Stereochemistry

stereoisomers - atomic connections are the same but 3-dimensional structures different

optical activity - rotation of plane polarized light

**concepts for chiral compounds**

1. stereoisomers not superimposable on mirror image, unique, mirror images are enantiomers

**enantiotopic** (http://www.iupac.org/goldbook/E02083.pdf)

“Constitutionally identical atoms or groups in molecules which are related by symmetry elements of the second kind only (mirror plane, inversion centre or rotation–reflection axis). For example the two groups c in a grouping Cabcc are enantiotopic. Replacement of one of a pair of enantiotopic groups forms one of a pair of enantiomers. Analogously, if complexation or addition to one of the two faces defined by a double bond or other molecular plane gives rise to a chiral species, the two faces are called enantiotopic.

1. enantiomers have identical physical and chemical properties except with asymmetric entities
2. racemate - equal mixture of enantiomers, not optically active
3. optical rotation: ,  = observed rotation, [] = specific rotation, l = pathlength in decimeters, c = concentration in grams per mL, [] depends on wavelength and temperature

<http://www.nsm.buffalo.edu/~jochena/research/opticalactivity.html>

1. chiral atom not required

(a) four different groups or electron pairs on atom with tetrahedral geometry, (C, S, P, N) amines invert as fast as 1011 s-1, slowed down by heteroatom (lone pairs) and small ring (why?)

(b) restricted rotation of disymmetric planes - biphenyls, allenes, spyro compounds both sides must be unsymmetrical



  

(c) restricted conformation/rotation - hexahelicene

(d) metallocenes

 

1. only a racemic mixture of chiral centers can be created by non-chiral reagents???



1. Fisher projection: simple 90 degree rotation in the plane not allowed
2. Cahn-Ingold-Prelog: R and S configuration based on atomic number
3. more than one chiral center - diastereomers can form: stereoisomers that are not enantiomers- examples

(a) diastereomers are chemically and physically different

(b) 2n isomers possible, sometimes internally racemic (meso), others are dl pairs

**diastereotopic** (http://www.iupac.org/goldbook/D01685.pdf)

Constitutionally equivalent atoms or groups of a molecule which are not symmetry related. Replacement of one of two diastereotopic atoms or groups results in the formation of one of a pair of *diastereoisomers*. In the example below the two hydrogen atoms of the methylene group C-3 are diastereotopic.

**Resolution**

1. convert enantiomers to diastereomers- derivatize with chiral reagent, diastereomers have different properties

2. chiral chromatography

3. enantioselective reaction/degradation

4. crystallization

**Optical purity**

1. % optical purity = 100[]obs/[]max

2. % enantiomeric excess = %R - %S = 100([R] -[S])/([R] + [S])

3. easily determined by NMR using chiral shift reagent or diastereomeric derivatives

**Cis-Trans** **Isomerization (diastereomers)**

1. double bonds, E and Z isomers

2. rings - cis and trans substituents (including other rings)

3. single bonds – delocalization in amides



4. bridging rings: endo substituent toward larger ring or other substitutent , exo away

**Enantiotopic pairs of groups/atoms – prochiral**

1. Enantiotopic ligands- identical groups - replacement of each by a new group gives enantiomers

2. ethanol, pro-R and pro-S



2. diastereotopic ligands - identical groups - replacement of each by a new group gives diastereomers: terminal alkene? groups near chiral center?

3. prochiral faces - clockwise face is Re and counter clockwise is Si



4. stereoselective process - one stereoisomer preferred over another

5. stereospecific - different stereoisomers leads to a different stereoproducts



**Asymmetric Synthesis -**



1. Asymmetric substrate- induction by chiral center

(a) Cram's rule - attack of carbonyl rotamer from small side

(b) chiral auxiliary *e. g.* convert acid to ester with chiral alcohol

2. asymmetric reagent - sellects prochiral faces or ligands

3. asymmetric catalyst

4. polarized light

|  |
| --- |
| rotantional barriers kcal/mol |
| CH3CH3 | 2.9 |
| CH3CH2CH3 | 3.4 |
| CH3NH2 | 1.98 |
| CH3NHCH3 | 3.6 |
| CH3OH | 1.07 |
| CH3OCH3 | 2.7 |

