Symmetry Breaking in Crystallizations: Different Polymorphic Selection by R- and S- Enantiomers in Achiral Media
(Missing Polymorph of the Melatonin Agonist)

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Answers That Matter.

Primary Nucleation (Classical Nucleation Theory)

Secondary Nucleation

Homogeneous nucleation

The free energy of formation of a spherical nucleus, ΔG_N, is given by the difference between the Interfacial (I) and volume (V) excess free energy (*aka* surface and the bulk),

$$\Delta G_N = \Delta G_I - \Delta G_V$$

$$\Delta G_I = +4\pi r^2\sigma \quad \text{and} \quad \Delta G_V = -\frac{4\pi r^3 \Delta G_{vol}}{3}$$

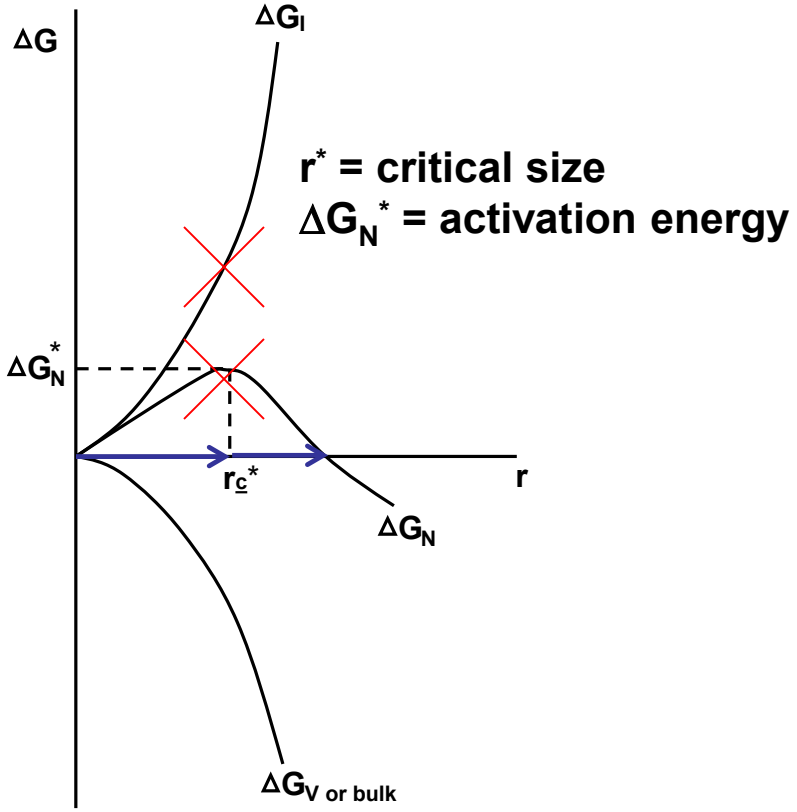
where σ = interfacial free energy per unit surface area, and

where ΔG_{Vol} = free energy change per unit volume.

$$\Delta G_N = +4\pi r^2\sigma - \left(-\frac{4\pi r^3 \Delta G_{vol}}{3}\right)$$

$$\frac{d\Delta G_N}{dr} = 8\pi r\sigma + 4\pi r^2 \Delta G_{vol} = 0$$

$$\Delta G_N^* = \frac{4\pi\sigma (r_c^*)^2}{3}$$



If you have "seed" crystals – you bypass the disfavored process

Pharmaceutical System 1

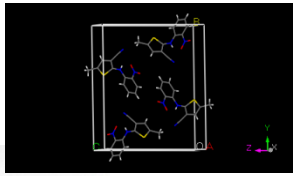
ROY

Thermochemistry and Conformational Polymorphism of a Hexamorphic Crystal System

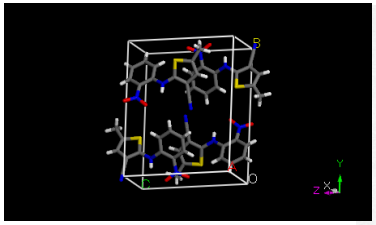
L. Yu, G.A. Stephenson,C.A. Mitchell, C.A. Bunnell, S. Snorek, J. Bowyer, T.B. Borchardt, J.G. Stowell, and S.R. Byrn

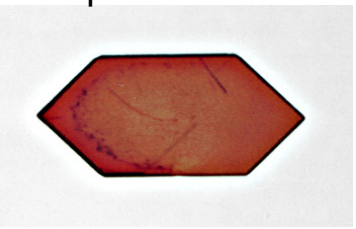
Journal of the American Chemical Society (2000), 122(4), 585-591.

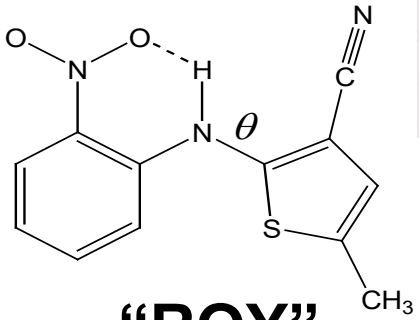
ON *P2₁/c*
mp 114.8°C



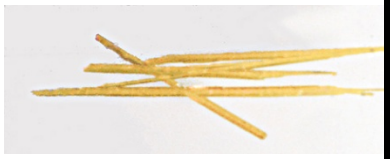
OP *P2₁/c*
mp 112.7 °C

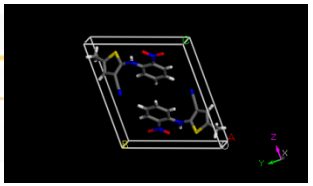


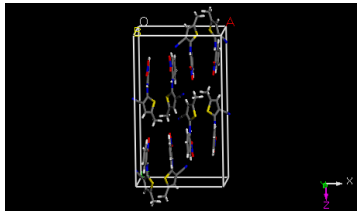


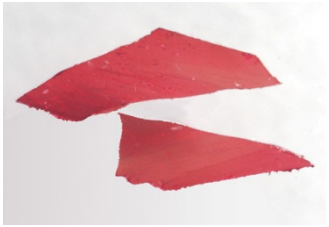


YN *P-1*
mp 99 °C

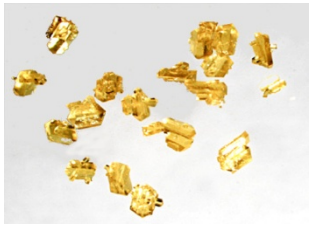


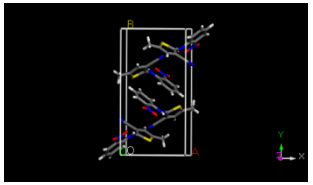




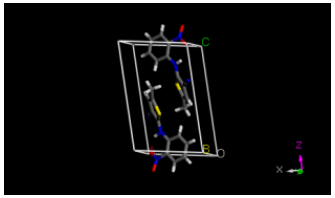


"ROY"





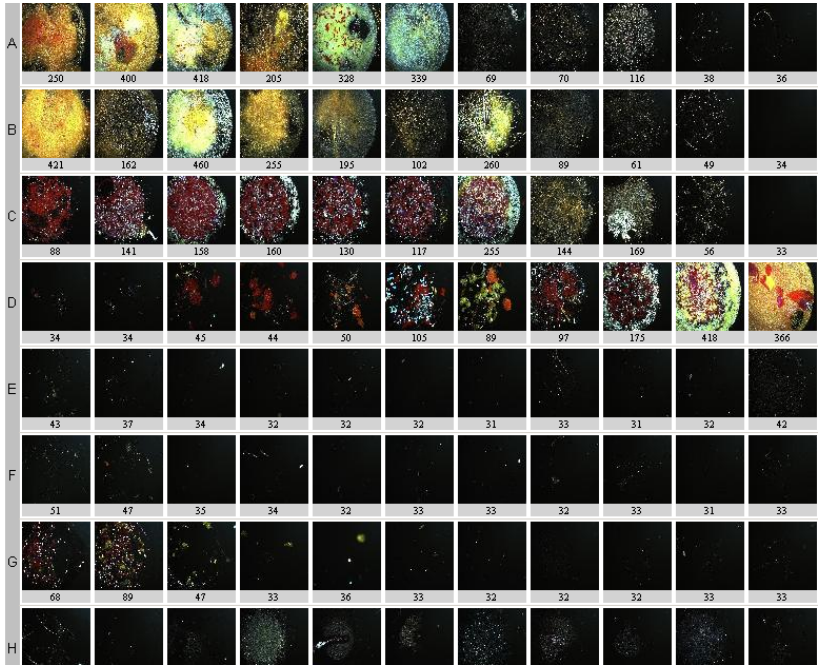
ORP *Pbca*
mp 97 °C



Y *P2₁/c*
mp 109.8 °C

R *P-1*
mp 106.2 °C

Concomitant Polymorphs – Multiple Crystal Forms Grow Simultaneously



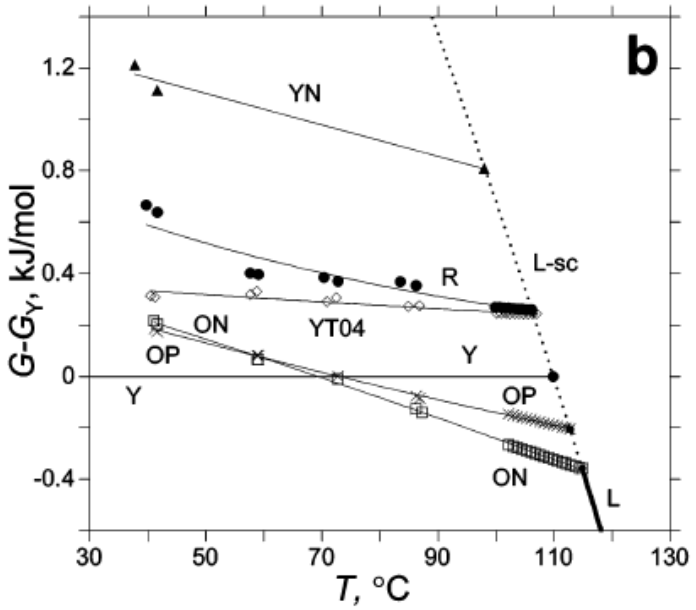


Figure 2. (a) Melting and eutectic melting data of YT04 and Y. (b) Free-energy difference between ROY polymorphs. Each line represents the free energy of a polymorph relative to Y (i.e., $G - G_Y$).

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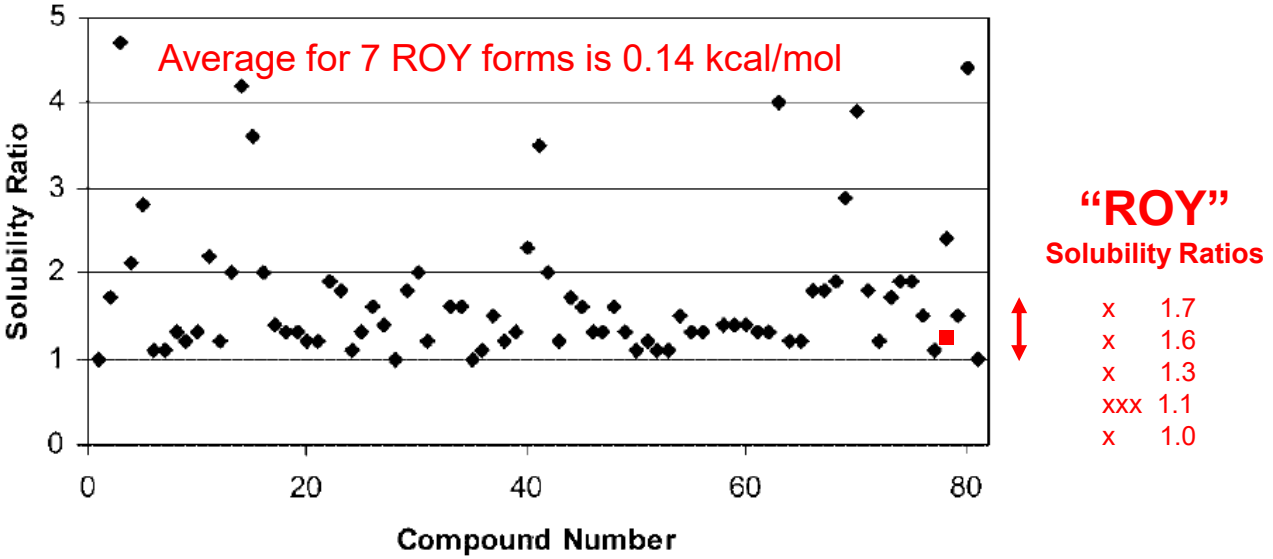
Polymorph Solubility Differences and Thermodynamic Stability

$$\Delta G_2 - \Delta G_1 = RT \ln \frac{X_1}{X_2}$$

Hoffman JD. 1958. Thermodynamic driving force in nucleation and growth processes. J Chem Phys 29: 1192–1193.

