stabilizes the staggered conformer.
- The steric repulsion between the vicinal protons scarcely contributes to rotational barrier.

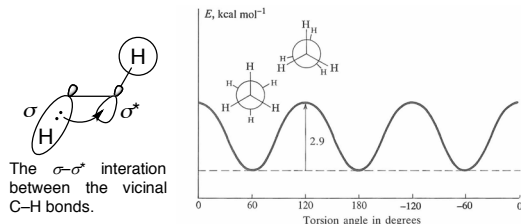


Figure 10.2. Potential energy of ethane as a function of the torsion angle

2) Butane

- Butane has two energy minima: one is anti, and the other is gauche.
- Anti conformer is more stable than gauche one ($\Delta E = 0.9$ kcal/mol).
- Each conformer, including unstable conformers, can be named with the dihedral angle θ as shown below.

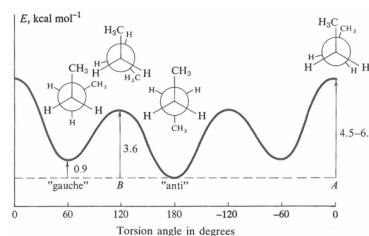
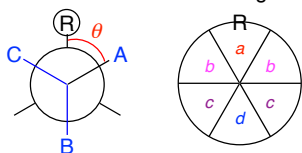


Figure 10.3. Potential energy of butane as a function of torsion angle.



- a:** synperiplanar (eclipsed, $-30^\circ < \theta < 30^\circ$)
- b:** synclinal (gauche, $30^\circ < \theta < 90^\circ$ (\pm))
- c:** anticlinal ($90^\circ < \theta < 150^\circ$ (\pm))
- d:** antiperiplanar (anti, $150^\circ < \theta < 180^\circ$ (\pm))

3) Pentane

- In the conformational analysis of pentane, the free rotations of C2-C3 and C3-C4 should be considered.

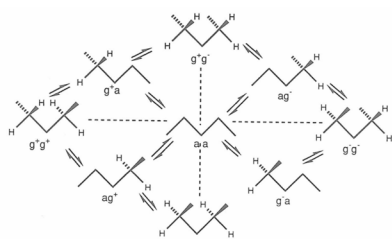


Figure 10.5. Pentane conformations.

- Conformer aa is the most stable conformer of pentane.
- Conformers g^+g^- and g^-g^+ are the least stable. The energies of these conformers has been estimated to lie over 3.3 kcal/mol above that of conformer aa.
- The steric repulsion is called 'syn-pentane interaction'.

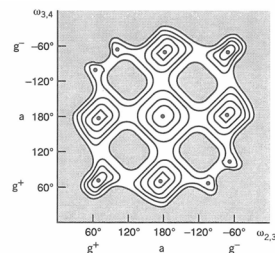
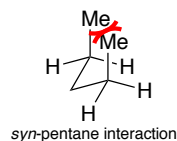


Figure 10.6. Energy contour diagram of *n*-pentane. [Reprinted with permission from Dale, J. (1978). "Stereochemistry and Conformational Analysis." Copyright © Universitetsforlaget, Oslo, Norway, p. 98.]

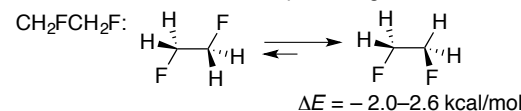


4) Effect of $\sigma - \sigma^*$ or $n - \sigma^*$ interaction

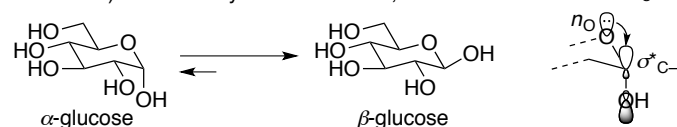
- Conformation involved with $C(sp^3) - C(sp^3)$ bond is affected by the hyperconjugation between

vicinal C-X bonds. In the hyperconjugation, one of the σ orbital of C-X bond donates electrons to σ^* -orbital of another C-X.

- Electron donating ability: $n_N > n_O > \sigma_{C-C}, \sigma_{C-H} > \sigma_{C-X}$ (X: N > O > S > Hal)
- Electron accepting ability: $\pi_{C=O} > \sigma^*_{C-Hal} > \sigma^*_{C-O} > \sigma^*_{C-N} > \sigma^*_{C-C}, \sigma^*_{C-H}$
- Gauche effect: In some compounds, gauche conformer is preferable to anti conformer.



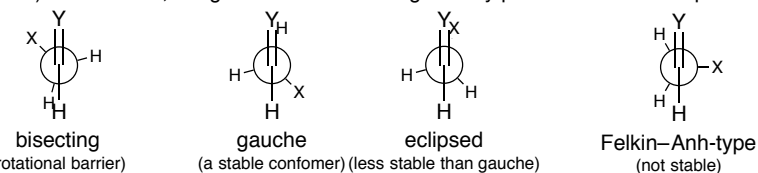
- Anomeric effect: The ratio of α - and β -glucose is 38:62 in water. The unusual ratio (A value of OH is 0.60) is caused by anomeric effect, the interaction between n_O and σ^*_{C-O} orbital.



