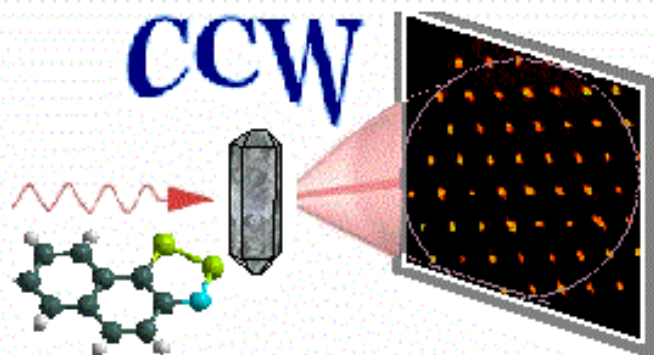




Canadian National Committee
for Crystallography (CNCC)

<http://www.canadiancrystallography.ca/>



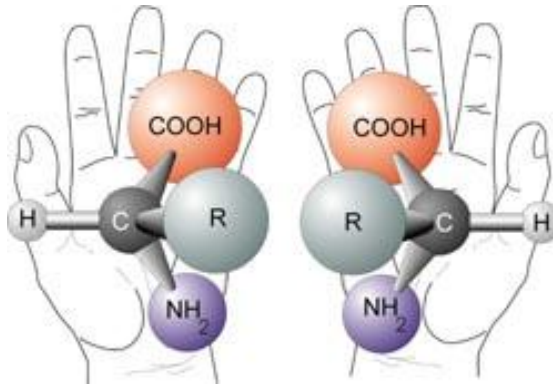
*3rd Chemical
Crystallography
Workshop*

Absolute Structure
Absolute Configuration

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



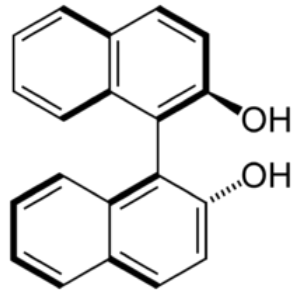
Molecules that cannot be superimposed with their mirror image

- Two mirror images of a chiral molecule are called *enantiomers*, they are optical isomers
- Determination of absolute configuration -> handedness of the molecule

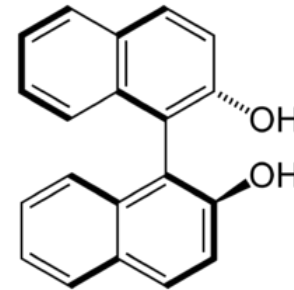
Origin of chirality

- Asymmetric carbon atoms (R/S)

- Axial chirality

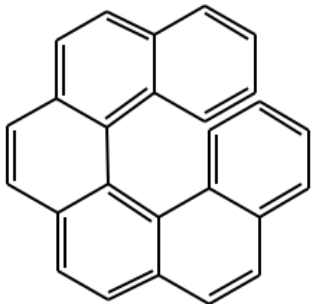


R-Binol

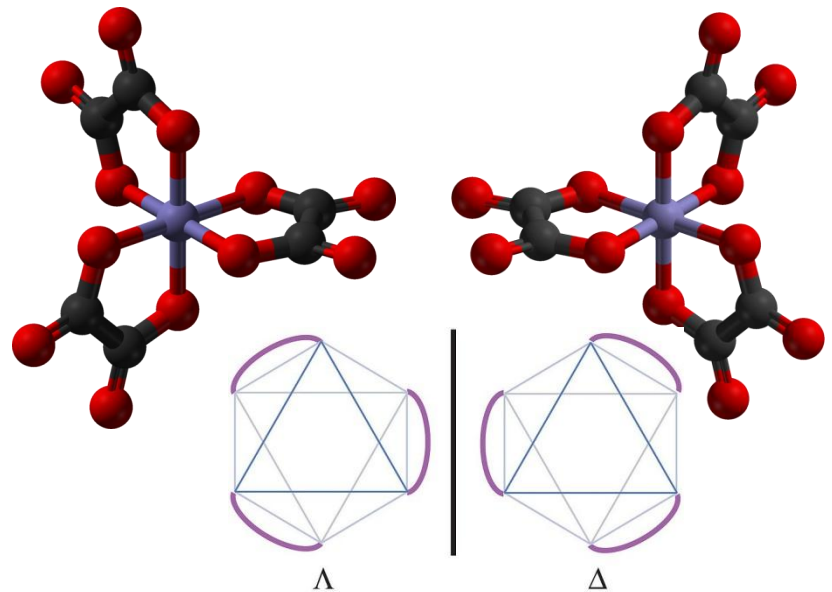
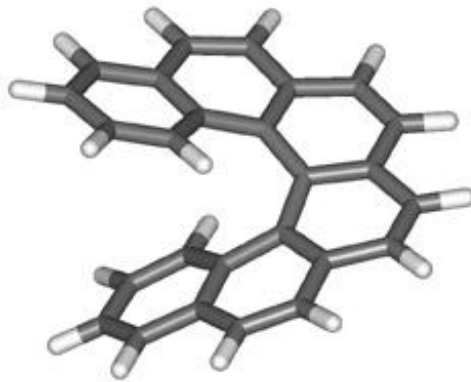


S-Binol

- Chiral Propeller Arrangement (P/M or Δ/Λ)



Helicenes



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 enantiomorph space groups
(screw axes of opposite handedness)

eg: $P4_1/P4_3$ or $P6_1/P6_5$

Space Group Restrictions

TRICLINIC

P 1

MONOCLINIC

P 2

P 21

C 2

ORTHORHOMBIC

P 2 2 2

P 2 2 21

P 21 21 2

P 21 21 21

C 2 2 21

C 2 2 2

F 2 2 2

I 2 2 2

I 21 21 21

85 %

TETRAGONAL

P 4

P 41

P 42

P 43

I 4

I 41

P 4 2 2

P 4 21 2

P 41 2 2

P 41 21 2

P 42 2 2

P 42 21 2

P 43 2 2

P 43 21 2

I 4 2 2

I 41 2 2

TRIGONAL

P 3

P 31

P 32

R 3

P 3 1 2

P 3 2 1

P 31 1 2

P 31 2 1

P 32 1 2

P 32 2 1

R 3 2

HEXAGONAL

P 6

P 61

P 65

P 62

P 64

P 63

P 6 2 2

P 61 2 2

P 65 2 2

P 62 2 2

P 64 2 2

P 63 2 2

CUBIC (minus sign in front of triade optional)