The Ratio of metastable solubility to stable polymorph is 1.7
Hence, energy difference for typical
organic polymorphic pairs is 0.33 kcal/mol



- Pudipeddi, M., Serajuddin Trends in Solubility of Polymorphs *J. PHARM. SCI.* **2005**, 94(5) 929-939.

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Disappearing and Late Appearing Polymorphs

Letter to the Editor: Woodward, G.D.; McCrone, W.C. *J.* **Unusual crystallization behaviour** *J. AppL Cryst. (1975). 8, 342.*

Compounds behaving respectably for many months or years until nucleation of a more stable form. After this occurs, the previously obtained crystal form cannot be made to crystallize often even in laboratories many miles away.

"most interesting to us is the fact that once one laboratory has recrystallized a compound, either for the first time or in a more stable form, other labs were able to do so, as though the seeds of crystallization, as dust, had been carried upon the winds from end to end of the earth."

comments made by C.P. Saylor to Woodward and McCrone which were then included in their Letter to the Editor

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Disappearing and Late Appearing Polymorphs

Disappearing Polymorphs Dunitz, J.D.; Bernstein, *Acc. Chem. Res.* **1995**, *28*, 193-200.

Tales of difficulties in obtaining crystals of a particular known form or in reproducing results from another laboratory (or even from one's own!) abound. Indeed, there are cases where it was difficult to obtain a given polymorphic form even though this had previously been obtained routinely over long time periods. Several monographs contain explicit or passing references to these problems, I but much of this lore has gone undocumented, especially in the last 30 years or so. In this Account we present and discuss old and new examples.

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Unintentional Seeding (Secondary Nucleation)

Anhydrous piezeoelectric crystals of ethylene diamine tartrate produced at industrial scale for many years until a monohydrate crystalline form nucleated and grew preferentially at one plant site. The “affliction” spread quickly to other plant sites many miles away.

Xylitol – first prepared in 1891, produced as an oil for 50 years until a new form crystallized that melted at 61°C, two years later a second crystalline form melting at 94°C was produced, never to be able to produce the lower melting form again.

(J.W. Mullins in Crystallization reprinted in 2002, pg. 200)

Pharmaceutical System 2

Ritonavir

Ritanovir Story: Late Appearing Polymorph

A new crystal form was found in the formulated product. This put Abbott into a market crisis. The supply of the semisolid capsules was depleting quickly. Form II crystals were brought into our laboratories to study its properties. Within a few days, all of the samples that were prepared in the lab turned out to be Form II. … A team of scientists who had been exposed to Form II visited our manufacturing facility in Italy to investigate if any significant changes had been made to our manufacturing process. Until this time, no detectable quantities of Form II had been detected in the bulk drug lots. ...soon after this visit significant amounts of Form II started showing up in Abbott Italy bulk drug during its manufacturing process.

The origin of Form II remains debatable, the fact was that this issue had to be addressed as soon as possible.

Chemburkar, S.R. et al. (2000). "Dealing with the impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development". *Org. Proc. Res. & Dev.* 4: 413-417.

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Ritonavir: Disappearing and Late Appearing Polymorphs

Theorized that an intermediate that had the disfavored conformation nucleated the stable polymorph.

Heterogeneous nucleation

Bauer J, et al. (2001). "Ritonavir: An Extraordinary Example of Conformational Polymorphism". *Pharmaceutical Research* **18** (6): 859–866.

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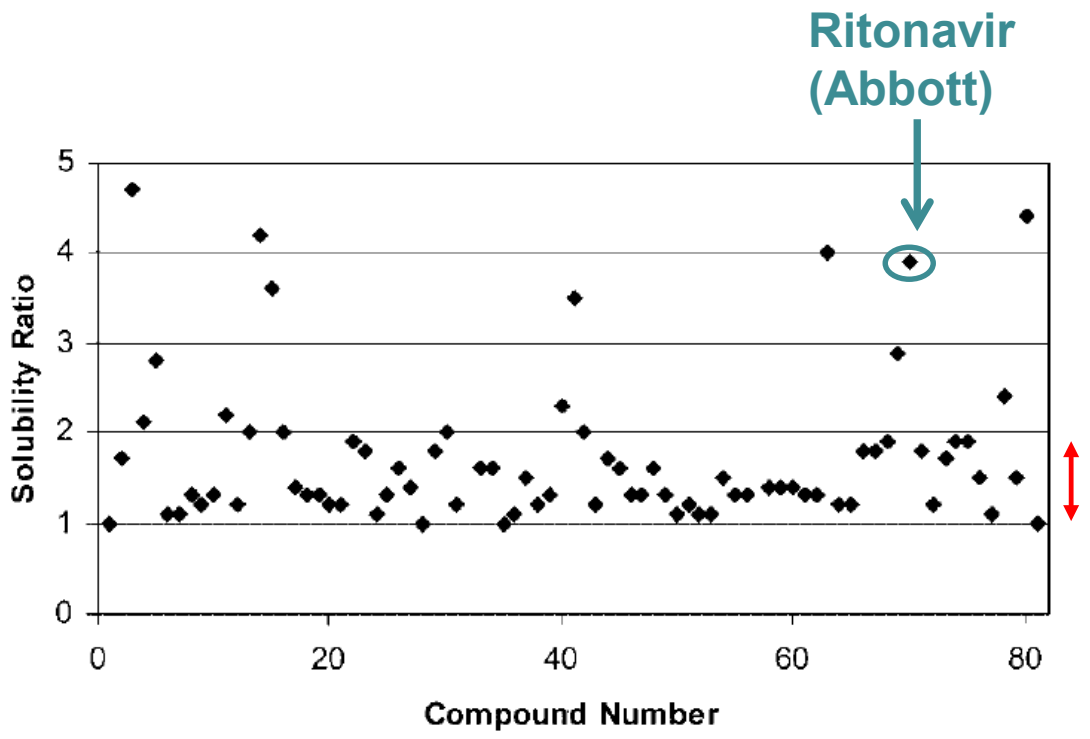
Contrast Late Appearing Polymorph to ROY's Concomitant Polymorphs

$$\Delta G_2 - \Delta G_1 = RT \ln \frac{X_1}{X_2}$$

Hoffman JD. 1958. Thermodynamic driving force in nucleation and growth processes. J Chem Phys 29: 1192–1193.



"ROY"
Solubility Ratios

x	1.7
x	1.6
x	1.3
xxx	1.1
x	1.0

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Pharmaceutical System 3

Symmetry Breaking in Crystallizations: Different Polymorphic Selection by R- and S- Enantiomers in Achiral Media

Melatonin Agonist

Just Accepted in Crystal Growth & Design

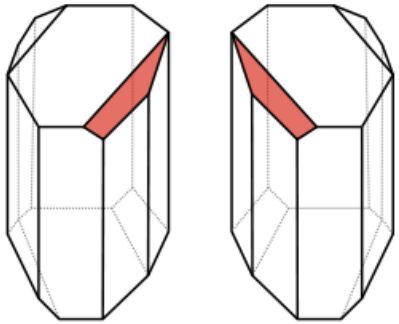
The compound was terminated in 1998 – I waited 14 years until it was OK to revisit!

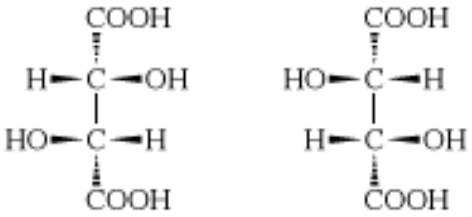
Enantiomers Produce the Same Crystalline Forms

Pasteur's crystals of sodium ammonium tartaric acid crystals demonstrate this nicely.

They have same melting point, same hardness, same solubility.

"Mirror image crystals"





D-tartaric acid L-tartaric acid

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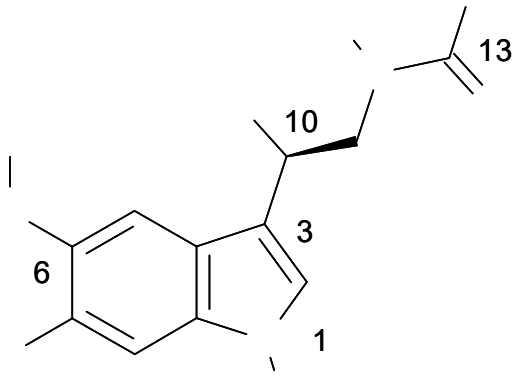
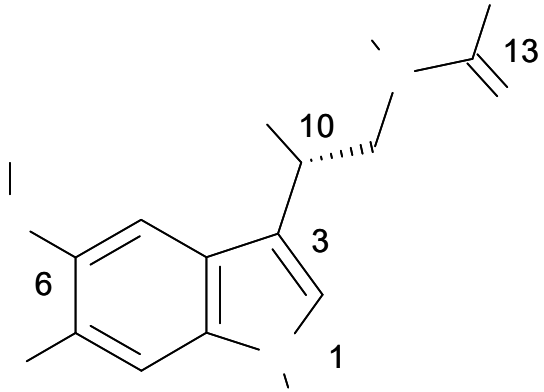
Enantiomers of Melatonin Agonist



Active Enantiomer



Inactive Enantiomer

Biological Systems are Chiral: different enantiomers have different activity and selectivity at receptor sites.

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Early Stage Supply Issues

Early synthesis usually at the 5-10 g scale. Many synthesis produce racemic mixtures of enantiomers that are separated by Liquid Chromatography using Chiral Columns

Conserve the active enantiomer for biological assays that are specific to the enantiomer used (toxicological testing etc.)

The Lead Scientist will often choose to do early crystallization studies using the inactive enantiomer.

In theory the crystallizations should produce the same forms!

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Melatonin Antagonist

Study of the Inactive Enantiomer

Three out of four initial batches were the metastable Form 1. The fourth batch was dramatically more stable, Form 2.

Extremely difficult to produce the metastable form after discovery of the stable Form 2

Form 1 is a Disappearing Polymorph in the inactive enantiomer

When the Active Enantiomer became available

Never produced as the Stable Polymorphic Form 2 despite thousands of recrystallizations and more than Ten multi kilogram scale lots!

The Missing Polymorph

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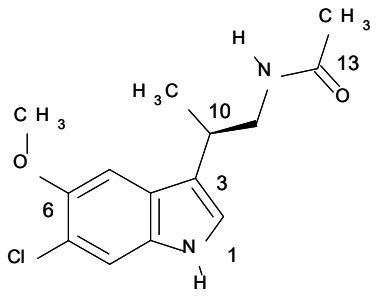
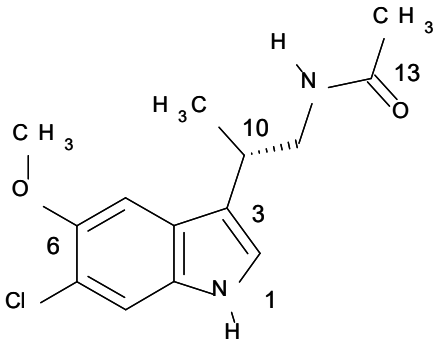
Comparative Evaporative Crystallization Results for the Active and Inactive Enantiomers.



