Some definitions

• Absolute Configuration -> spatial arrangement of the atoms for a chiral molecule (R/S, P/M or D/L assignment).

• Absolute Structure -> spatial arrangement of atoms in a noncentrosymmetric crystal structure (unit-cell, space group)
• Chiral molecules

Molecules that cannot be superimposed with their mirror image

• Two mirror images of a chiral molecule are called *enantiomers*, they are optical isomers

• Determination of absolute configuration -> handness of the molecule
Origin of chirality

- Asymmetric carbon atoms (R/S)
- Axial chirality
- Chiral Propeller Arrangement (P/M or $\Delta/\Lambda$)

Helicenes

R-Binol

S-Binol
In the solid state

• Chiral molecules can crystallize as an enantiopure bulk sample or as a racemic mixture.

• For enantiopure crystals → Space group restriction:

  Only 65 space groups allowed for chiral molecules:
  No Inversion Center / No Mirror / No Glide Plane

  These include 11 pairs of eniantomorph space groups
  (screw axes of opposite handedness)
  eg: P4₁/P4₃ or P6₁/P6₅
# Space Group Restrictions

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Racemic mixture In the solid state

1) **Conglomerate**: a mixture of well-resolved crystals of both enantiomers
   - Chiral space group
   - Individual crystals have an optical activity 5-10%

2) **Racemates**: One type of crystal containing the two enantiomers in a well defined stoechiometry.
   - No optical activity
   - Usually centrosymmetric space group 90-95%
Racemates
Racemic mixture In the solid state

• 3) **Inversion twin**: twinned crystals of both enantiomers. Chiral space group

• 4) **Disordered solid-solution**: Crystal containing the two enantiomers in a disordered arrangement. Usually centrosymmetric space group
• Louis Pasteur Experiment (1848): Separation of the two enantiomers by the visual sorting of crystals of a conglomerate

D(-) levotartaric acid  L(+) dextrotartaric acid  Sodium ammonium tartrate crystals
The two enantiopure samples and the conglomerate give the same powder X-ray diffraction pattern.
Powder diffraction

Ammonium Hydrogen Tartrate
$P_{2_12_12_1}$

Intensity (u.a.)

2θ (degrees)

Ammonium Hydrogen Tartrate
$P_{2_1/c}$

Intensity (u.a.)

2θ (degrees)
Polar structures

Achiral molecules can crystallize in chiral and non-centrosymmetric space groups

Helical arrangement of SiO$_4$ tetrahedra in $\alpha$-quartz (P3$_1$21)
How we determine Absolute Configuration?

- Method 1: Internal Chiral Reference
- Method 2: From Absolute Structure
Absolute configuration from an internal chiral reference

Co-crystallisation with a compound of known absolute configuration

Iding et al.,
Absolute configuration from Absolute Structure

- Method based on the *anomalous scattering*
- Friedel’s Law is not respected:

\[ F(h, k, l) \neq F(\bar{h}, \bar{k}, \bar{l}) \]

- “Heavy” atom should be present:
  Light atoms usually show only a small anomalous dispersion effect

\[ \text{MoK}\alpha: \text{ element } > \text{P (15)} \]
\[ \text{CuK}\alpha: \text{ element } > \text{O (8)} \]
Absolute Configuration from Absolute Structure

Refine the structure and its inverse, compare the R-factors

Calculated pairs of reflections $hkl \ vs \ \overline{hkl}$ (Friedel / Bijvoet Pairs) can be examined

Refinement of the Flack Parameter $x$

$$I_{calc}(h, k, l) = (1 - x) \cdot |F_{calc}(h, k, l)|^2 \cdot x \cdot |F_{calc}(\overline{h}, \overline{k}, \overline{l})|^2$$

$$0 \leq x \leq 1$$

Diffraction from a crystal twinned by inversion
Reporting absolute structure

- Report $x$ and its esd $u$
- If $u > 0.3$ : absolute structure cannot be determined reliably.
- $0 < x < 1$
- $x \approx 0$: correct absolute structure
- $x \approx 1$: wrong absolute structure $\rightarrow$ invert structure!
- $x \approx 0.5$: inversion twin
Refinement in Shelx

\[
\begin{array}{cccccccccccccccc}
\text{rms sigma} & 0.000 & 0.000 & 0.000 & 0.020 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 \\
\text{rms deviation} & 0.000 & 0.000 & 0.000 & 0.010 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 & 0.000 \\
\end{array}
\]

\[ \text{GooF} = S = 1.028; \quad \text{Restrainted GooF} = 1.020 \text{ for } 21 \text{ restraints} \]

\[ \text{Weight} = 1 / \left[ \text{sigma}^2(Fo^2) + (0.0337 \times P)^2 + 0.22 \times P \right] \quad \text{where} \quad P = (\text{Max}(Fo^2, 0) + 2 \times Fc^2) / 3 \]

\[ R1 = 0.0268 \text{ for } 1243 \text{ Fo} > 4\text{sig}(\text{Fo}) \text{ and } 0.0268 \text{ for all } 1245 \text{ data} \]

\[ wR2 = 0.0688, \quad \text{GooF} = S = 1.028, \quad \text{Restrainted GooF} = 1.020 \text{ for all data} \]

\[ \text{Flack x parameter} = 0.0683 \quad \text{with esd} \quad 0.2363 \]

Expected values are 0 (within 3 esd's) for correct and +1 for inverted absolute structure.

Note that this rough estimate ignores correlation with other parameters; if the above value differs significantly from zero, it is ESSENTIAL to test the inverted structure or refine x as a full-matrix parameter using TWIN and BASF.

Occupancy sum of asymmetric unit = 11.00 for non-hydrogen and 9.00 for hydrogen atoms

Principal mean square atomic displacements U

\[
\begin{array}{cccc}
0.0282 & 0.0247 & 0.0195 & \text{C1} \\
0.0299 & 0.0266 & 0.0193 & \text{C2} \\
\end{array}
\]
Refinement in Shelx

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Refinement in Shelx

L.S. 4

BOND $H

TWIN

BASF 0.0674

FMAP 2
PLAN 5
ACTA

WGHT 0.033700  0.22360

FVAR 0.63488

MOLE 1
C1  1  0.520368  0.124011  0.630898  11.000000  0.01969  0.02799 =
    0.02473 -0.00013   0.00023  -0.00137
C2  1  0.331654  0.188750  0.637001 11.0000000  0.01956  0.02677 =
    0.02943  0.00099  -0.00139   0.00077

AFIX 13
H2  2  0.279971  0.174102  0.556762  11.00000  -1.20000
AFIX  0
Refinement in Shelx

_refine_ls_matrix_type full
_refine_ls_weighting_scheme calc
_refine_ls_weighting_details 'calc \( w = \frac{1}{(s^2 + (F_0^2)^2 + 0.0337P^2 + 0.2236P)} \) where \( P = (F_0^2 + 2F_c^2)/3 \)'
_atom_sites_solution_primary direct
_atom_sites_solution_secondary difmap
_atom_sites_solution_hydrogens geom
_refine_ls_hydrogen_treatment mixed
_refine_ls_extinction_method none
_refine_ls_extinction_coef ?

_refine_ls_abs_structure_details
- 'Flack H D (1983), 487 Friedel Pairs'

_chemical_absolute_configuration rmmad
_refine_ls_abs_structure_Flack 0.1(2)

_refine_ls_number_reflns 1245
_refine_ls_number_parameters 120
_refine_ls_number_restraints 21
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_refine_ls_R_factor_gt 0.0268
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_refine_ls_wR_factor_gt 0.0688
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_refine_ls_restrained_S_all 1.021
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_refine_ls_shift/su_mean 0.000

loop_
_atom_site_label
Hooft parameter


• Run SHELX *without* refining the Flack parameter.

• Generate the CIF file and the corresponding .fcf reflection file (ACTA instruction).

• Run PLATON and open the CIF File.

• On the Graphical Menu, select the “ByVoetPair” option.
Hooft parameter
Space Group: P2_12_12_1
Wavelength: 1.54178
Flack x .... 0.1
Flack (su) .. 0.2
Bijvoet Pairs: 497
Coverage ...... 99
QffCalcMax. .. 4.95
Outlier Crit. .. 9.91
Scatter Plot:
Sigma Crit. .... 0.25
Select Pairs .. 260
Number Plus .. 203
Number Minus .. 57
Average Ratio .. 0.907
AC ............ 0.914
Normal Prob. Plot:
Sample Size .. 462
Corr. Coeff. .. 0.996
Intercept .... -0.065
Slope ........ 0.676
Bayesian Statistics:
Type .......... Gaussian
Select Pairs .. 482
P2(true) ...... 1.000
P3(true) ...... 1.000
P3(roc-twin) .. 0.4E-33
P3(false) ... 0.8-149
G ............ 0.9054
G (su) ....... 0.0726
Haas (y) ...... 0.05
Haas (eu) .... 0.04

INPUT INSTRUCTIONS via KEYBOARD or LEFT-MOUSE-CLICKS (HELP with RIGHT CLICKS)
Absolute Configuration from Absolute Structure

Once you have determined the absolute structure and the absolute configuration of the molecule, you should ensure that the bulk sample is enantipure i.e. contains only the enantiomer found. (eg. circular dichroism, chromatography)

Useful References:

