

---

# Complementary Crystallography and X-ray Powder Diffraction Methods

Greg Stephenson  
Research Advisor  
Eli Lilly and Company  
Preformulations

The Lilly logo is written in a red, cursive script font.

Answers That Matter.

---

# Solid-State Pharmaceuticals

---

Identify a phase that is suitable for a product

“Safe and Efficacious”

Bioavailable – sufficiently soluble to achieve efficacy

Physically and Chemically Stable no-phase transitions  
and less than 2% decomposition when stored for 2  
years with 5 to 10 other excipients and exposed to  
20-75%RH

Crystalline, Soluble, Non-solvated, filters well, non-  
hygroscopic, is flowable.....is that all?.....um...with just 2g of  
material in less than 30 days?

# Non-discrete phases (continuous)

---

In that quest – we find many phases that are not discrete

Iso-structural Solvates: drug packs in the same arrangement in the crystal lattice with many different solvents

(or Iso-structural desolvates or “variable hydrates”)

Less commonly Iso-structural Salts

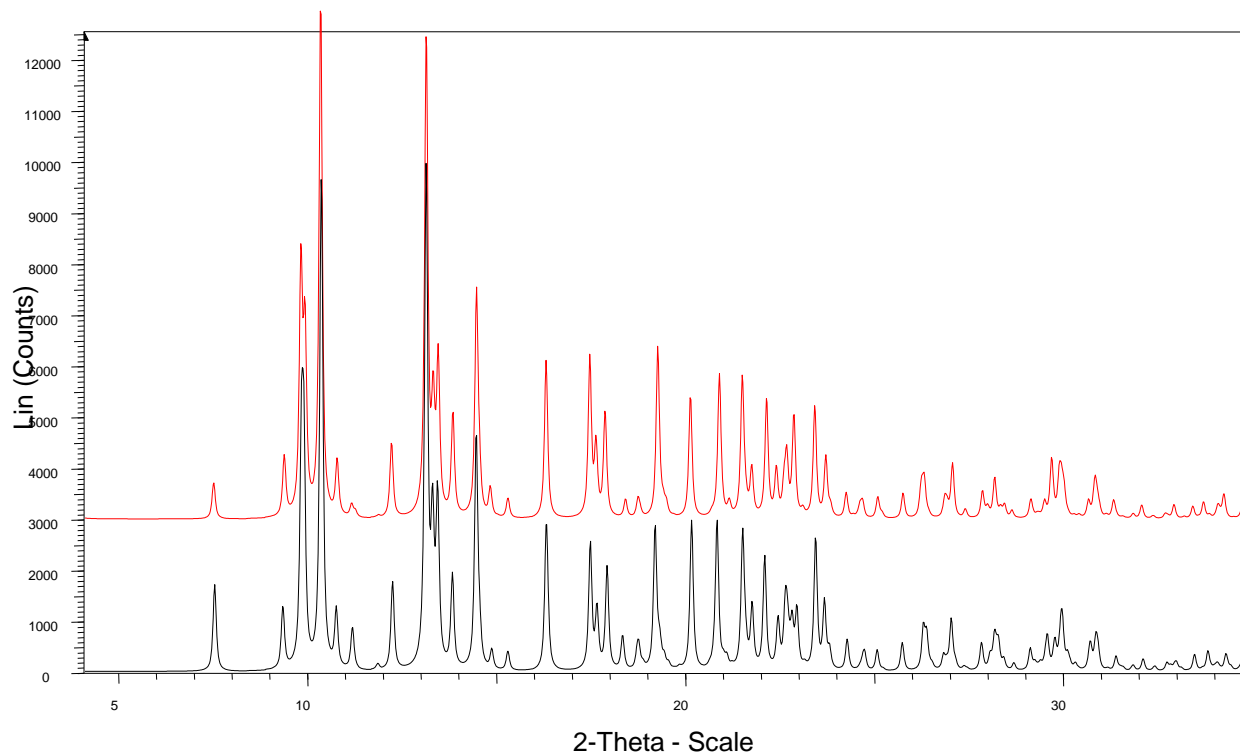
and Solid-Solutions

Also talk about:

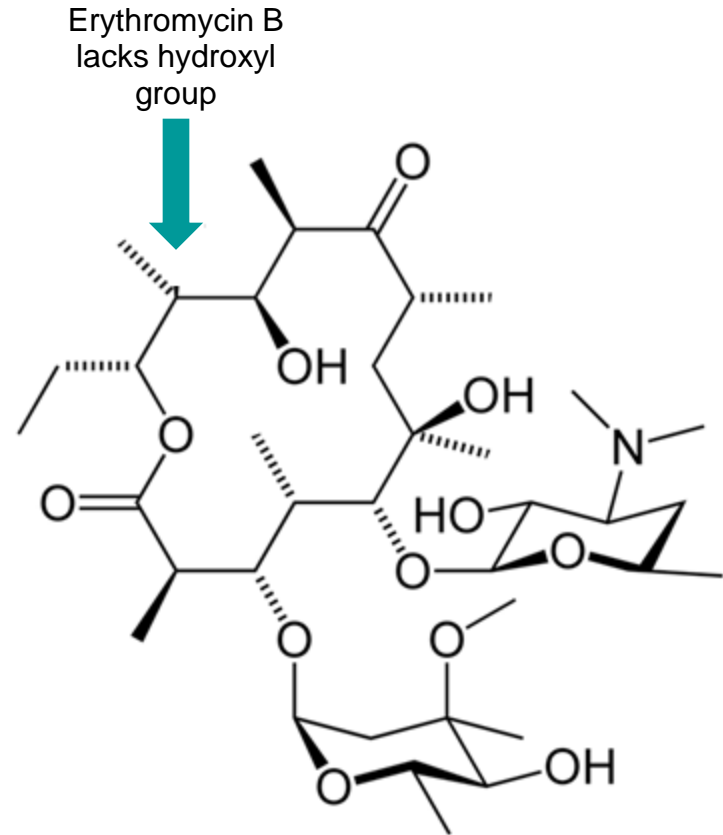
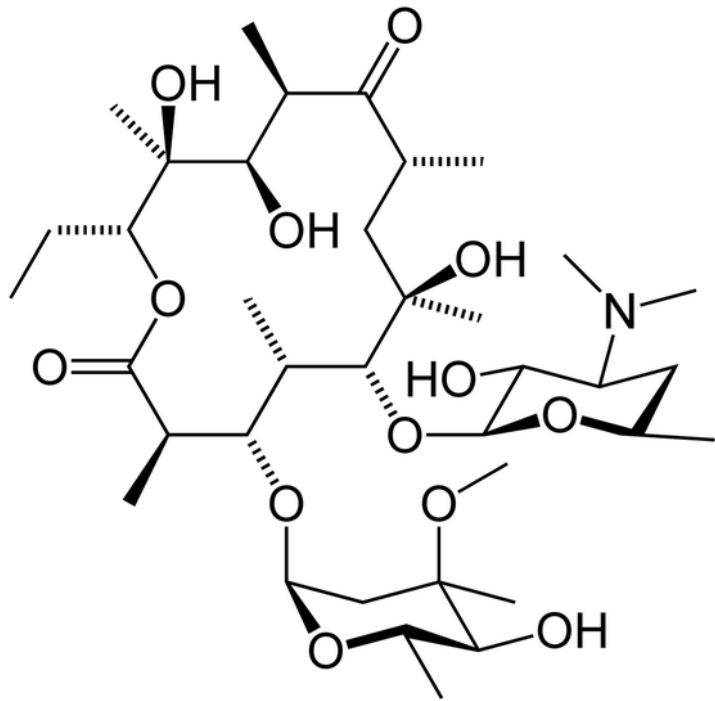
Discuss a couple of Discrete Phases, one quite interesting