Active Enantiomer

Solvent	Active	Inactive
acetone	Form 1	Form 2
acetonitrile	Form 1	oil*
ethanol	Form 1	oil*
methanol	Form 1	Form 2
2-propanol	Form 1	Form 2
1-butanol	Form 1	Form 2
ethyl acetate	Form 1	Form 2
isopropyl acetate	Form 1	Form 2
methyl ethyl ketone	Form 1	Form 2
methylene chloride	Form 1	Form 2
cumene	Form 1	Form 2
n-amyl acetate	Form 1	Form 2
3-methyl butanol	Form 1	Form 2
toluene	Form 1	Form 2
cyclohexanone	oil*	oil*
anisole	Form 1	Form 2
methyl acetate	Form 1	Form 2
n-propanol	Form 1	Form 2
tetrahydrofuran	Form 1	Form 2
acetic acid	oil*	oil**
methyl isobutyl ketone	Form 1	Form 2
chloroform	Form 1	Form 2
dioxane	Form 1	Form 2
"wet" ethyl acetate	Form 1	Form 2



Inactive Enantiomer

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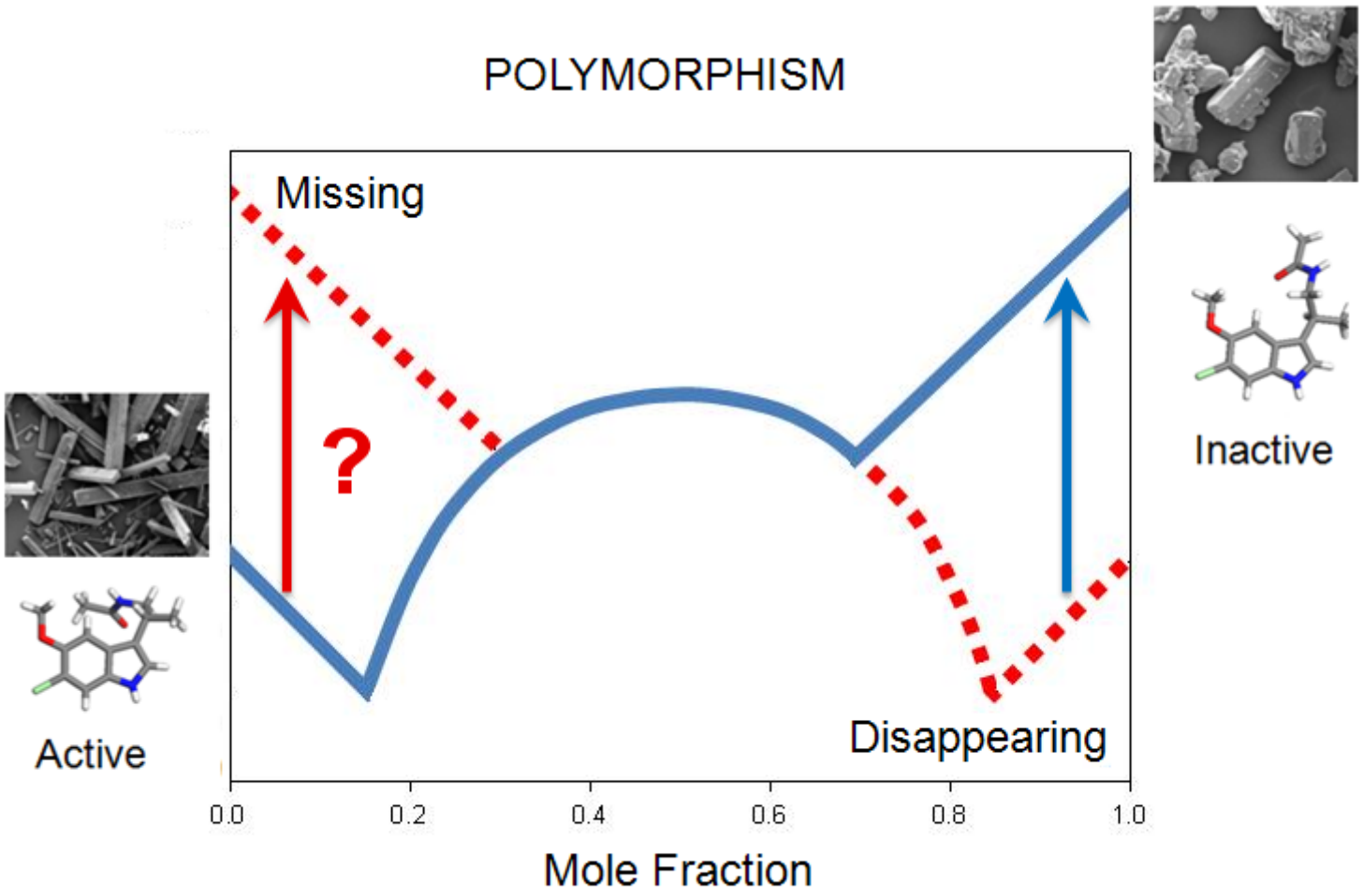
Symmetry Breaking in Crystallizations: Different Polymorphic Selection by R- and S- Enantiomers in Achiral Media

(Missing Polymorph of the Melatonin Agonist)



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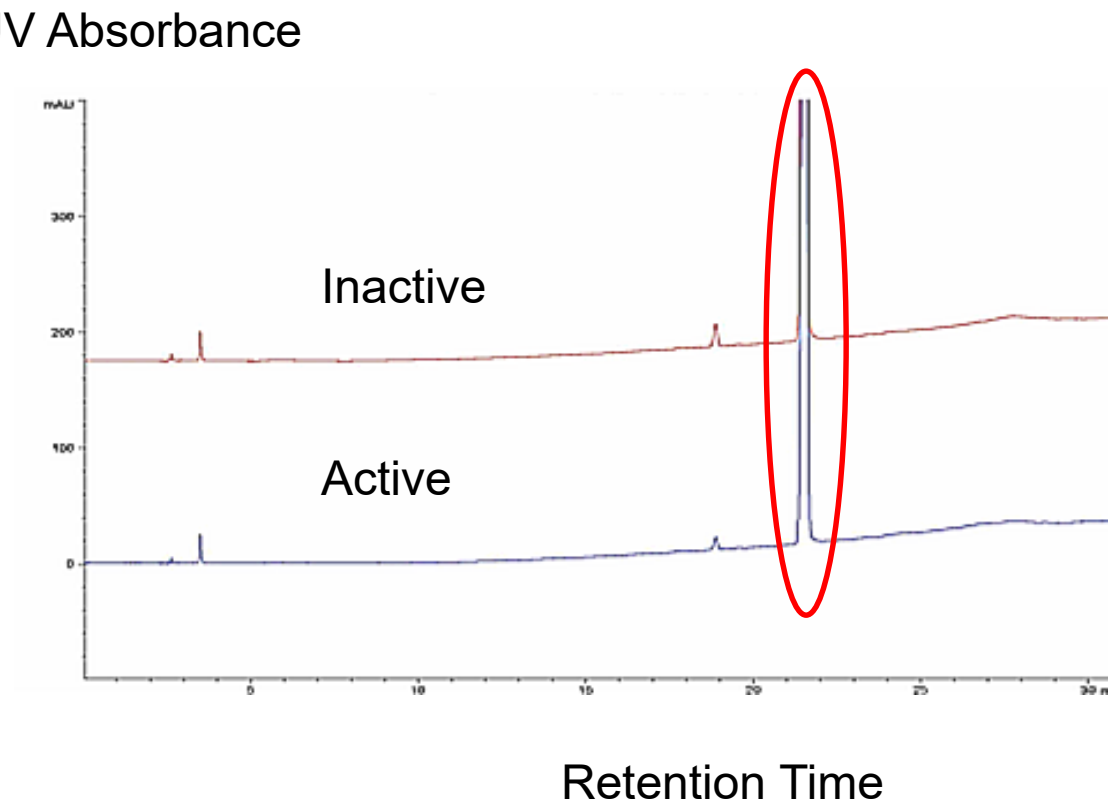
Related Substances and Purity are Nearly Identical (HPLC assay)

	Purity by % Area	
Time	**active**	**inactive**
3.47	0.2129	0.2055
17.58	0.0284	0.0287
18.70	0.2463	0.4383
19.44	0.0428	0.0436
21.37	99.4697	99.2839



Purity does not readily account for their differing crystallization behavior

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X-ray Powder Diffraction Used Initially To Identify Forms

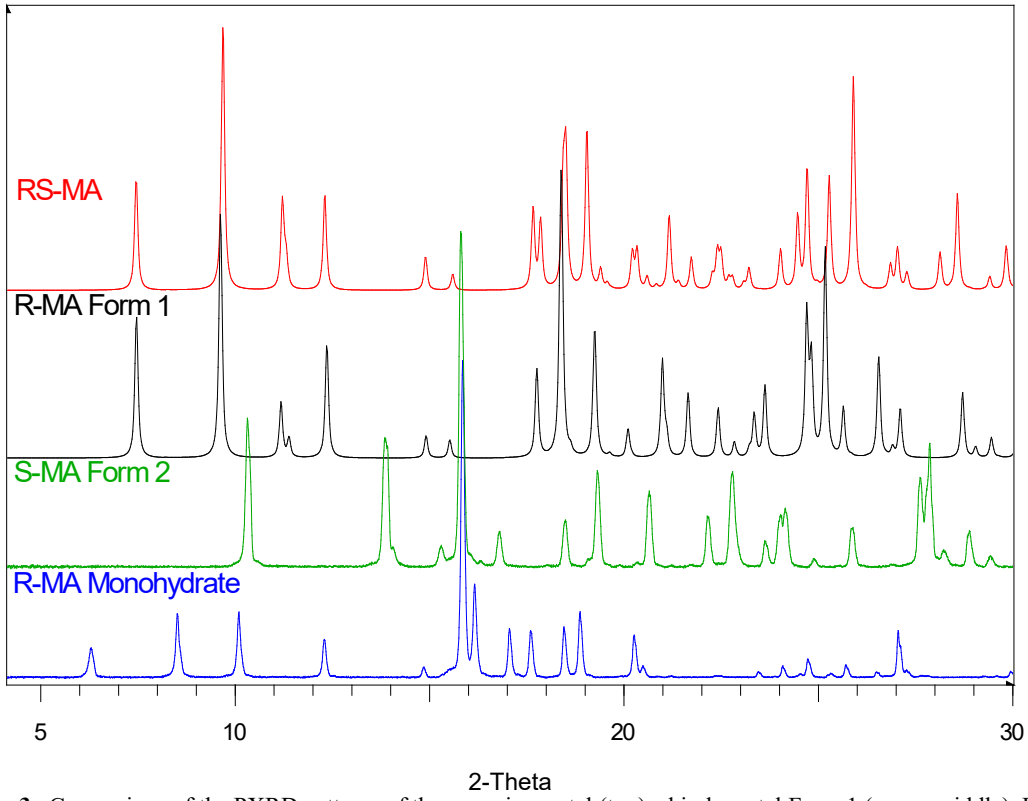

Figure 3. Comparison of the PXRD patterns of the racemic crystal (top), chiral crystal Form 1 (upper-middle), Form 2 (lower-middle), and the monohydrate form (bottom).

The active Form 1 will form a monohydrate in water.

The inactive Form 2 will not form the hydrate!

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Crystal Morphologies Differ

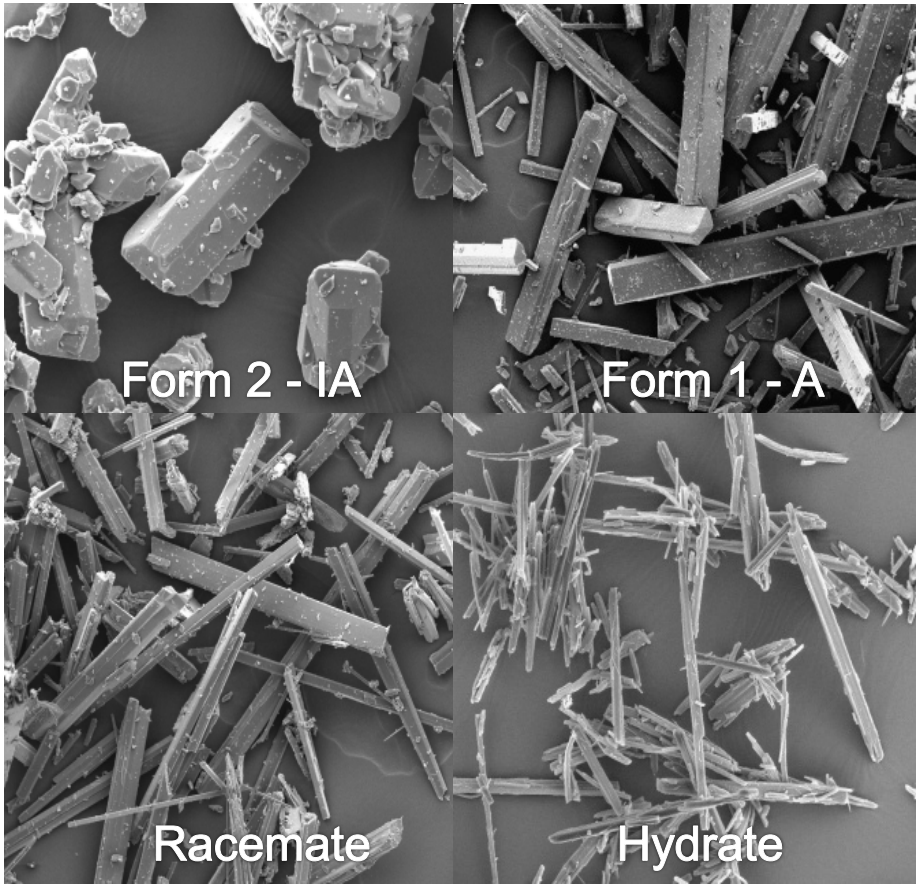
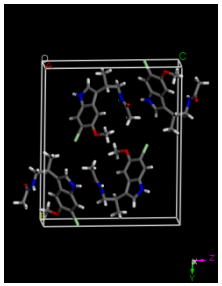
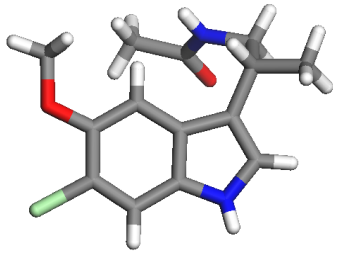


Figure 2. MA crystal habits; Form 2 (top left), Form 1 (top right), Racemate (lower left), Hydrate (lower right).

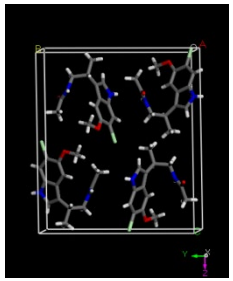
Answers That Matter.

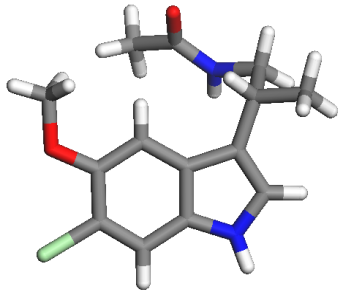
Single Crystal Diffraction: Conformational Polymorphs, Racemate and Hydrate



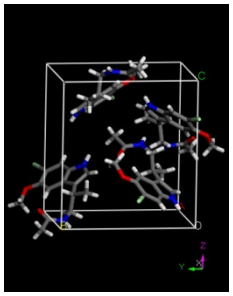


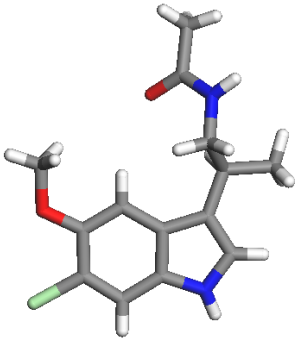
Form 1



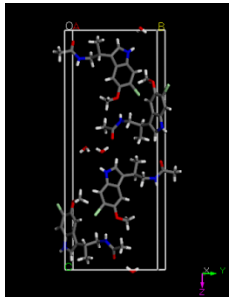


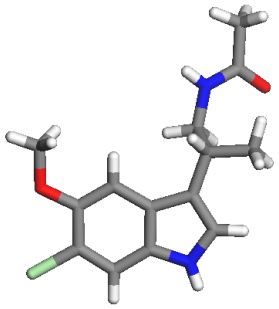
Racemate





Form 2





Hydrate

Torsion	RS-MA	R-MA Form 1	S-MA Form 2*	R-MA H2O
T1: C2-C3-C10-C11	87.4°	99.8°	128.6°	111.1°
T2: C3-C10-C11-N12	52.3°	64.1°	160.6°	173.0°
T3: C10-C11-N12-C13	78.0°	-122.2°	-76.3°	101.7°
T4: C11-N12-C13-C14	175.2°	179.2°	-177.8°	178.8°

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Both metastable and stable polymorphs are more dense than the racemic crystalline form

Identification	RS-MA	R-MA -Form 1	S-MA Form 2	R-MA Hydrate
Empirical formula	$C_{14}H_{17}ClN_2O_2$	$C_{14}H_{17}ClN_2O_2$	$C_{14}H_{17}ClN_2O_2$	$C_{14}H_{17}ClN_2O\,H_2O$
Formula weight	280.75	280.75	280.75	298.76
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic
Space group	P2(1)/c	P2(1)2(1)2(1)	P2(1)2(1)2(1)	P2(1)2(1)2(1)
a, Å,	4.93520(10)	4.96890(10)	9.1740(4)	4.61780(10)
b, Å,	18.1423(4)	15.5039(2)	11.5383(5)	11.1219(2)
c, Å,	15.6111(3)	17.9606(3)	12.7475(5)	28.1075(6)
β, °	92.9510(10)	90	90	90
Density, g/cm^3 (calculated)	1.336	1.348	1.382	1.375
Crystal size, mm^3	0.40 x 0.21 x 0.18	0.69 x 0.11 x 0.07	0.20 x 0.20 x 0.20	0.30 x 0.07 x 0.07
Theta range for data collection, °	3.74 to 70.22	3.77 to 65.01	5.17 to 69.09	3.14 to 58.80
Reflections collected	7897	4789	7148	4186
Independent reflections	2337	2075	2362	1911
Goodness-of-fit on F2	1.09	1.066	1.12	1.008
Final R indices [I>2sigma(I)]	R1 = 0.0450 wR2 = 0.1427	R1 = 0.0409 wR2 = 0.1079	R1 = 0.0419 wR2 = 0.1031	R1 = 0.0439 wR2 = 0.1074
Largest diff. peak and hole e.Å^{-3}	0.274 and -0.348	0.355 and -0.196	0.252 and -0.301	0.231 and -0.317

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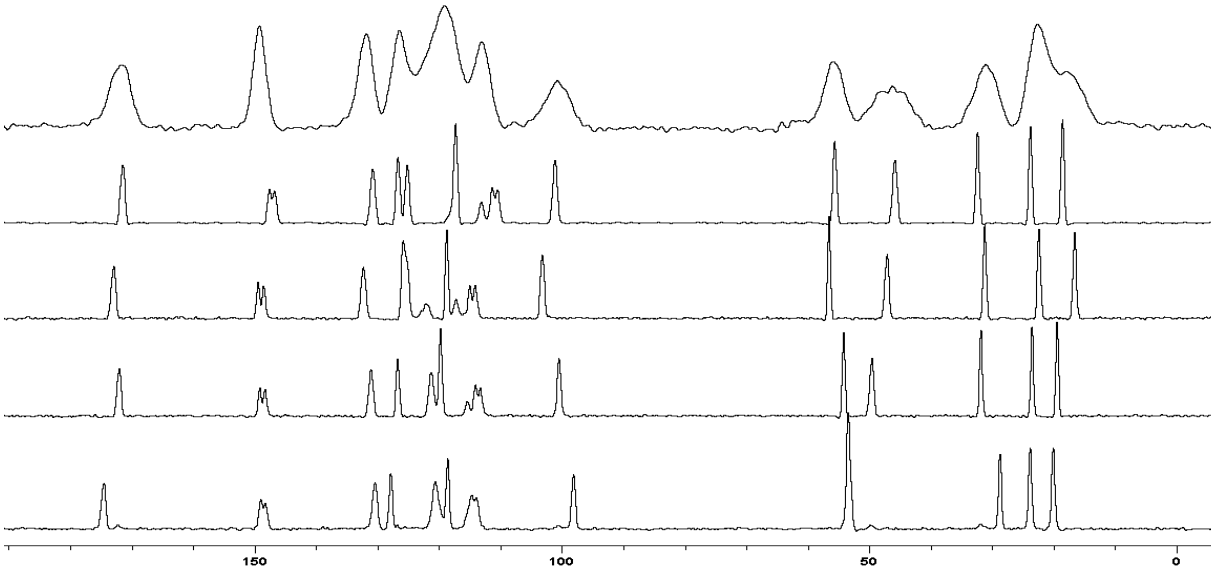
The Reluctance to Nucleate

Ritonavir, it was concluded that the molecule had to convert from an energetically stable conformation in solution to a disfavored conformation in the crystal lattice of the stable polymorph, inferred responsible for its reluctance to nucleate as the stable polymorphic form.

Answers That Matter.

Crystallography and CP/MAS 13C Solid-State NMR used to establish conformation in solution state



Amorphous Form

R-MA Monohydrate

S-MA Form 2

R-MA Form 1

RS-MA

Figure 6. ^{13}C CPMAS Solid-State NMR spectra of crystalline forms and that of the melt of R-MA in its "glassy-state", R-MA Monohydrate, S-MA Form 2, R-MA Form 1, and the RS-MA Racemate (top to bottom).

Table 4. Correlation of Torsion Angles with ^{13}C Chemical Shift Values of the MA Forms.

Torsion	RS-MA	Form 1	Form 2	Hydrate	Melt	Solution
C15-O6-C6-C5 (°)	-0.1	3.6	9.5	-5.4		
C15 Methoxy (ppm)	53.4	54.1	56.5	55.5	55.9	58.23
N12-C11-C10-C2 (°)	52.3	64.1	160.6	173		
C11 methylene (ppm)	53.4	49.5	47	45.8	46.2	45.45
C16-C10-C3-C2 (°)	-35.5	-23.2	1.8	-11.1		
C16 methyl (ppm)	20	19.4	16.5	18.5	17.9	18.39

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Ab initio Conformational Analysis

Conformational analysis was performed with Materials Studio (Accelcrys) using the Dreiding force field and Gasteiger charges
A grid scan was performed of with the 4 most important torsion angles
The resulting 13,824 structures were clustered and re-optimised to generate a list of unique conformers
The 61 lowest energy conformers were re-optimised using Orca with Moller Plesset 2nd order perturbation theory (MP2) and a double zeta plus polarisation basis set

The conformer in the Form 2 “missing polymorph” is lower in energy than Form 1.

Frank Leusen and John Kendrick

Answers That Matter.

The Reluctance to Nucleate the Missing Polymorph

Ritonavir, it was concluded that the molecule had to convert from an energetically stable conformation in solution to a disfavored conformation in the crystal lattice of the stable polymorph, inferred responsible for its reluctance to nucleate as the stable polymorphic form.

Melatonin Agonist, the average conformation in the amorphous form and in solution state is more similar to the stable form than the metastable form

ab initio calculations agree that the most stable conformer is that found in the stable Form 2 “missing polymorph”

If anything, solution conformation favors nucleation of the stable polymorph!

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Evaluation of Thermodynamic Relationship of the Two Polymorphs Relative to the Racemate

$$G_c = G_A + RT \ln 2 = RT (\ln x_A + \ln 2) \quad (1)$$

$$G_R = RT \ln x_R \quad (2)$$

$$\Delta G_{C\text{-}R} = RT (\ln x_A + \ln 2 - \ln x_R) \approx RT (\ln c_A/c_R + \ln 2) \quad (3)$$

Using Solubility Data

When $T^f_R > T^f_A$, as with Form 1 evaluated at its melting point

$$\Delta H^{\Phi}_{T\,A}{}^{f} = \Delta H^f_A - \Delta H^f_R + (C^l - C^s_R)(T^f_R - T^f_A) \quad (4)$$

$$\Delta S^{\Phi}_{T\,A}{}^{f} = \Delta S^f_A - \Delta S^f_R + R \ln 2 + (C^l - C^s_R)(\ln T^f_R/T^f_A) \quad (5)$$

$$\Delta G^{\Phi}_{T\,A}{}^{f} = \Delta H^f_{T\,R} (T^f_A/T^f_R - 1) - T^f_A R \ln 2 + (C^l - C^s_R)(T^f_R - T^f_A - T^f_A \ln T^f_R/T^f_A) \quad (6)$$

Using Melting Data

When $T^f_A > T^f_R$, as with Form 2 evaluated at its melting point

$$\Delta H^{\Phi}_{T\,R}{}^{f} = \Delta H^f_A - \Delta H^f_R + (C^l - C^s_A)(T^f_R - T^f_A)$$

$$\Delta S^{\Phi}_{T\,R}{}^{f} = \Delta S^f_A - \Delta S^f_R + R \ln 2 + (C^l - C^s_A)(\ln T^f_R/T^f_A)$$

$$\Delta G^{\Phi}_{T\,R}{}^{f} = \Delta H^f_A (1 - T^f_R/T^f_A) - T^f_R R \ln 2 + (C^l - C^s_A)(T^f_R - T^f_A - T^f_R \ln T^f_R/T^f_A) \quad (7)$$

Jacques, J.; Collet, A.; Wilen, S.H. *Enantiomers, Racemates, and Resolutions*; Krieger Publishing Company: Malabar, FL, **1991**.

When the Gibbs free energy curves of two forms cross, ΔG is zero

Transition Temperature-Determined by Extrapolation of Solubility data and/or Thermal Data

$$T_t \approx \Delta H^{\Phi}_{T\,R}{}^{f}/\Delta S^{\Phi}_{T\,R}{}^{f}$$

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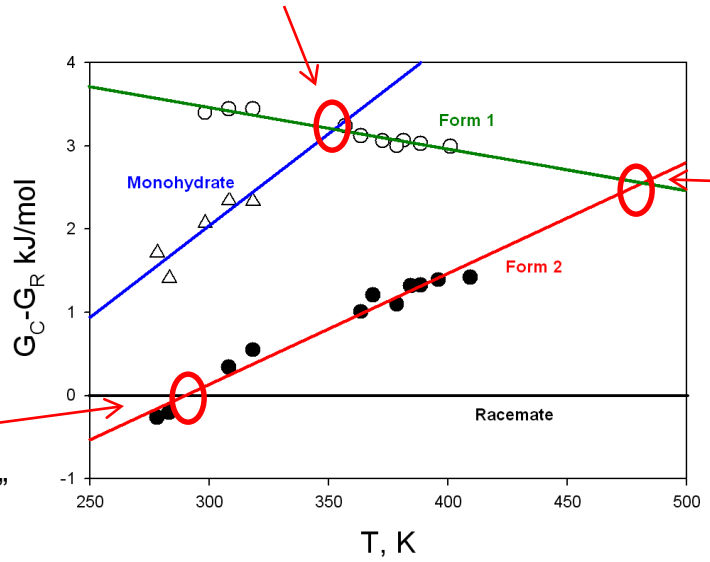
Thermodynamic Relationship of Solid-State Forms

"At Constant Pressure"

In water the monohydrate converts to the anhydrate at elevated temp



Virtual Transition Point well above either form's melting point
Form 2 More Stable Than Form 1
"monotropically related"

Rare!

"spontaneous resolution" of racemic crystal to conglomerate mixture at low temp is predicted

Form 2 is more stable than the monohydrate in water:
An example of how discovery of a new form can completely change the landscape of "accessible" crystalline forms

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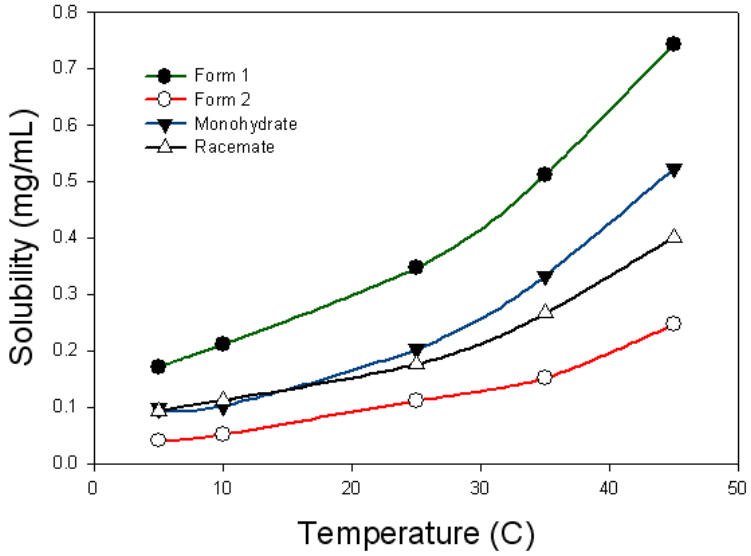
Comparison of Physical Properties



Form 2 is less soluble than either Form 1 as well as the monohydrate form in water!

Figure 7. Water solubility of MA versus temperature for crystalline forms of MA.

Property	Form 1	Form 2
Density (g/cm3)	1.348	1.382
Melting point (°C)	127.9	147.0
Solubility (mg/mL)	0.4	0.1

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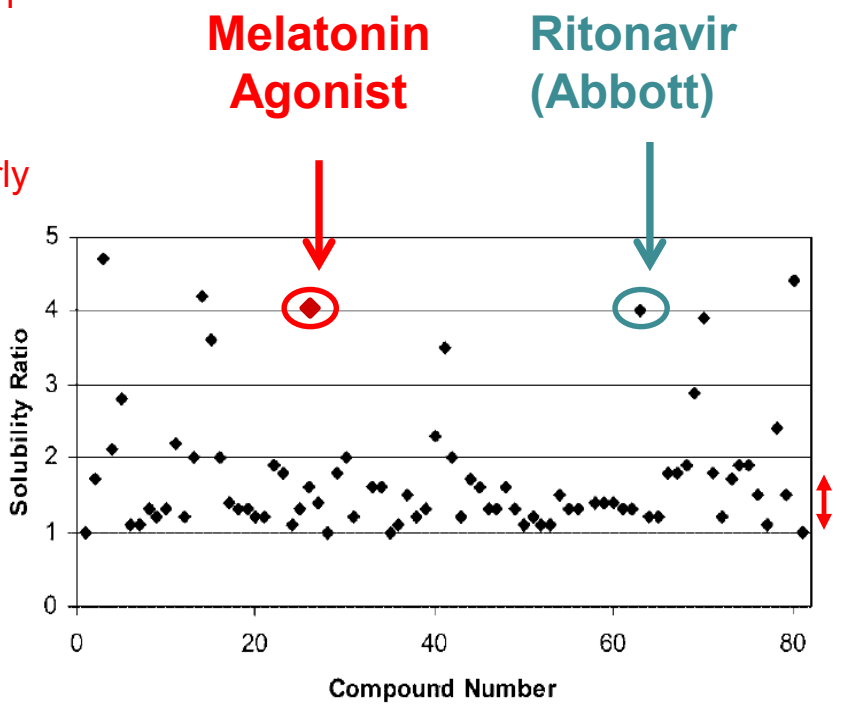
Late Appearing Polymorphs vs. Concomitant Polymorphs

$$\Delta G_2 - \Delta G_1 = RT \ln \frac{X_1}{X_2}$$

Hoffman JD. 1958. Thermodynamic driving force in nucleation and growth processes. J Chem Phys 29: 1192–1193.

0.8 kcal/mol difference for Melatonin Agonist
0.14 kcal/mol for "ROY"

Late appearing polymorphs are nearly 4 std dev away from the average energy difference for organic polymorphs!



"ROY"
Solubility Ratios

x 1.7
x 1.6
x 1.3
xxx 1.1
x 1.0

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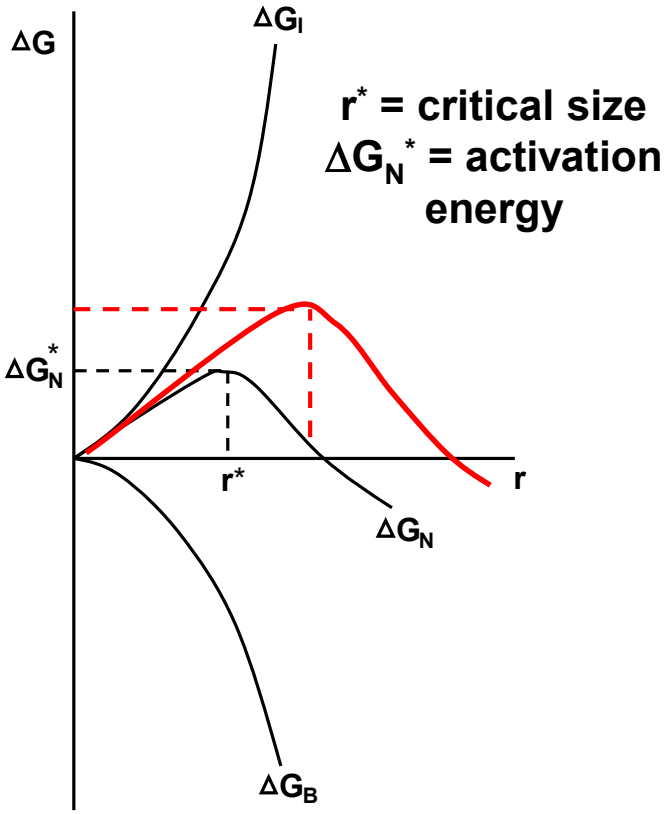
Primary Nucleation (Classical Nucleation Theory)

Homogeneous Primary Nucleation

Nucleation Rate; $J_N = A\exp(-\Delta G_N^*/kT)$



In the absence of seeds –when the energy difference between polymorphs are small their nucleation rates are likely to be similar and (concomitant polymorphs likely)

In the absence of seeds -very large energy differences may result in very large differences in nucleation rate

Induction times may be prohibitively long for the stable polymorph to appear

Late appearing are more likely.

Conclusions to Melatonin Antagonist

The primary nucleation rate for the stable polymorph is much slower than that of the metastable form due to its exceptional thermodynamic stability (much greater entropic cost of surface formation).

The active and inactive enantiomers of the melatonin agonist have been exposed to the same substances, the same labs, the same glassware etc.

Conclusion – the first crystallization of the stable polymorph of the inactive enantiomer is a result of heterogeneous nucleation by a chiral substance, that is a substance capable of nucleating the inactive enantiomer but not the active (chiral recognition).

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Conclusions to Melatonin Antagonist

1. Studies with the inactive enantiomer predict that a dramatically more stable polymorph exists for the active compound that has not been isolated to date (the missing polymorph of the active).
2. Once this form is nucleated in the active enantiomer, the metastable form will “disappear” and the compound will only be isolated in the more stable form.
3. Unlike Ritonavir, the predominant conformer in solution is the same as in the stable form.
4. Purity of the substance does not account for their differing behavior.
5. Heterogeneous nucleation by a chiral substance is likely responsible for initial nucleation of the stable polymorph.

A Very Rare System:

A Disappearing Polymorph in one hand, A Missing Polymorph in the other

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Acknowledgements

Craig Wolfangel
Jennifer Runyan
David Jackson
Lian Yu

Eli Lilly and Company

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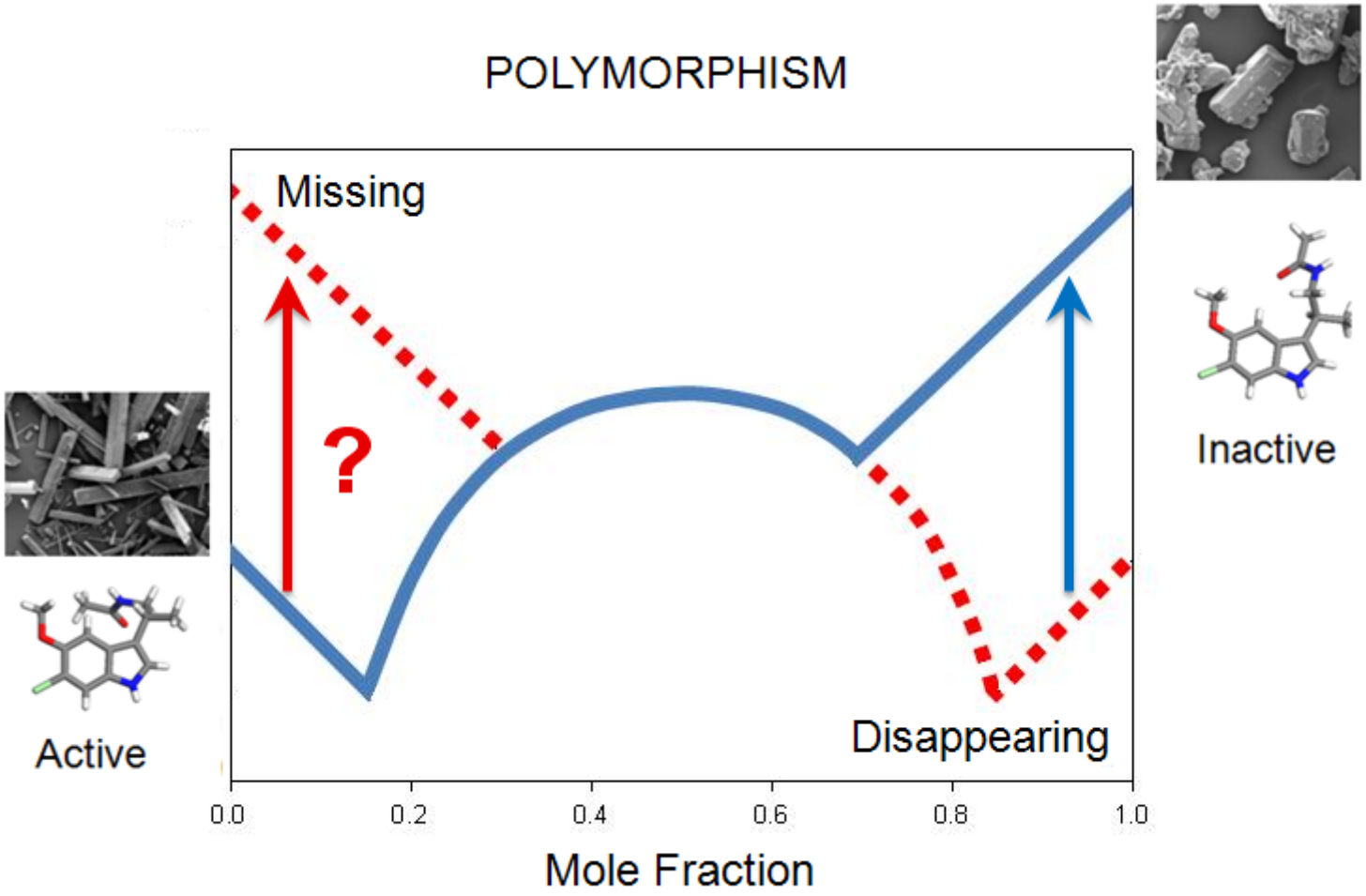
Symmetry Breaking in Crystallizations: Different Polymorphic Selection by R- and S- Enantiomers in Achiral Media

(Missing Polymorph of the Melatonin Agonist)



Answers That Matter.

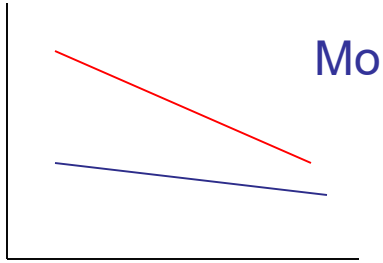
Stable vs. Metastable

1. Metastable Form – The form that is less stable under a given set of condition (Temp, Pressure)

2. Stable Form – The form that is most stable under a set of conditions

At a given Pressure

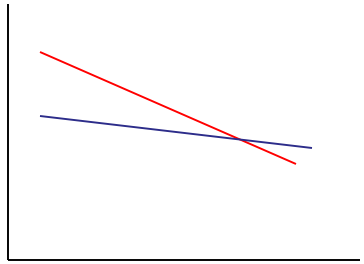
G – free energy



Monotropic

Temperature

G – free energy



Enantiotropic

Temperature

Disappearing Polymorphs

"We believe that once a particular polymorph has been crystallized it is always possible to obtain it again; it is only a matter of finding the right experimental conditions."

Disappearing Polymorphs Dunitz, J.D.; Bernstein, *Acc. Chem. Res.* **1995**, *28*, 193-200.

Because of the appearance of secondary nuclei, the difficulty of obtaining a the metastable crystal form with a high degree of reproducibility may be severely compromised (when the energy difference is great).

One must rely on isolation from nuclei-free environment and isolation under kinetic control

generally not the most robust processes at large scale.

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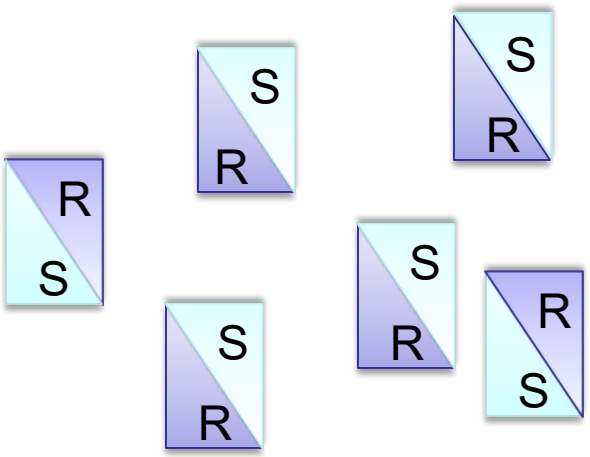
Crystallization of Racemic Compounds

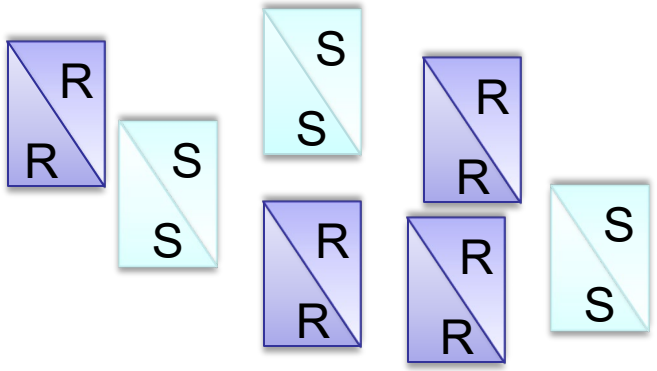
Crystallization From a Racemic Solution of Enantiomers

~90% of the time

~10% of the Time



Racemic Crystals



Conglomerate Mixture of Crystals of opposite "Handedness"

Wallach's Rule[1] states that racemic crystals tend to be denser than their chiral counterparts

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

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Conclusions to Melatonin Antagonist

The primary nucleation rate for the stable polymorph is much slower than that of the metastable form due to its exceptional thermodynamic stability (much greater entropic cost of surface formation). Like ritonavir, in the absence of heterogeneous nucleation by an appropriate substance, its late appearance (induction time) may become prohibitively long.

The pair-wise study of the crystallization of enantiomeric substances may lead to new understanding of primary nucleation because it affords the researcher an opportunity to approach crystallization of a given form twice (free of homogeneous primary nucleation).

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Early Stage Challenges

Very new (young) materials – likely never made before, let alone crystallized. There is a lot to learn relatively little time.

Relatively small quantities exist to work with, initially and tight time lines.

Often complex synthetic routes are involved: the by-products of the reactions or “related substances” are changing in proportion to one another and in proportion to the desired product.

Usually > 95-98% pure substance early on, however very small levels of impurities can have a very large influence on nucleation.

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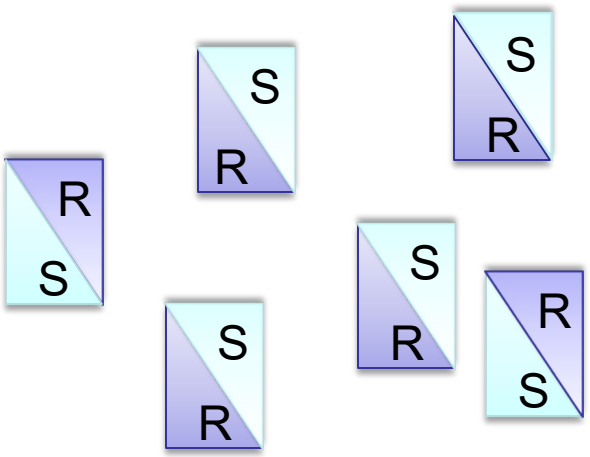
Crystallization of Racemic Compounds

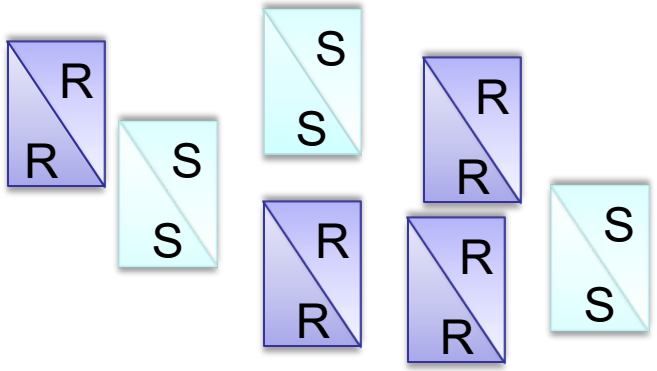
Crystallization From a Racemic Solution of Enantiomers

~90% of the time

~10% of the Time



Racemic Crystals



Conglomerate Mixture of Crystals of opposite "Handedness"

Wallach's Rule[1] states that racemic crystals tend to be denser than their chiral counterparts

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

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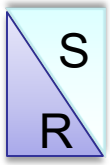
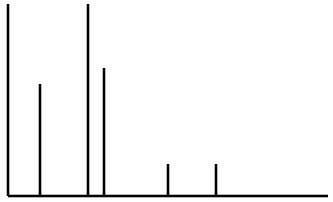
Differentiation of Racemic Crystals vs. a Conglomerate Mixture

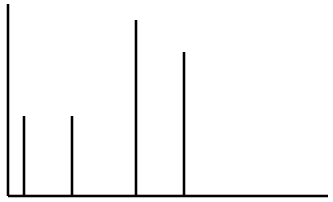
Racemic Crystals



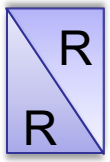


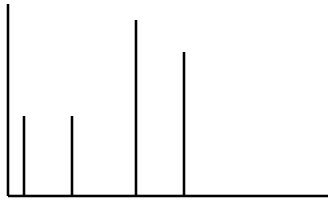
Conglomerate Crystals

Same Crystal Packing



Mirror Image Structures





1. Separate, Recrystallize a Pure Enantiomer
2. Compare its Pattern to the Crystals Growm From the Racemic Solution

If Patterns Same, it is a Conglomerate Mix

If Patterns Differ, the are Racemic Crystals

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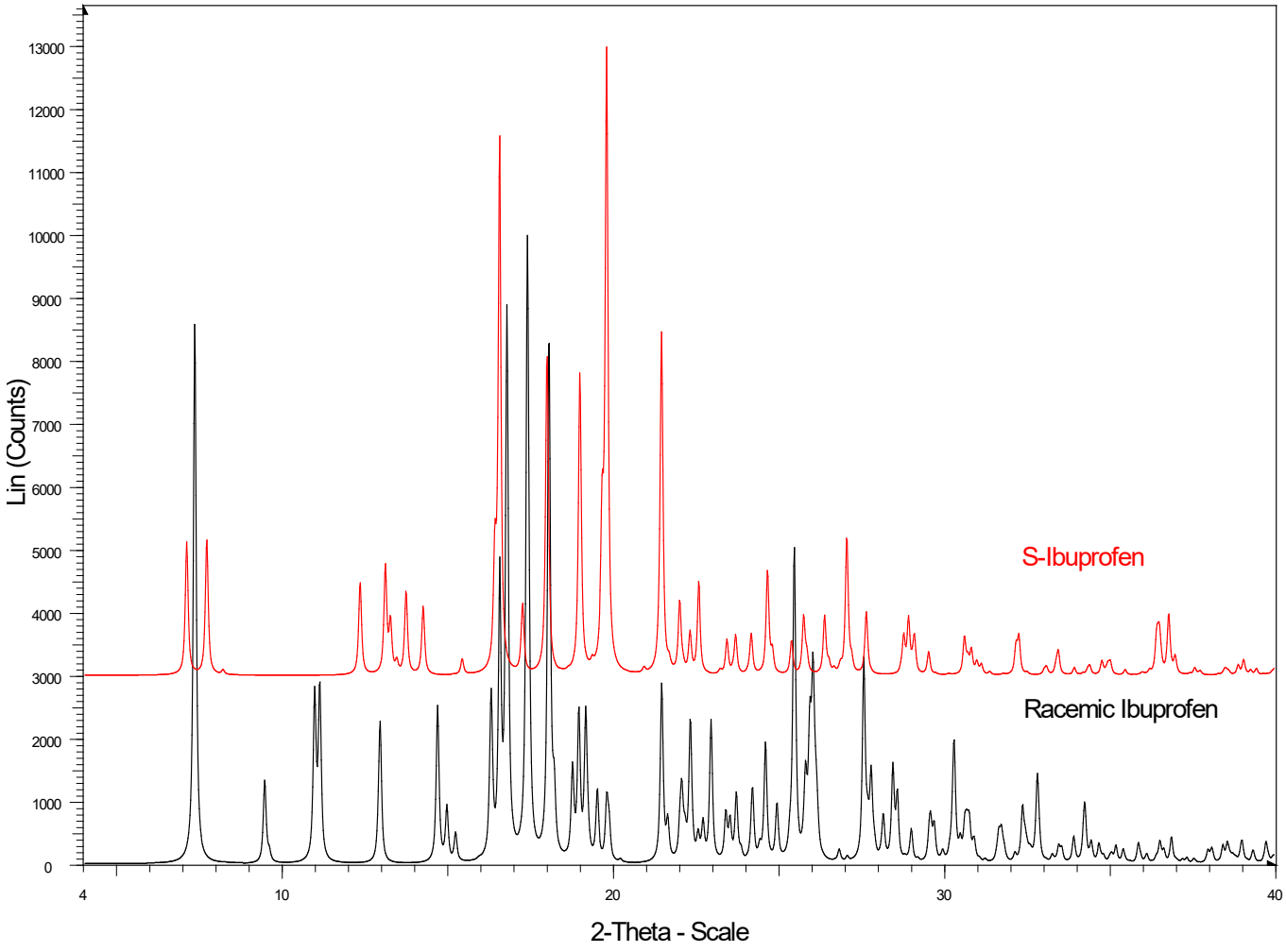
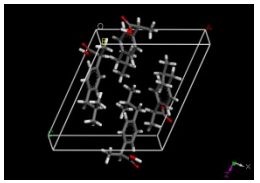
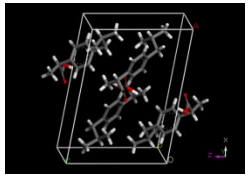
Classic Example (You see this 90% of the time)
True Racemic Crystal Versus its Pure Enantiomer





Monoclinic Space Group $P2_1$
a = 12.46 Å b = 8.08 Å c = 13.54 Å
Beta = 112.89



Monoclinic Space Group $P2_1/c$
a = 14.67 Å b = 7.89 Å c = 10.73 Å
Beta = 99.43°

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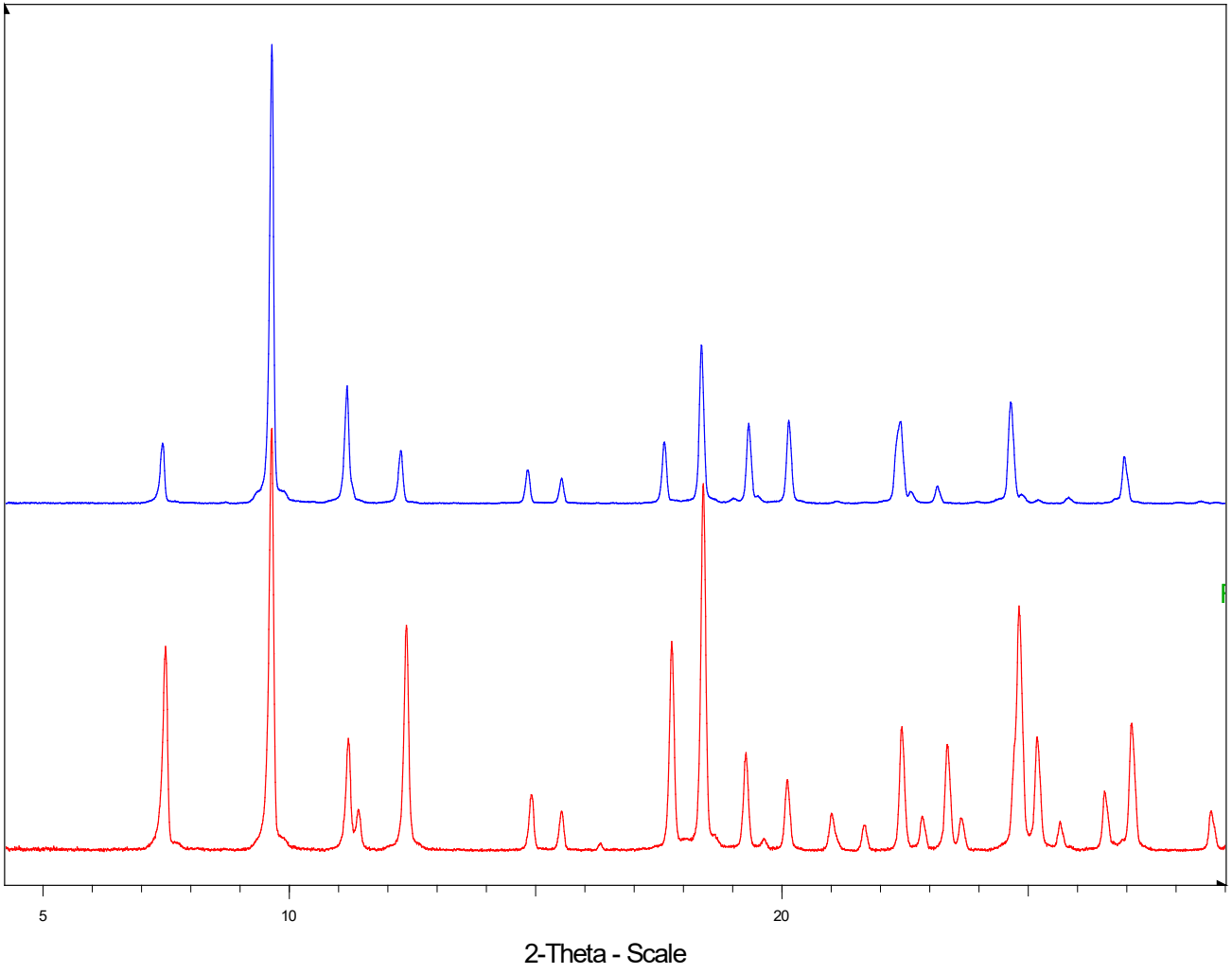
Similar Powder Patterns of Racemate and Form 1



Racemic Material
(Chiral LC 50%R/50%S)

ChiralPurity > 98%
R-enantiomer

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Differentiation of Conglomerate Mixtures from Racemates and Solid Solutions

Von H.W. Roozeboom

Zeit. Phyzik. Chemie **1899**, 28, 494.

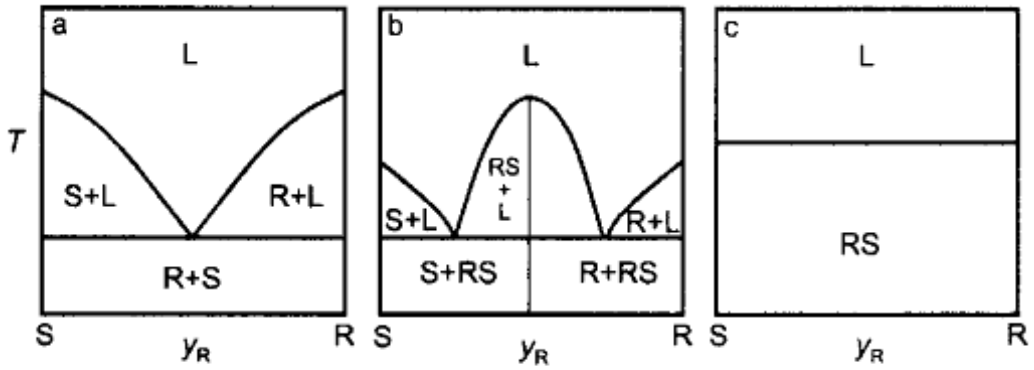

Figure 1. Binary phase diagram of enantiomer mixtures forming (a) a conglomerate, (b) a racemic compound, and (c) a solid solution.[2] *R*, *S*, *RS*, and L represent respectively solid *R*-enantiomer phase, solid *S*-enantiomer phase, racemic compound *RS*, or solid solution *RS* and liquid phase.

CRYSTAL GROWTH & DESIGN Article
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Sukanya Srisanga and Joop H. ter Horst*

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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:

Equation. 1 $\ln x = \Delta H^f_A / R \ (1/T^f_A - 1/T^f)$

where R = 1.9869 cal mol^{-1} K^{-1}, where x is the mole fraction of the more abundant enantiomer ($0.5 <= x <= 1$) of a mixture whose melting terminates at T^f (degrees K). ΔH^f_A, and T^f_A .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:

Eqn. 2 $\ln 4x\,(1-x) = 2\,\Delta H^f_R / R \ (1/T^f_R - 1/T^f)$

The same variables are used, however the enthalpy of fusion, ΔH^f_R, of the racemate and the temperature of melting of the racemic crystal, T^f_R, is used throughout this region of the phase diagram.

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

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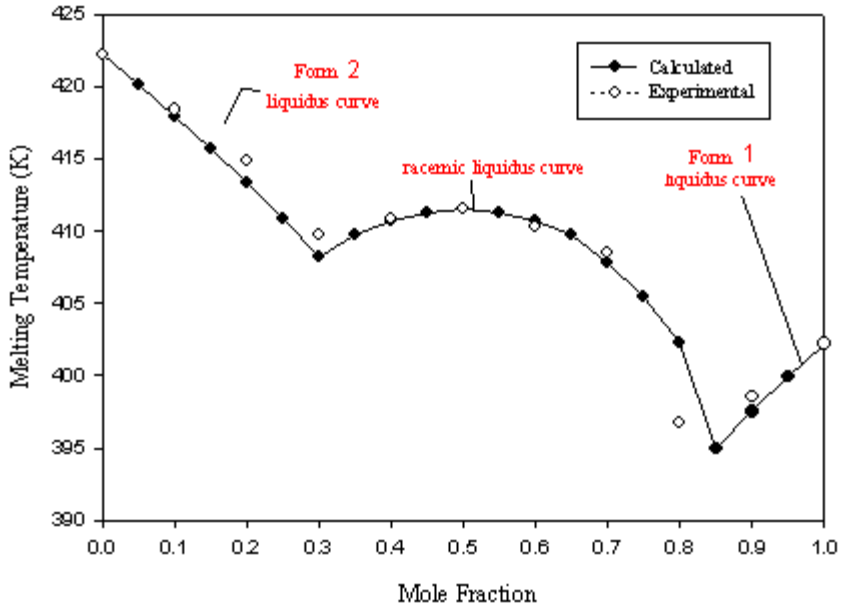
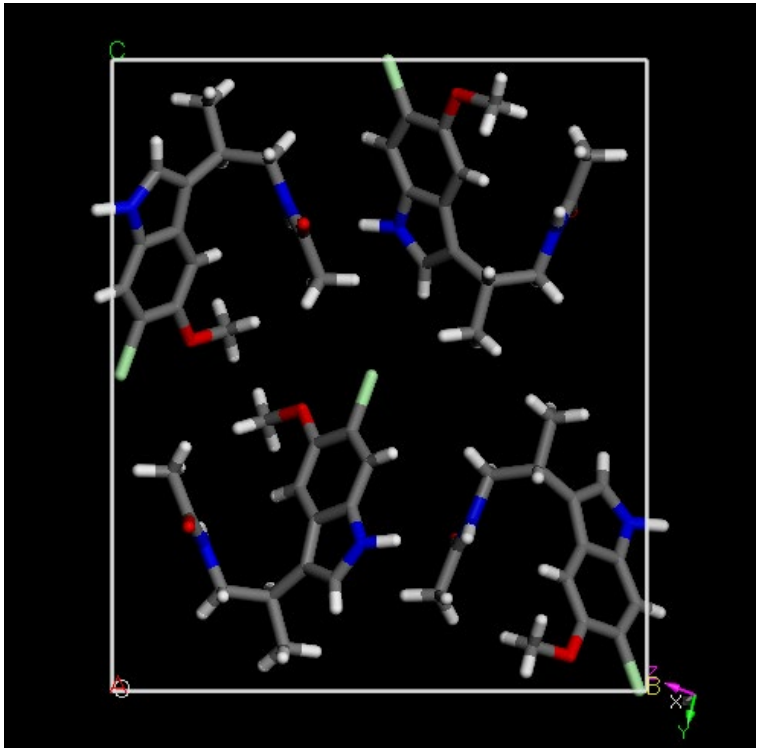
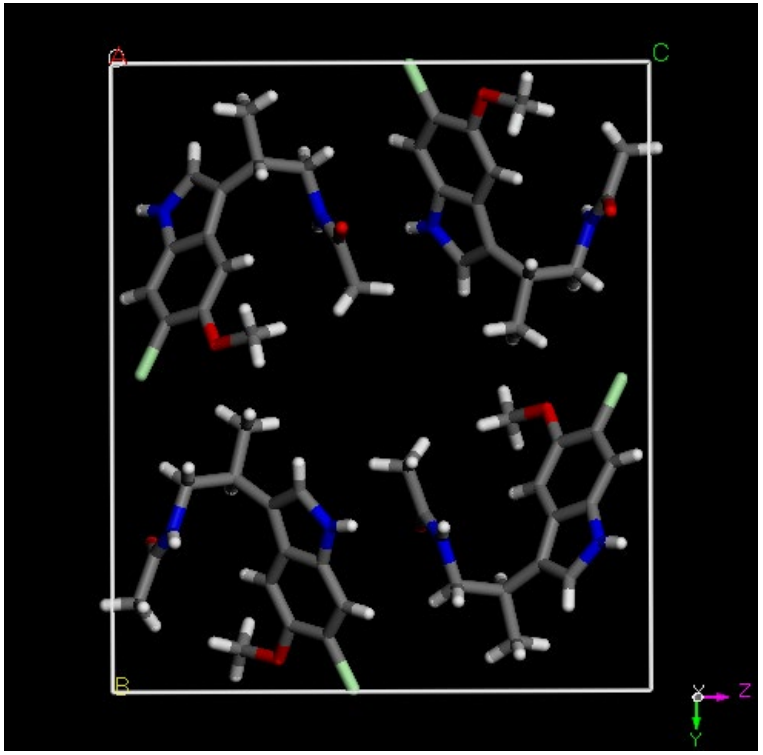
Melting Phase Diagrams Can Be Used to Establish Racemate Relation to Polymorphs