(b) Acyclic unsaturated compounds

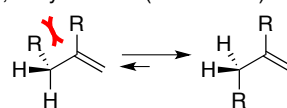
1) X-CH₂-CH=Y (Y = CH₂, O)

- Energy minima appear when the $C(sp^3) - X$ (or H) bond overlaps to the $C=Y$ bond in the Newman projection. Another conformer, in which the C-X bond overlaps to the $C(sp^2) - H$ bond, is a torsional barrier.
- Steric repulsion between X and Y is often considerable in the eclipsed conformer (1,3-allylic strain). Therefore, the gauche conformer is generally preferable to the eclipsed one.

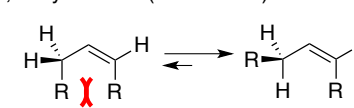


- The gauche or eclipsed conformation is stable in substituted benzenes.
- Allylic strain:

1,2-allylic strain (A(1,2)-strain)

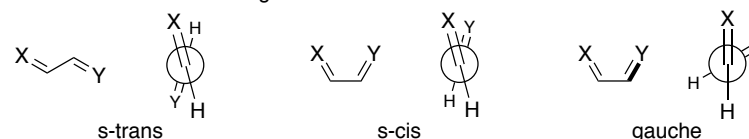


1,3-allylic strain (A(1,3)-strain)



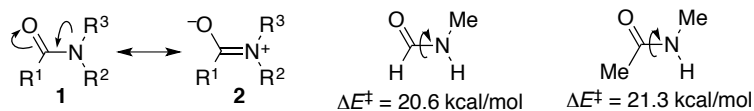
2) X=CH-CH=Y

- In general, s-trans conformer is more stable than s-cis, when there is no steric repulsion in the conjugated molecule.
- However, gauche conformer is preferable to s-cis one, if X and/or Y have a substituent and both double bonds have Z-configuration.



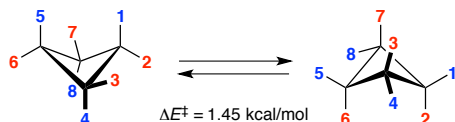
3) Carboxamides

- C–N bond of carboxamide possesses double bond character, because structure **2** remarkably contributes to the resonance hybrid. Therefore, the rotation of C–N bond is relatively slow.
- In NMR analysis, a set of signals are often observed because the *Z–E* isomerization of amide is slow in NMR time scale.



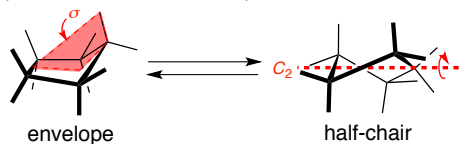
(c) 4-Membered rings

- In 4-membered rings, planar structure is unfavorable because torsional strain is maximum.
- Puckered structure is preferable to planar one in order to escape the strain. The 4-membered ring is released from the eclipsed conformation.
- The angle of pucker is 28° and the barrier of ring inversion is 1.45 kcal/mol in cyclobutane.



(d) 5-Membered rings

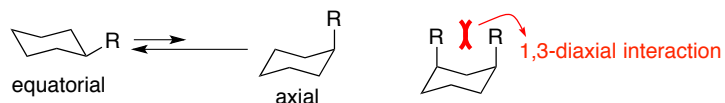
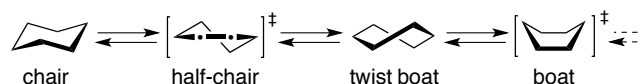
- Conformation analysis of 5-membered rings is significantly complicated as compared to those of 4- and 6-membered rings, because their conformation is very flexible.
- Stable conformations of cyclopentane are envelope and half-chair conformations. The former is more stable than latter, but the energy difference of both conformers is very small (0.5 kcal/mol).
- The envelope conformer is C_5 -symmetry, and the half-chair conformer is C_2 -symmetry.
- Equilibrium between envelope and half-chair conformers is remarkably affected by substituents.



(e) 6-Membered rings

1) Saturated rings

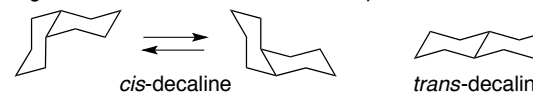
- Stable conformations of saturated 6-membered rings are chair and twist boat. Boat configuration is the transition state of the interconversion between two twist boat conformers.
- In most cases, chair conformer is more stable than twist boat conformer. Rarely, twist boat is preferable to chair in order to avoid large 1,3-diaxial interaction.



- Stability of conformer of substituted 6-membered rings is affected by A-value, 1,3-diaxial interaction, and the presence of gauche conformation *etc.*

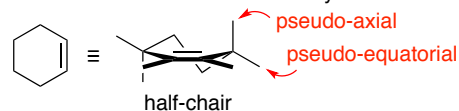
Fused ring systems

- Bicyclic system of cis-fused cyclohexane, such as *cis*-decaline, is possible to invert. In contrast, ring inversion of the *trans*-isomer is impossible.

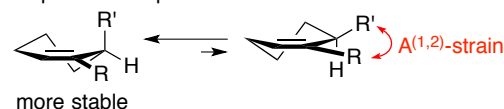


2) Cyclohexene

- The most stable conformation of cyclohexene is half-chair.



- In 1,6-disubstituted cyclohexenes, substituent R' at the 6-position induces considerable $A^{(1,2)}$ -strain if it occupies the pseudo-equatorial position. To avoid the strain, R' tends to occupy the pseudo-axial position.



3) Cyclohexanone

- Cyclohexanones prefer chair conformation. Their conformations are affected by the dipole and planar structure of carbonyl group.