End with a Structure solution from Powder Diffraction

# Erythromycin Dihydrate: Same or Different Form Based on X-ray Powder Diffraction?



# Molecular Structures of Erythromycin A and Erythromycin B



# Erythromycin A and Erythromycin B Dihydrate Crystal Forms



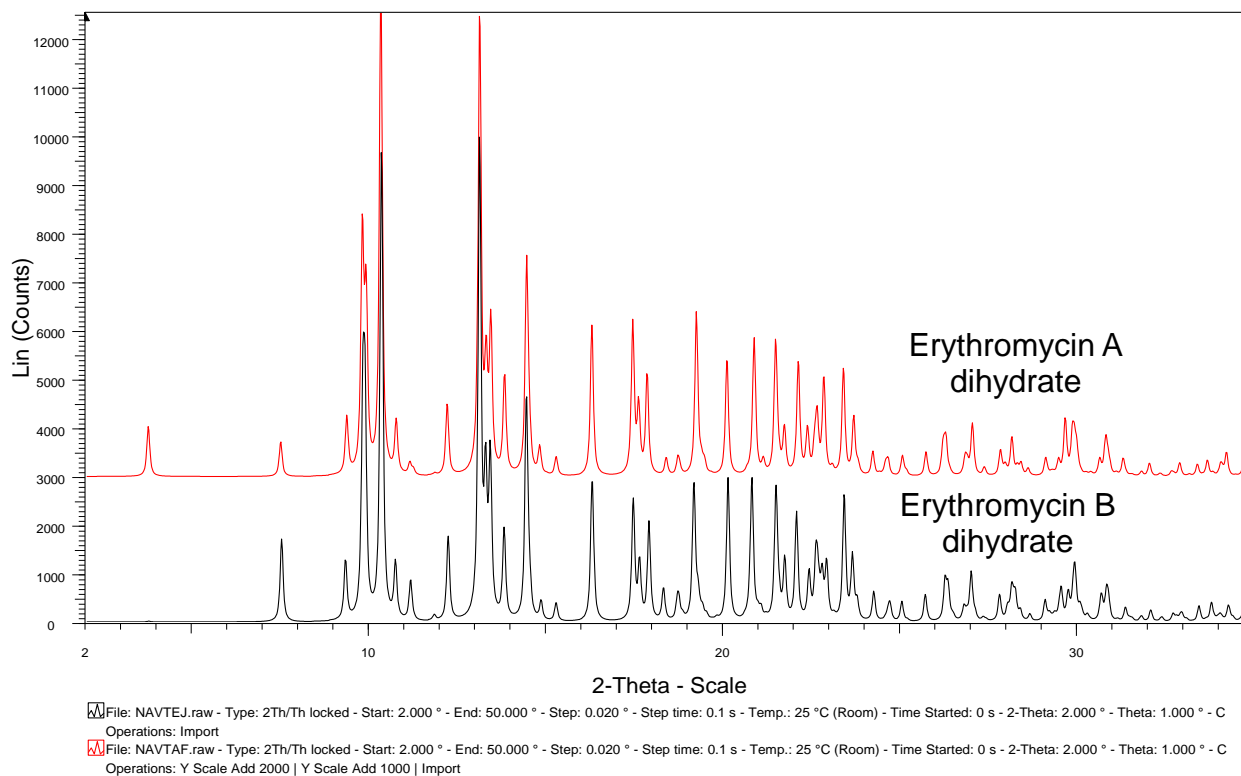
Isostructural Dihydrates

Erythromycin A dihydrate  
Orthorhombic, S.G. P 2<sub>1</sub> 2<sub>1</sub> 2<sub>1</sub>  
a = 9.1829(8) Å  
b = 9.6316(7) Å  
c = 47.151(13) Å

Erythromycin B dihydrate  
Orthorhombic, S.G. P 2<sub>1</sub> 2<sub>1</sub> 2<sub>1</sub>  
a = 9.170(1) Å  
b = 9.672(1) Å  
c = 46.985(1) Å

G.A.Stephenson, J.G.Stowell, P.H.Toma, R.R.Pfeiffer, S.R.Byrn  
J.Pharm.Sci. (1997), 86, 1239. CCDC Ref Code NAVTAF and NAVTEJ

# Erythromycin A dihydrate versus Erythromycin B dihydrate



# Different

---

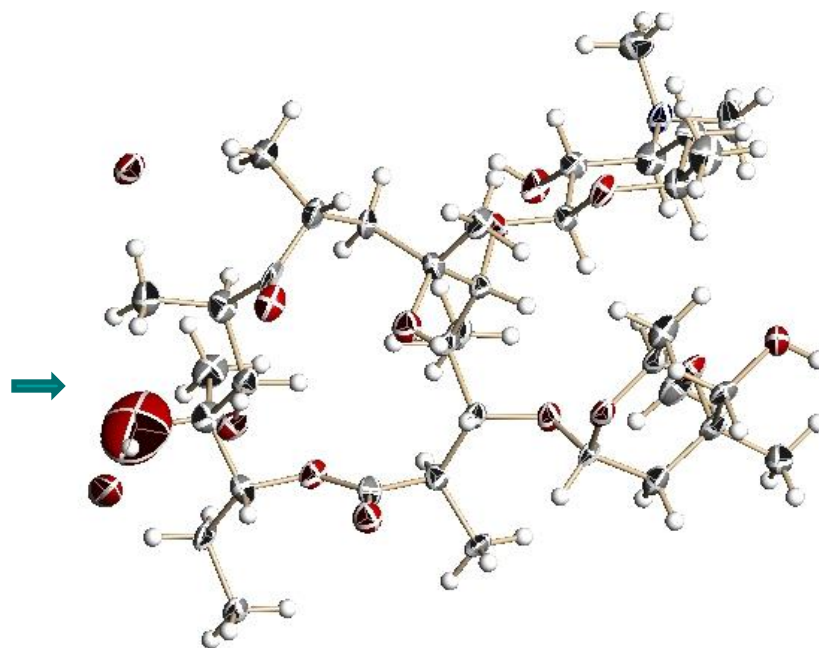
Unit cell metrics nearly identical

Unit cell contents nearly identical

Molecular Packing nearly identical



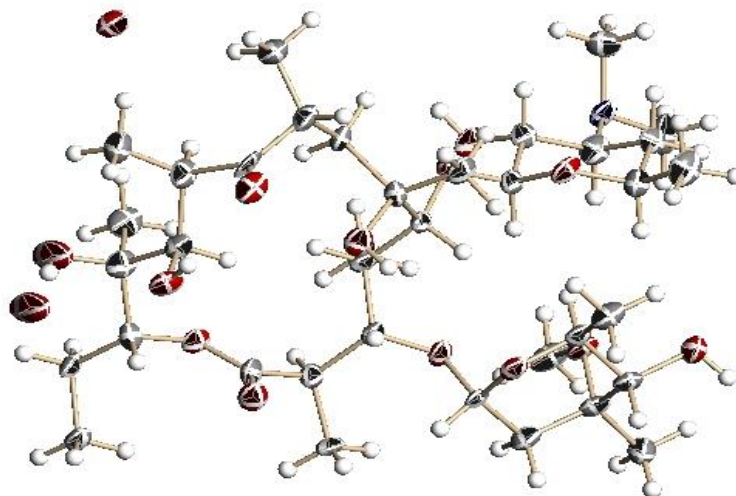
# Much information in a Thermal Ellipsoid diagram



Something Wrong with  
Hydroxyl group during  
refinement

# Refine Hydroxyl Group Site Occupancy

This is actually a solid solution formed upon crystallization of the two molecule's



38% Erythromycin A, 62% Erythromycin B  
Well Behaved Structure  
(Thermal ellipsoid plot)

All atoms have similar thermal parameters  
other than where expected

# Solid-Solution Formation, Reasonably Common with Related Substances or Natural Products

---

Solid-Solutions are reasonably common, however are often overlooked

Commonly found in crystallization processes

- That related substance that you just can't seem to reject

Need to find conditions that result in phase separation

- Screen for a solvent that results in different crystal forms for the two different substances, those conditions should afford separation

# Coefficient of Isomorphism<sup>1</sup>

---

Kitaigorodskii defines a coefficient of isosterism - compares molecular volumes common to two molecules that are arranged in such a fashion as to maximize the superposition of constituent groups

$$\epsilon = 1 - (V_{no-overlap} / V_{overlap})$$

No Solid solution is likely to form when  $\epsilon < 0.8$ , but is likely when  $\epsilon > 0.9$ <sup>2</sup>

Hence larger molecules and related substances

1. Jacques, Collet, Wilen in *Enantiomers, Racemates, and Resolutions*, Kreigers Publishing, 1991, p128
2. A.I. Kitaigorodskii, *Organic Chemical Crystallography*, Consultants Bureau, New York, 1968, p 453.