	Racemate	Form 1	Form 2	Hydrate
Onset Tm (°C)	136.08(0.41)	127.16(0.09)	147.39(0.08)	
Enthalpy of Fusion (kJ/mol)	32.9(.25)	28.2(0.4)	36.4(0.8)	NA
Density (g/cc @ 100K)	1.336	1.348	1.397	1.375

Comparison of Unit Cells Shows Similarity of Metrics





Enantiomer: Orthorhombic $P2_12_12_1$
a = 4.97 Å, b = 15.50 Å, c = 17.96 Å

V= 1383.64 Å ^{3}, Z=4, Z' =1

Racemate: Monoclinic $P2_1/c$
a = 4.94 Å, b = 18.14 Å, c = 15.61 Å
β = 92.951°
V = 1395.90 Å ^{3}, Z = 4, Z'= 1

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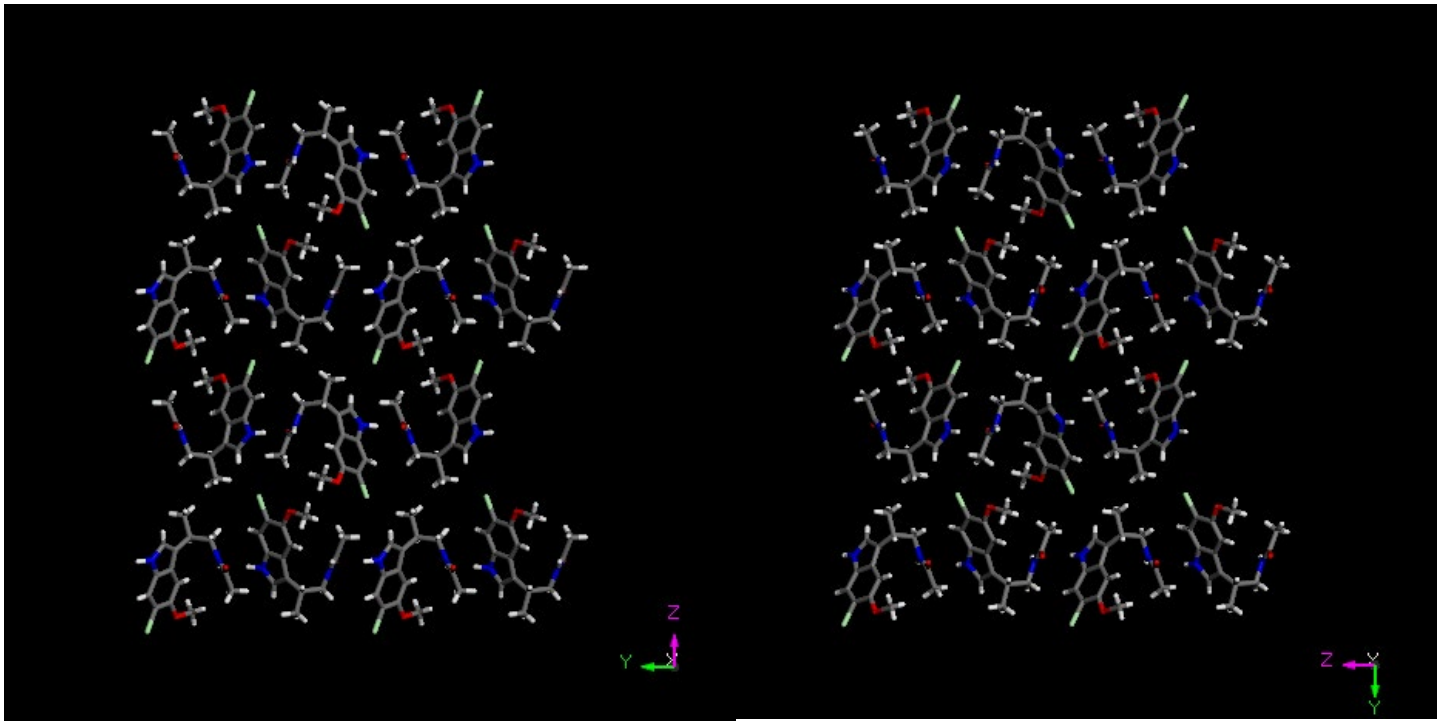
Answers That Matter.

Super Cell: Similarity of Structure is More Apparent

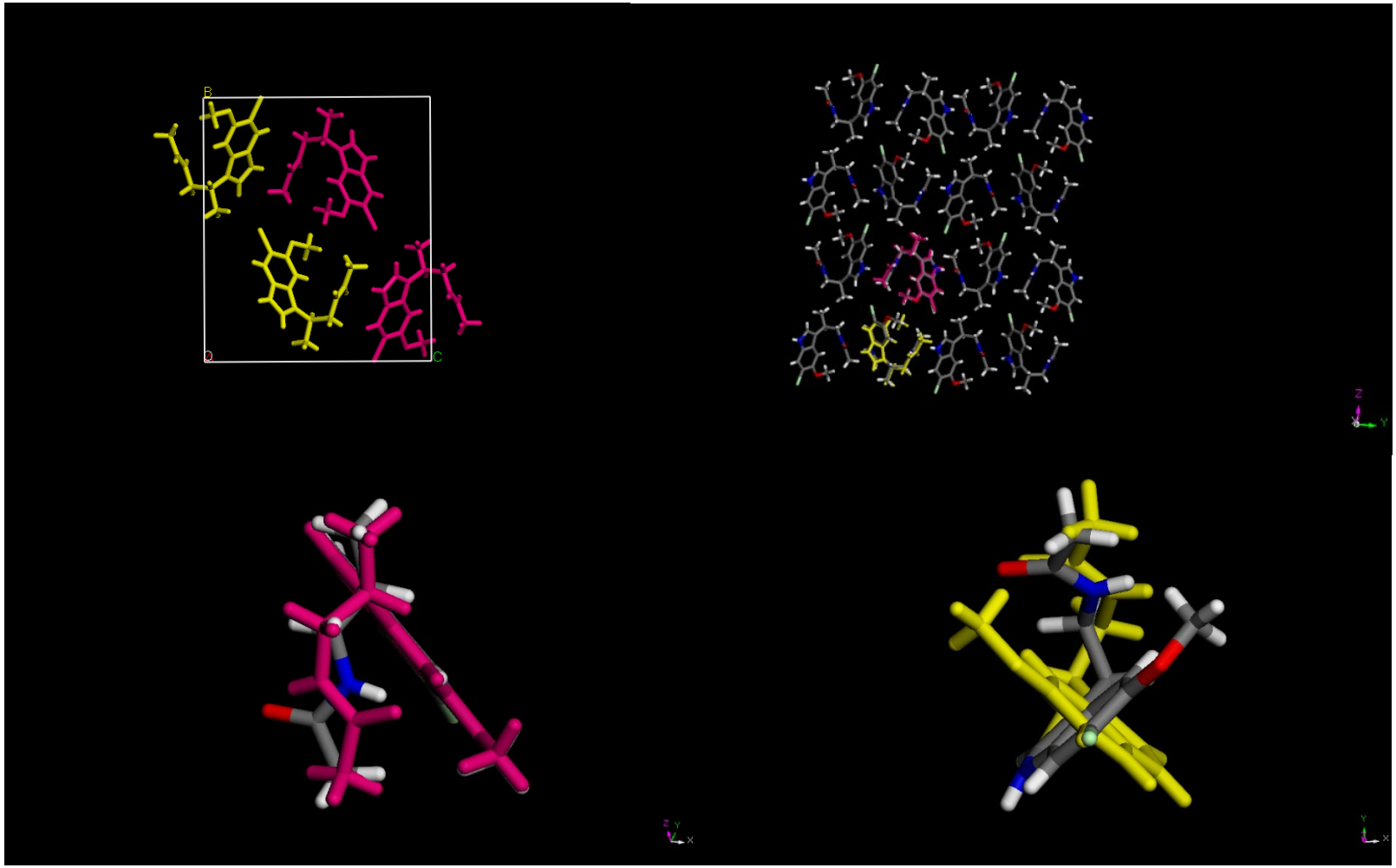


Chiral, Enantiopure
$P2_12_12_1$

Racemic, both enantiomers present in unit cell
$P2_1/c$

Answers That Matter.

A Closer Look Comparing Racemic Crystal Versus Chiral Form 1



Answers That Matter.

Comparison of Physical Properties

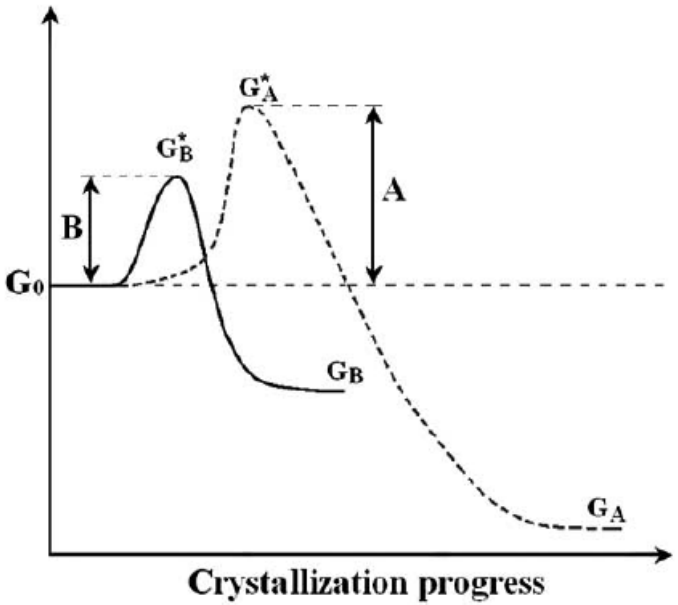


Fig. (3). Schematic diagram for the crystallization progress in a dimorphic system from the initial state, G_0, to two different polymorphs A or B. [6,8].

Diagram from Jie Lu and Sohrab Current Medicinal Chemistry, 2009, 16, 884-905.

Lilly
Answers That Matter.

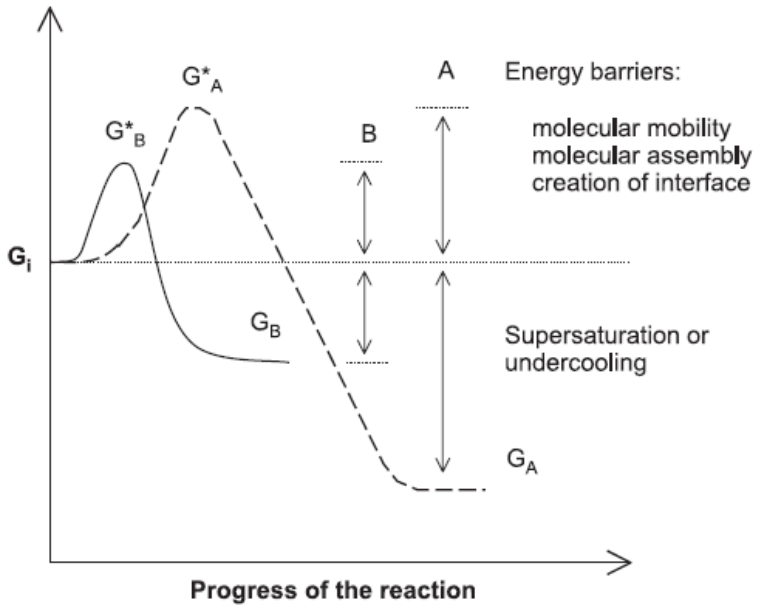


Fig. 5. Schematic diagram for a hypothetical transition from the initial state, G_i, to two different solid forms A or B, with free energies G_A and G_B. Form A is more stable and less soluble than B. A transition from the initial state G_i to state A or B will depend on the energy barrier and according to this reaction pathway the height of the energy barrier for structure A, $(G_A^* - G_i)$ is greater than that for B, $(G_B^* - G_i)$. Because the rate of nucleation is related to the height of the energy barrier on the reaction path, B will nucleate at a faster rate than A even though the change in free energy is greater for A $(G_A - G_i)$ than for B $(G_B - G_i)$.

Braun, Doris E.; Karamertzanis, Panagiotis G.; Arlin, Jean-Baptiste; Florence, Alastair J.; Kahlenberg, Volker Tocher, Derek A.; Griesser, Ulrich J.; Price, Sarah L. **Solid-State Forms of b -Resorcylic Acid: How Exhaustive Should a Polymorph Screen Be? Crystal Growth & Design (2011), 11(1), 210-220.**