**Conformational Analysis**

1. conformers - rapid rotation interconvert structures

2. ethane -2.9 kcal/mol barrier, staggered and eclipsed, average CH interaction is 0.9 kcal/mol

3. butane - gauche - anti = 0.9 kcal/mol, 3.4 and 6 kcal/mol barriers, non bonding interaction of two methyls = 4 kcal/mol

4. propene - eclipsed 2 kcal < bisected, repulsion of methyl  component with  bond

 carbonyl behaves similarly (propanal?)



5. butadiene - s-trans favored, same for acrolein (propenal) but not bulky ketones



**cyclohexane** - chair, twist-boat

1. substituents often prefer equitorial position to avoid gauche (1,3 diaxial) interactions with ring

examine relative free energies for substitutents: Me, Et, iPr, tBu, OH, COOMe, HgBr

2. multiple substitutents also avoid each other, transannular interaction (cis 1,3)???

3. rapid chair-chair interconversion - makes racemic mixture of conformations

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|  |
| --- |
| equitorial - axial equilibrium of monosubstituted cyclohexane |
| Me | 1.8 kcal/mol |
| Et | 1.8 |
| iPr | 2.1 |
| tBu | >4.5 |
| CN | 0.15-0.25 |
| CH=CH2 | 1.7 |
| CO2H | 1.35 |



|  |  |
| --- | --- |
| OH | 0.5 (acetone) |
| OH | 0.9 (methanol) |
| HgBr | 0 |

**other rings**

1. heteroatoms in 6 membered rings - anomeric effect - lone pair - \*

2. cyclopropane –planar, eclipsed, angle strain

3. cyclobutane – butterfly, angle strain

4. cyclopentane - envelope and half chair

**molecular mechanics**

computer programs use potential energy functions based on simple molecules

optimize conformations, bond angles, lengths of complex molecules

not applicable to molecules with structures not available in potential energy functions

**Strain**

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1. energy difference between actual structure and hypothetical molecule

2. (heat of combustion of ring compounds)/(# CH2 groups) cyclopropane>cyclobutane>cyclopentane>cyclohexane

3. cyclopropane, banana bond, -analogy

(a) sp3 orbitals cannot point along internuclear axis (60o vs. 109o)

(b) increase p character to decrease interorbital angle, rehybridize to sp5

(c) orbitals toward H have more s character about sp2

(d) high p character of orbitals seen in conjugation with bonds

(e) react with electrophilic reagents, Br2 forms 1,3-dibromopropane



*Angewante Chemie, Int. Ed*. *47* (2008) 1107

 



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(f) multiple strained rings: tricyclo[1.1.1.01,3]pentane has all bonds directed to one side of plane

4. medium rings -

(a) cyclohexane - chair has gauche interactions?

(b) 5,7-13 member rings, either trans-annular interaction, large angle strain, or eclipsing interactions

5. larger rings (>14 members) have no strain

6. cyclopropene - polymerizes at -80 oC, less stable than cyclopropane

7. small rings only have cis double bonds, smallest ring with trans double bond has 8 atoms

Bredt's rule

double bond does not form at bridgehead unless trans ring has at least 8 atoms





smallest ring with triple bond without strain has 9 carbons

8. steric crowding - restricted rotation move

# Baldwin’s Rules

1. exo ring closure - electrons move out of ring

2. endo ring closure - electron move in ring

3. ring closure classified according to geometry

tetrahedral, trigonal, digonal

4. tetrahedral - favored for all exo (endo is rare)

5. trigonal - favored except for 3-5 endo

6. digonal - favored except for 3 and 4 exo

7. rules based on steric requirements of nucleophilic attack

 



Campbell, Pohlhaus, Min, Ohmatsu,Johnson, JACS *130* (2008) 9180 – 9181

**Torsional Effects on Reactivity**

1. Small nucleophiles preferentially attack axial to avoid eclipsing of O with equitorial H in TS
2. Large nucleophiles prefer equitorial attack to avoid 1,3 type of interaction