# Crystallization of Racemic Compounds

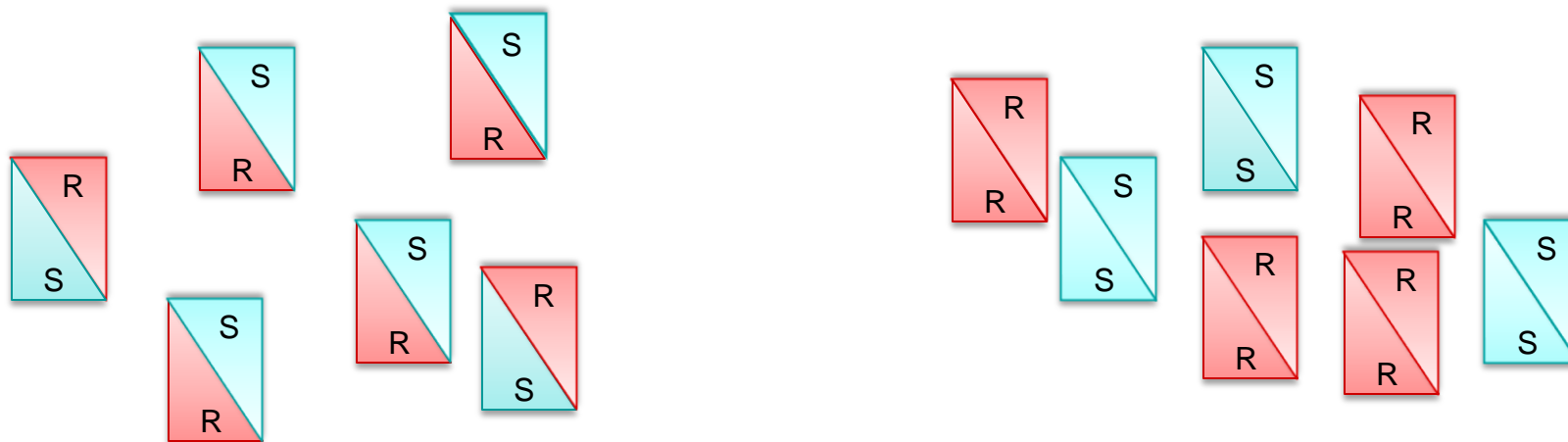
## Solution of Two Enantiomers

Wallach's Rule<sup>1</sup>  
states that racemic crystals tend  
to be denser than their chiral  
counterparts

~90% of the time

~10% of the Time

Wallach, O. Liebigs Ann. Chem.  
1895, 286, 90-143.

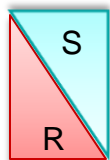


Racemic Crystals

Mixture of Chiral Crystals of Opposite  
"Handedness"  
Conglomerate Mixture

# Analytical Differentiation of Racemic Crystals versus a Conglomerate

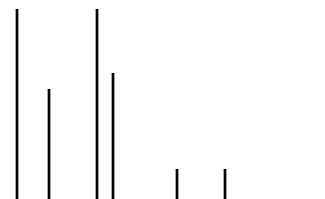
Racemic Crystals



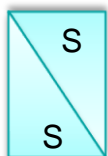
Single Crystals Method

Structure (molecular arrangement) differs from Chiral Forms

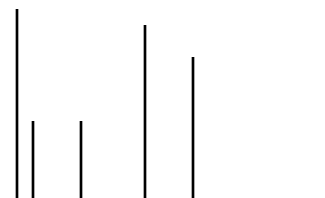
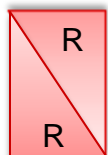
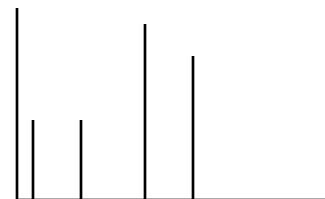
Powder Diffraction  
(ssNMR, IR, Raman, mp)



Chiral Crystals

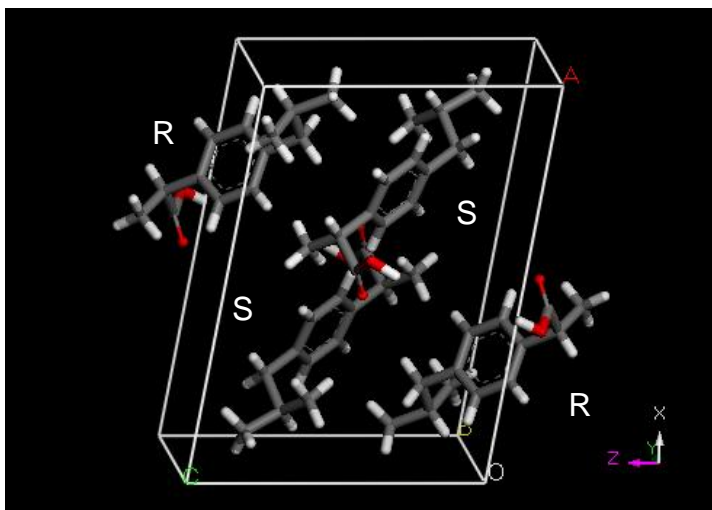


Same Crystal Packing, however Mirror Image Structures



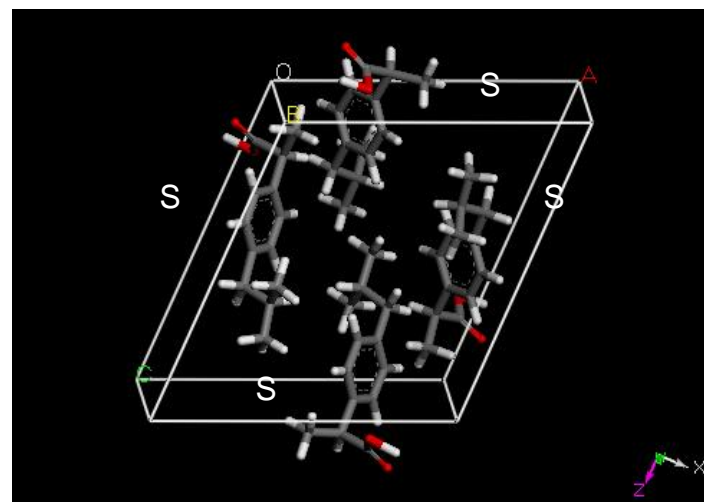
# Racemic Ibuprofen and its S Enantiomer

Monoclinic Space Group  $P2_1/c$   
 $a = 14.67 \text{ \AA}$   $b = 7.89 \text{ \AA}$   $c = 10.73 \text{ \AA}$   
Beta =  $99.43^\circ$



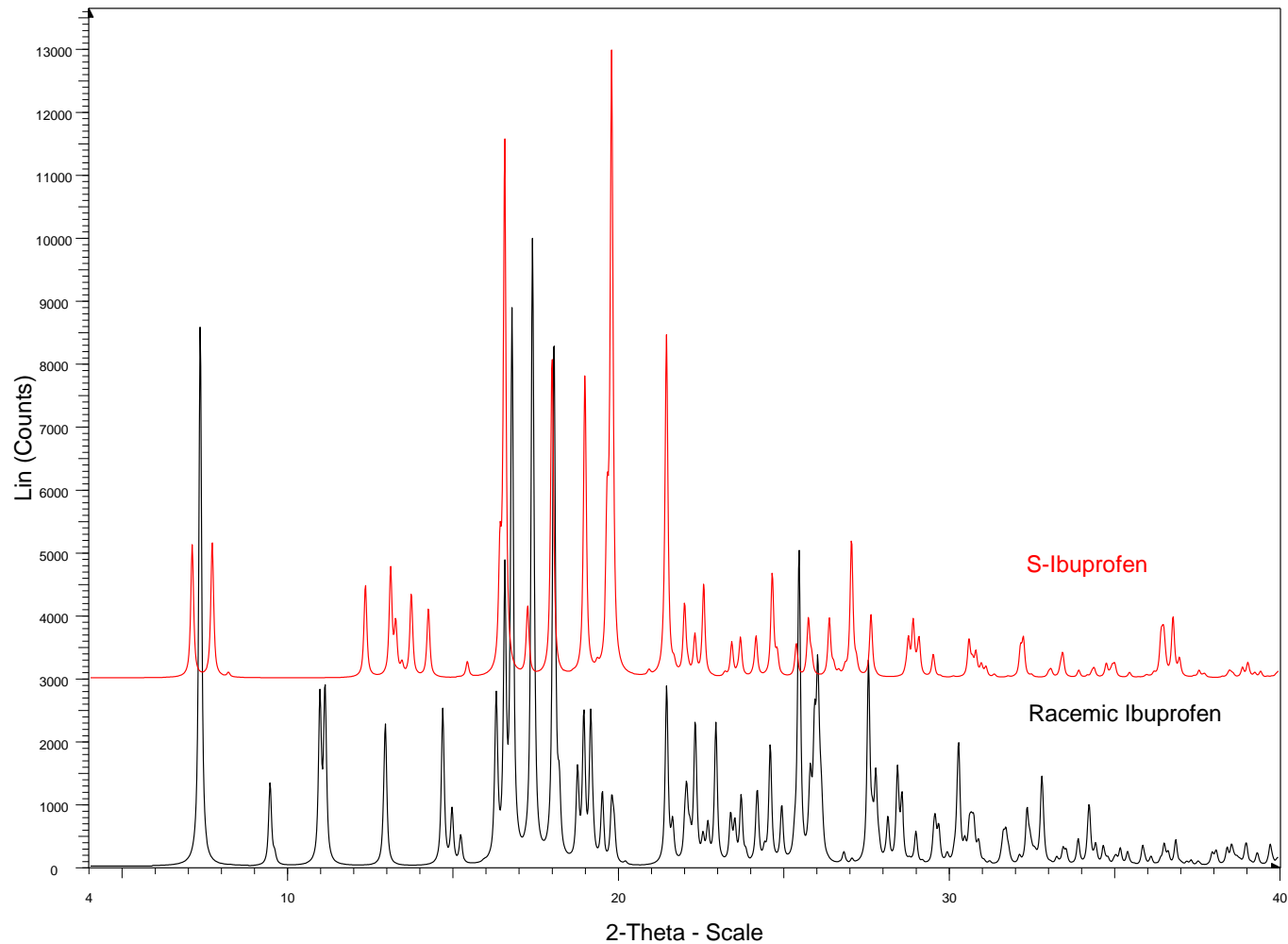
CCDC Structure COTYOA01K.H.Stone, S.Lapidus, P.W.Stephens  
J.Appl.Crystallogr. (2009), 42, 385

Monoclinic Space Group  $P2_1$   
 $a = 12.46 \text{ \AA}$   $b = 8.08 \text{ \AA}$   $c = 13.54 \text{ \AA}$   
Beta =  $112.89^\circ$



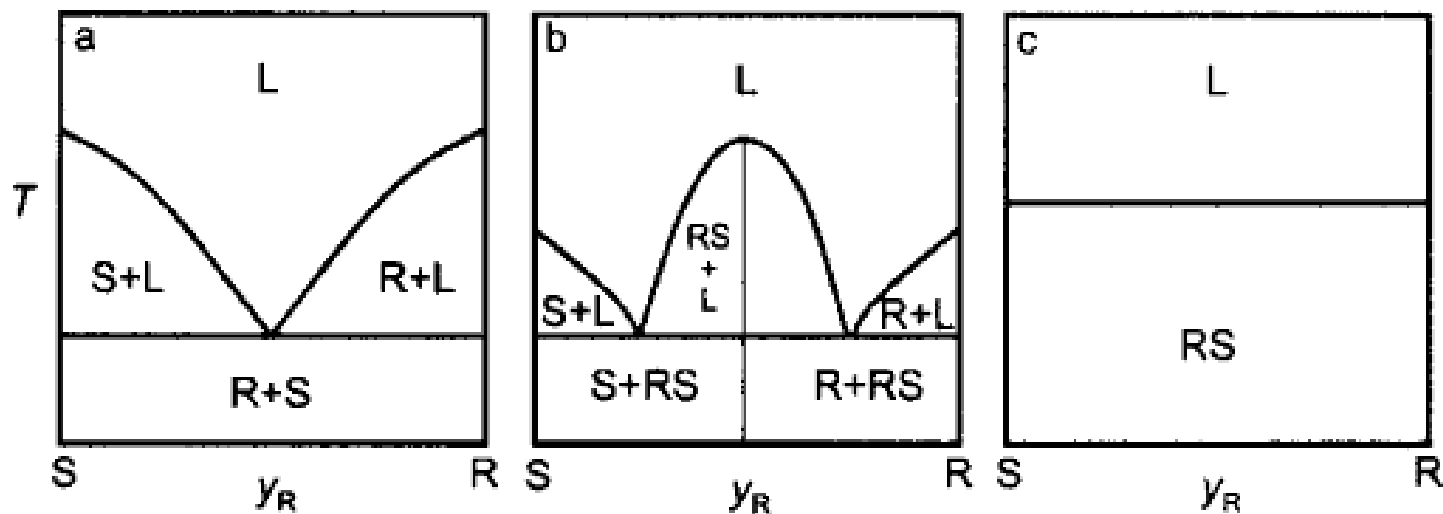
CCDC Structure JEKNOC10  
A.A.Freer, J.M.Bunyan, N.Shankland, D.B.Sheen Acta  
Crystallogr.,Sect.C:Cryst.Struct.Commun. (1993), 49, 1378

# Racemic Crystal Versus Enantiomer





# Phase Diagram of Solid Solution

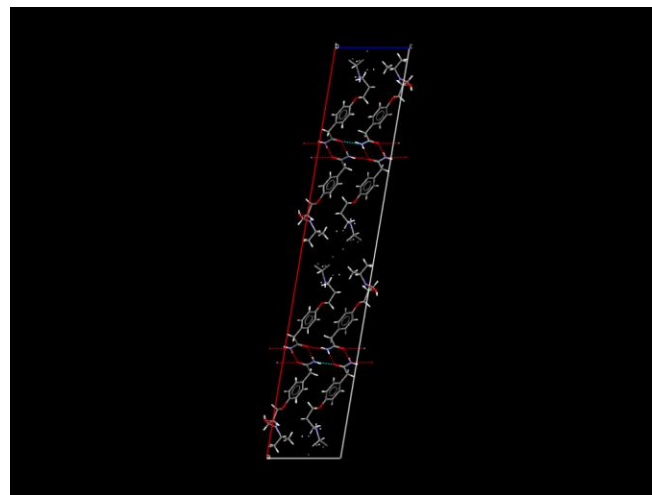
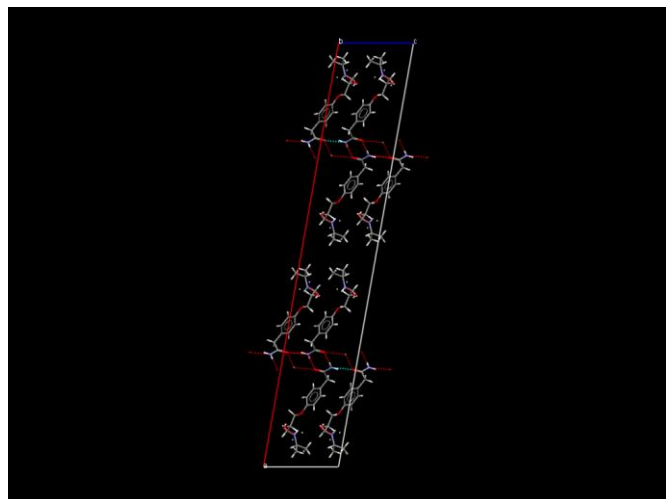


**Figure 1.** Binary phase diagram of enantiomer mixtures forming (a) a conglomerate, (b) a racemic compound, and (c) a solid solution.<sup>2</sup> *R*, *S*, *RS*, and *L* represent respectively solid *R*-enantiomer phase, solid *S*-enantiomer phase, racemic compound *RS*, or solid solution *RS* and liquid phase.

