Understanding the challenges associated with crystallising fluorinated APIs and intermediates

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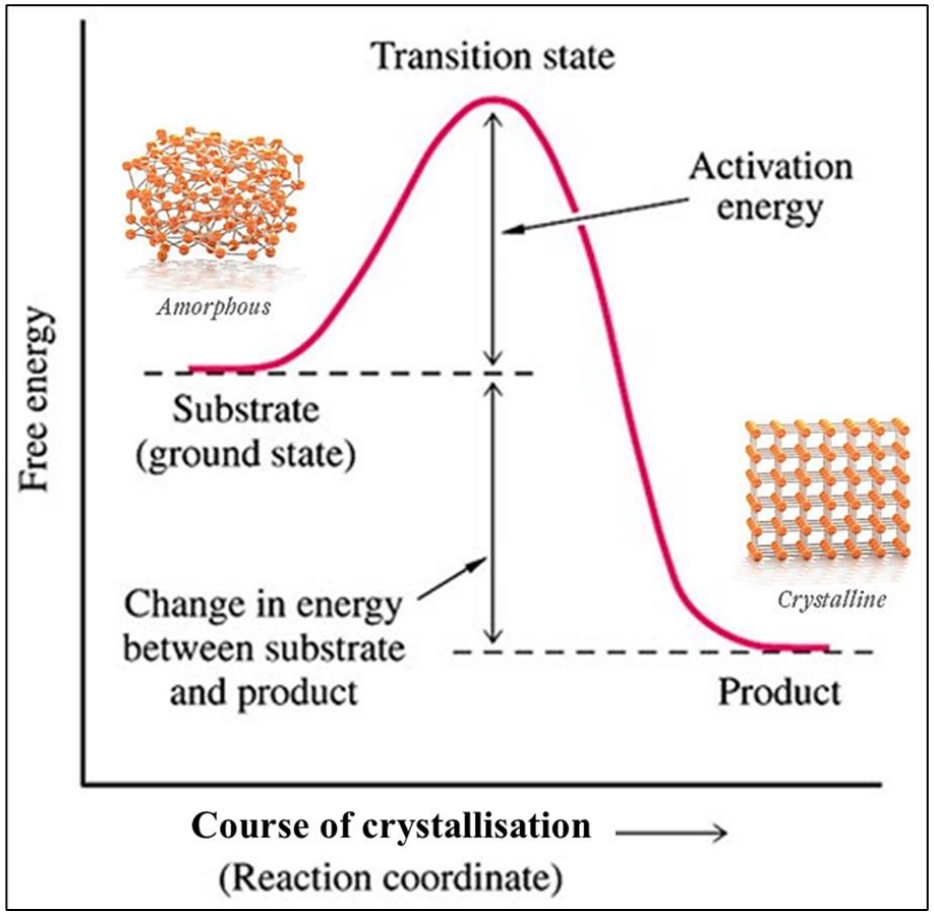
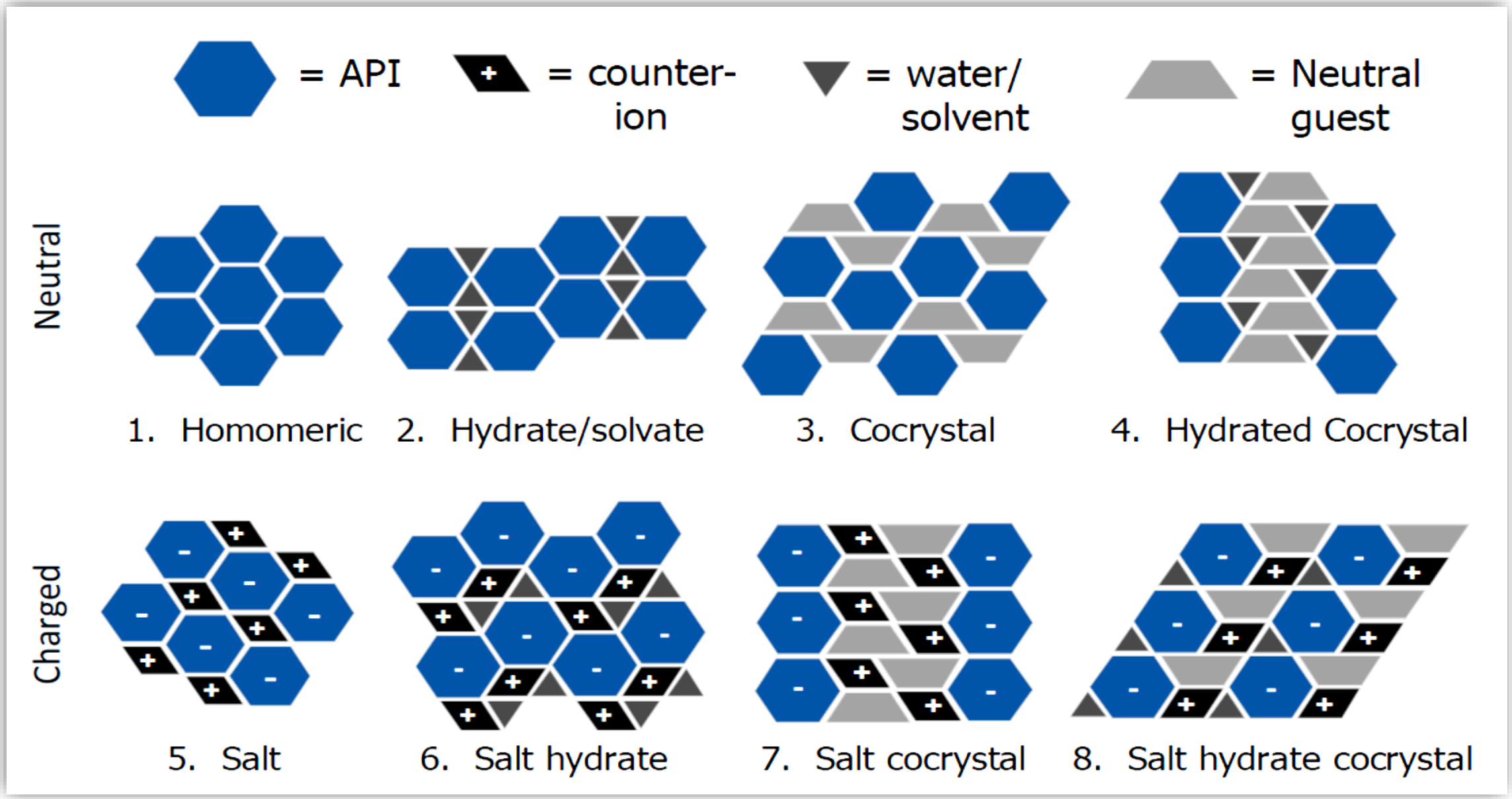
Crystallisation is *Difficult*

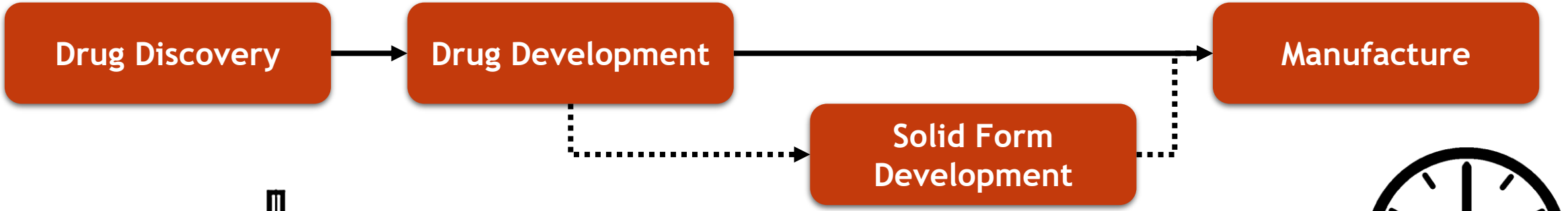
- Crystallisation involves the installation of directional intermolecular bonds. While energetically favoured, the process is not entropically favoured according to 2nd Law of Thermodynamics.
- Therefore, requires an energy input to overcome an energy barrier.

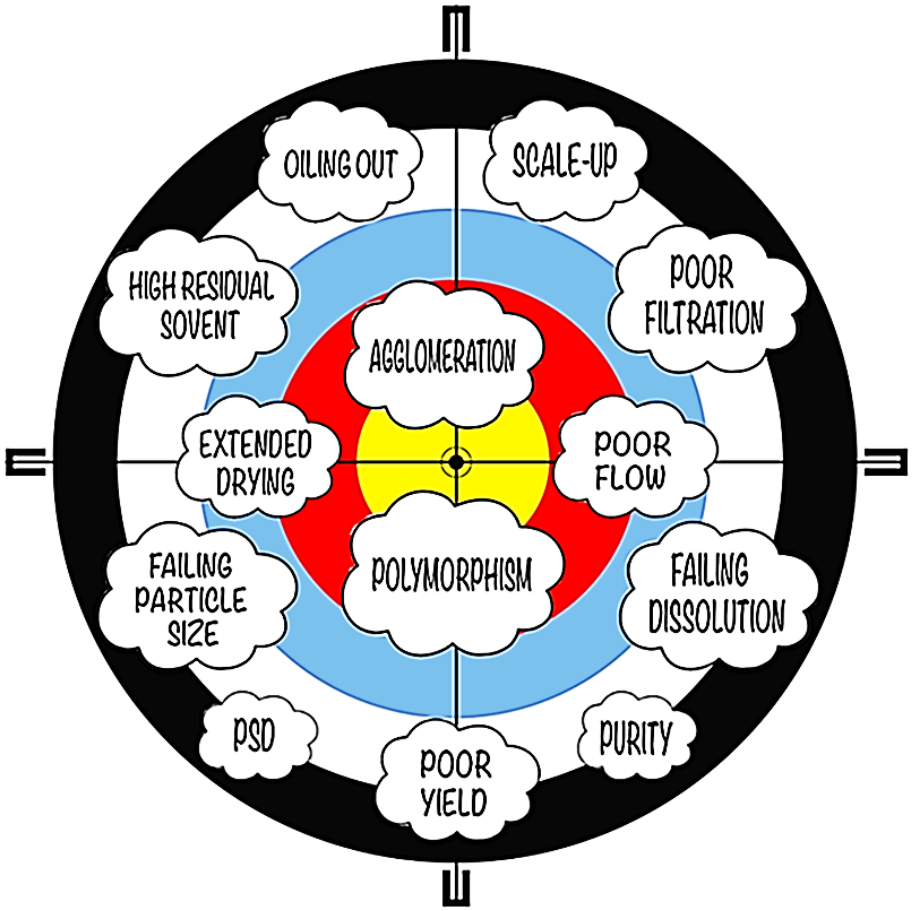


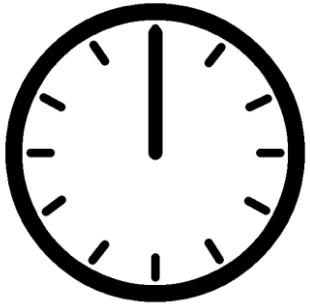
Crystalline Solid Forms

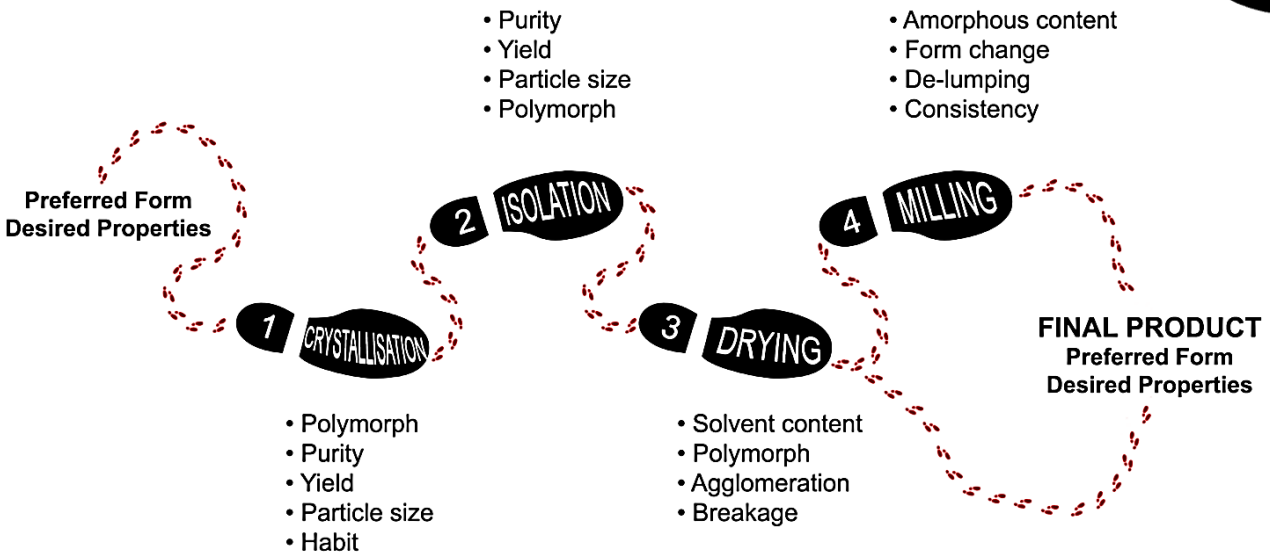


Solid Form Selection in Development





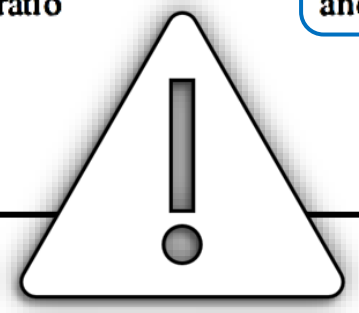




Methods for Crystallisation

Composition type		Process variables[a]				
Polymorph/ solvates	Salts/ co-crystals	Thermal	Anti-solvent	Evaporation	Slurry conversion	Other variables
▪ Solvent/ solvent combinations	▪ Counter-ion type	▪ Heating rate	▪ Anti-solvent type	▪ Rate of evaporation	▪ Solvent type	▪ Mixing rate
▪ Degree of supersaturation	▪ Acid/base ratio	▪ Cooling rate	▪ Rate of anti-solvent addition	▪ Evaporation time	▪ Incubation temperature	▪ Impeller design
▪ Additive type	▪ Solvent/ solvent combinations	▪ Maximum temperature	▪ Temperature of anti-solvent addition	▪ Carrier gas	▪ Incubation time	▪ Crystallization vessel design (including capillaries, etc.)
▪ Additive concentration	▪ Degree of super-saturation ▪ Additive type and concentration ▪ pH ▪ Ionic strength	▪ Incubation temperature(s) ▪ Incubation time	▪ Time of anti-solvent addition	▪ Surface-volume ratio	▪ Thermal cycling and gradients	

[a] Applicable to all types of screens.



Lots of experiments

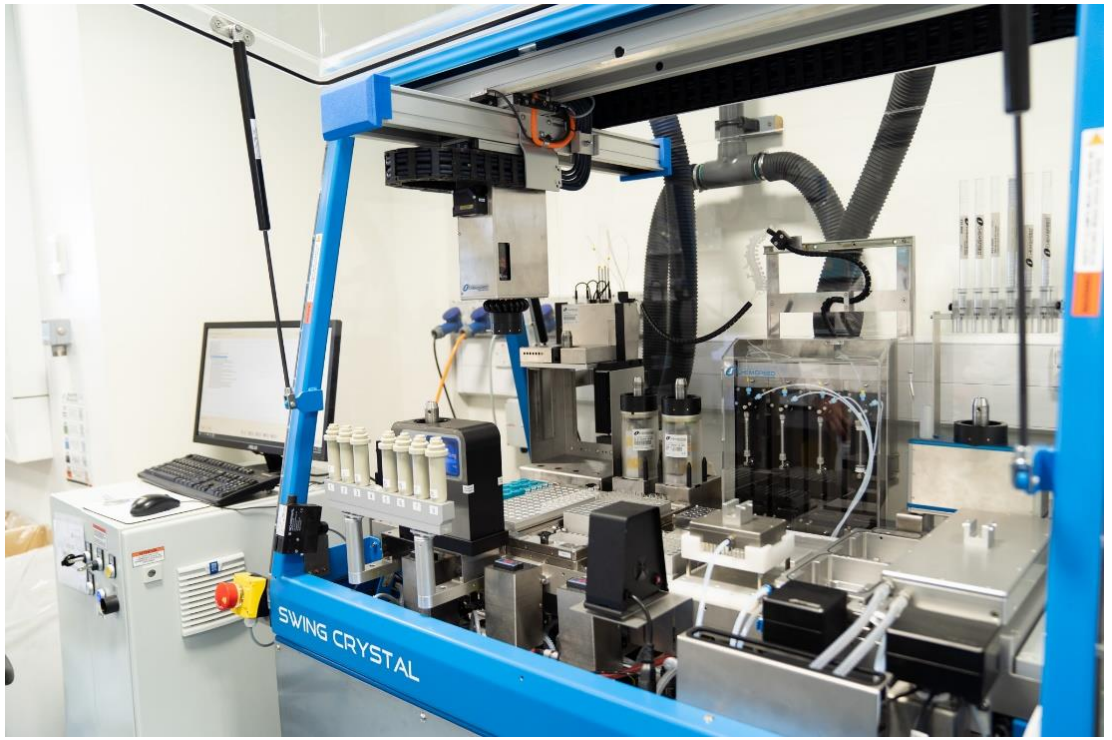
Adv. Drug Delivery Rev. **2004**, ***56***, 275

High Throughput Screening

- Robotic screening is a very useful tool when used in conjunction with manual solid form screening processes.
- By automating processes, a wider variety and combinations of solvents, counterions, coformers, and temperatures can be screened.
- The thermodynamic form can be identified quicker, in less experiments.

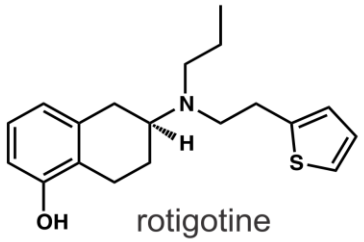
A robot chemist at the University of Liverpool, UK, sifts through thousands of materials to find a photocatalyst.
Credit: Univ. Liverpool

Nature, **2019**, *568*, 577

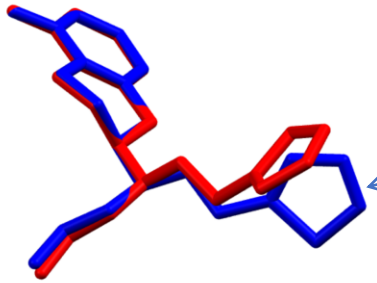


Crystallising the Wrong Form: Rotigotine

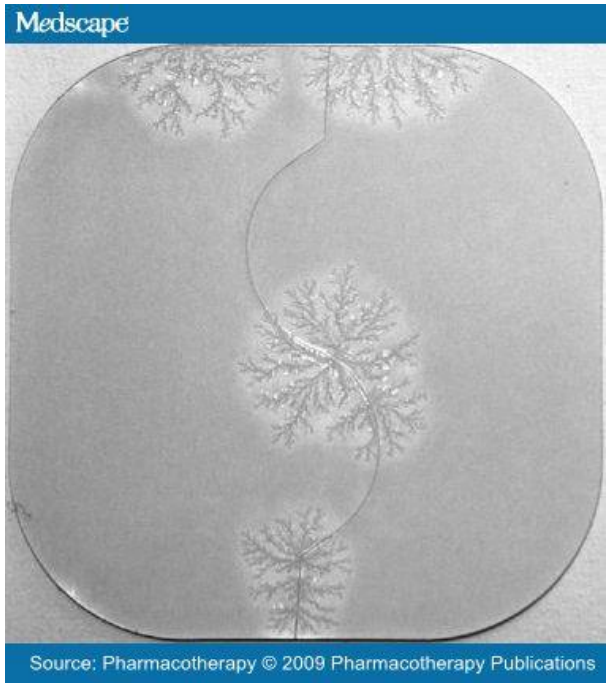
- Dopamine agonist initially prescribed for the treatment of Parkinson's disease, and later approved for moderate-to-severe cases of restless-legs syndrome (*Neupro*, UCB)
- Administered through a transdermal patch to minimize the unpleasant side effects of the drug
- Approved by the European Medicines Agency (EMEA) for use in Europe and then by the FDA for the US market in 2007.
- 2008: new crystal form - unexpected, as the drug had been established since the 1980s and no polymorphism had been observed
- UCB continued to supply *Neupro*® in Europe, specific batches were recalled and replaced by batches that were refrigerated immediately after manufacture
- *Neupro*® became temporarily unavailable in the US
- 2012: Return on the market (new formulation)
- Origin of the phase transition is still not known



rotigotine



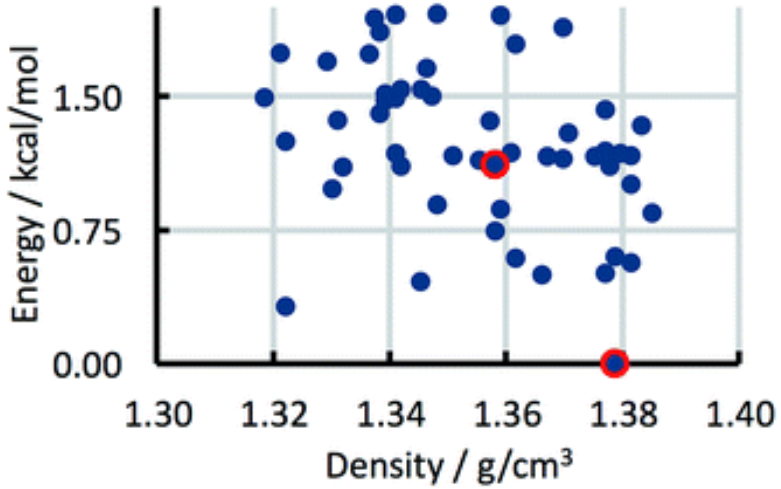
New form



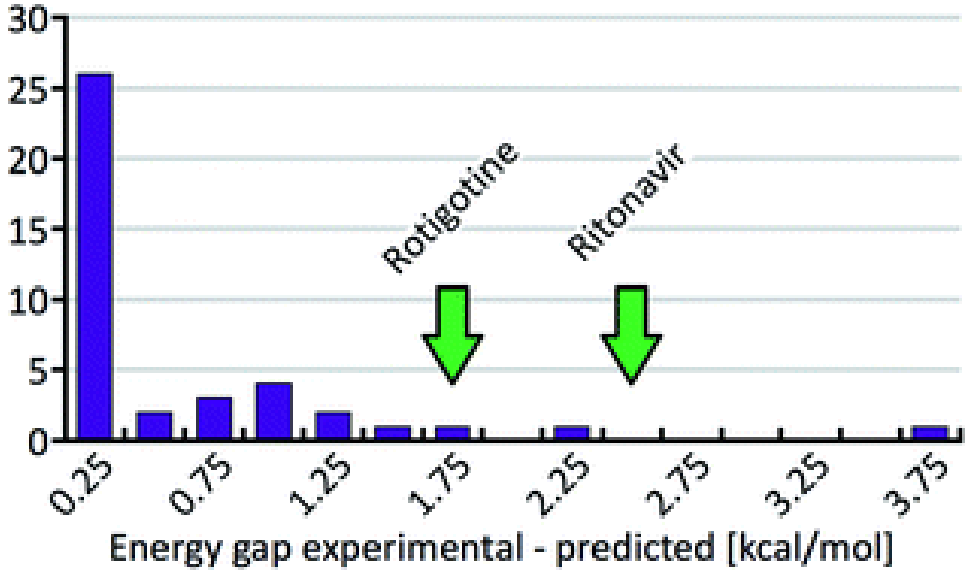
J. Pharm. Sci. **2015**, *104*, 4117

Could Rotigotine Happen Again?

"Based on a thorough and critical analysis of the commercial crystal structure prediction studies of 41 pharmaceutical compounds, we conclude that for between 15 and 45% of all small molecule drugs currently on the market, the most stable experimentally observed polymorph is not the thermodynamically most stable crystal structure and that the appearance of the latter is kinetically hindered"



Example energy landscape

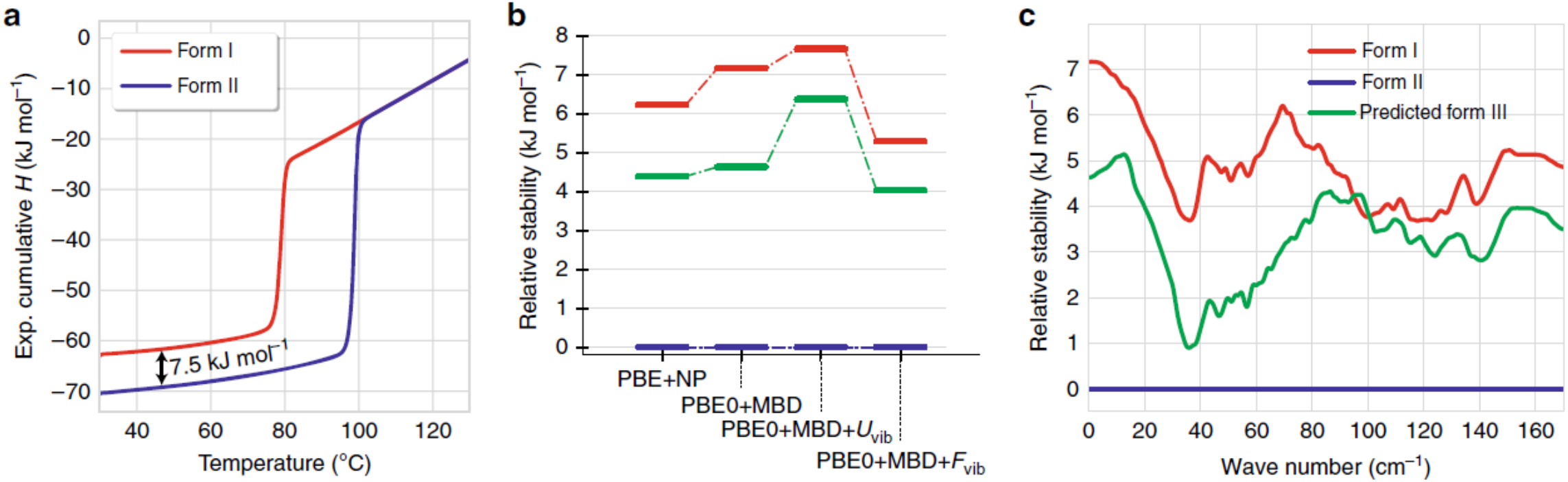


Histogram summary of the study

Commun. Chem. **2019**, *2*, 70

Rotigotine: Predicted Form III….

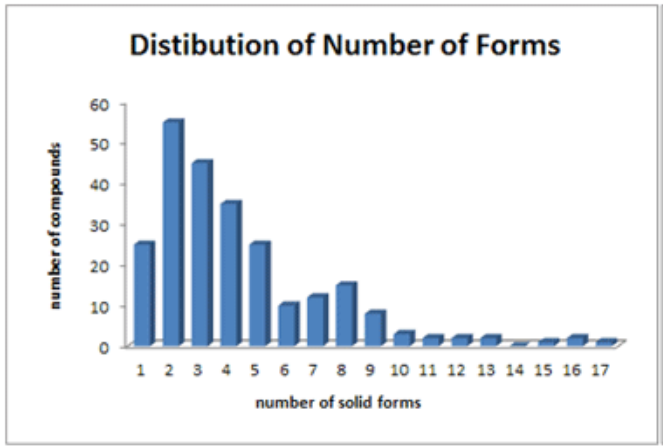
- The relative stabilities of predicted rotigotine structures were refined using DFT using many-body van der Waals dispersion interactions, electron exchange, and vibrational free energies
- Energy difference between Forms I and II predicted to be 7.5 kJ.mol^{-1}, in excellent agreement with experimentally derived difference of 7.6 kJ.mol^{-1}
- Form III was predicted to be approximately 2 kJ.mol^{-1} from Form I…

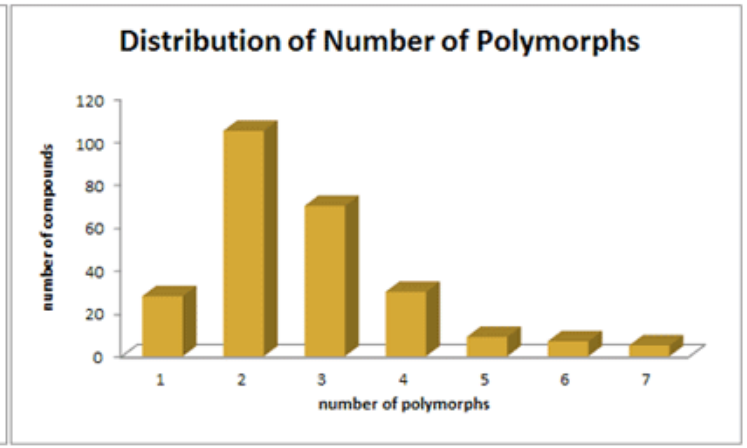


Commun. Chem. **2019**, *2*, 70

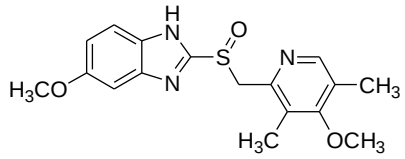
Many Different Types of Polymorphism

Solid crystalline phases of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state; polymorphs are indistinguishable in the liquid, gaseous, or dissolved states

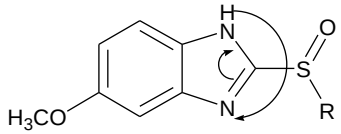


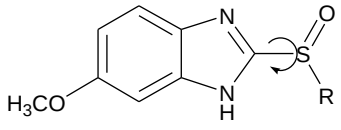


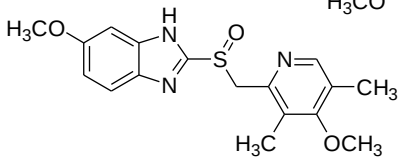
Tautomeric Polymorphism (omeprazole)



5-methoxy

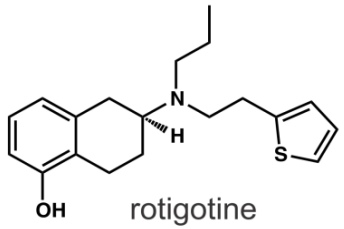




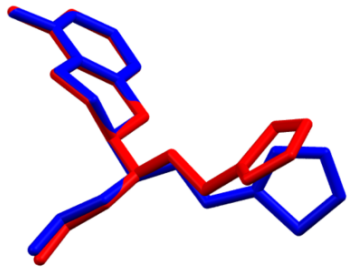


6-methoxy

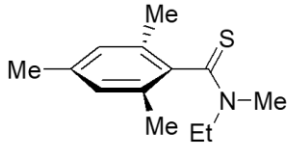
Conformational Polymorphism

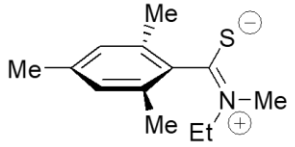


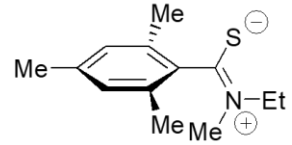
rotigotine



Configurational Polymorphism





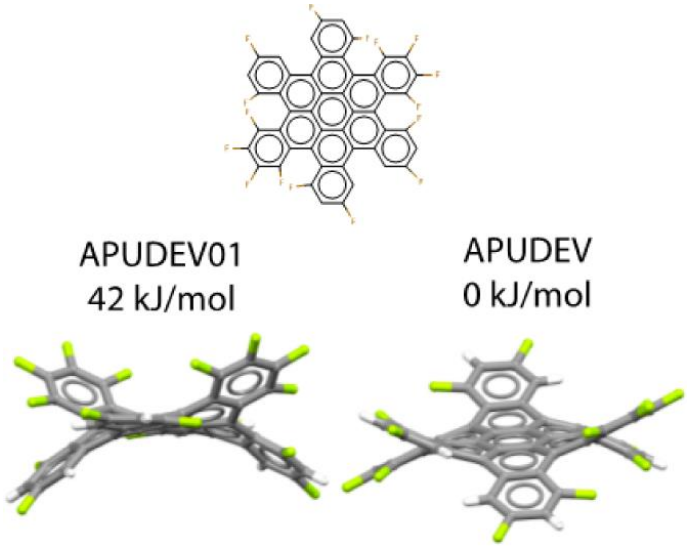


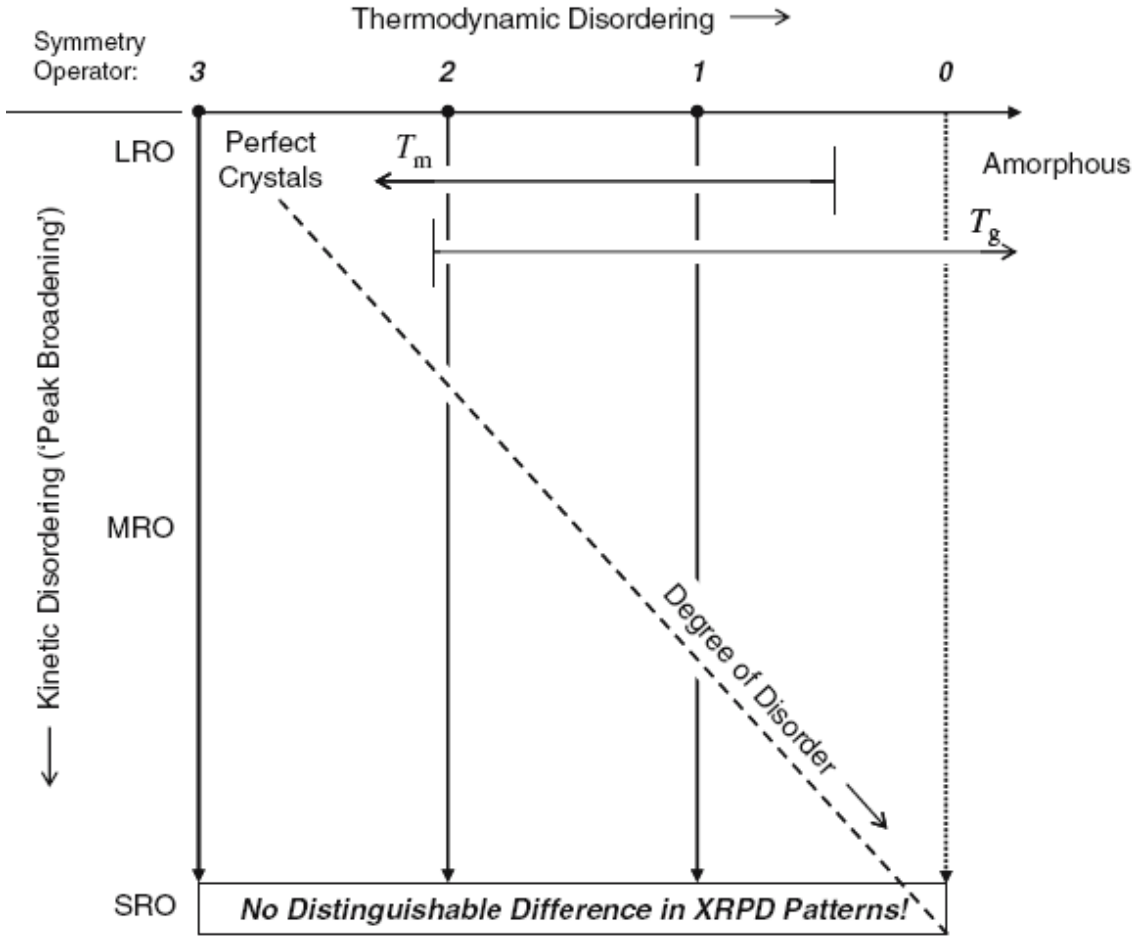
68% in solution at equilibrium 32%

mp 59-60 °C solid mp 98-99 °C

Conformational Polymorphism vs Disorder

- Conformational polymorphism arises due to molecular flexibility about certain bonds
- A review of the Cambridge Structural database showed conformational polymorphism is exhibited by 36.2% of molecules and 39.1% of flexible polymorphs
- Conformational polymorphism may lead to differences in crystallinity and select physical properties
  - Solubility
  - Dissolution
  - Melt point
  - Stability

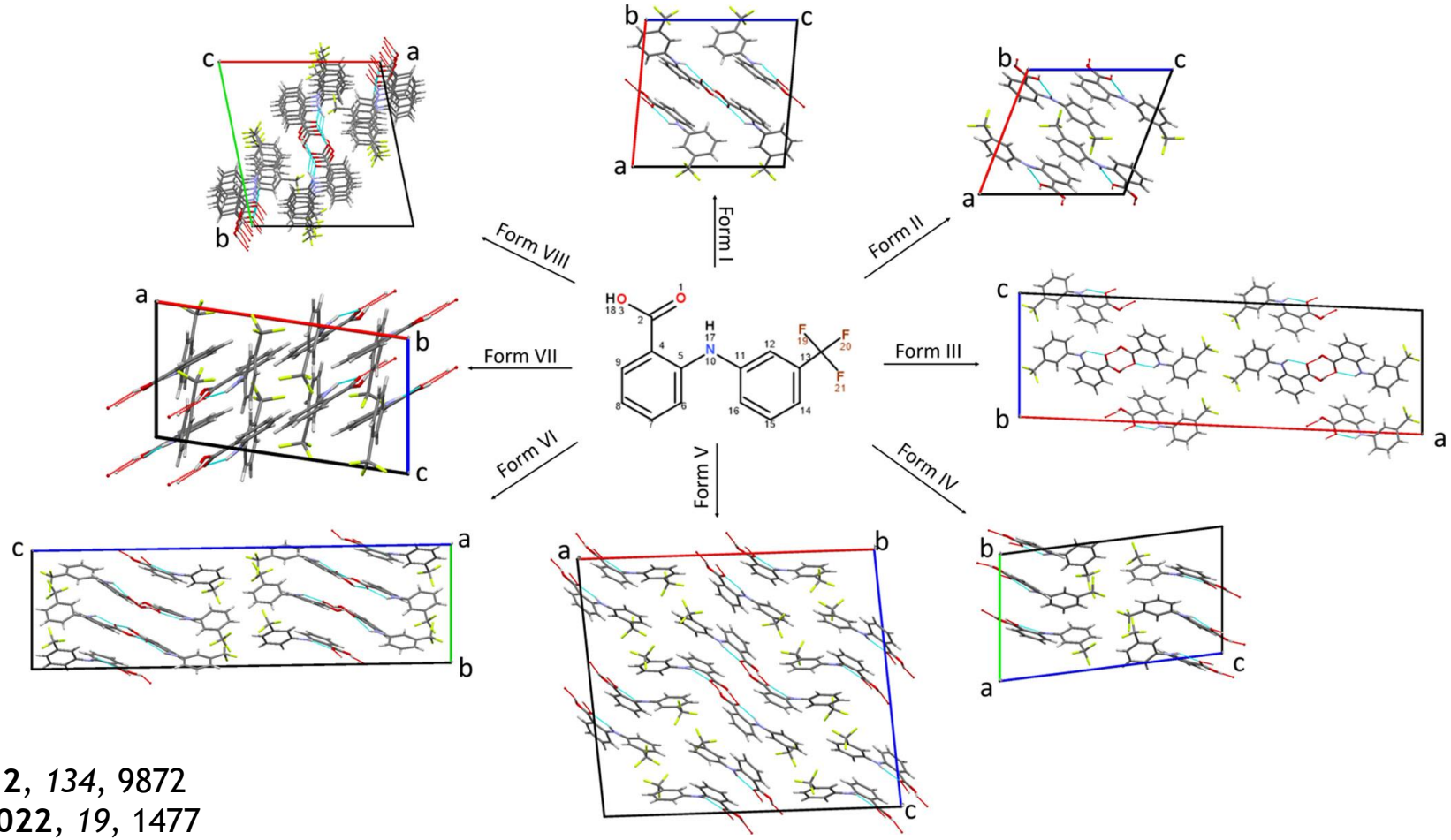




Chem. Pharm. Res. ***2006***, *23*, 2333
Chem. Rev. **2014**, *114*. 2170
Org. Lett. **2010**, *12*, 4840

The Polymorphic Landscape of Flufenamic Acid

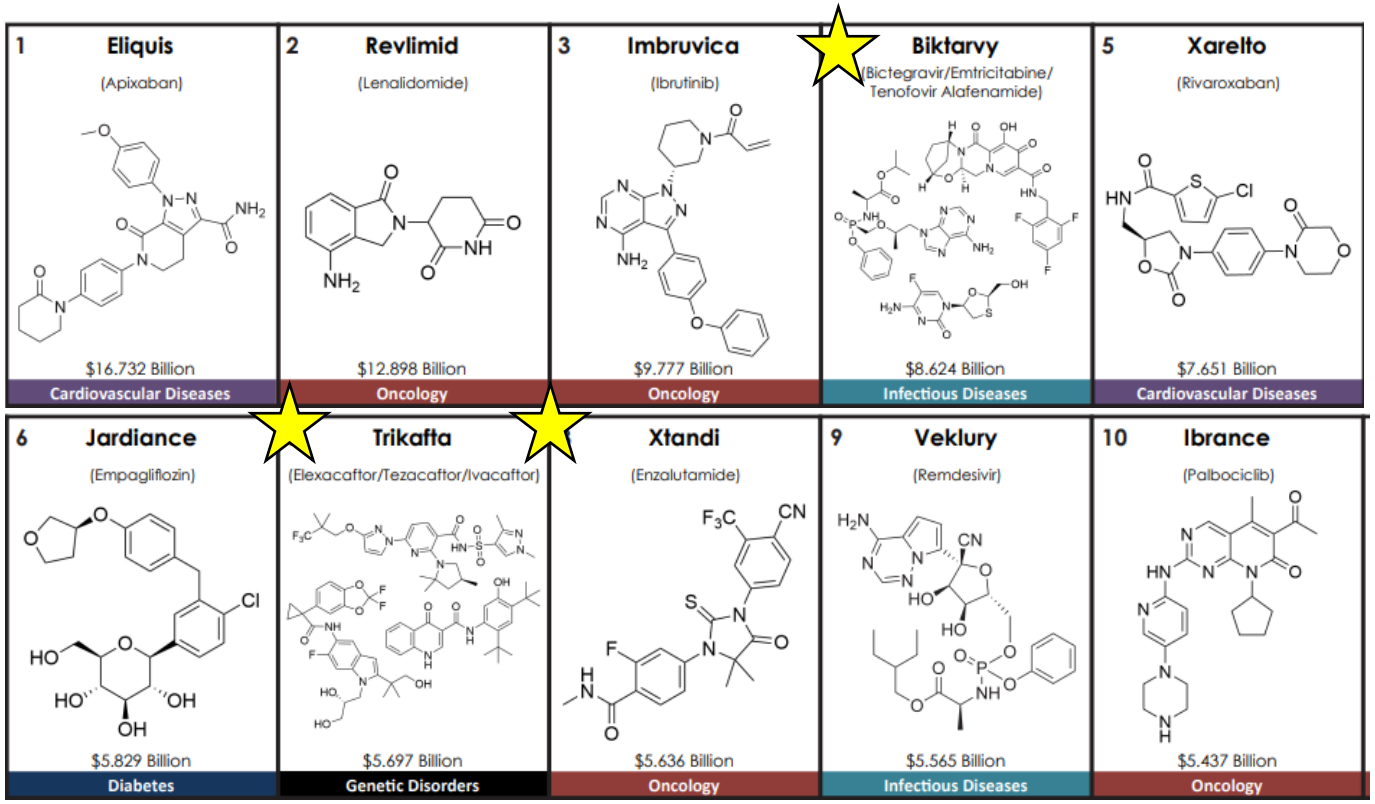
- A polymorphic non-steroidal anti-inflammatory.
- Elucidation of the first crystal structure was performed in 1973 and all nine polymorphs were accessed through polymer-induced heteronucleation in 2012 by Matzger *et al*. All contained strong hydrogen bonded dimers.



J. Am. Chem. Soc **2012**, *134*, 9872
Mol. Pharmaceutics **2022**, *19*, 1477

Fluorinated APIs

- In 2021, three of the ten top selling small molecule APIs were fluorinated:
  - Biktarvy for infectious diseases (HIV/AIDS), combined sales of $8.6B
  - Trikafta for genetic disorders, combined sales of $5.7B
  - Xtandi for oncology, combined sales of $5.6B



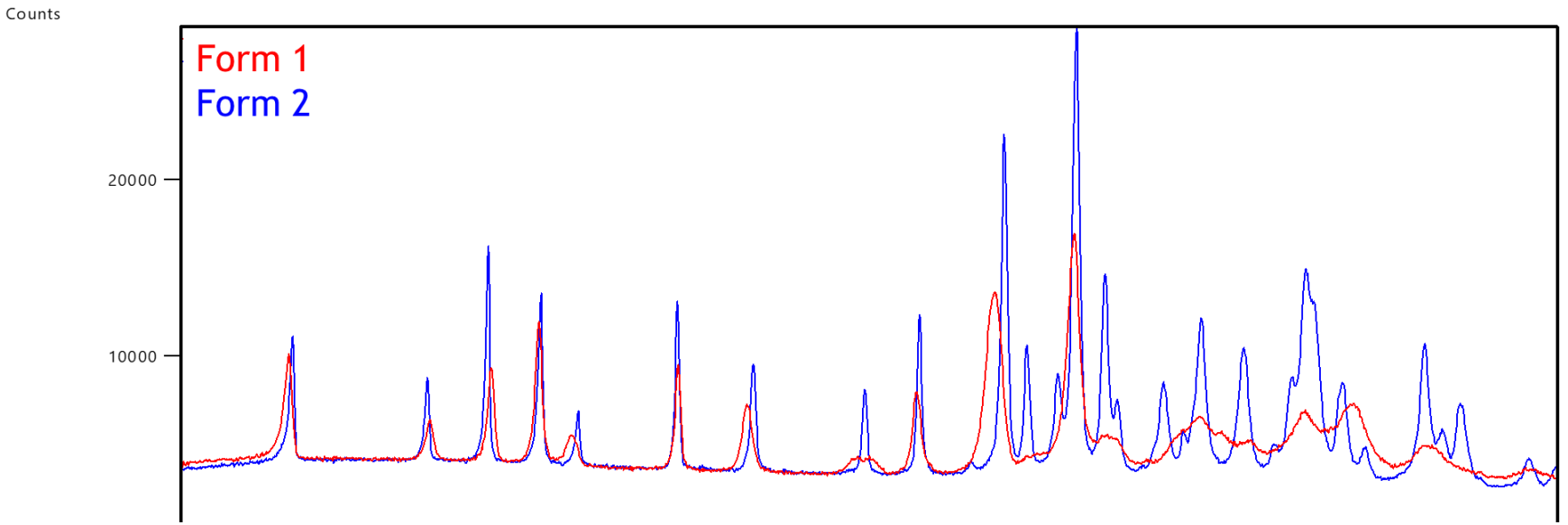
https://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/files/Top%20200%20Small%20Molecules%202021V3.pdf

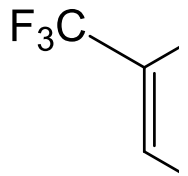
Fluorinated Approvals in 2023

- So far in 2023, 7 of the 22 FDA approvals are fluorinated:
  - Pfizer's **Paxlovid**, a combination of nirmatrelvir and ritonavir, for the treatment of COVID-19.
  - Blue Earth Therapeutic's **Posluma** (Flotufolastat F18), for PET of a target specific to prostate cancer.
  - Bausch + Lomb and Novaliq's **Miebo**, perfluorocyclohexyloctane, for the treatment of dry eye disease.
  - Astellas' **Veozah**, containing fezolinetant, for the treatment of vasomotor symptoms due to menopause.
  - Pharming's **Joenja**, containing leniolisib, for the treatment of APD syndrome.
  - Reata's **Skyclarys**, containing omaveloxolone, for the treatment of Friedreich's ataxia.
  - Lilly's **Jaypirca**, containing pirtobruntinib, a kinase inhibitor for the treatment of refractory mantle cell lymphoma.

Crystallisation of a Challenging API

- Polymorphism exhibited by a fluorinated API isn't always as obvious, nor easy to identify.
- A detailed polymorph screen was conducted on a rigid, fluorinated API using a range of standard and non-standard techniques. Multiple solvated and hydrated forms were identified.
- Of these, two forms, Form 1 and Form 2, were found to be closely related.
- A request was made to clarify the two forms due to their substantial differences by XRPD.

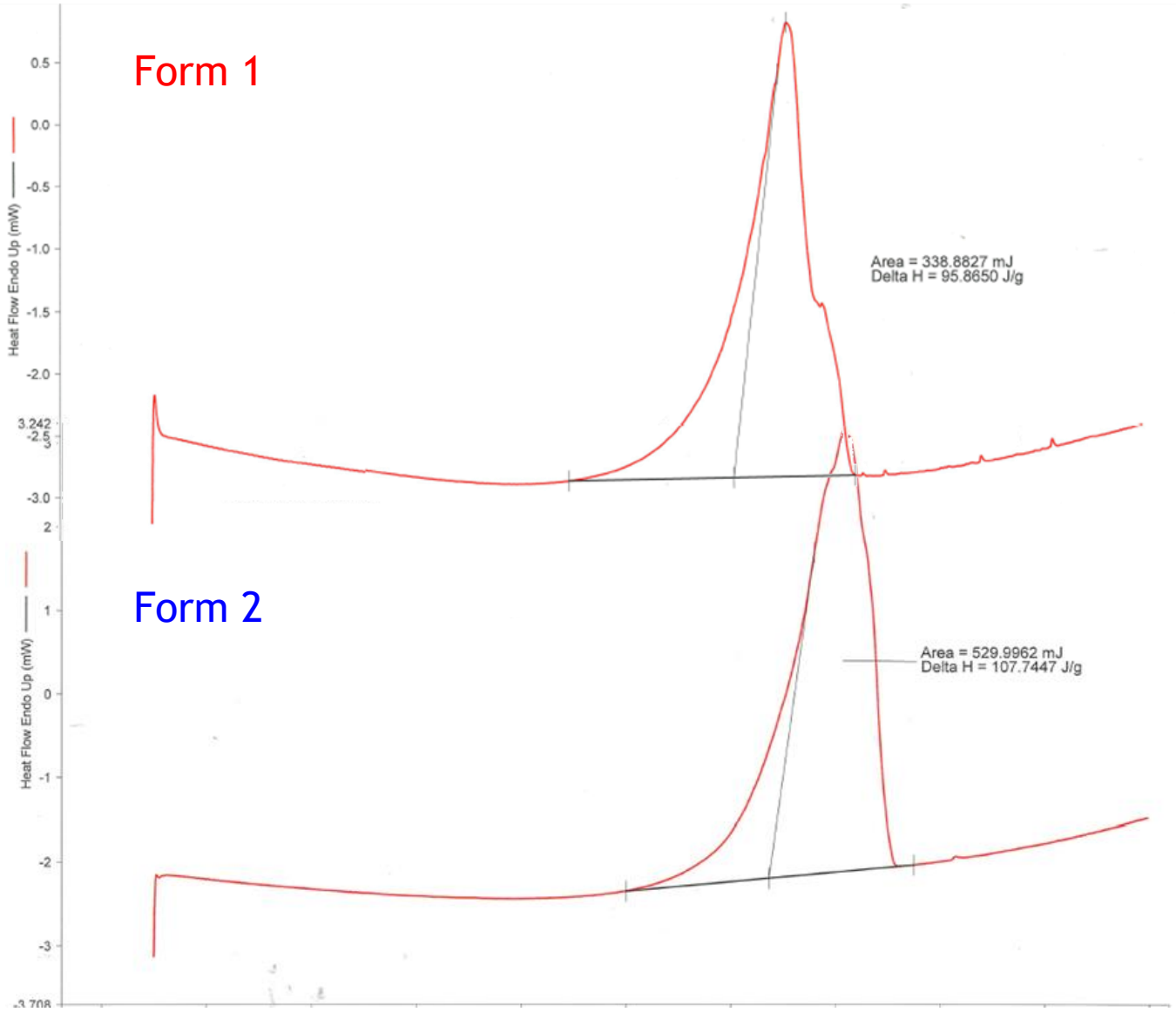




Close Thermal Relationships Between Polymorphs

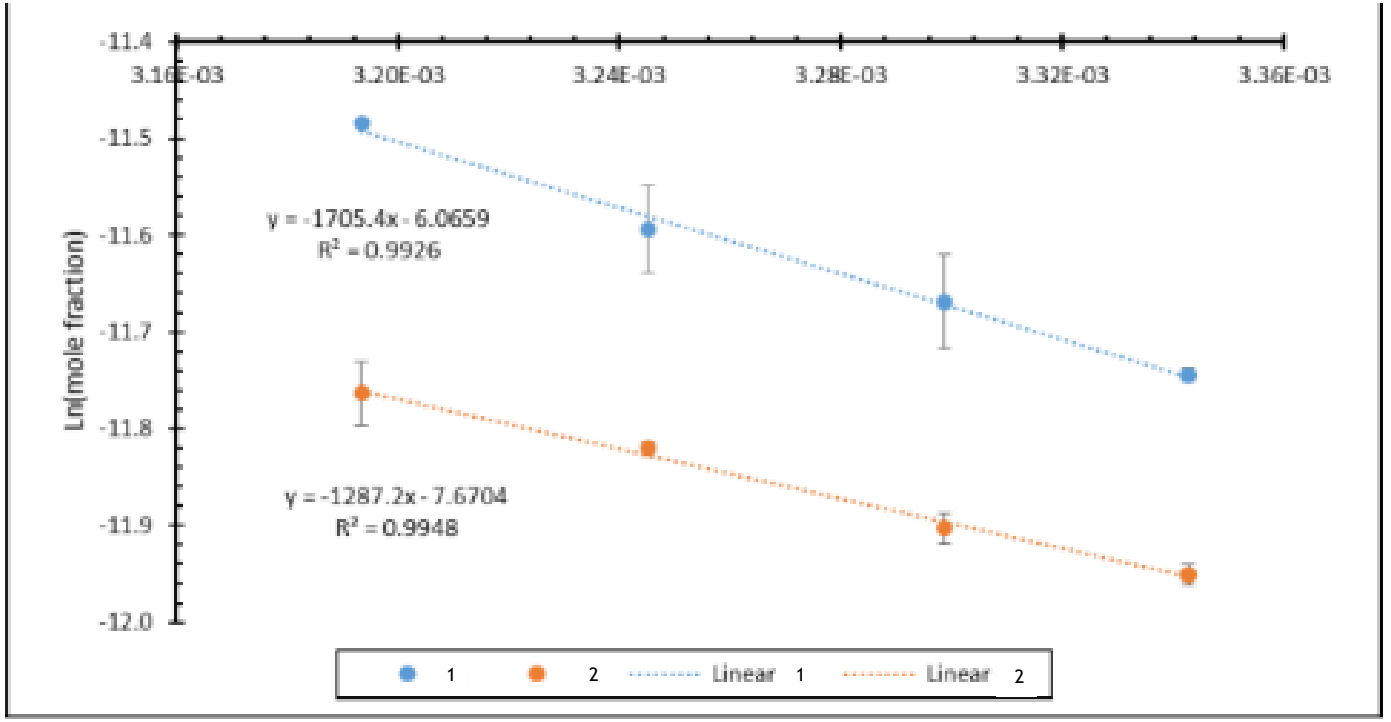
- Thermal analysis of the two forms found them to be closely related, exhibiting only a 11.9 J/g difference in enthalpy
  - Form 1: 95.9 J/g
  - Form 2: 107.7 J/g
  - 5.5 KJ/mol energy difference

- Further investigation into the relationship showed a key thermal relationship:
  - Form 1 was most stable below 22°C
  - Form 2 was most stable above 50°C



van’t Hoff Solubility

- A key method of evaluating the thermodynamic relationship between forms is *via* a solubility *versus* temperature study (ln mole fraction vs 1/absolute temperature)
- van’t Hoff solubility measurements in MIBK confirmed a difference in solubility between the two forms whereby both increased in solubility as temperature increased
- A lack of intersection between the lines suggested a montropic relationship between the two but it would be likely that the lines intersect at sub-zero temperatures



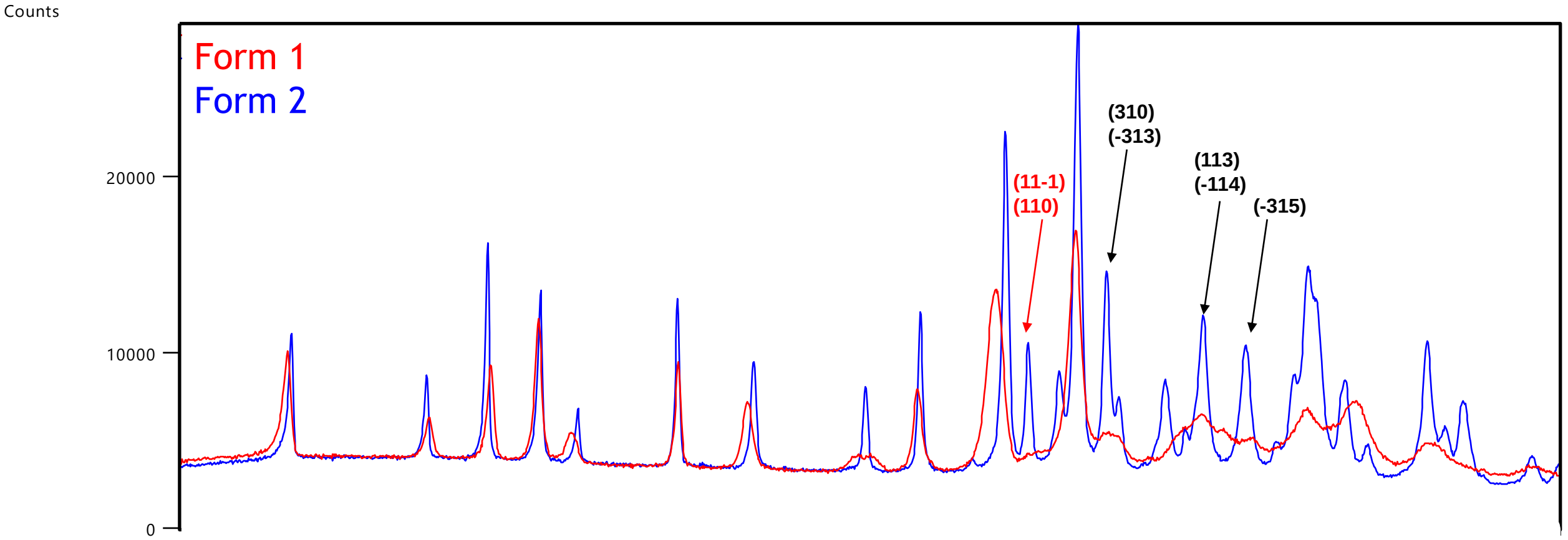
Single Crystal X-ray Analysis and Plane Analysis

- Single crystal analysis of Form 2 showed a common feature of -CF_3 containing moieties.

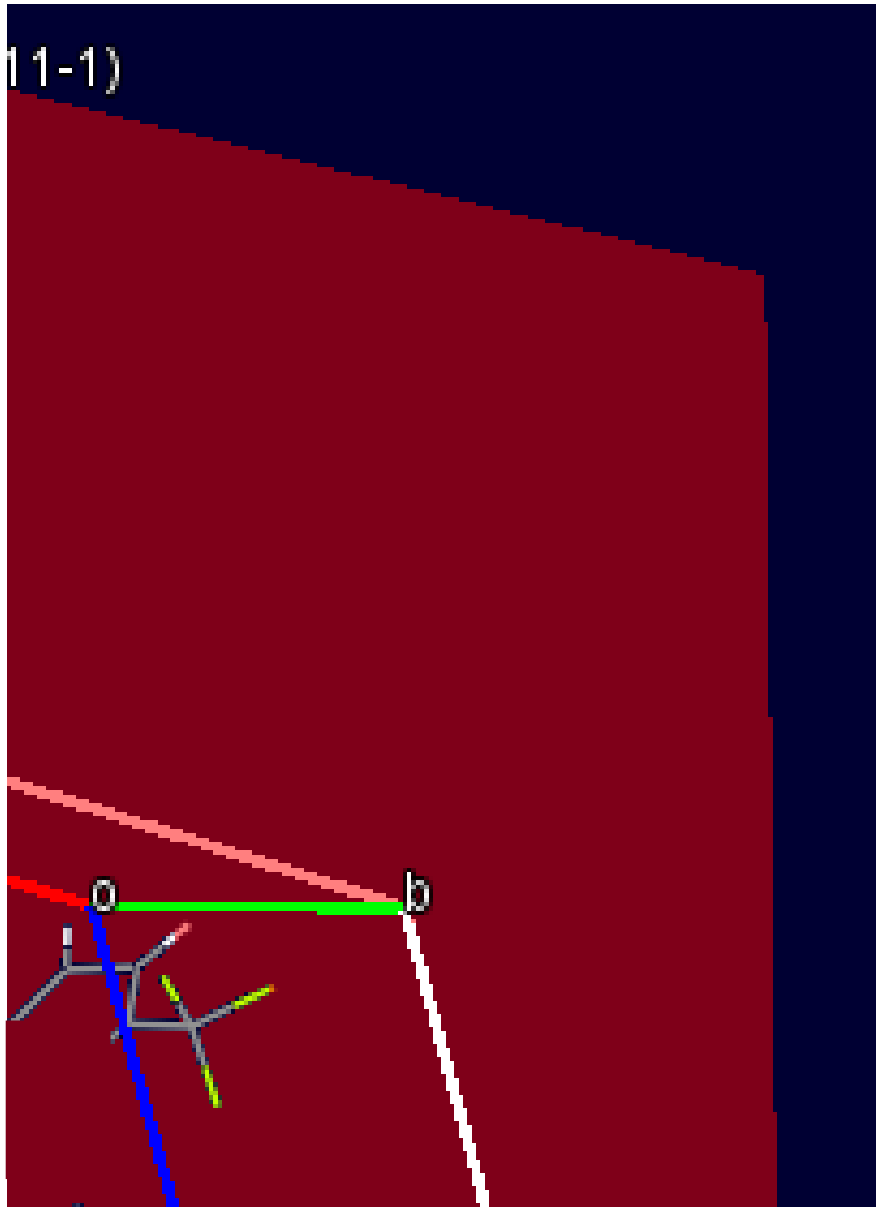
- Calculation of select planes of electron density within the crystal structure of Form 1 indicated that shifted peak positions between Forms 1 and 2 was due to configurational disorder within the aromatic CF_3 moiety.

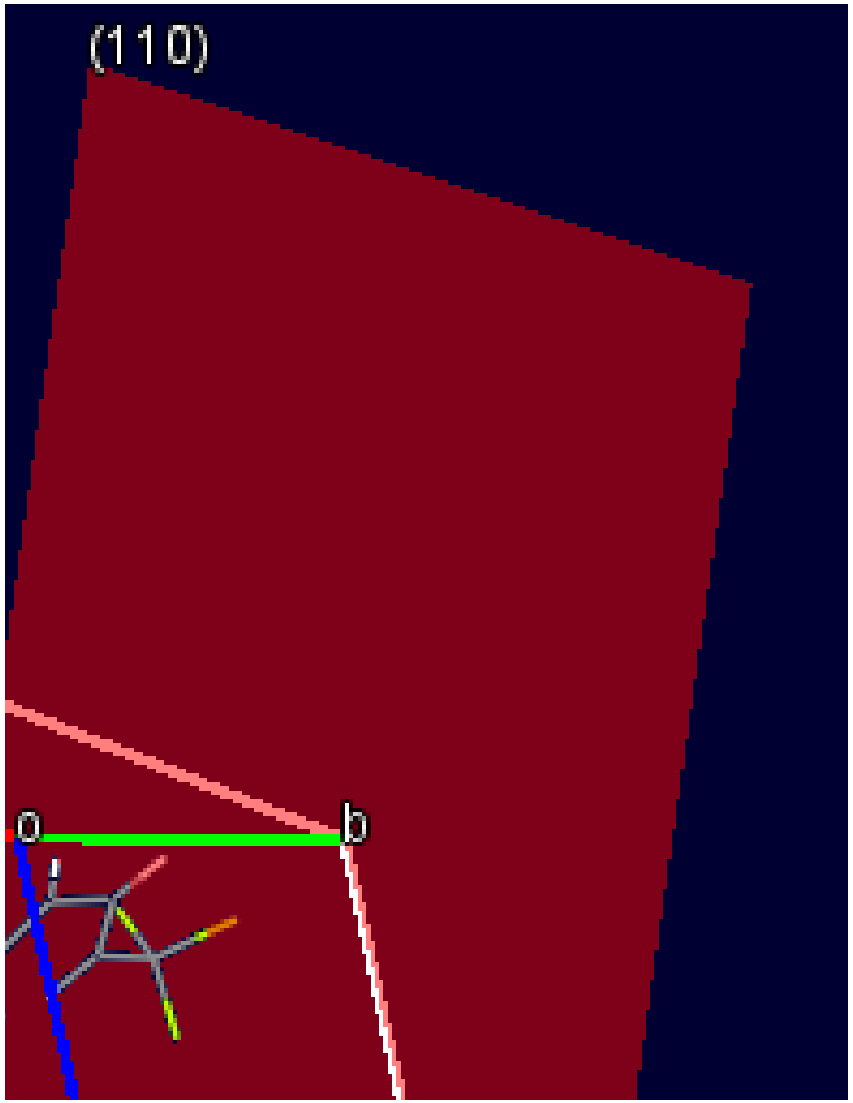
- Key planes were identified:
  - (113) and (-114); Form 2 peak
  - (310) and (-313); Form 2 peak
  - (11-1) and (110); Form 2 peak
  - (-315); Form 2 peak

XRPD Plane Calculations

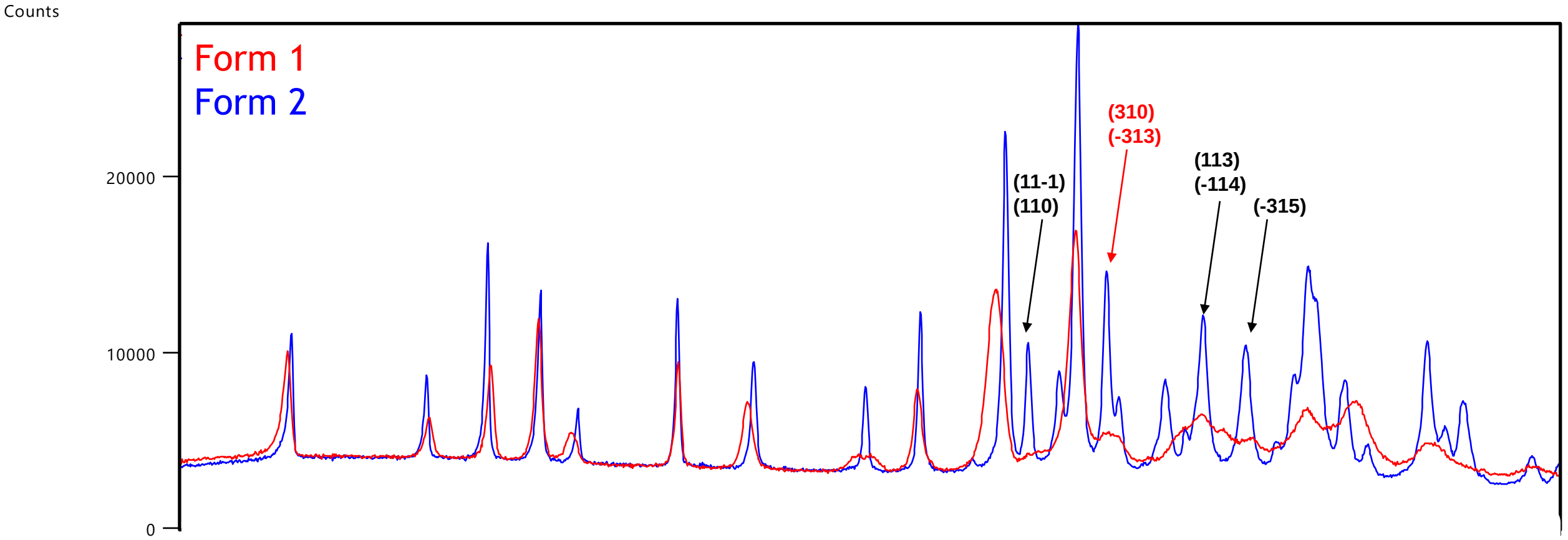


(11-1) and (110); Form 2 peaks

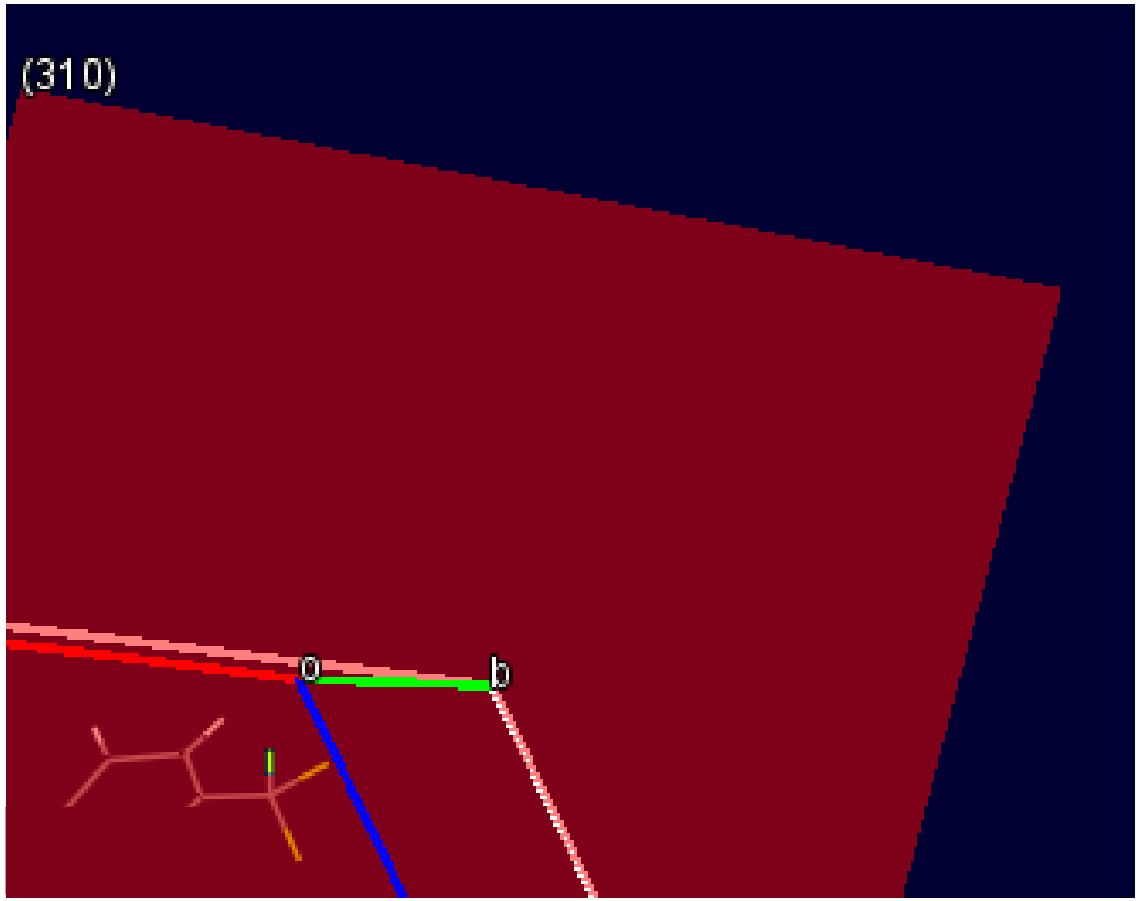


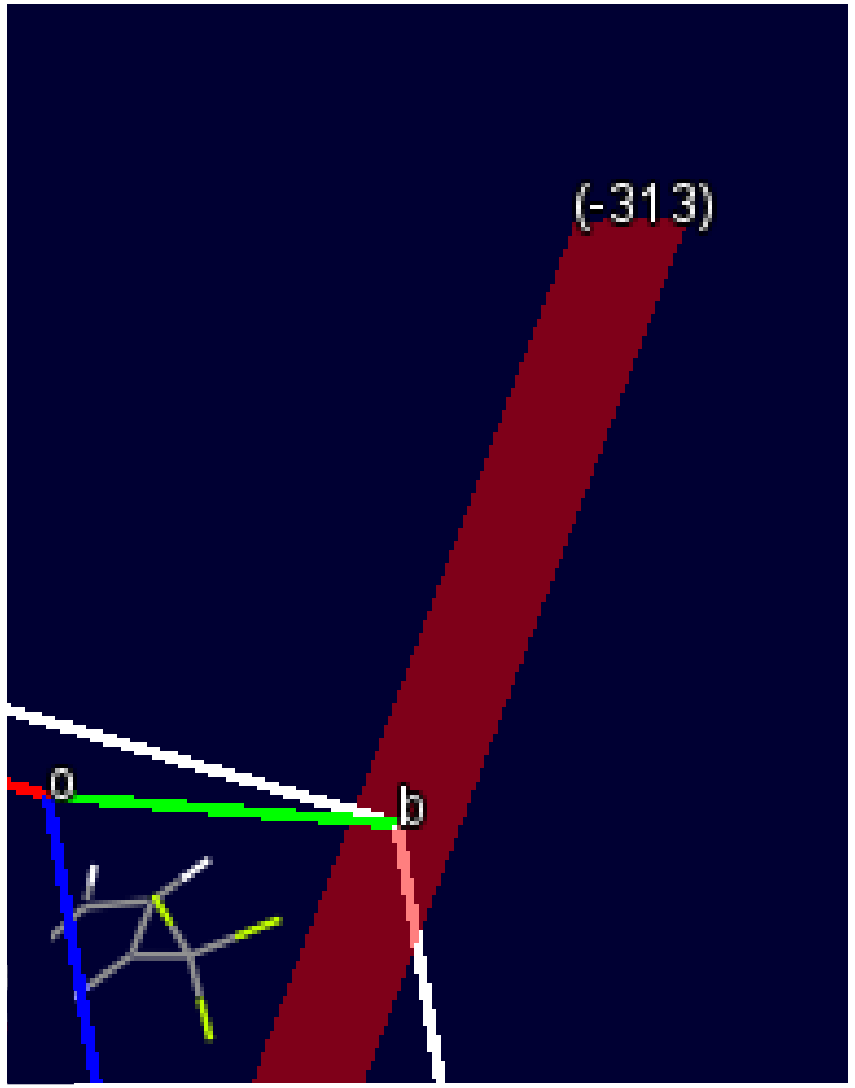


XRPD Plane Calculations

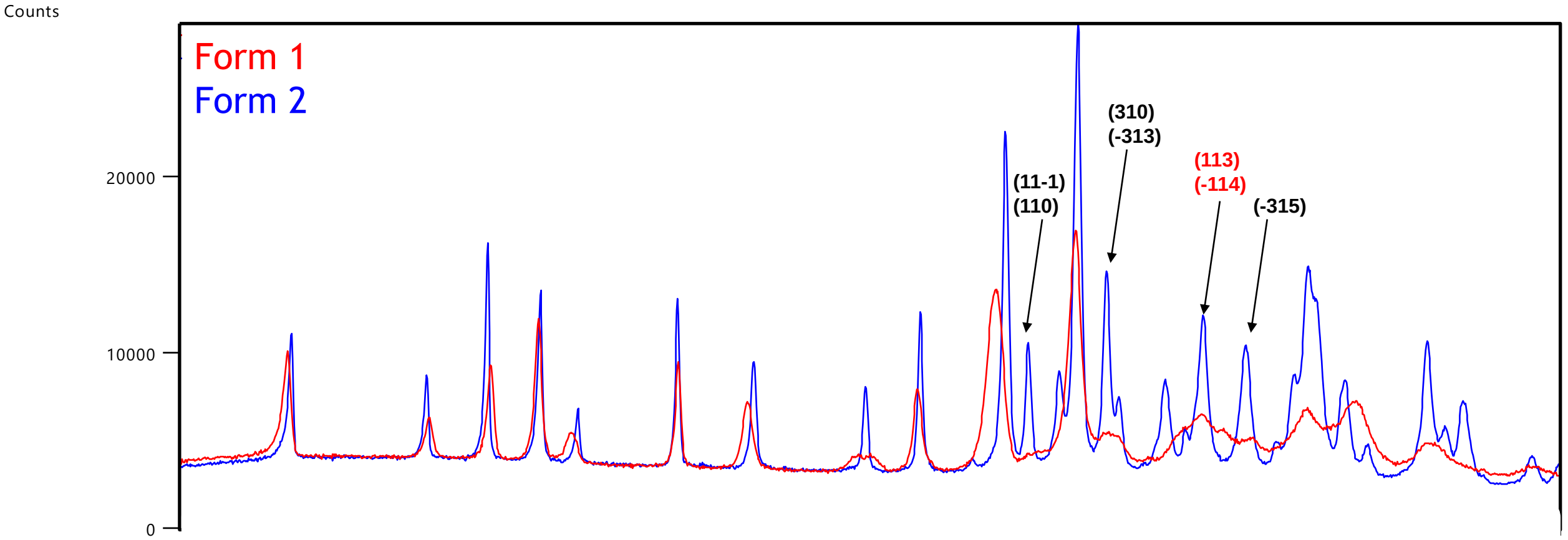


(310) and (-313); Form 2 peaks

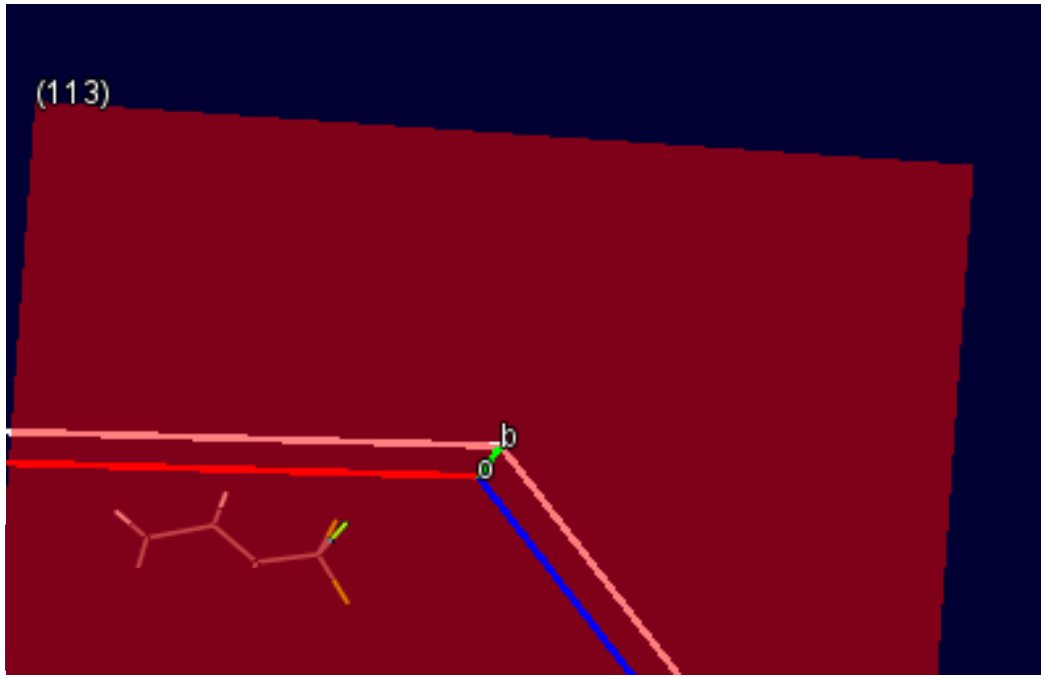


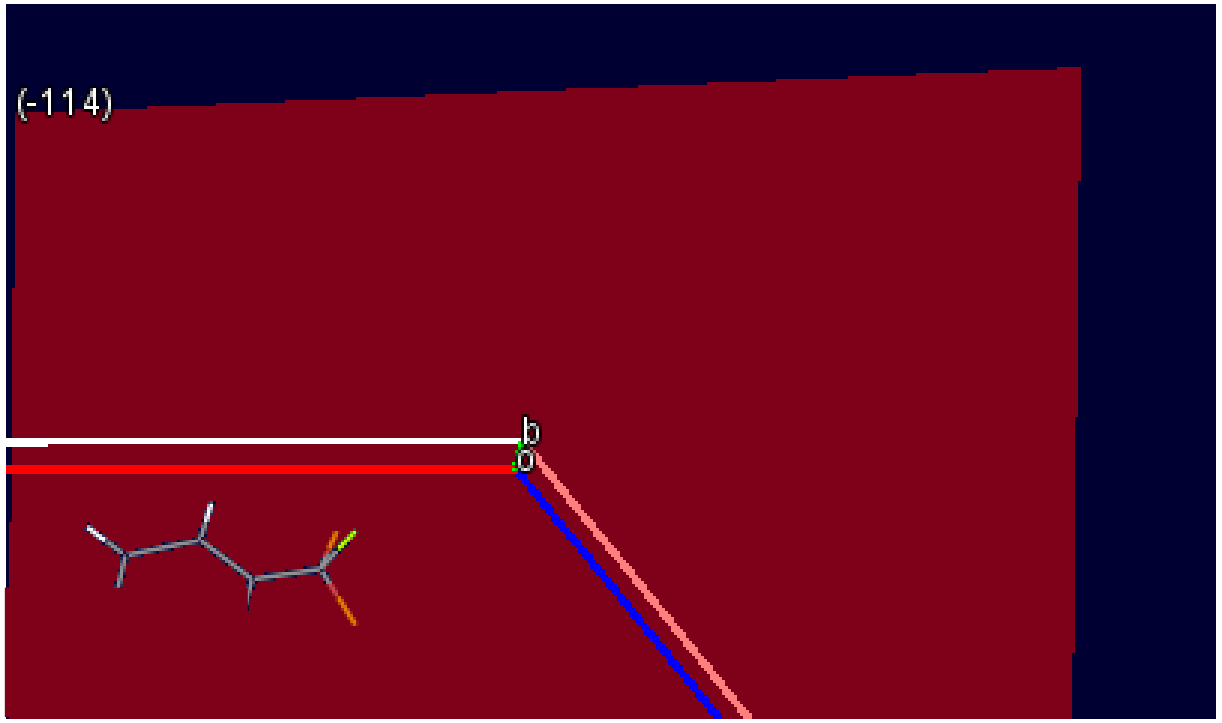


XRPD Plane Calculations

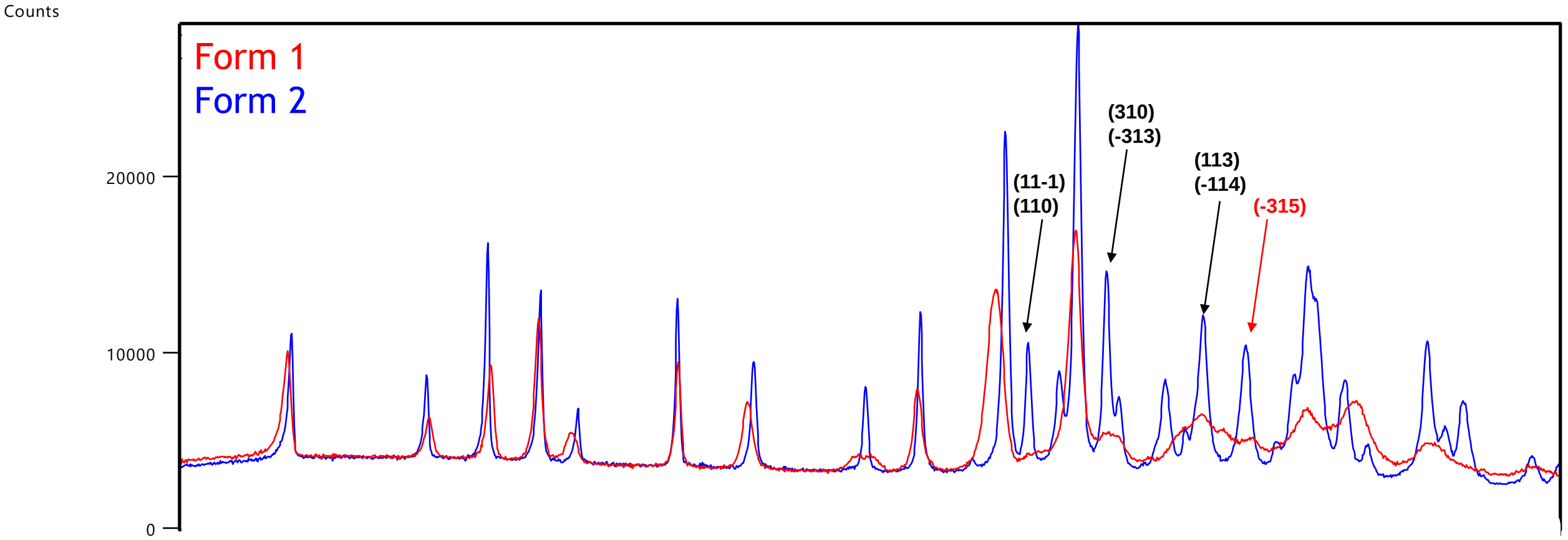


(113) and (-114); Form 2 peaks

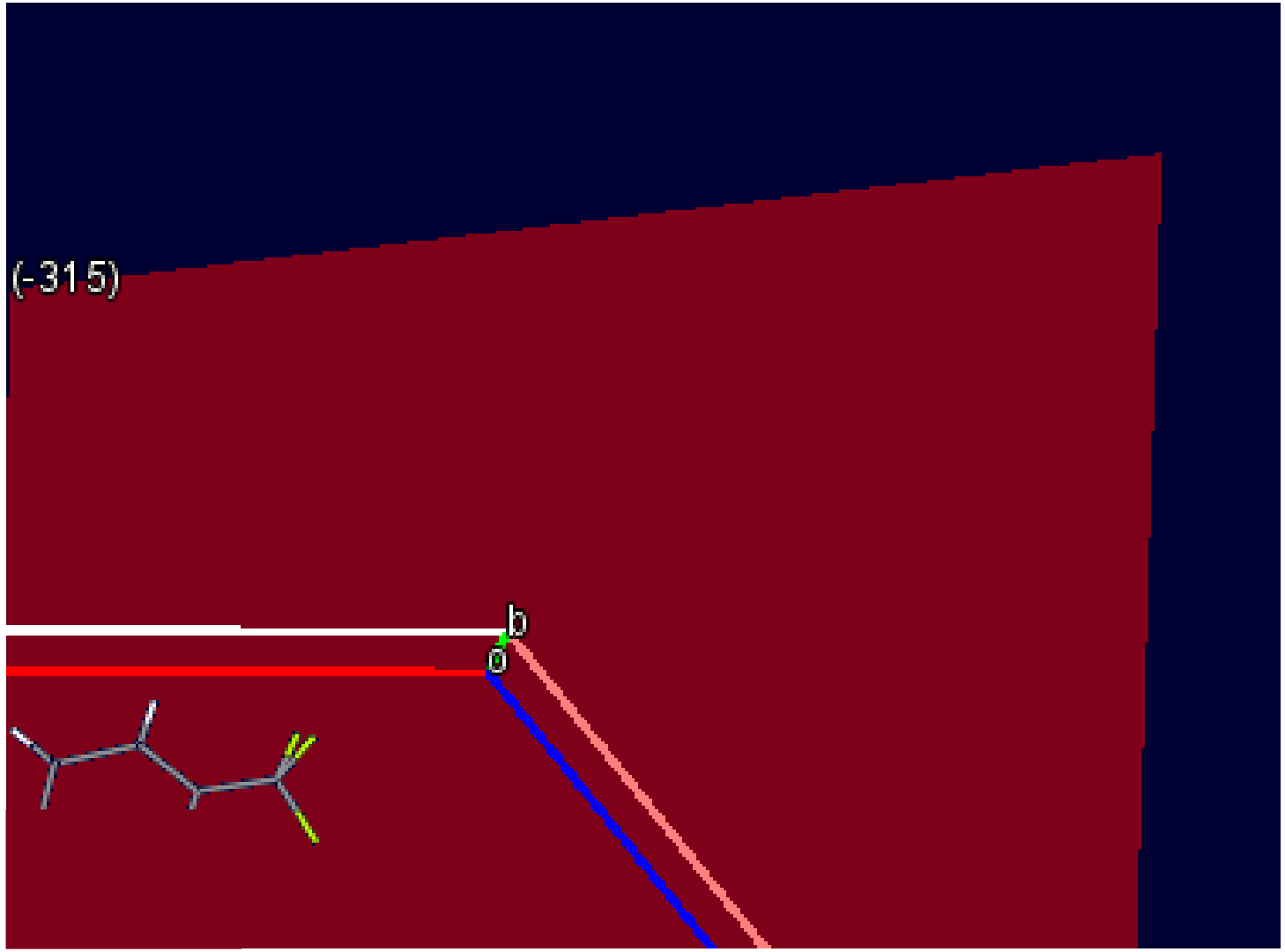




XRPD Plane Calculations

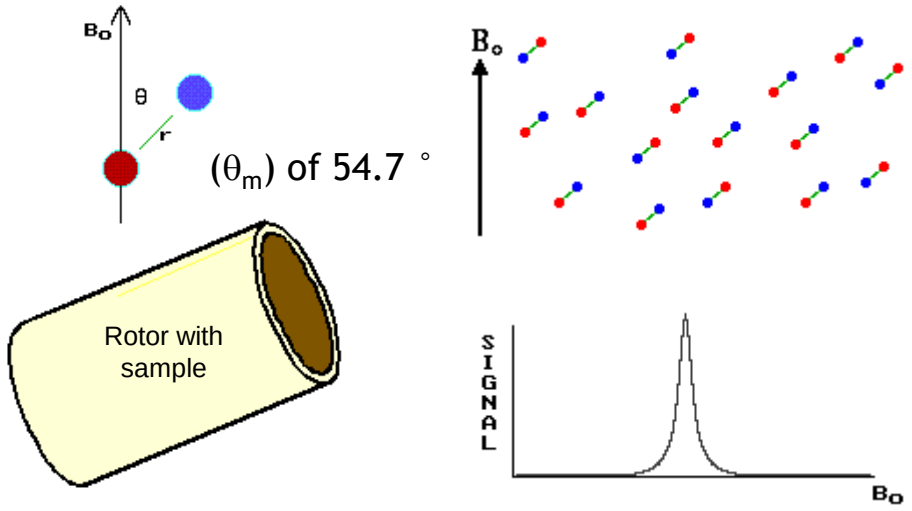


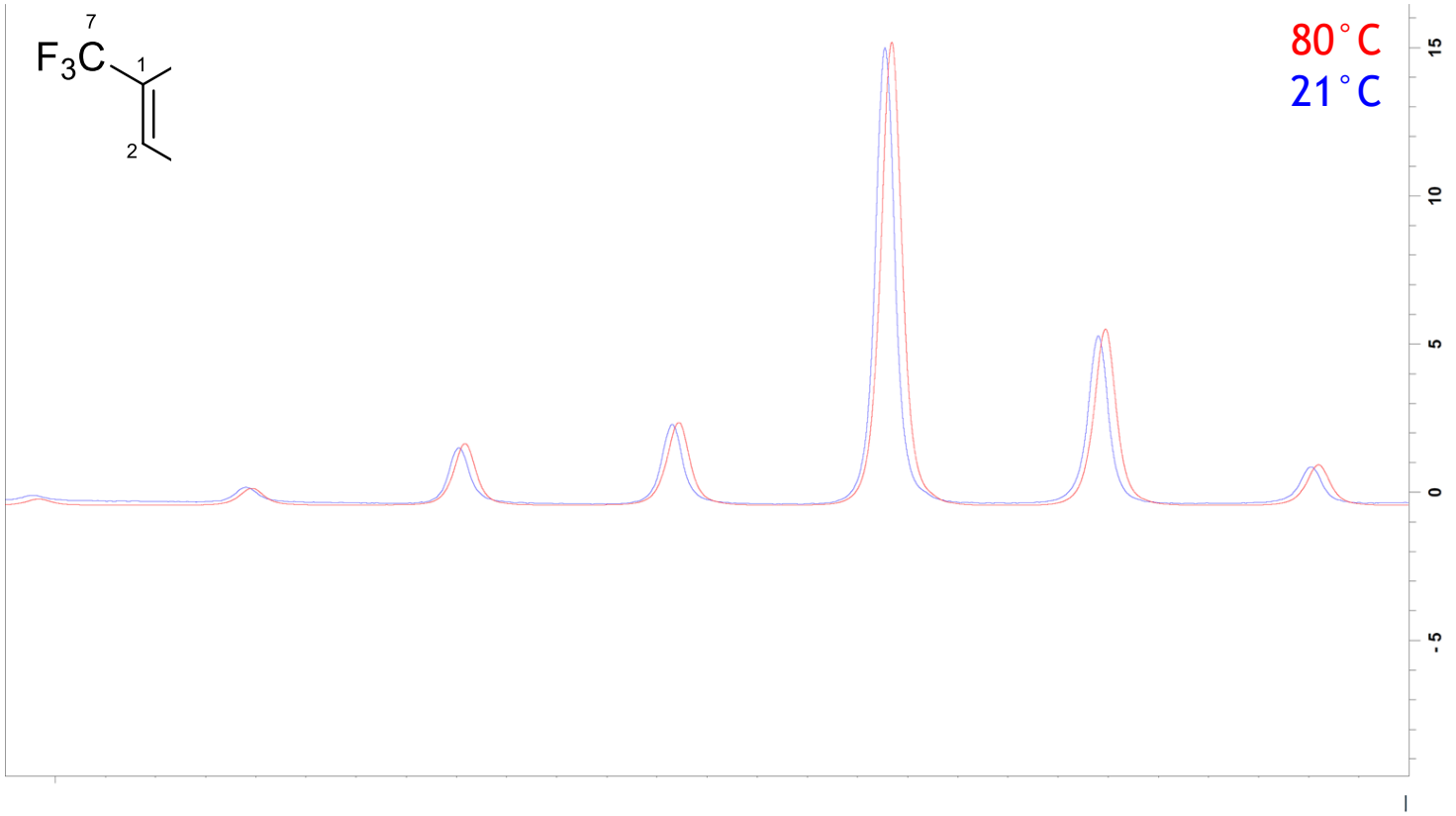
(-315); Form 2 peak



Solid State NMR

- Analysis of the spectroscopic and crystallographic data showed it was difficult to conclusively determine whether or not the difference between Forms 1 and 2 were true polymorphs.
- The data actually suggested that Form 1 is a phase of Form 2, with some disorder and a nanocrystalline component within the crystals that cannot be determined by XRPD alone.[1]
- As such, a technique more sensitive to the local environment of the nucleus and the average electronic distribution around it.[2]



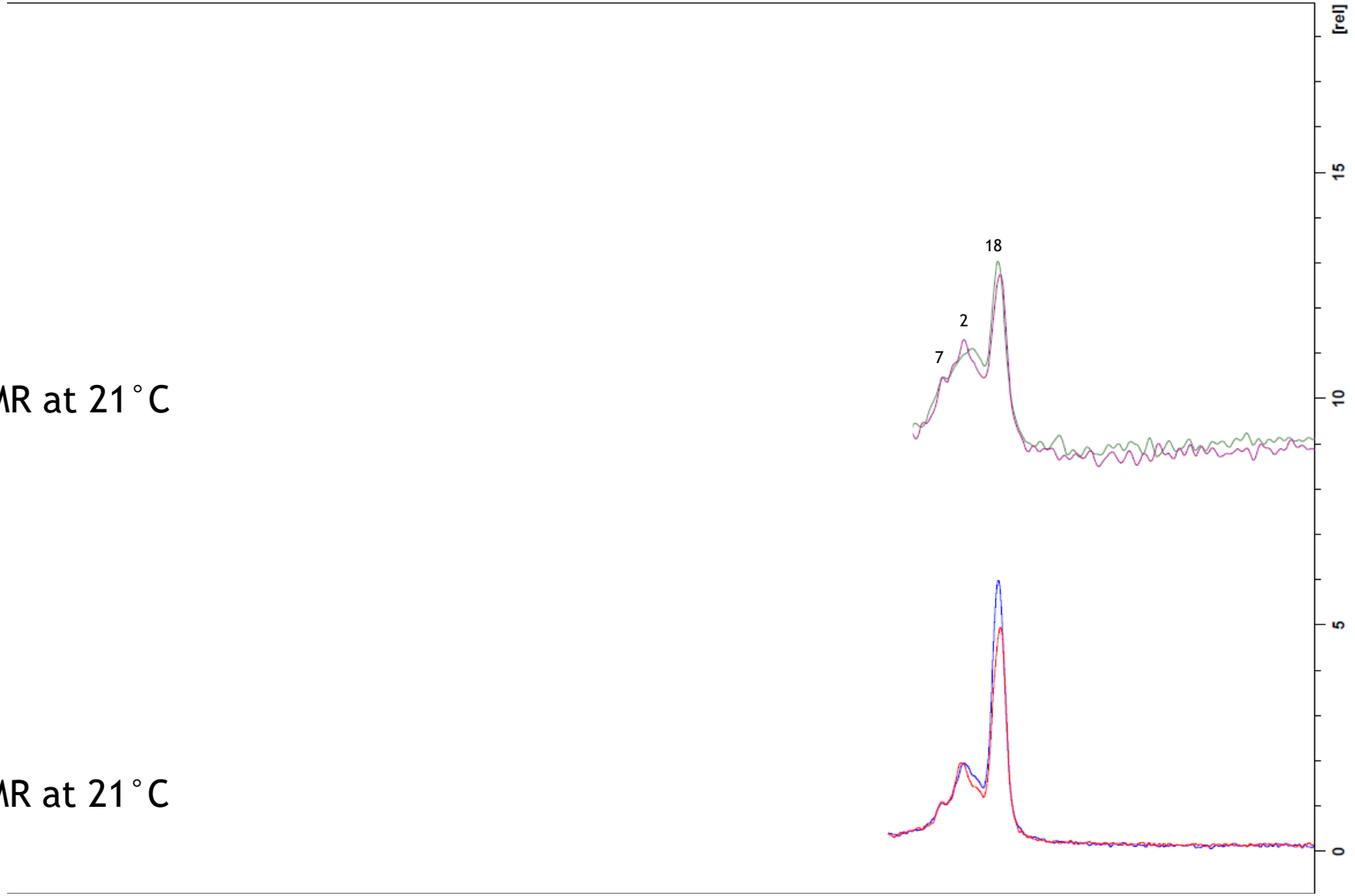


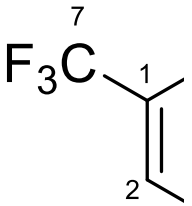
1. *Mag. Res. Chem.* **1994**, *32*, 118
2. *Cryst. Growth Des.* **2008**, *8*, 3474
3. *Study of disorder by solid-state nmr spectroscopy* in Disordered Pharmaceutical Materials **2016**, Ch. 14 pp 427.

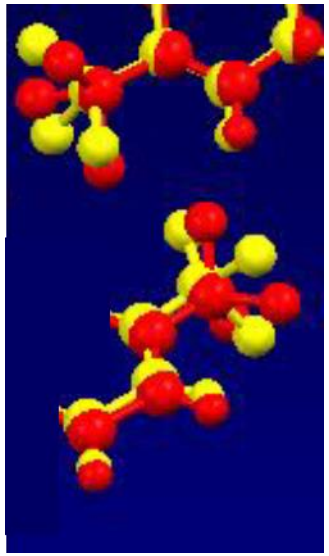
SS-NMR at 21°C

HPDEC ^{13}C ss-NMR at 21°C

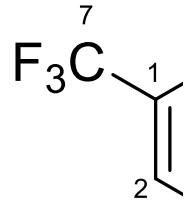
CPMAS ^{13}C ss-NMR at 21°C



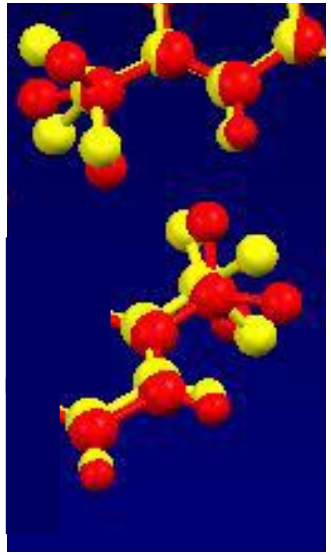




Outcome



- Despite there being substantial differences in the XRPD 2θ diffractograms of Forms 1 and 2, it was suspected that the differences between the forms was due to dynamic disorder.
- Literature precedence exists for rings flexing from planarity by as much as 15%.[1]
- Furthermore, the powerful electron withdrawing effect of the $-CF_3$ may reduce the aromaticity of the ring, leading to further ring flexibility.[2]
- Finally, $-CF_3$ moieties are known to undergo rotational disorder due to high symmetry and low energy barrier for rotation.
- This example highlights the complex behaviour that can be encountered with fluorinated compounds and despite there being substantial shifts in the XRPD diffractograms, this was not classed as a case of “true” polymorphism.
- The FDA accepted this approach, confirming the path forward allowing manufacture of the forms without prejudice as both were equally soluble in the intended aqueous media.



1. *J. Mol. Struct.* **2002**, *616*, 159
2. *Ch. J. Phys. Chem.* **2020**, *33*, 53
3. *Acta Cryst.* **2022**, *B78*, 333
4. *Crystallog. Rev.* **2009**, *15*, 57

Thank you

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