Fundamental Studies of Crystallization of Organic Materials

- New phenomena
- New tools
- New technological demands

Crystallization of organic materials

Lian Yu (School of Pharmacy) and Mark Ediger (Department of Chemistry)

- US pharmaceutical industry ~ $70 Billion/year
- New drug candidates are becoming more potent, but less soluble and bioavailable
- 1/3 of drug candidates fail because of bioavailability issues
- Most current products contain crystalline drugs; amorphous drugs have higher bioavailability
- Recent success story: AIDS drug Kaletra (Abbott), amorphous drugs dispersed in PVP/VA. No refrigeration required - successful in Africa

Crystal growth in glasses

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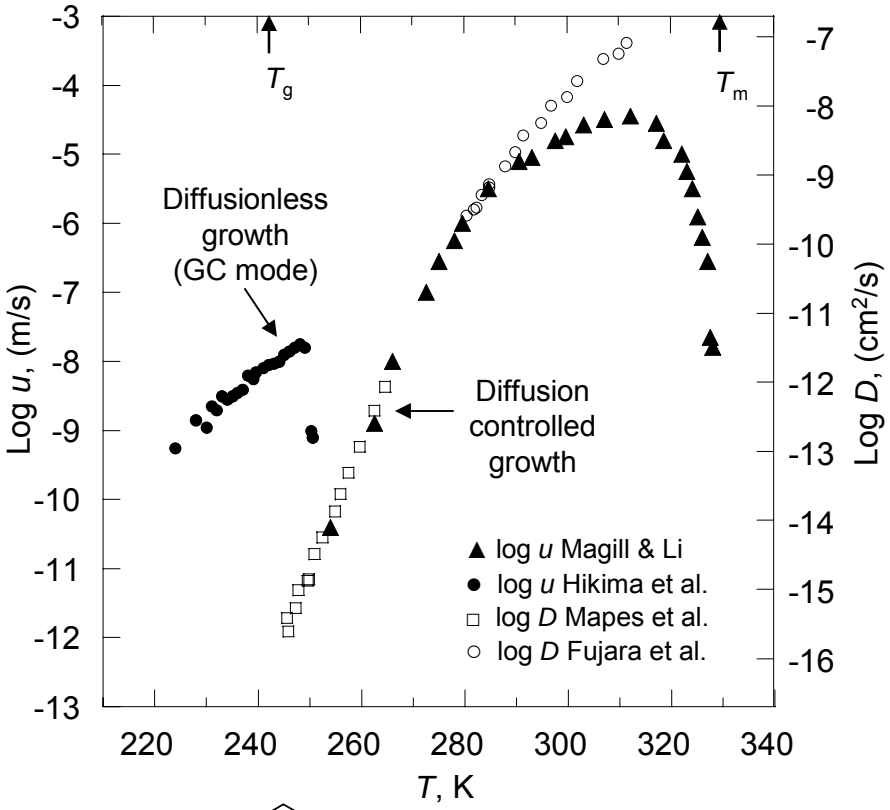
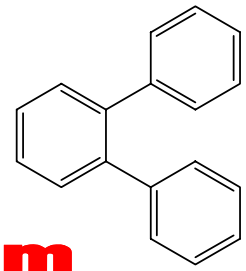


- Glasses should not crystallize!
- Faster crystal growth in glass!!
- Major implications for delivery of glassy pharmaceuticals
- Transition to fast GC growth only seen in organic systems



o-terphenyl

Magill & Li. *J. Crystal Growth* **1973**
Hikima et al. *Phys. Rev. B* **1995**
Mapes et al. *J. Phys. Chem. B* **2006**
Fujara et al. *Z. Phys. B*: *Condens. Matter* **1992**

Crystal growth in glasses

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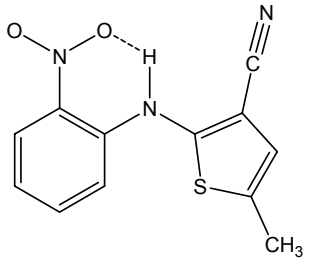
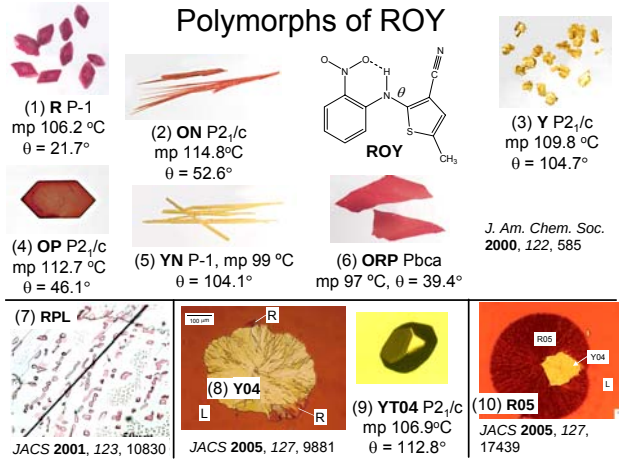
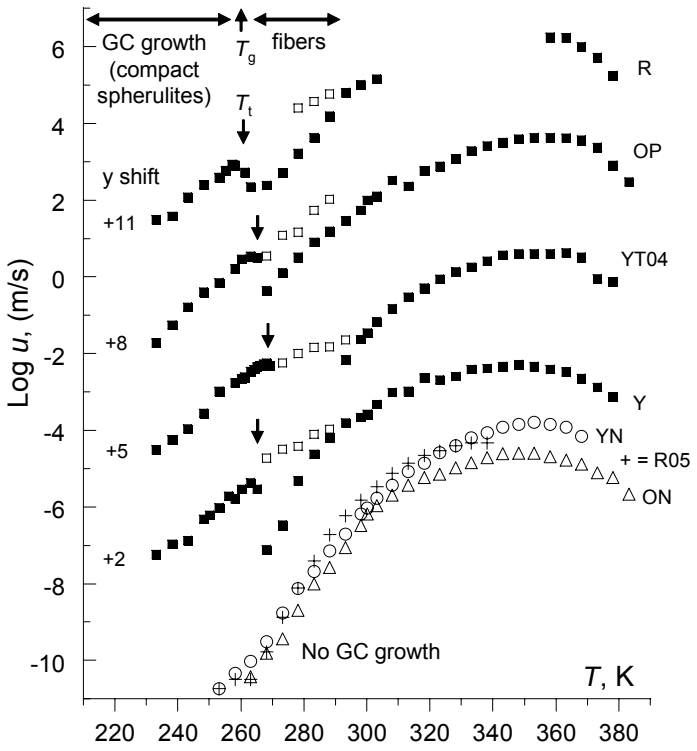
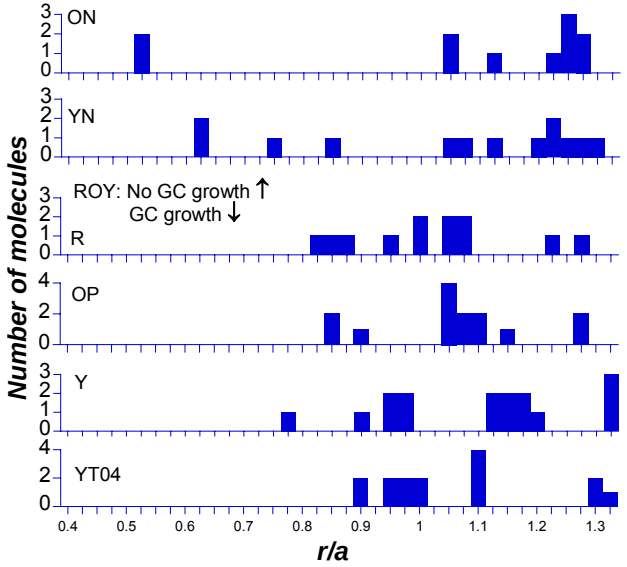