2. Jacques, Collet, Wilen in *Enantiomers, Racemates, and Resolutions*, Kreiglers Publishing, 1991

# Atenolol

## Racemate versus Enantiomer



R.A.E.de Castro, J.Canotilho, R.M.Barbosa, M.R.Silva, A.M.Beja,  
J.A.Paixao, J.S.Redinha Cryst.Growth Des. (2007), 7, 496

(RS)-Atenolol

C 2/c

$a = 55.83(3)\text{\AA}$   $b = 5.559(3)\text{\AA}$   $c = 9.734(2)\text{\AA}$

$\alpha = 90^\circ$   $\beta = 100.042(6)^\circ$   $\gamma = 90^\circ$

Volume =  $2974.75\text{\AA}^3/\text{cm}^3$

Z: 8 Z': 1

(S)-Atenolol

C 2

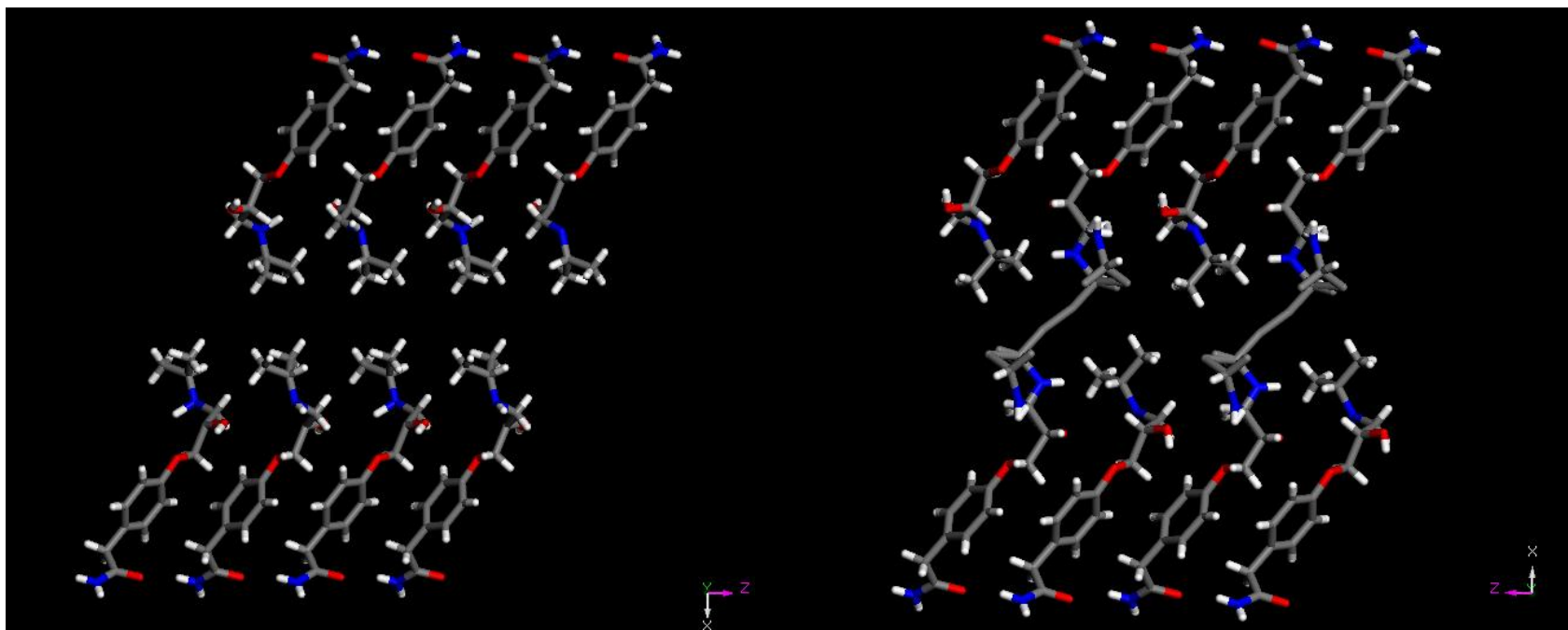
$a = 54.43(3)\text{\AA}$   $b = 5.712(3)\text{\AA}$   $c = 9.676(2)\text{\AA}$

$\alpha = 90^\circ$   $\beta = 99.510(6)^\circ$   $\gamma = 90^\circ$

Volume =  $2966.96\text{\AA}^3/\text{cm}^3$

Z: 8 Z': 2

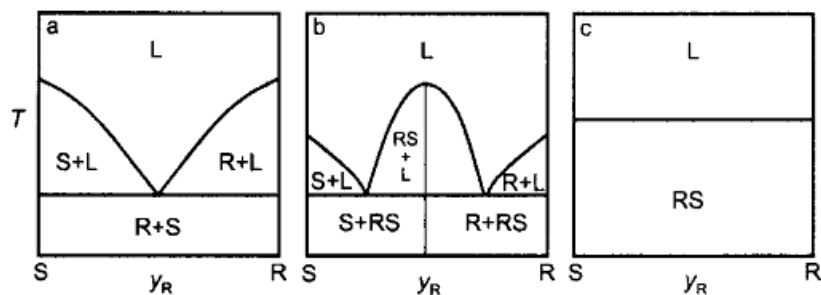
# Chiral Structure Disordered “Pseudo-Symmetry”



(RS)-Atenolol  
C 2/c  
 $a = 55.83(3)\text{Å}$   $b = 5.559(3)\text{Å}$   $c = 9.734(2)\text{Å}$   
 $\alpha = 90^\circ$   $\beta = 100.042(6)^\circ$   $\gamma = 90^\circ$   
Volume =  $2974.75 \text{Å}^3/\text{cm}^3$   
Z: 8 Z': 1

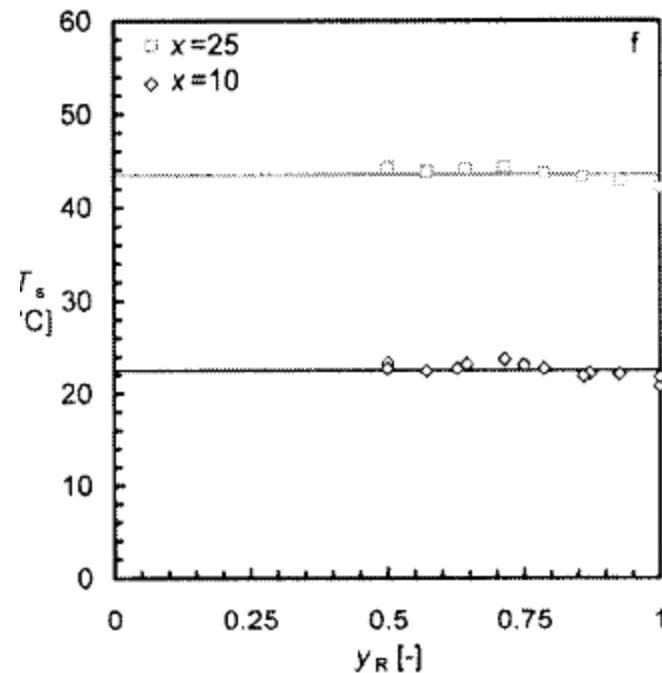
(S)-Atenolol  
C 2  
 $a = 54.43(3)\text{Å}$   $b = 5.712(3)\text{Å}$   $c = 9.676(2)\text{Å}$   
 $\alpha = 90^\circ$   $\beta = 99.510(6)^\circ$   $\gamma = 90^\circ$   
Volume =  $2966.96 \text{Å}^3/\text{cm}^3$   
Z: 8 Z': 2