P 2 3

F 2 3

I 2 3

P 21 3

I 21 3

P 4 3 2

P 42 3 2

F 4 3 2

F 41 3 2

I 4 3 2

P 43 3 2

P 41 3 2

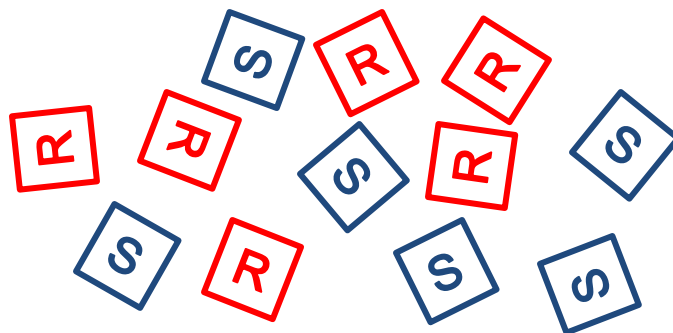
I 41 3 2

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 %

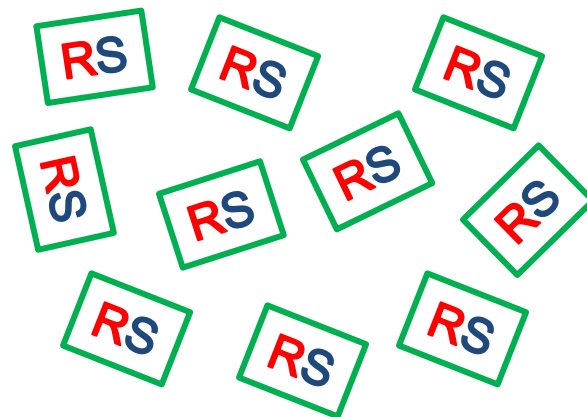


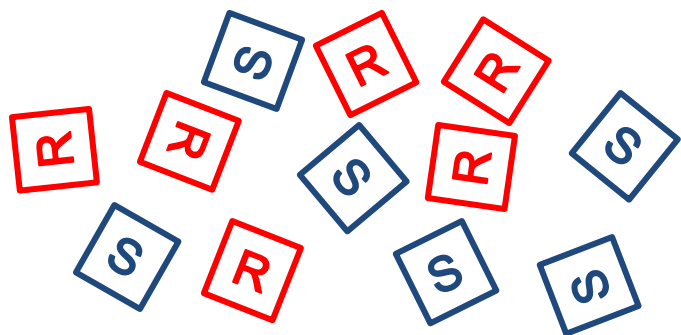
- 2) **Racemates**: One type of crystal containing the two enantiomers in a well defined stoichiometry.

