Chapter 2. Stereochemistry

- Conformation & configuration
  - whether or not interconvertible between two different 3D arrangements of atoms by single-bond rotation
- Configuration
  - double bonds: *Z* & *E*; 📖 120
    - nonbonding electron pair: the lowest priority; 📖 121 top
  - cycles: *cis* & *trans*; 📖 121 bottom

Configuration (I)

- Configuration
  - tetrahedral atoms: *R* & *S* (CIP rules); 📖 122-123
    - stereogenic centers (stereocenters): chirality
    - enantiomers: optical activity; $[\alpha]_D^{20} = 100\alpha / (c(\text{g}/100\text{mL}) \times l(\text{cm}))$
      - different activity with another chiral compounds
    - racemate (racemic mixture): different properties; 📖 124 Fig. 2.1
    - ee (enantiomeric excess; e.e.) = optical purity
    - ORD (optical rotatory dispersion): 📖 125 Fig. 2.2
      - α vs λ; determination of absolute configuration
    - CD (circular dichroism): circularly polarized light; 📖 126 Fig. 2.3

Configuration (II)

- Multiple stereogenic centers: 📖 126-129
  - diastereomers: 2^n; different physical properties
    - epimers: different at only one stereocenter
    - Fisher, extended & Newman projections: 📖 128 Fig. 2.5
      - erythro/threo & syn/anti: relative configuration
- Other stereogenic elements
  - centers: sulfur, nitrogent, phosphorus; 📖 129 top & middle
  - axis: allenes, spiro cyles, atropisomers; 📖 129-30
  - planes & helices: *E*-cyclooctene & helicenes; 📖 130-31
    - $t_{1/2}$ = 1 h at 183.9 °C vs 4 min 0 °C (*E*-cyclononene)

Configuration (III)

- Chirality & symmetry: 📖 132
  - achiral compounds with either a center of symmetry or a plane of symmetry: *meso*
- Prochiral centers: sp^3 atoms with the same two groups
  - enantiotopic (homotopic): pro-*R* & pro-*S*; 📖 133 bottom
    - diastereotopic (heterotopic): nonequivalent; 📖 135 Fig. 2.6
- Prochiral faces: cabonyls and alkenes
  - two different groups on the sp^2 atoms: *re* & *si* face; 📖 134
  - selectivity with chiral environment: enzymes; 📖 135-136

❖ Resolution

- Separation of enantiomers: under chiral environment
  - types: conglomerate, racemic compound, pseudoracemate
  - formation of diastereomeric relationship: 🕮 137 Scheme 2.2
    - diastereomeric salts: resolving agent; 🕮 138 Scheme 2.3
    - chiral stationary phase (CSP): differential adsorption; 🕮 137 Fig. 2.7 [Home Study] Topic 2.1
    - kinetic resolution: differential reaction rate; 🕮 138 Scheme 2.4
      - enzymatic kinetic resolution: 🕮 141 bottom
      - ee depends on relative rate & conversion: 🕮 138 Fig. 2.8
      - [Home Study] Topic 2.2

❖ Preparative Column Separation

CHIRAL CHROMATOGRAPHY Simulated moving bed installation at CarboGen subsidiary of Solutia, Aarau, Switzerland, separates 4 kg of racemate per day.

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❖ Conformational Analysis (I)

- Conformation of acyclic compounds
  - ethane: torsional barrier, 2.88 kcal/mol; 📖 142 Fig. 2.10
    - butane: van der Waals repulsion; 📖 144 Fig. 2.11
  - rotational barriers in alkanes: 📖 145 top
    - heteroatoms: 📖 145 middle & 📖 146 Table 2.1
  - rotational barriers in alkenes: 📖 146 middle
    - more stable eclipsed conformation: 2.7 kcal/mol
    - more substituted alkenes: 1,3-allylic strain ($A^{1,3}$) vs 1,2-allylic strain ($A^{1,2}$): 📖 147

❖ Conformational Analysis (II)

- Conformation of acyclic compounds
  - rotational barriers in carbonyls: aldehydes; 🕮 148 middle
    - ketones: alkyl eclipsed; 🕮 148-150
  - 1,3-dienes: coplanar = π-π overlap; 🕮 150 middle
    - *s-trans* (3.9 kcal/mol) < *skew* ≤ *s-cis*
  - conjugated enones: *s-trans* & *s-cis*; 🕮 151 top
    - aldehydes: propenal, only *s-trans* conformation
    - ketones: steric repulsion between C1 & C4; 🕮 151-152