# Phase Diagram of Solid Solution

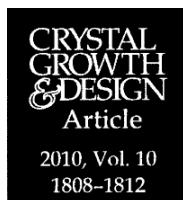


**Figure 1.** Binary phase diagram of enantiomer mixtures forming (a) a conglomerate, (b) a racemic compound, and (c) a solid solution.<sup>2</sup> *R*, *S*, *RS*, and *L* represent respectively solid *R*-enantiomer phase, solid *S*-enantiomer phase, racemic compound *RS*, or solid solution *RS* and liquid phase.

2. Jacques, Collet, Wilen in *Enantiomers, Racemates, and Resolutions*, Kreiglers Publishing, 1991, p128

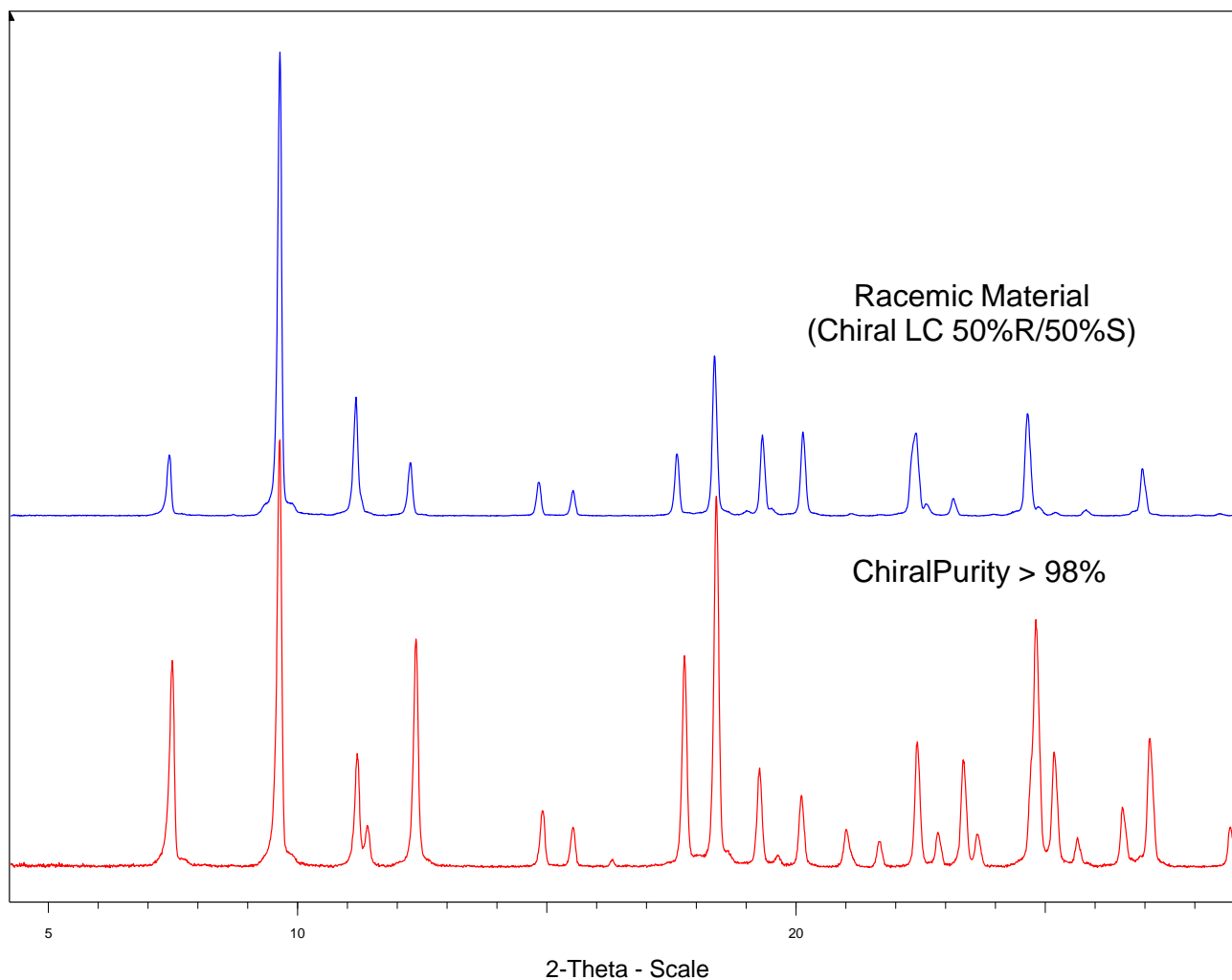


Atenolol Solid-Solution

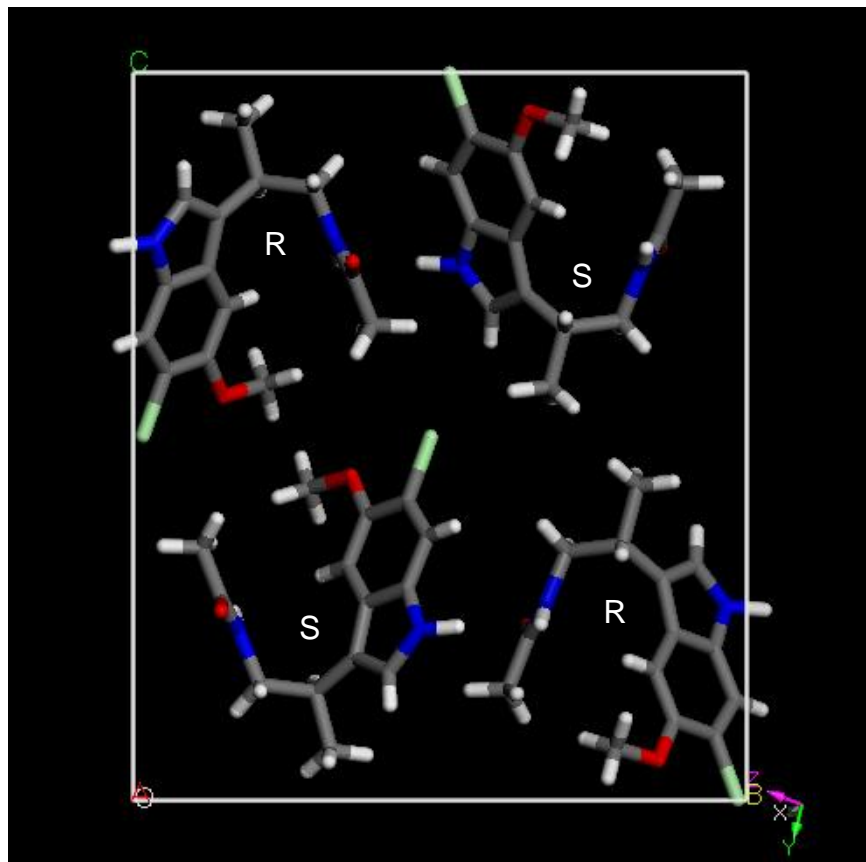


Sukanya Srisanga and Joop H. ter Horst\*

# Racemic or Conglomerate?

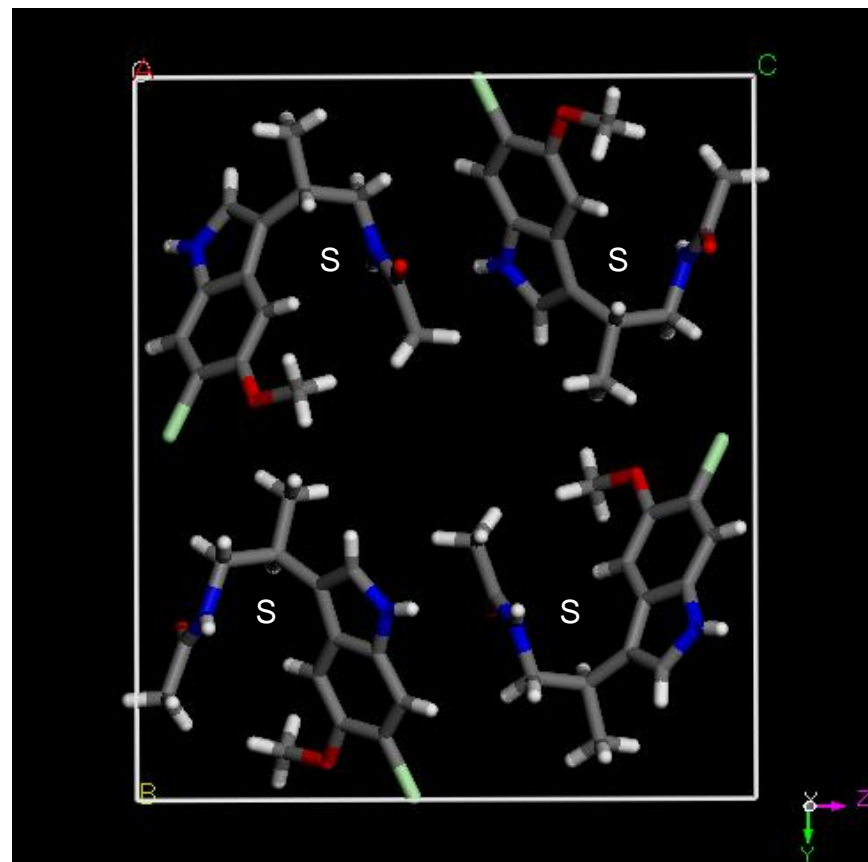


# Chiral vs Racemic Crystals: Unit Cells



Enantiomer: Orthorhombic  $P2_12_12_1$   
 $a = 4.97 \text{ \AA}$ ,  $b = 15.50 \text{ \AA}$ ,  $c = 17.96 \text{ \AA}$

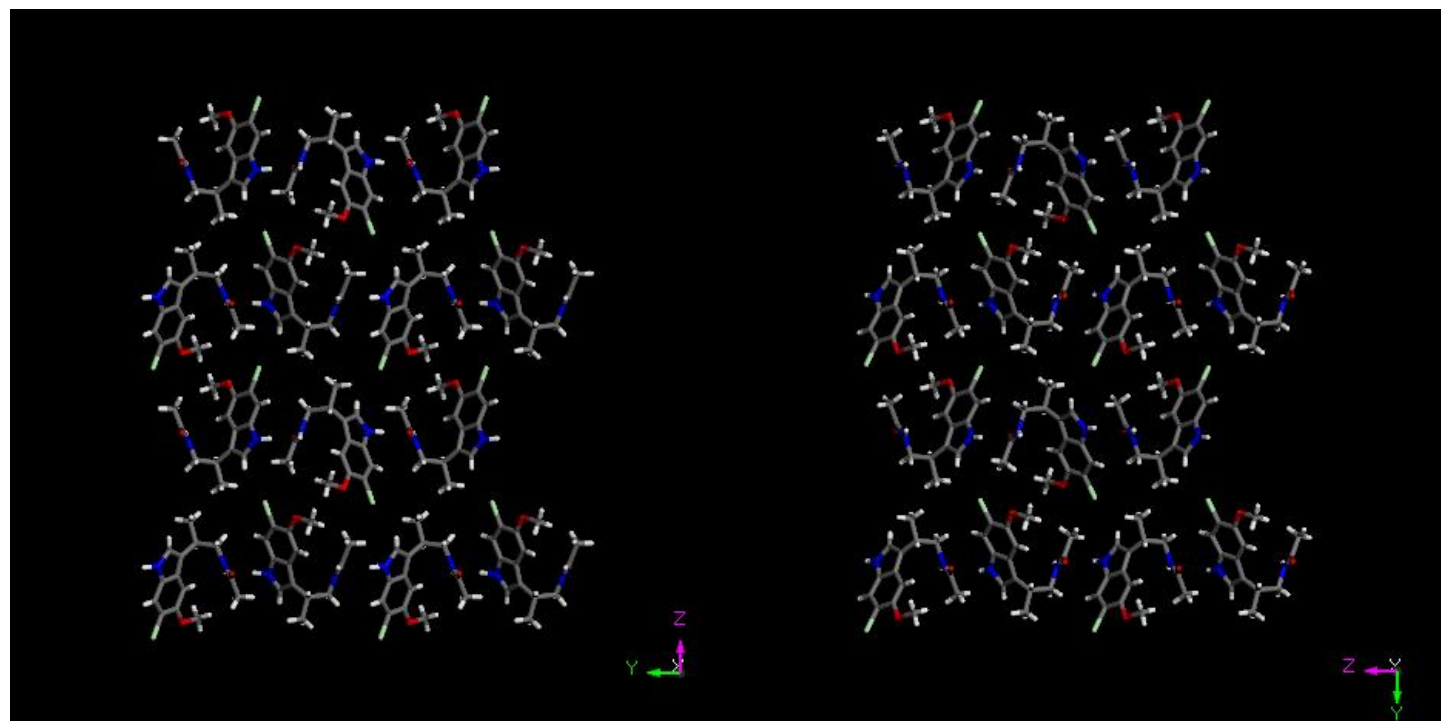
Volume =  $1383.64 \text{ \AA}^3$ ,  $Z=4$ ,  $Z'=1$ , density =  $1.348 \text{ g/cc}$   
Enthalpy of Fusion  $99.43 \text{ J/g}$ ,  $T_m 127.16^\circ\text{C}$



Racemate: Monoclinic  $P2_1/c$   
 $a = 4.94 \text{ \AA}$ ,  $b = 18.14 \text{ \AA}$ ,  $c = 15.61 \text{ \AA}$   
 $\beta = 92.951^\circ$

Volume =  $1395.90 \text{ \AA}^3$ ,  $Z = 4$ ,  $Z' = 1$ , density =  $1.336 \text{ g/cc}$   
Enthalpy of Fusion  $102.19 \text{ J/g}$ ,  $T_m 136.09^\circ\text{C}$