ROY







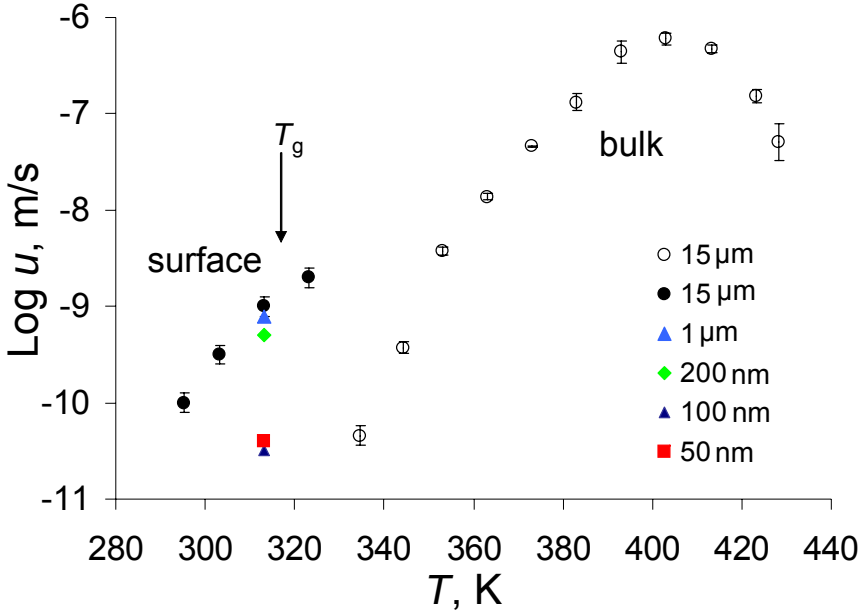
Hypothesis: Good match between crystal and liquid packing leads to GC growth

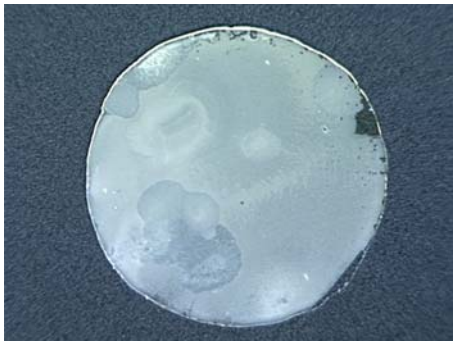
Understanding the connection between polymorph structure and crystal growth in glasses would be major advance

Sun, Xi, Ediger, Yu, *J. Phys. Chem. B* **2008**, *112*, 661.
Sun, Xi, Ediger, Yu, L. *J. Phys. Chem.* **2008**, *112*, 5594.

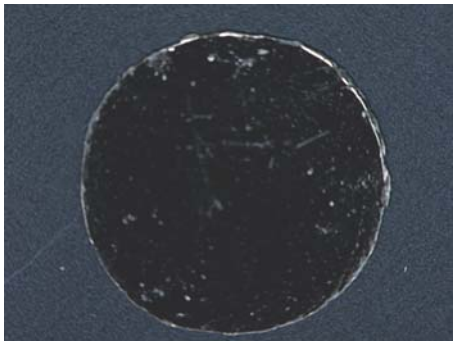
Fast surface crystal growth

Lian Yu (School of Pharmacy) and Mark Ediger (Department of Chemistry)



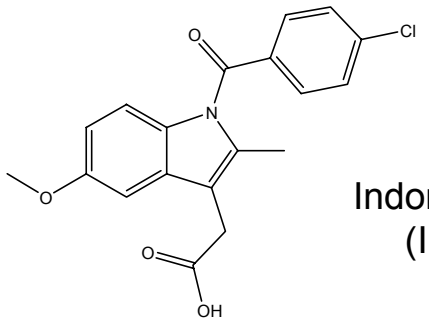


Uncoated amorphous IMC. Surface crystallization complete in 2 weeks at 40 °C. Diameter of circle = 15 mm



Amorphous IMC coated with 3 nm polyelectrolyte or 10 nm gold. No surface crystallization observed. Coating stops growth of existing crystals.

- Major implications for amorphous pharmaceuticals - high surface area
- Not reported for other materials
- Film thickness effects - organic electronics



Indomethacin (IMC)

Wu, Sun, Li, de Villiers, Yu, *Langmuir* **2007**.

Fast surface crystal growth

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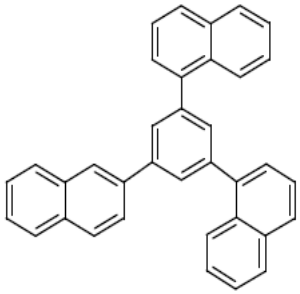
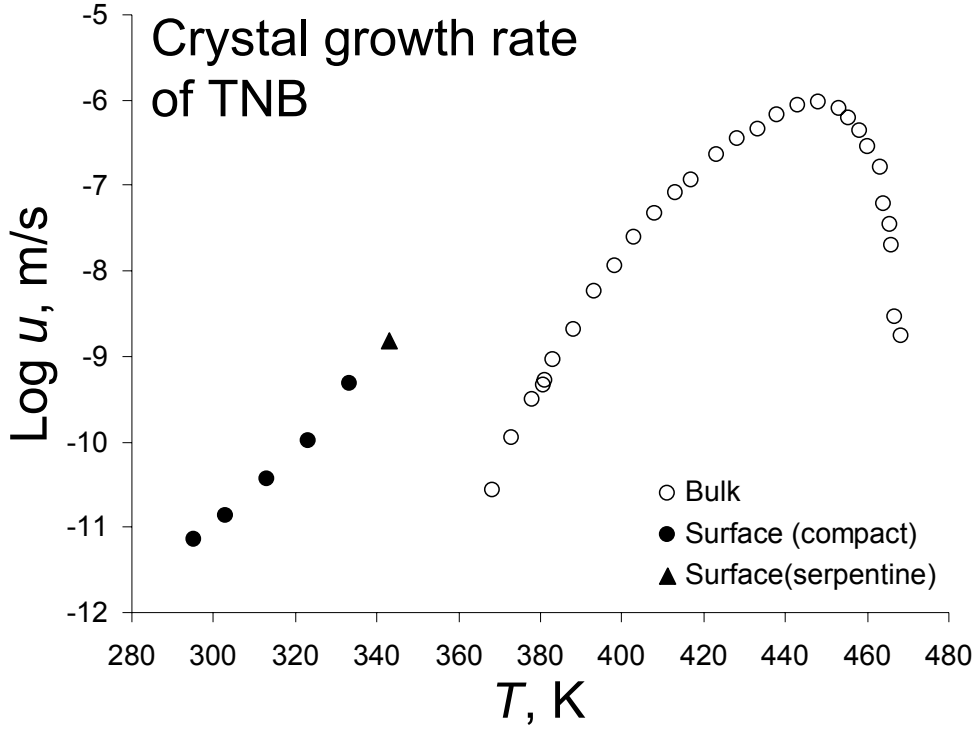
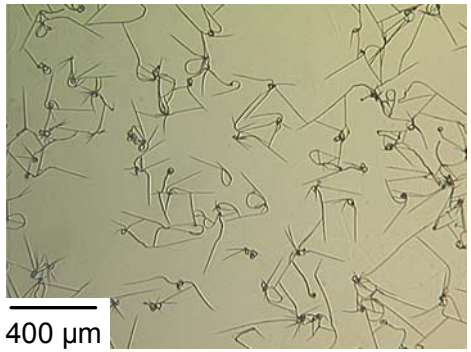


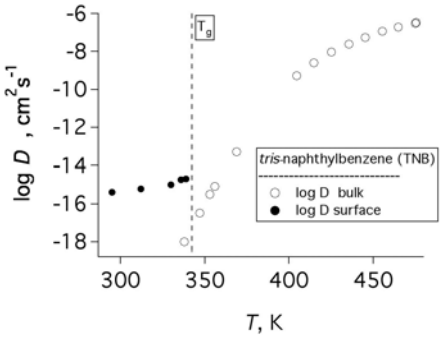
tris-naphthylbenzene (TNB)



Hypothesis: High mobility at glass surface leads to fast crystal growth

Supported by independent experiments on TNB



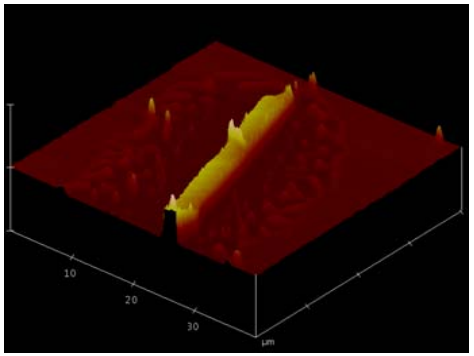


Results anticipated in next 12 months

Lian Yu (School of Pharmacy) and Mark Ediger (Department of Chemistry)

Crystal growth in glasses:

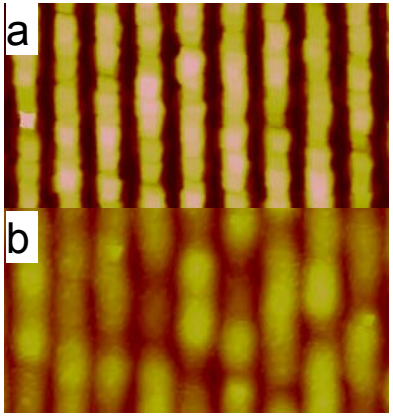
- Simulation of ROY liquid (de Pablo): test structural hypothesis for GC growth
- Characterize diffusion-controlled growth in ROY, compare with liquid dynamics (dielectric and enthalpy relaxation)
- Simulation of polymorph growth rates (de Pablo)
- Effect of polymer additives on GC growth (new postdoc)



Crystal grown in 50 nm IMC film is 400 nm high, surrounded by depletion zone

Fast surface crystal growth:

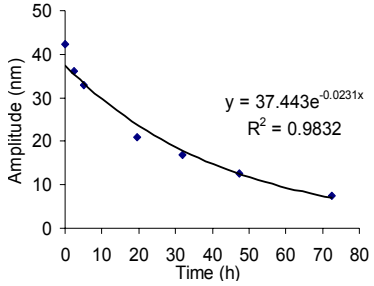
- AFM study of growth morphology
- AFM measurement of IMC surface mobility via grating decay
- Isotope concentration expt (new postdoc)



IMC surface grating (1000 lines/mm)

Initial

After 2 days at 30 ºC



Decay kinetics show surface viscosity is much smaller than bulk viscosity

A larger interdisciplinary effort on crystallization of organic materials might include:

- Simulations (de Pablo)
- Better surface characterization (Hamers): Polymorph selectivity and other evidence suggest “surface reconstruction” of amorphous material
- Controlling polymorphism (Hamers and Yu): Expertise with polymorphs, functionalized amorphous carbon surfaces…
- Understanding interfacial structure as it controls crystal growth (Voyles and de Pablo): Fluctuation electron microscopy
- Connection with organic electronics (Evans)
- Connections with other classes of materials - metallic glasses, amorphous silicon, others?
- Other technological issues for which these phenomena might be particularly relevant

Why is this a “materials” problem?

Lian Yu (School of Pharmacy) and Mark Ediger (Department of Chemistry)

- We seek to make connections with other classes of materials, e.g., diffusion-controlled growth rates depend systematically on fragility.
- Why are the transition to GC growth mode and fast surface crystal growth reported only in organics?
- Organic molecules, with their well-defined internal structure, can exhibit more complex behavior than inorganic and metallic systems.
- We seek general principles, not optimization of a particular system

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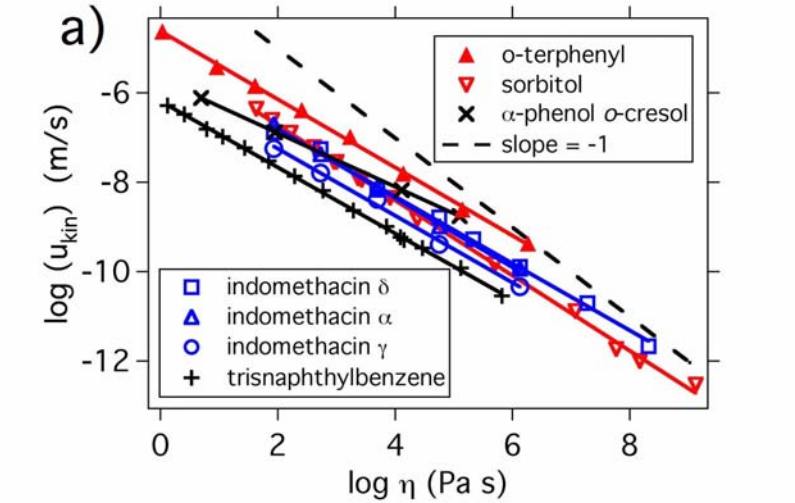

Ediger, Harrowell, Yu, JCP 2008