No optical activity

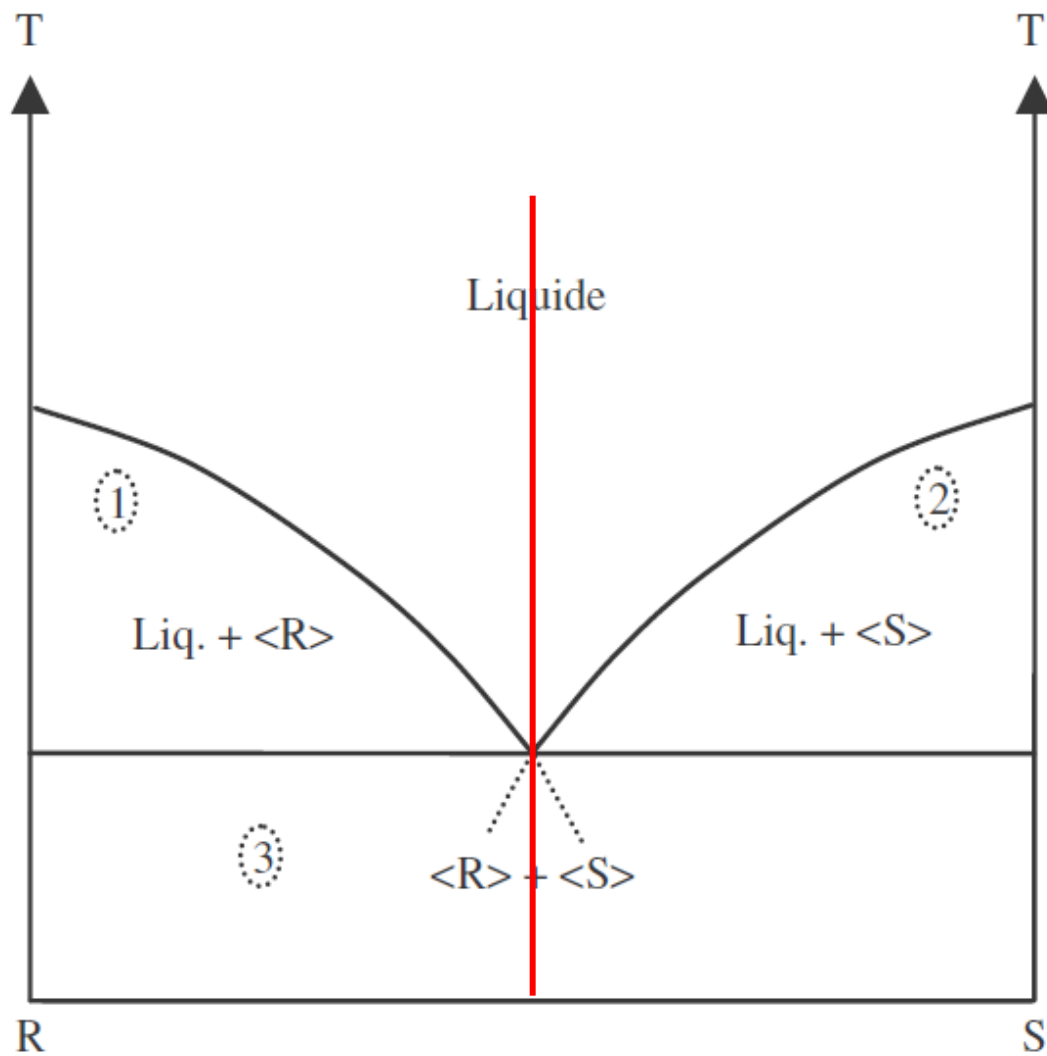
Usually centrosymmetric

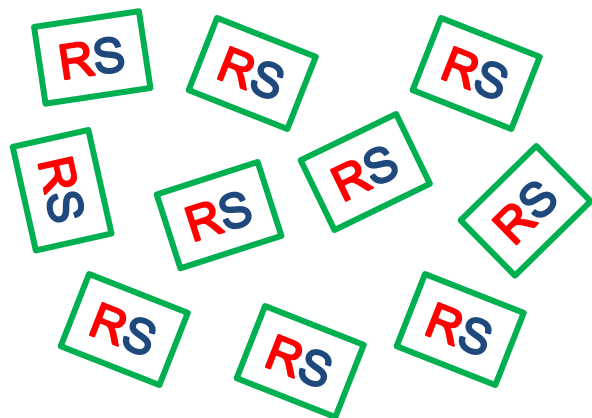
space group 90-95 %



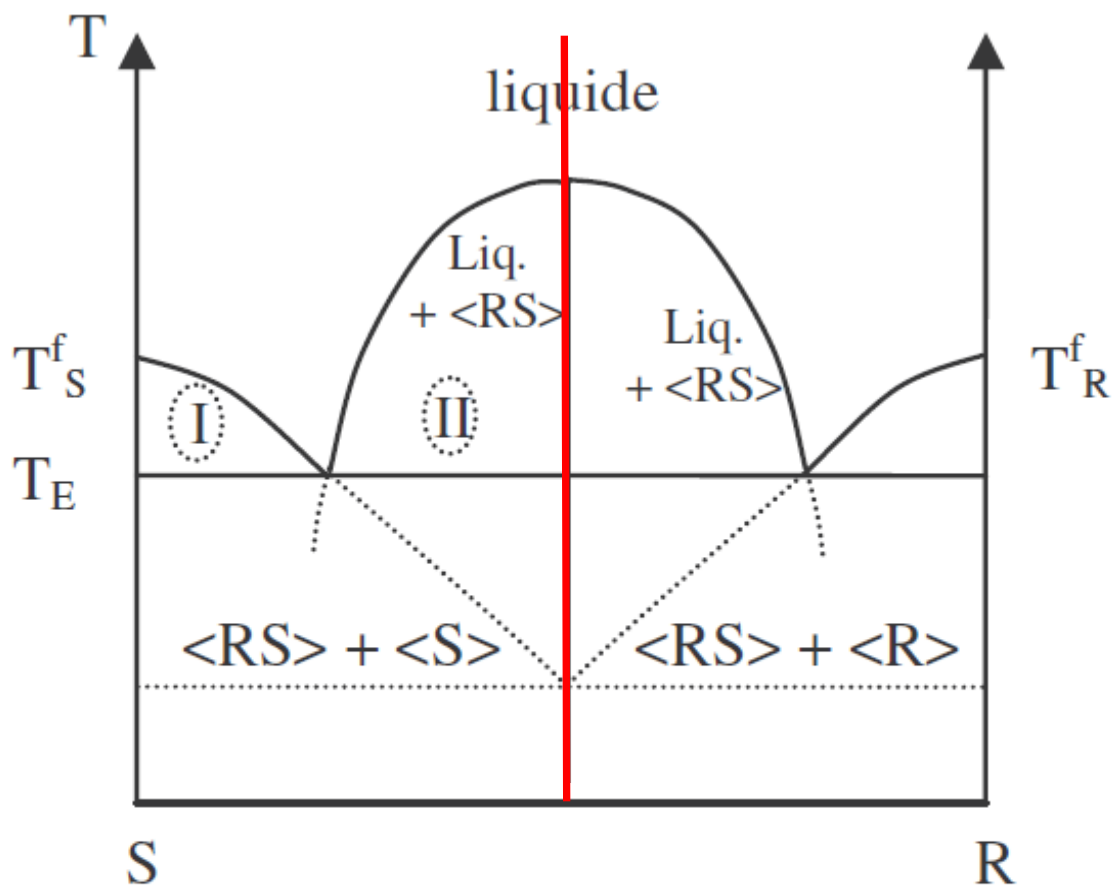


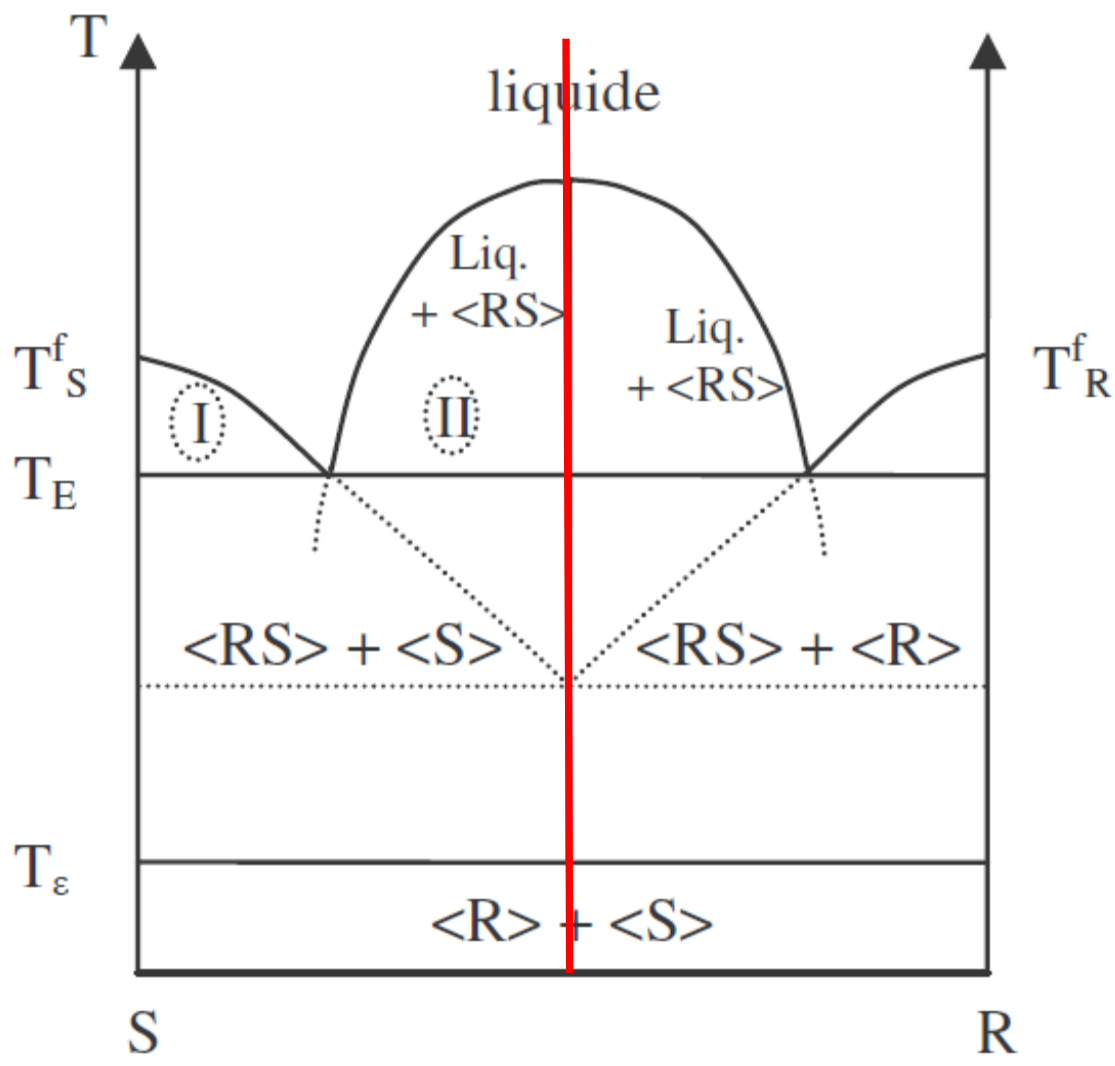
Conglomerate





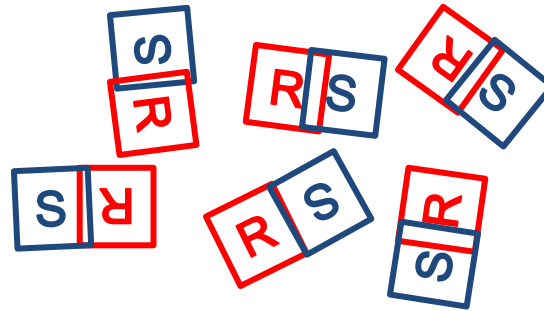
Racemates



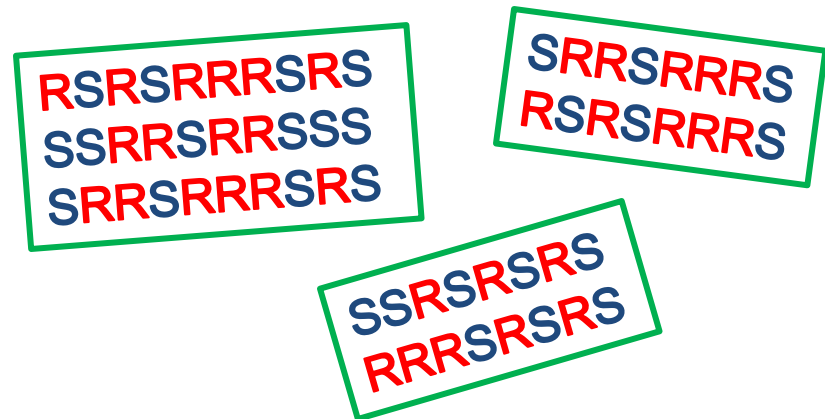


Racemic mixture In the solid state

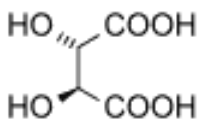
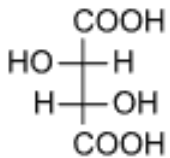
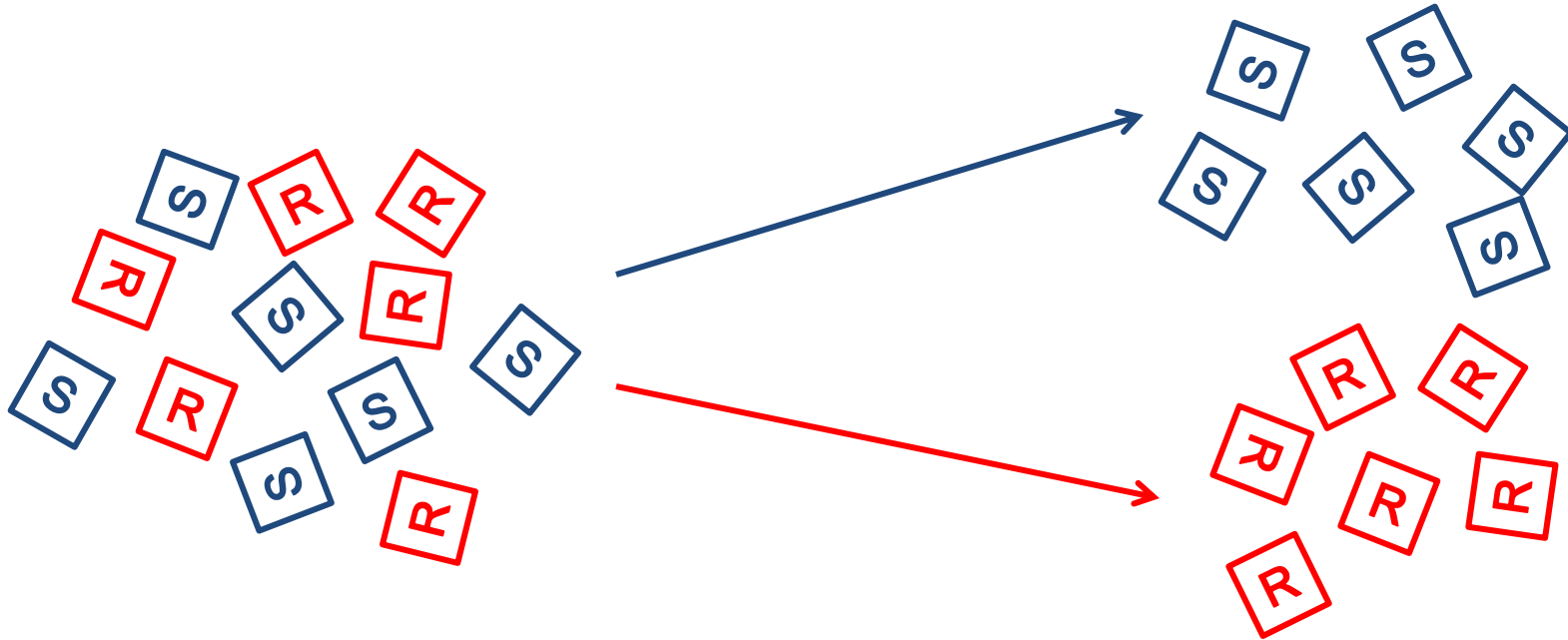
- 3) **Inversion twin** : twinned crystals of both enantiomers
Chiral space group



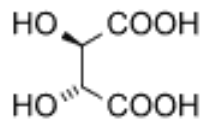
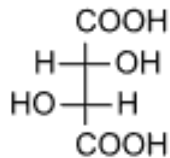
- 4) **Disordered solid-solution**: Crystal containing the two enantiomers in a disordered arrangement.
Usually centrosymmetric
space group



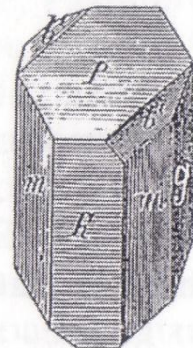
- Louis Pasteur Experiment (1848): Separation of the two enantiomers by the visual sorting of crystals of a conglomerate



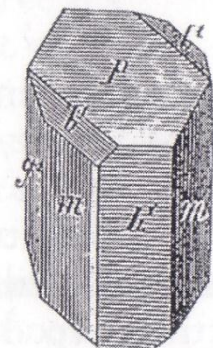
D-(-) levotartaric acid



L-(+) dextrotartaric acid

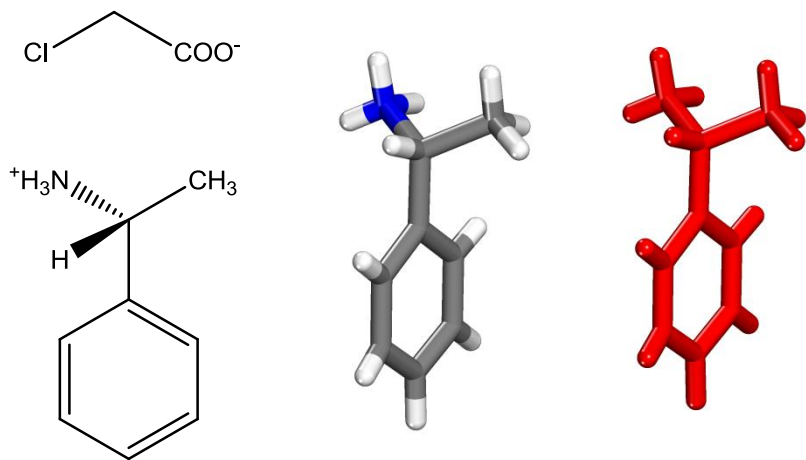


(Droit.)

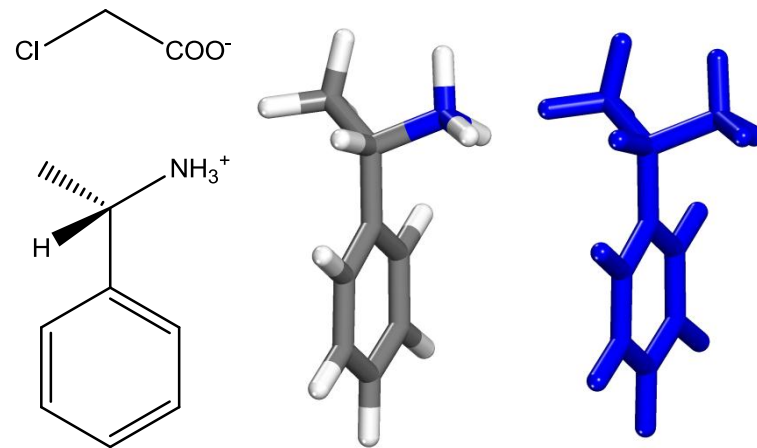


(Gauche.)

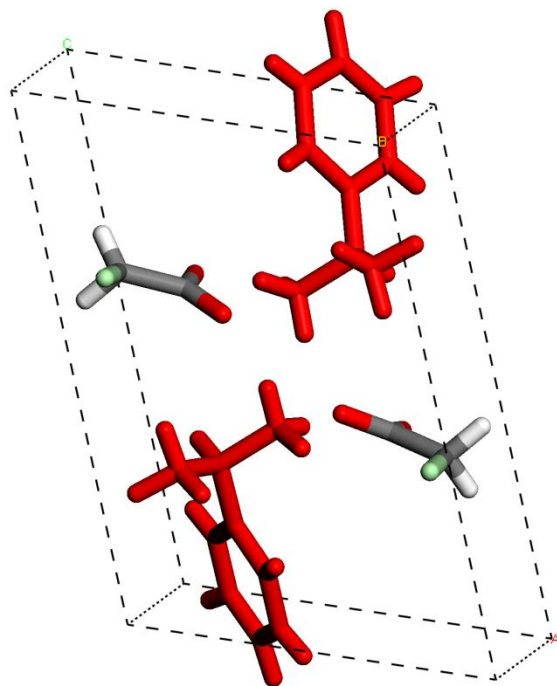
Sodium ammonium tartrate crystals



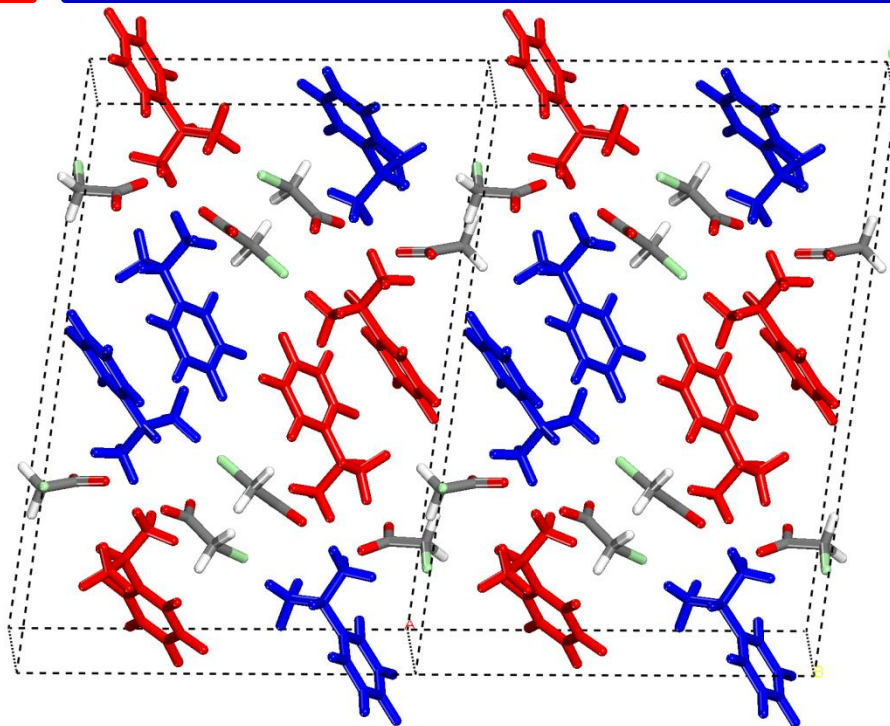
(R)-1-phenylethylamine



(S)-1-phenylethylamine

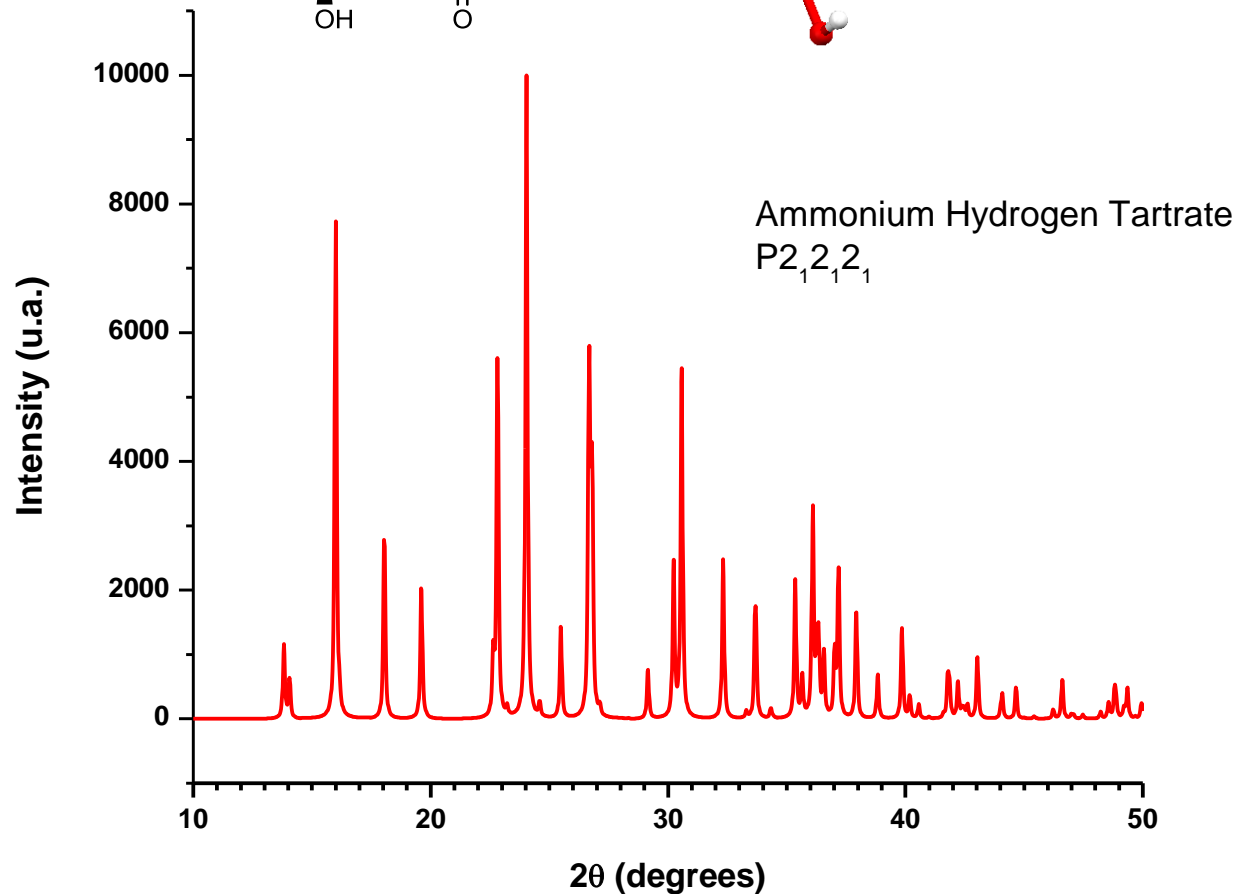
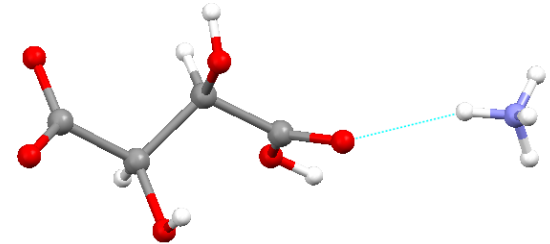
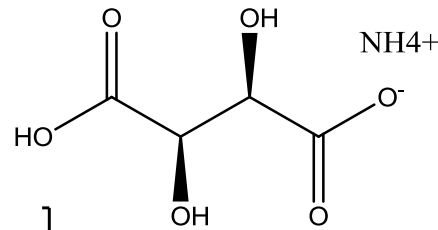
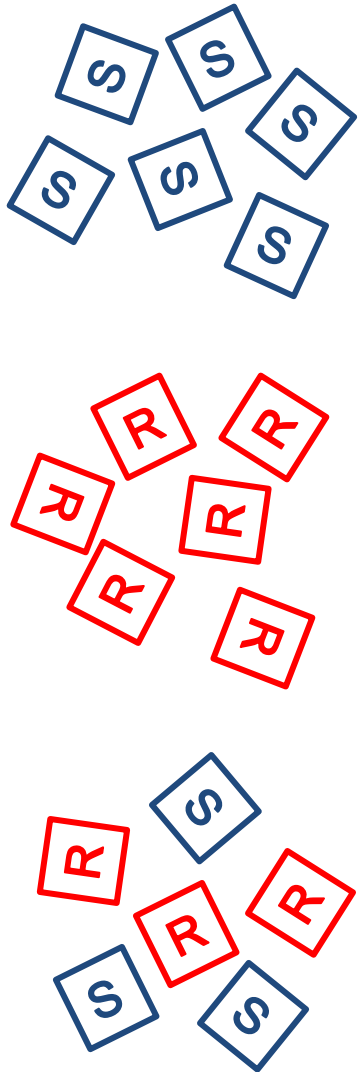


$P2_1$



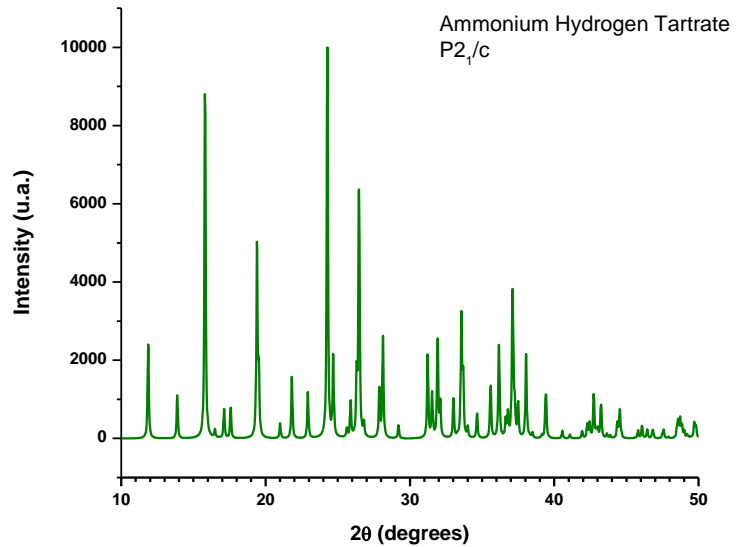
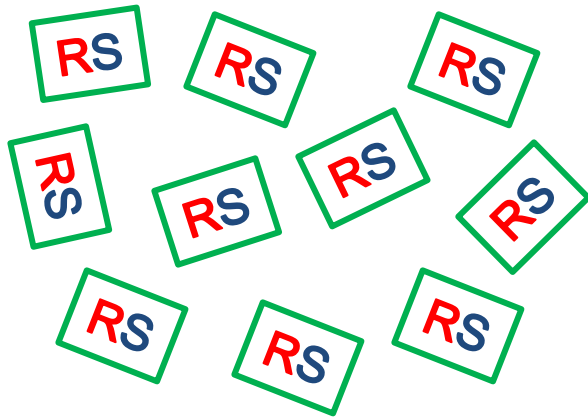
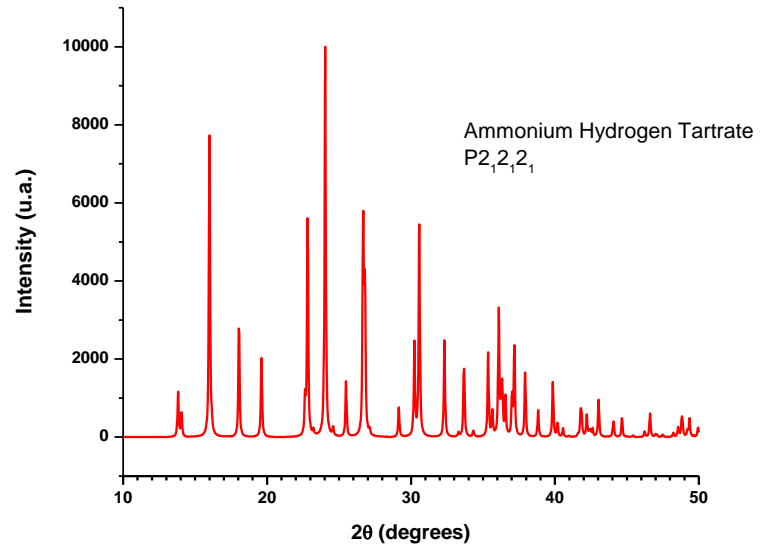
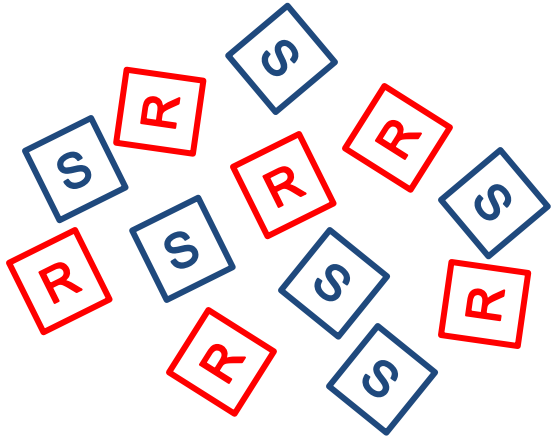
$P2_1/c$

Powder diffraction



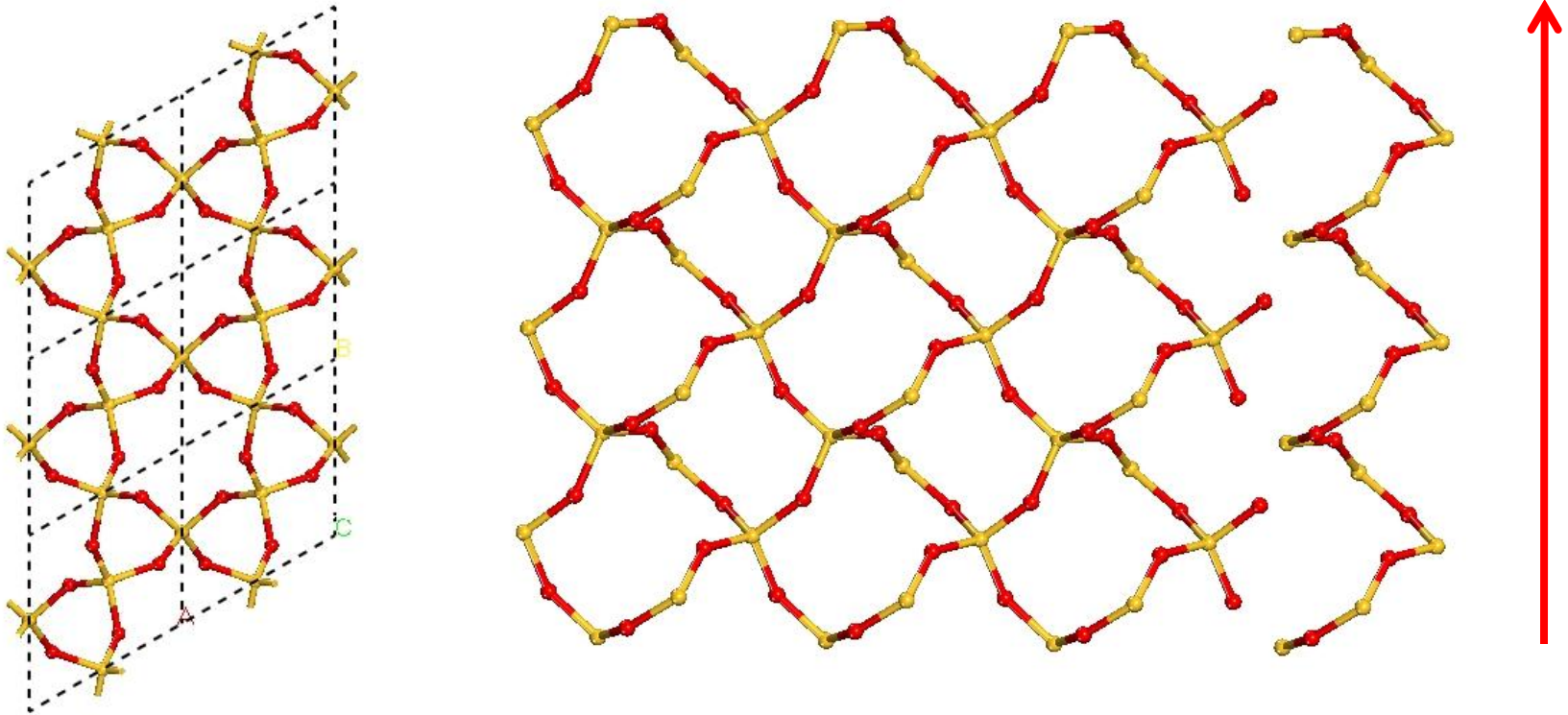
The two enantiopure samples and the conglomerate give the same powder X-ray diffraction pattern

Powder diffraction



Polar structures

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



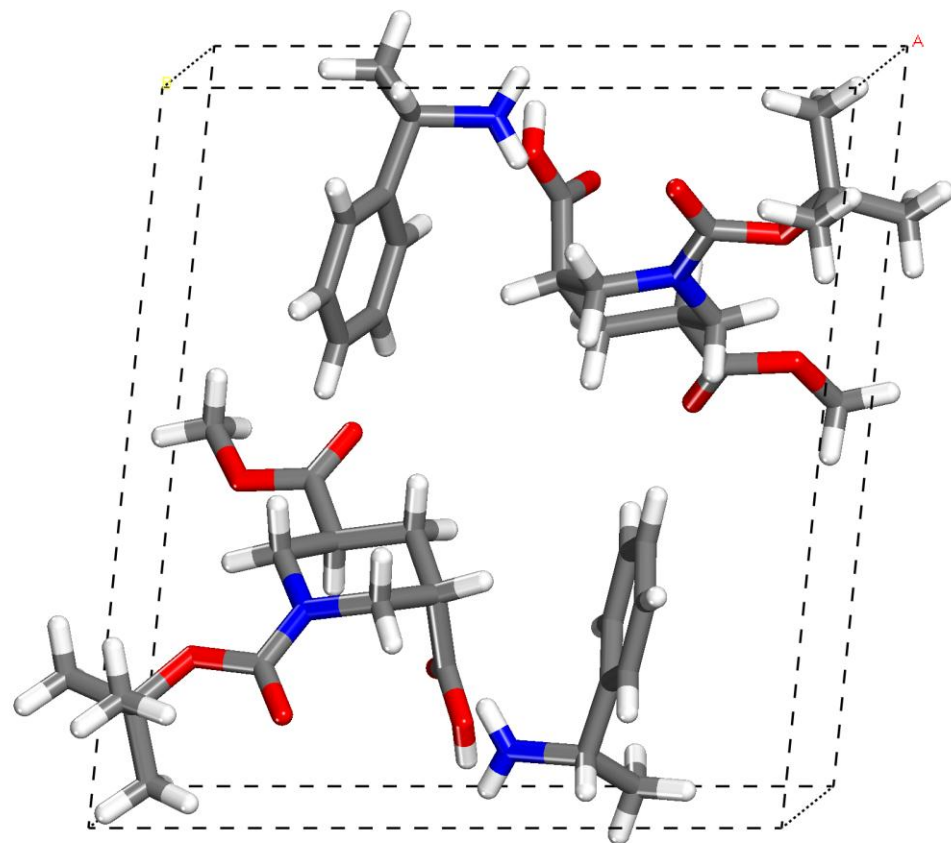
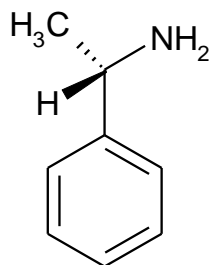
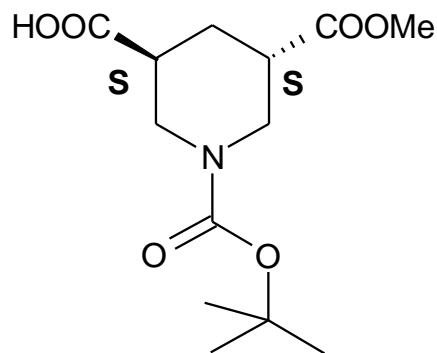
Helical arrangement of SiO_4 tetrahedra in α -quartz ($P3_121$)

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.*,
Tetrahedron Asymmetry 14 (2003) 1541-1545

Absolute configuration from Absolute Structure

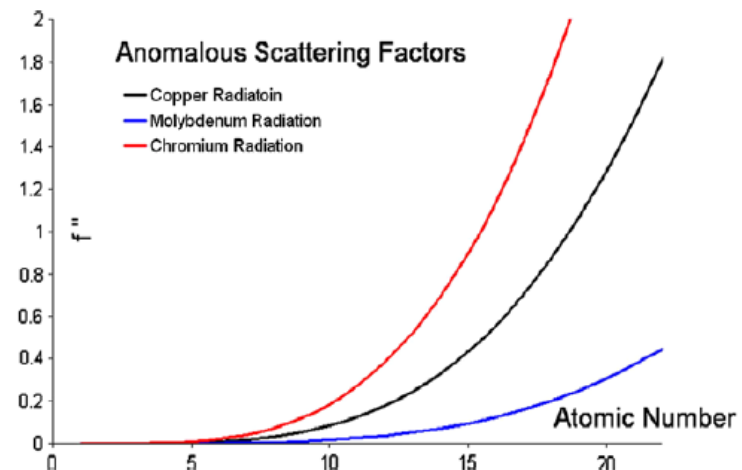
- Method based on the *anomalous scattering*
- Friedel's Law is not respected:

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

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

MoK α : element > P (15)

CuK α : element > O (8)



Absolute Configuration from Absolute Structure

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

Calculated pairs of reflections hkl vs $\bar{h}\bar{k}\bar{l}$
(Friedel /Bijvoet Pairs) can be examined

Refinement of the Flack Parameter x

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

$$0 \leq x \leq 1$$

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

rms sigma	0.000	0.000	0.000	0.020	0.000	0.000	0.000	0.000	0.000	0.000	0.000
rms deviation	0.000	0.000	0.000	0.010	0.000	0.000	0.000	0.000	0.000	0.000	0.000

GooF = S = 1.028; Restrained GooF = 1.020 for 21 restraints

Weight = 1 / [sigma^2(Fo^2) + (0.0337 * P)^2 + 0.22 * P] where P = (Max (Fo^2, 0) + 2 * Fc^2) / 3

R1 = 0.0268 for 1243 Fo > 4sig(Fo) and 0.0268 for all 1245 data

wR2 = 0.0688, GooF = S = 1.028, Restrained GooF = 1.020 for all data

Flack x parameter = 0.0683 with esd 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

0.0282	0.0247	0.0195	C1
0.0299	0.0266	0.0193	C2

Refinement in Shelx

L.S. 4

BOND \$H

TWIN

BASF 0.1

FMAP 2

PLAN 5

ACTA

WGHT 0.033700 0.22360

FVAR 0.63488

MOLE 1

C1	1	0.520368	0.124011	0.630898	11.00000	0.01969	0.02799 =
		0.02473	-0.00013	0.00023	-0.00137		

C2	1	0.331654	0.188750	0.637001	11.00000	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

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	11.00000	0.01969	0.02799 =
		0.02473	-0.00013	0.00023	-0.00137		

C2	1	0.331654	0.188750	0.637001	11.00000	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=1/[\s^2^(Fo^2^)+(0.0337P)^2^+0.2236P] where P=(Fo^2^+2Fc^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 rmad
_refine_ls_abs_structure_Flack   0.1(2)
_refine_ls_number_reflns        1245
_refine_ls_number_parameters    120
_refine_ls_number_restraints    21
_refine_ls_R_factor_all         0.0268
_refine_ls_R_factor_gt          0.0268
_refine_ls_wR_factor_ref        0.0688
_refine_ls_wR_factor_gt         0.0688
_refine_ls_goodness_of_fit_ref  1.028
_refine_ls_restrained_S_all     1.021
_refine_ls_shift/su_max         0.000
_refine_ls_shift/su_mean        0.000

loop_
  _atom_site_label
```

Hooft parameter

Hooft R. B. W., Straver L. H., Spek A. L. Determination of absolute structure using Bayesian statistics on Bijvoet differences. *J. Applied Cryst.* (2008) 41, 96-103.

- 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

P.L.A.T.O.N

PLATON

A Multipurpose Crystallographic Tool
 (C) 1980-2010 A.L.Spek - 40M-Version: 310310

GRAPHICS	GEOM-CALC	VOIDS FLIP	SYMMETRY	ABSORPTION	REPORT	MISC-TOOLS
PLUTONauto	Calc ALL	Calc Solv	ADDSYM	MULscanABS	Validation	SYSTEM-S
ORTEP/ADP	Calc Intra	Calc K.P.I	ADDSYM-EQL	ABSPslScan	ASYM-VIEW	FCF2HKL
NewmanPlot	Calc Inter	SQUEEZE	ADDSYM-EXT	ABSTempa	FCF-Valid	Expand2P1
Ring-Plots	Calc Coord	CALC-FCF	ADDSYM-PLT	ABSGauss	Diffraction	FCF-Gener
Plane-Plot	Calc Metal	Contour-SQ	ADDSYM-SHX	ABSXtal	ANALSVAR	HKL-Gener
Polyhedra	Calc Geom	SOLV F3D	NEWSYM	ABSSphere	ByvoetPatr	HKL-Transf
ContourDiff	Calc Hbond	SOLV PLOT	NONSYM	SHXABS	ASYM-EXPECT	EXOR-RES
Contour-Fo	Calc TMA	CavityPlot	LePage		ASYM-Valid	ANIS-RES
AutoMolFit	L.S.-PLANE		DelRed		SupplMater	Rename-RES
HKL2Powder	DihedAngle		MOLSYM		EXPECT-HKL	Auto-Renum
SlmPowderP	AngleLines	FLIP MENU	SPGRfromEX		CSD-CELL	SPF -eld
RadDistFun	AngleSplLn	FLIP SHOW	ASYM		CSD-QUEST	SHELXL-res
Patterson	CremerPopl	FLIP PATT	ASYMaverFR		StructTidy	CIF -acc
	BondValenc	FLIPPER 25	LePageTwln		StrainAnal	PDB -pdb
PLUTONatlv	HFIX - RES	STRUCTURE?	TwlnRotMat	Xtal Hablt	LocCIF-acc	CIF2SHELXL

Xtal Data (CIF) tartar.cif- Set 1(): tartar
 Refl Data (SHELXL) tartar.fcf [NO-DIAC] (): tartar
 No check.def file found for CIF-Validation

Browser - HELP

INPUT INSTRUCTIONS via KEYBOARD or LEFT-MOUSE-CLICKS (HELP with RIGHT CLICKS)

>>

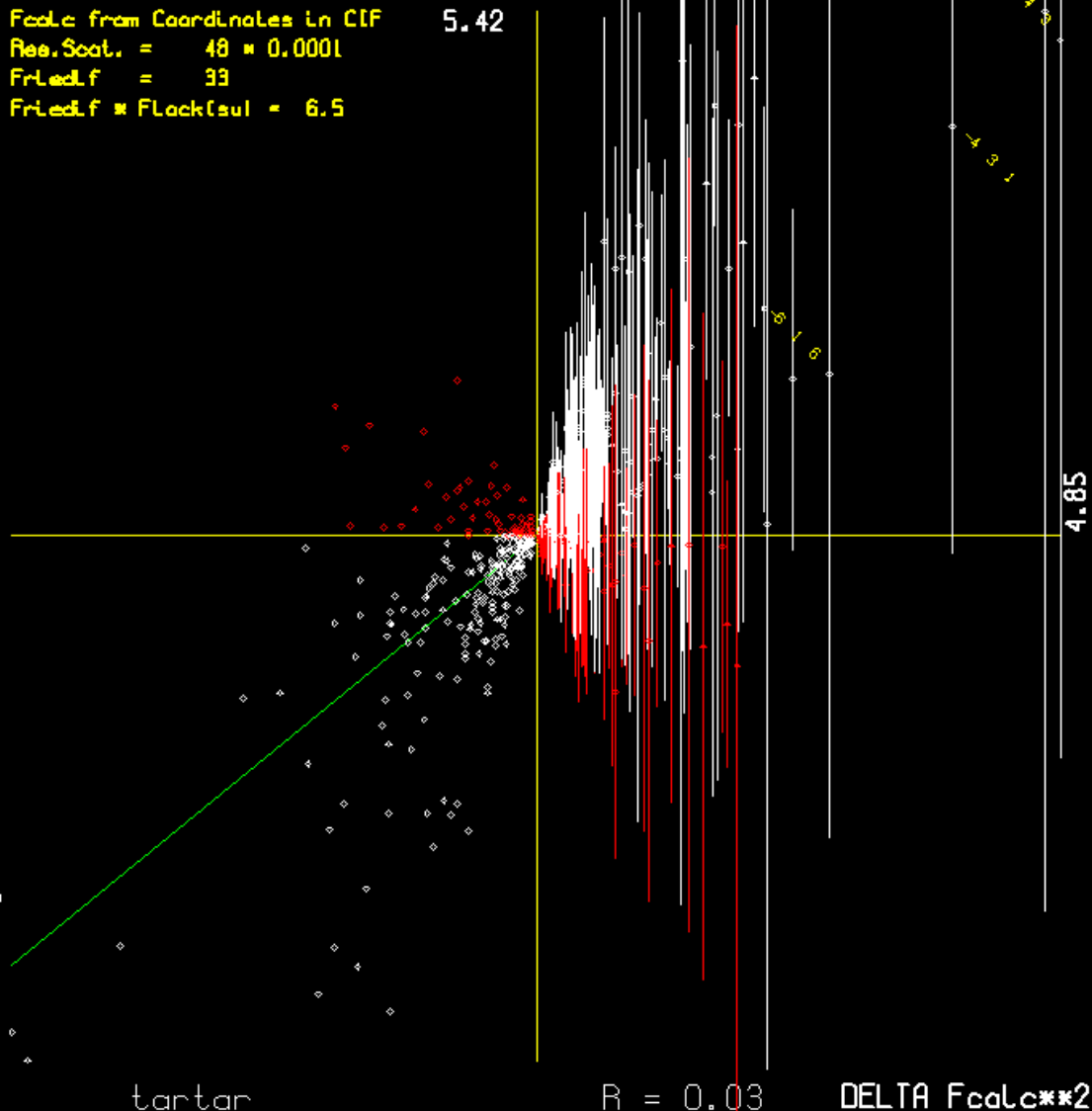
PLATON MENU

- OptionMenus
- NoMove
- Join-Expand
- Organic
- Round
- Parentheses
- Label-Atias
- R/S-Determ
- Norm-H-bond
- NoSymm
- NoDisorder
- LstARU RCel
- LstCellSymm
- ListAtoms
- ListBonds
- LstFlagRadi
- Exclude H
- MinQPeakHgt
- MinQPeakDis
- Q-Peak-Incl
- KeyInstruct
- Prev Next
- SAVE-InstrS
- ENTRY-LIST
- Reset End
- Exit
- MenuActive

BIJVOET-PAIR SCATTER PLOT

PLATON-May 22 07:59:48 2010 - (310310) DELTA Fcalc**2

Fcalc from Coordinates in CIF 5.42
 Res.Scot. = 48 * 0.0001
 Friedlf = 33
 Friedlf * Flack(su) = 6.5



Space Group	P212121	BIJVOETMENU
Wavelength	1.54178	alFromFCF
Flack x	0.1	inclWghtPar
Flack (su)	0.2	
BIJVOET PAIRS	497	
Coverage	99	
DLffCalcMax.	4.95	
Outlier Crit	9.91	OutlierCrit
Scatter Plot		
Sigma Crit.	0.25	SigmaCriter
Select Pairs	260	
Number Plus	203	
Number Minus	57	
Aver. Ratio	0.907	
RC	0.914	
Normal Prob. Plot		NPP-Bijvoet
Sample Size	482	
Corr. Coeff.	0.996	ApplySlope
Intercept	-0.065	
Slope	0.676	
Bayesian Statistics		NU-Value
Type	Gaussian	Gaussian
Select Pairs	482	
P2(true)	1.000	
P3(true)	1.000	
P3(rac-twin)	0.4E-33	
P3(false)	0.8-149	
G	0.9054	
G (su)	0.0726	
Hoofst y	0.05	EPS-File
Hoofst (su)	0.04	End

INPUT INSTRUCTIONS via KEYBOARD or LEFT-MOUSE-CLICKS (HELP with RIGHT CLICKS)

MenuActive

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 enantiopure i.e. contains only the enantiomer found. (eg. circular dichroism, chromatography)

Useful References:

H.D. Flack, G. Bernardinelli, Absolute structure and absolute configuration. *Acta Cryst* , (1999) A55, 908-915.

H.D. Flack, G. Bernardinelli, Reporting and evaluating absolute structure and absolute configuration determinations. *J. Applied Cryst.* (2000) 33, 1143-1148.

Thompson A. L., Watkin D. J. X-ray crystallography and chirality: understanding the limitations. *Tetrahedron: Asymmetry* (2009) 20, 712 - 719