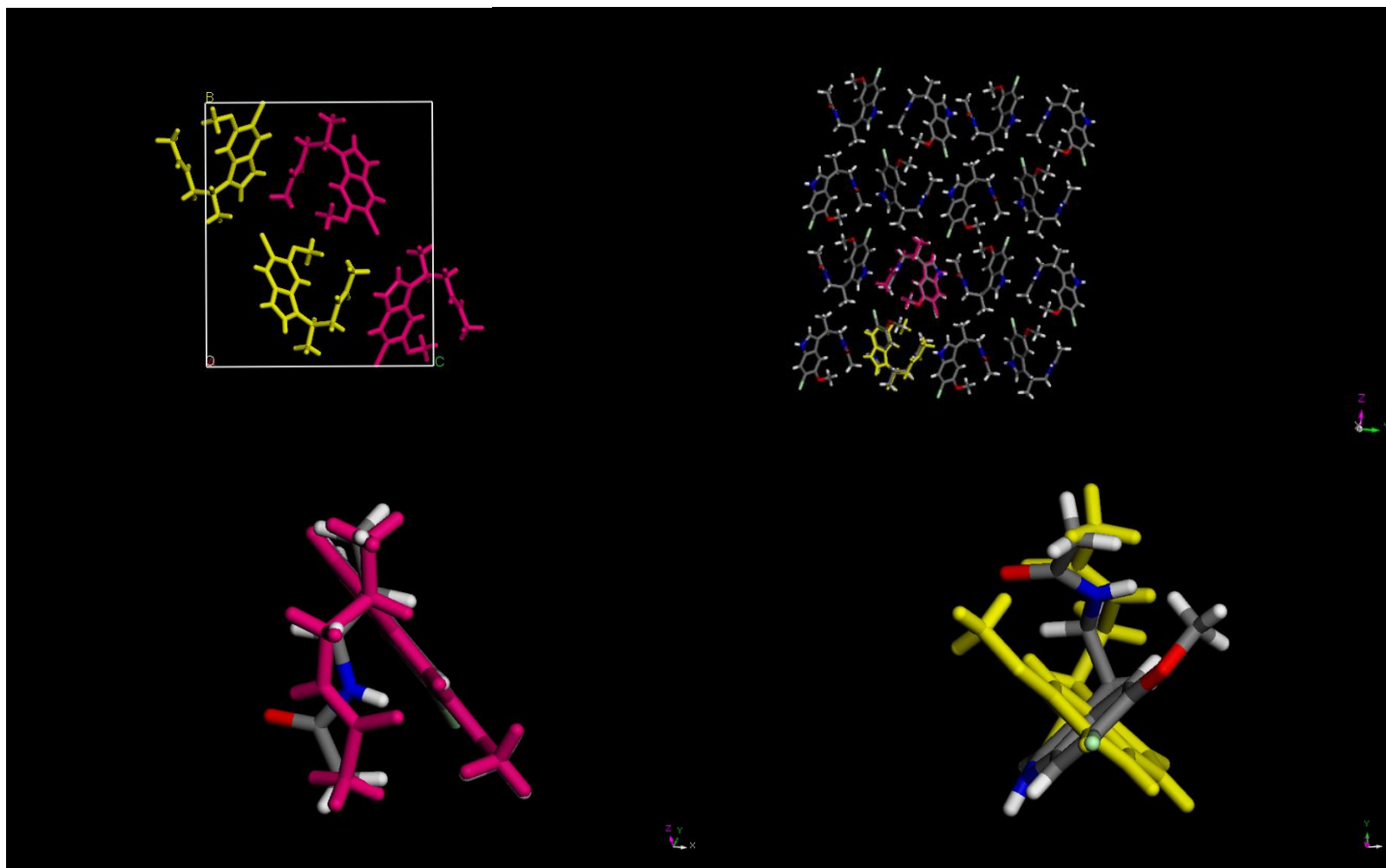
# Looking at Super Structure



Chiral, Enantiopure  
P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>

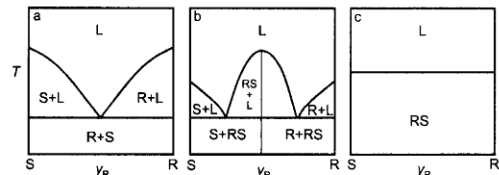
Racemic, both enantiomers  
present in unit cell  
P2<sub>1</sub>/c

# A Closer Look



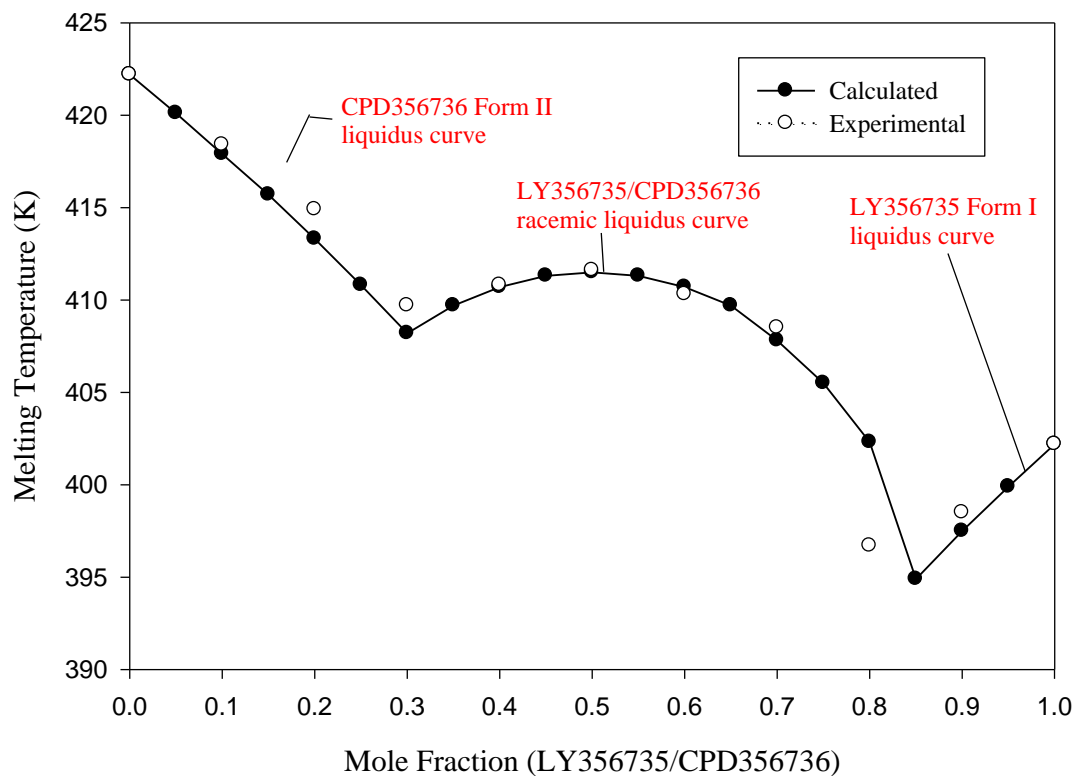


# Truly Racemic Crystal Not a Solid Solution Confirmed by Thermal Analysis



**Figure 1.** Binary phase diagram of enantiomer mixtures forming (a) a conglomerate, (b) a racemic compound, and (c) a solid solution.<sup>2</sup> R, S, RS, and L represent respectively solid R-enantiomer phase, solid S-enantiomer phase, racemic compound RS, or solid solution RS and liquid phase.

Phase Diagram for LY356735 and LY356736



# Phase Diagram of Enantiomeric Mixtures

The phase diagram for a mixture of two enantiomers can be calculated using the Schroder Van-Laar equation to determine the liquidus curve for the portion of the phase diagram which is at the extremes of chiral purity as expressed below:

$$\text{Equation. 1} \quad \ln x = \Delta H_A^f / R (1/T_A^f - 1/T^f)$$

where  $R = 1.9869 \text{ cal mol}^{-1} \text{ K}^{-1}$ , where  $x$  is the mole fraction of the more abundant enantiomer ( $0.5 \leq x \leq 1$ ) of a mixture whose melting terminates at  $T^f$  (degrees K).  $\Delta H_A^f$  and  $T_A^f$  are the enthalpy of fusion and the melting point of the pure enantiomer. Usually these curves are symmetrical at the two extremes. In the case of LY356735 versus LY356736, the enantiomerically pure regions are not the same, since the stable form of LY356736 is the more stable crystalline form, whereas the form used for LY356735 is the metastable polymorphic form. The two polymorphs have different melting points and enthalpies of fusion, hence the curves are not symmetrical.

The Prigogine and Defay equation can be used for calculating the liquidus curve for the racemic portion of the curve (from  $x=0.5$  to where the mole fraction defines the two eutectic points) as define below:

$$\text{Eqn. 2} \quad \ln 4x(1-x) = 2 \Delta H_R^f / R (1/T_R^f - 1/T^f)$$

The same variables are used, however the enthalpy of fusion,  $\Delta H_R^f$ , of the racemate and the temperature of melting of the racemic crystal,  $T_R^f$ , is used throughout this region of the phase diagram.

Experimental data was collected at 10 percent intervals and was used to validate the calculations.