❖ Conformational Analysis (III)

- Conformation of cyclic compounds
  - cyclohexane: chair << twist < boat; 🕮 152 mid -153 top
    - conformational inversion & energy barrier: 🕮 153 Fig. 2.13
  - monosubstituted cyclohexane: chair; 🕮 154
    - equatorial < axial (1.8 kcal/mol): 1,3-diaxial interactions
  - conformational free energies: A values; 🕮 158 Table 2.2
    - measurement by ^{1}H NMR: the inversion rate; 🕮 155 Fig. 2.14
      - – iodocyclohexane: 🕮 157 Fig. 2.16
    - equilibration between diastereomers: 🕮 157 top
      - – large A value for ^{t}Bu: conformationally biased equilibrium

❖ Conformational Analysis (IV)

- Conformation of cyclic compounds (continued)
  - dimethylcyclohexanes: 3 regioisomers; 🕮 158 bottom
    - both Me groups at equatorial: ca. 1.8(1.9) for each axial Me
    - 1,3-diaxial Me-Me repulsion: 1.9(1.8) kcal/mol; 🕮 159 top
  - decalins: configurational isomers: *trans* < *cis*; 🕮 159 bottom
    - *trans*: conformationally locked vs *cis*: flexible (ΔG^* = 12.3-12.4)
  - cycles with sp^2 atoms: smaller barriers; 🕮 160
    - cyclohexene (7.7, half chair), cyclohexanone (4.9)
    - axial Me at C-2 of alkylidenecyclohexane: A1,3 strain; 🕮 161
    - cyclohexanone: axial Me at C-2 (ca 1.8), axial Me at C-3 (1.3-4)

❖ Conformational Analysis (V)

- Conformation of other cyclic compounds
  - strain energies for cycloalkane: 📖 162 Table 2.3
    - small rings: 3- & 4-ring; torsional & angle strains
    - medium rings: 8- to 11-ring; cross-ring repulsions
  - cyclopropane: planar; bent C-C 1.50 Å, ∠H-C-H 115°
  - cyclobutane: puckered; 📖 162 bottom
    - smaller inversion barrier and energy preference for *cis*
  - cyclopentane: half-chair vs envelope; 📖 163 top
    - less angle strain but large torsional strain
  - cycloheptane: 4 conformations; 📖 163 bottom

❖ Conformational Analysis (VI)

- Conformation of other cyclic compounds
  - cyclooctane: 5 conformations; 🕮 165 Fig. 2.18
    - inversion barriers: 5-8 kcal/mol
  - cyclodecane: 18 conformers; transannular strain
    - the lowest energy conformers: boat-chair-boat; 🕮 166
  - larger rings: many conformers; 🕮 166 Fig. 2.19
    - diamond lattice: the most stable; cf: adamantane
  - anomeric effect: [Home Study] Topic 2.3
  - molecular mechanics: $E_{strain} = E(r) + E(\theta) + E(\phi) + E(d)$

❖ Dynamic Stereochemistry

- Stereospecific reactions: mechanism; 🕮 169
  - stereoisomeric reactants afford stereoisomerically different products under the same reaction conditions
- Stereoselective reactions: 🕮 171 Scheme 2.6
  - a single reactant could give two or more stereoisomeric products in principle, one of which is formed preferentially
  - catalytic hydrogenation: entries 1-3, Scheme 2.6
    - usually *syn* addition but some exceptions: mechanism; 🕮 172
    - directed hydrogenation: hydroxy(l) groups; 🕮 173
    - homogeneous catalysts: Ir^+ & Rh^+

❖ Stereoselective Reactions

- Reduction of cyclic ketones: entries 4-6, Scheme 2.6
  - carbonyl: prochiral face; 🕮 176 bottom
  - axial attack: kinetically favored but sterically congested
    - relief of torsional strain between carbonyl and C-$H_{(eq)}$: 🕮 177
  - small Nu: axial vs bulky Nu: equatorial: 🕮 178 Table 2.4
- Addition to acyclic carbonyls: entries 7-8, Sch. 2.6
  - 1,2-asymmetric induction: Cram's rule; 🕮 179 top
    - Felkin-Ahn model: 🕮 179 middle; [Home Study] Topic 2.4
  - 1,3-asymmetric induction: R_L/C-O ⊥ C=O; 🕮 181 top
  - chelation control: