Amorphous Solids

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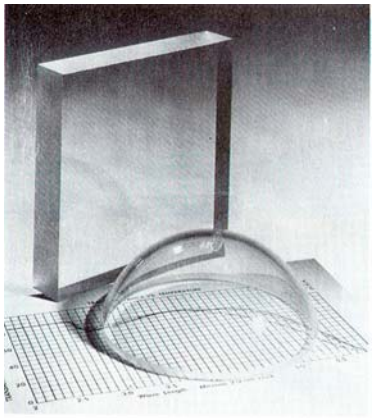
With thanks to NSF and Abbott

Crystalline and amorphous solids

Crystalline SiO_2 (quartz)
Density 2.65 g/cm^3



Amorphous SiO_2
or silica glass
Density 2.20 g/cm^3

This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

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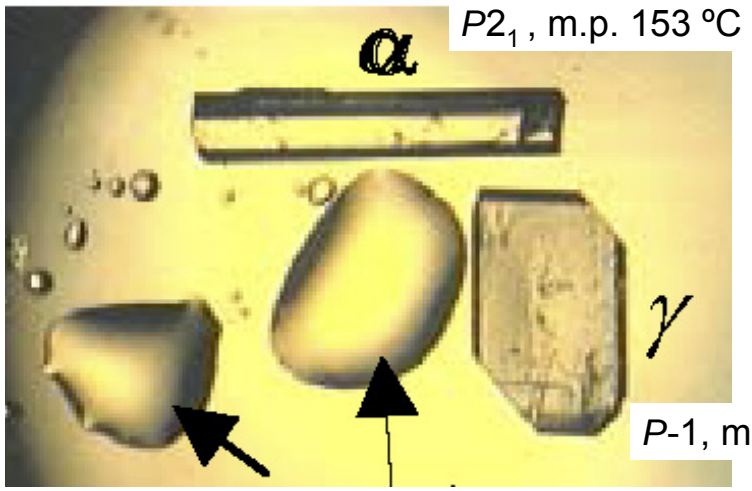
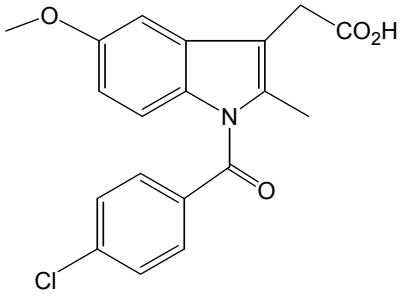
PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

Crystalline and amorphous indomethacin



$P2_1$, m.p. 153 ºC



P-1, m.p. 160 ºC

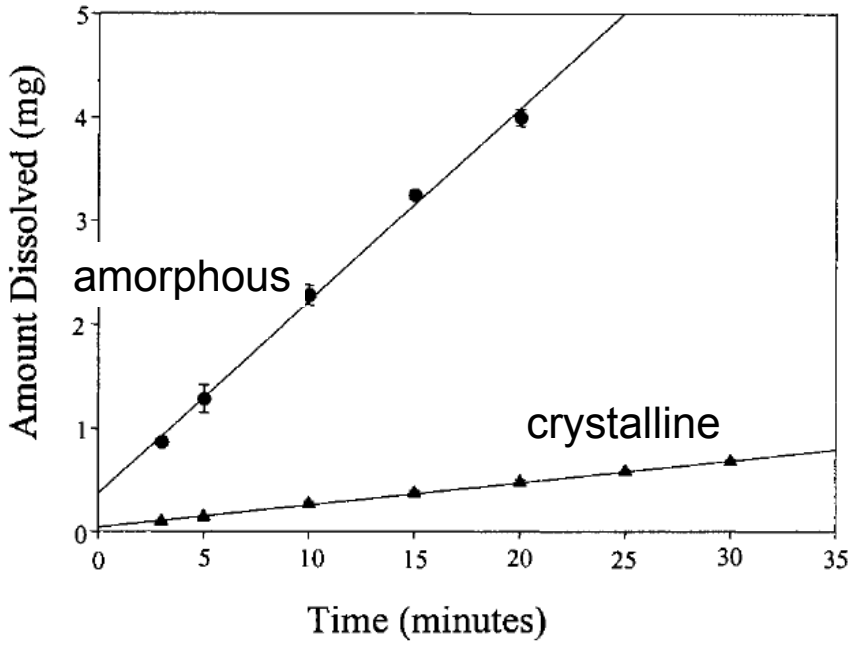
Amorphous solid (glass). T_g = 42 ºC
More soluble than crystals (5 – 17 x)

Figure from Chen, …, Stowell. JACS 2002. Solubilities from Hancock & Parks 2000, Murdande et al.. 2010, Alonzo et al. 2010

Most pharmaceuticals are crystals.

Amorphous drugs are of interest because they are:

- More soluble – useful for delivering poorly soluble drugs
- Often less stable chemically
- Often produced by freeze drying, spray drying, milling, and other processes
- Occasionally the “only” solid form available

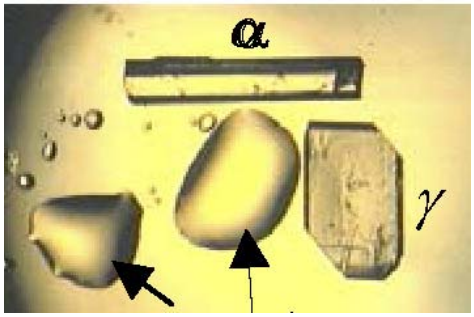


Ritonavir (Abbott)
A low solubility, low permeability drug (BCS Class IV)

Figure 2. Intrinsic dissolution rates of ritonavir in 0.1*N* HCl at 37°C: (a) amorphous (0.3 mg/cm^2-min, $n = 3$) and (b) crystalline (0.03 mg/cm^2-min, $n = 4$).

Law et al., J. Pharm. Sci. 93 (2004) 563

Organic glasses have many applications



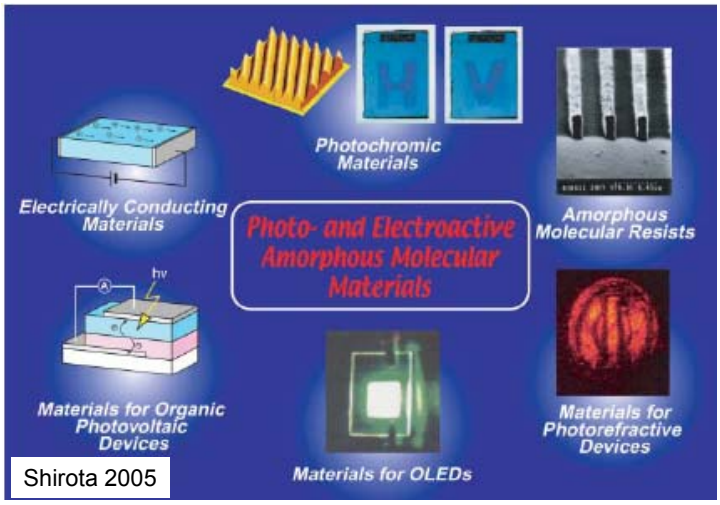
Drug delivery
Glasses are more soluble than crystals

Food

Bio-preservation

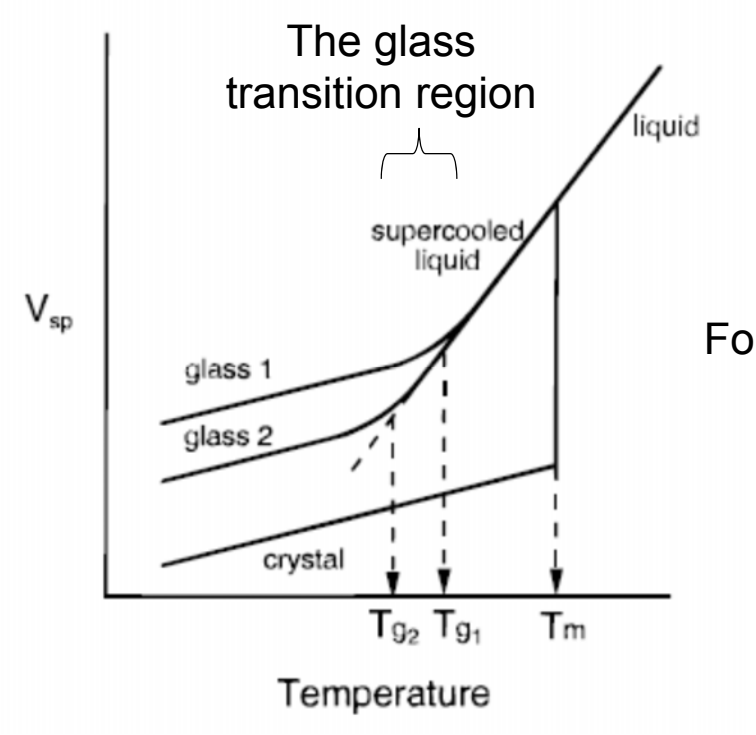
In sugar glasses

In amber



Shirota 2005

The standard way to make a glass: Cooling a liquid without crystallization



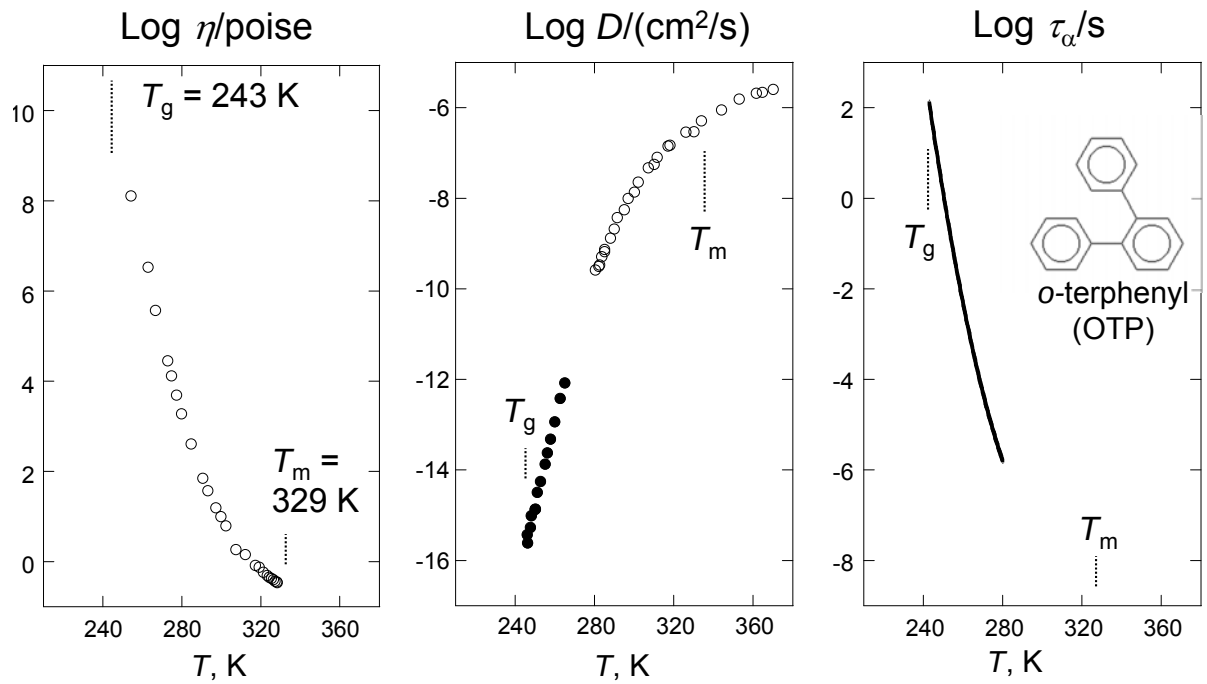
For many liquids,
$T_g \approx 0.7\ T_m$

Glassmaking in Nature

http://www.volcanoman.com/

Obsidian: Natural glass with chemical composition similar to that of granite

Slowdown of molecular motions as T_g is approached from above

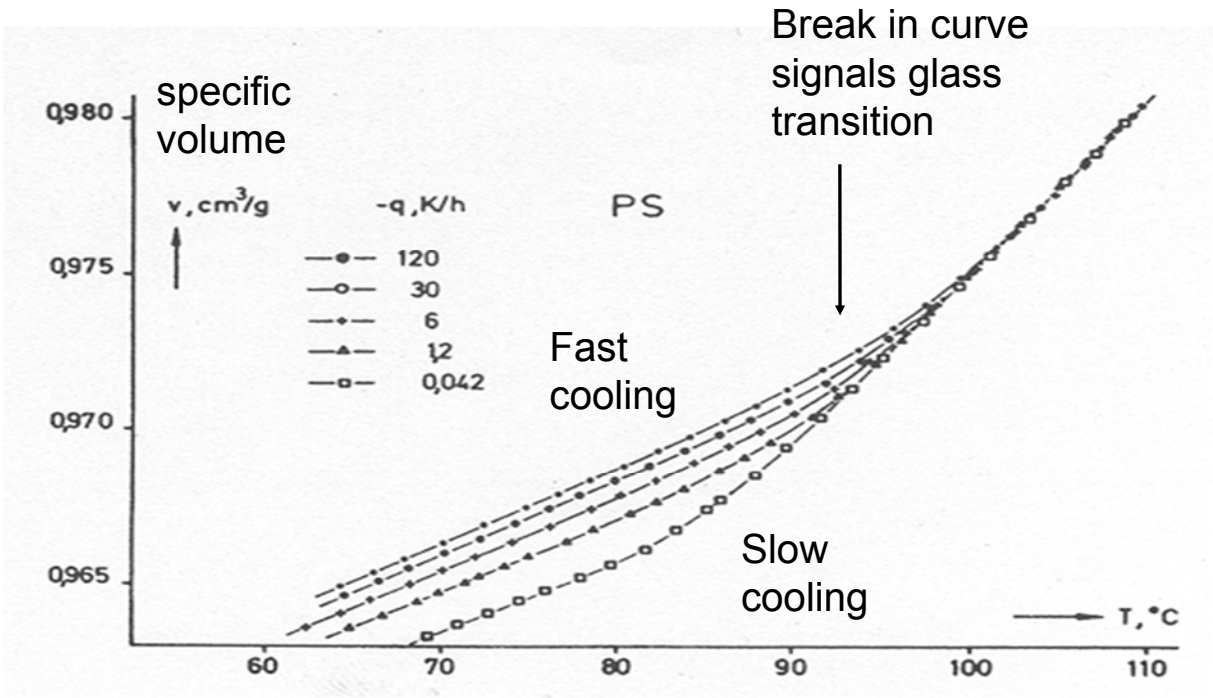


Magill & Li 1973

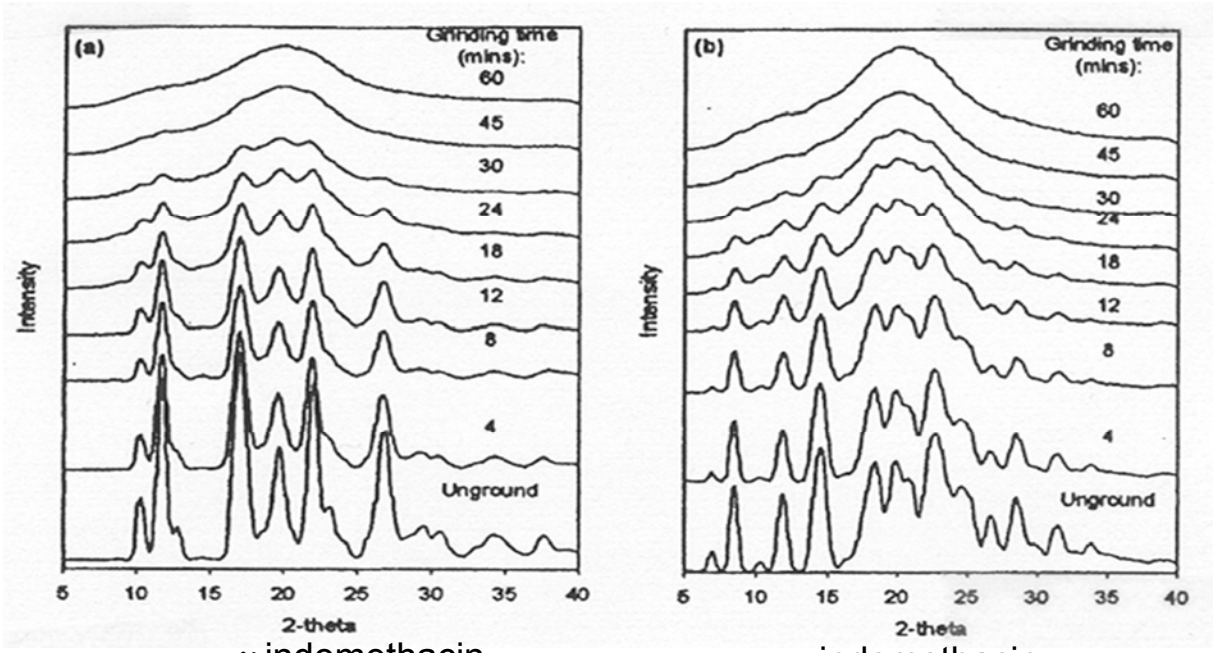
Fujara et al. 1992
Mapes et al. 2006

Wagner & Richert 1999

Cooling rate affects the glass formed



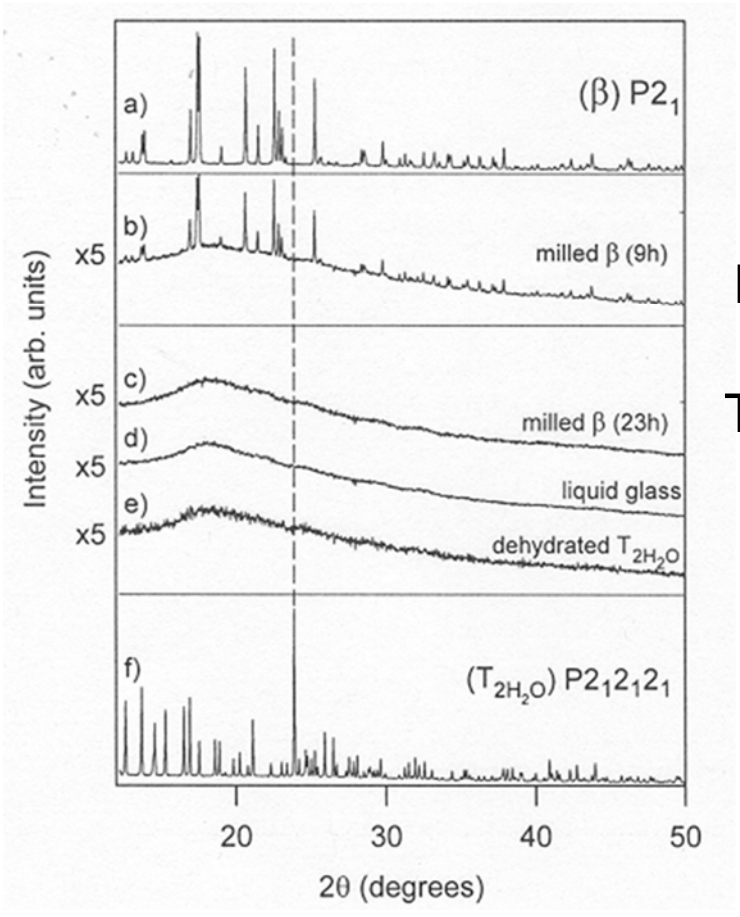
Grinding crystals can make amorphous solids



γ indomethacin

α indomethacin

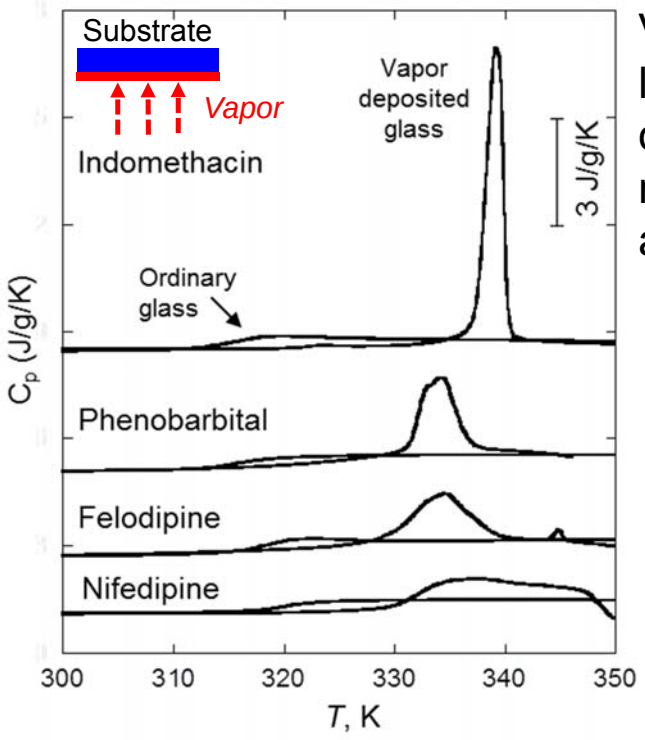
Crowley and Zografi, J.Pharm. Sci. 91 (2002) 492



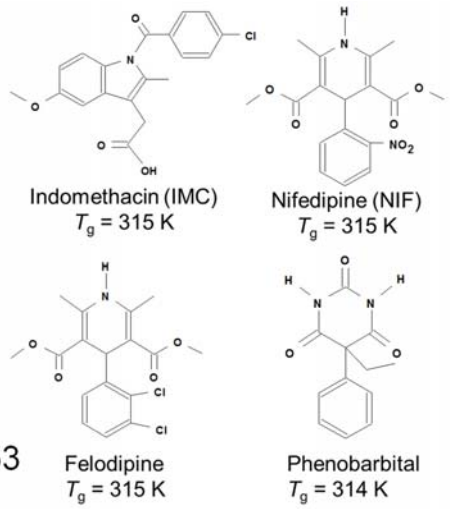
Drying crystalline hydrates can make amorphous solids: Trehalose dihydrate

Willart et al., *Solid State Comm.* 119 (2001) 501

Vapor deposition can produce stable glasses

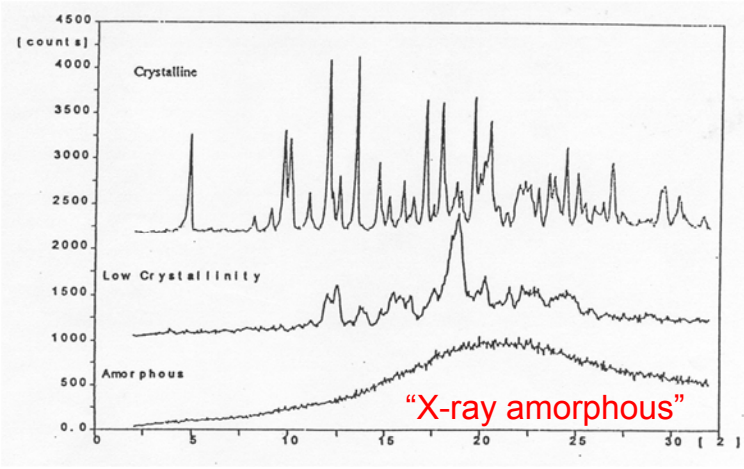


VD glasses can be 14 J/g lower in energy than ordinary glasses – a level reached only after very long aging (perhaps 10^6 years)



Swallen, Ediger, et al. *Science* **2007**, *315*, 353
Zhu & Yu *Chem. Phys. Lett.* **2010**, *499*, 62

Standard method to distinguish crystals and amorphous solids: X-ray diffraction



Other methods:
LM: Amorphous solids lack birefringence and crystal-like morphologies

DSC: Amorphous solids lack well-defined melting points and heats of melting, may show glass transition

IR, Raman, SSNMR: Amorphous solids tend to show broader peaks

What is being studied?

Structure

Molecular packing

H bonding

…

Thermodynamics

Driving force to crystallize

Miscibility with polymers, …

Amorphous drugs

Kinetics and transformation

Glass relaxation (aging)

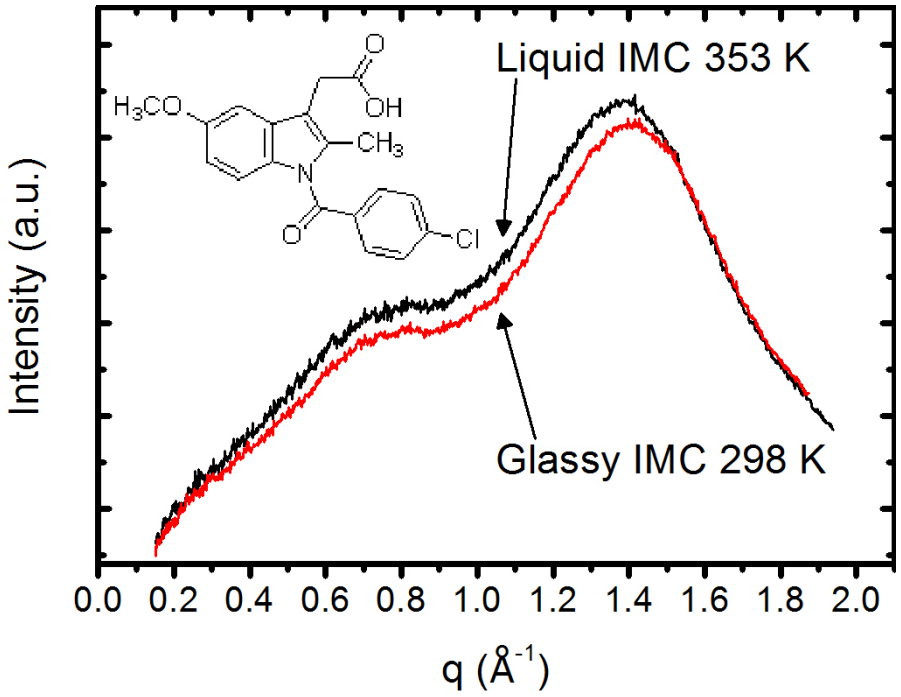
Molecular mobility (bulk and surface)

Crystallization (nucleation, growth)

Chemical reaction

Stabilization

Glasses have liquid-like structures.
Glassy IMC diffracts X-ray similarly as liquid IMC



Dawson, K. J; Kearns, K. L; Yu, L.; Steffen, W.; Ediger, M. D. *Proc. Nat. Acad. Sci.* **2009**, *106*, 15165

Glasses are generally less dense than crystals

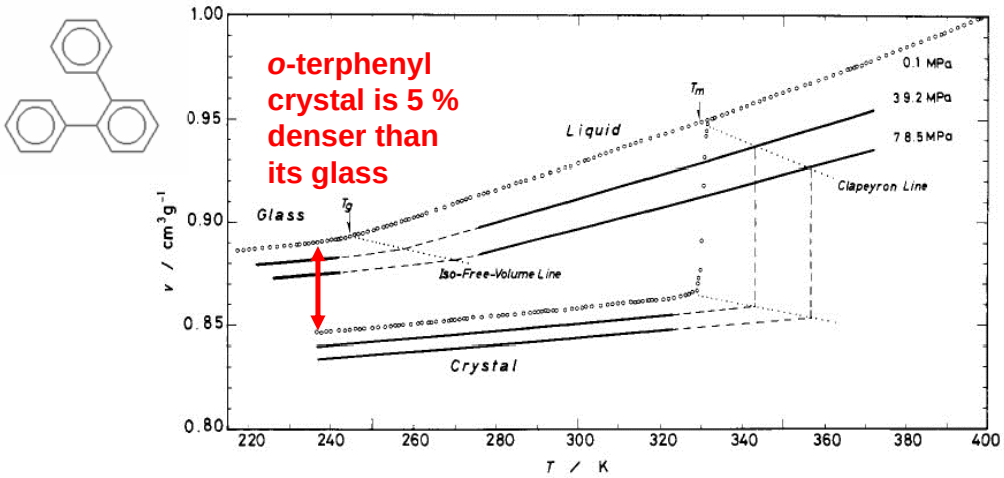


Figure 1. Variations of the specific volumes of the liquid, the supercooled liquid, the glass, and the crystal for *o*-terphenyl as a function of temperature. The thick solid lines are the representatives of the isobars under the elevated pressures. The iso-free-volume line is the intersection between the liquid and glass surfaces. The Clapeyron line is the trace of the melting temperature estimated as shown in the text.

Crystalline vs. amorphous structures

- Crystalline: Local structure is repeated in space
- Amorphous: Local structure might be “crystal like”, but is not repeated in space

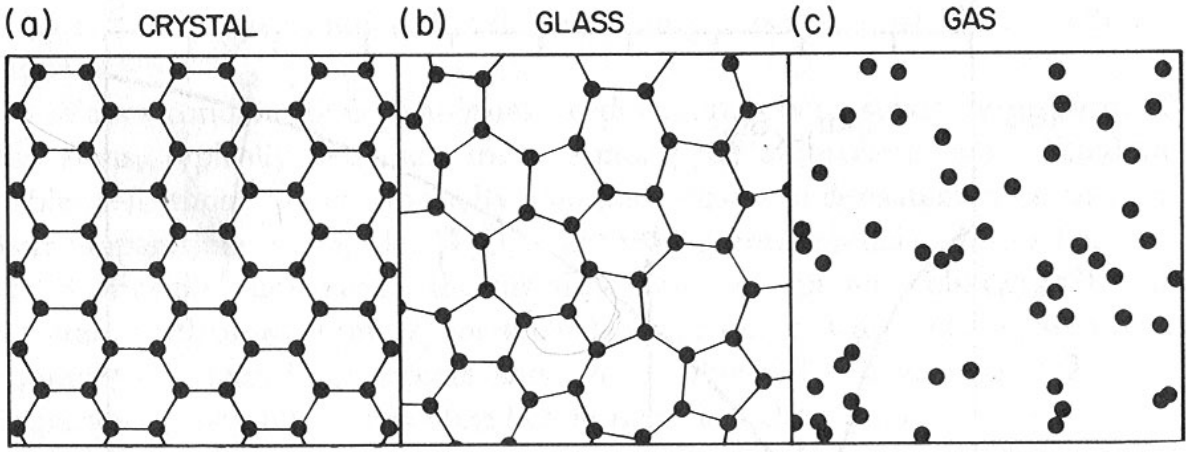
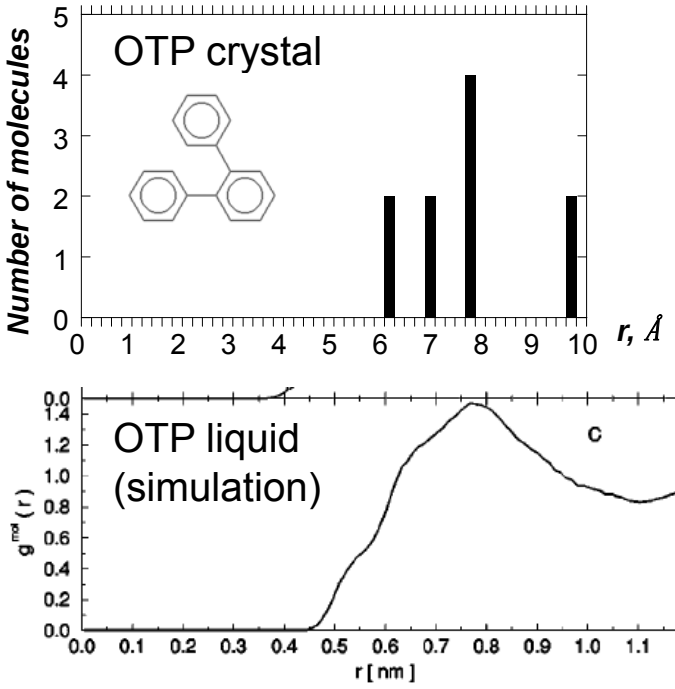


Figure 1.6 Schematic sketches of the atomic arrangements in (*a*) a crystalline solid, (*b*) an amorphous solid, and (*c*) a gas.

Zallen, *The Physics of Amorphous Solids*, 1998

One descriptor of the structure of an amorphous solid: Radial distribution function (RDF) or pair distribution function (PDF)

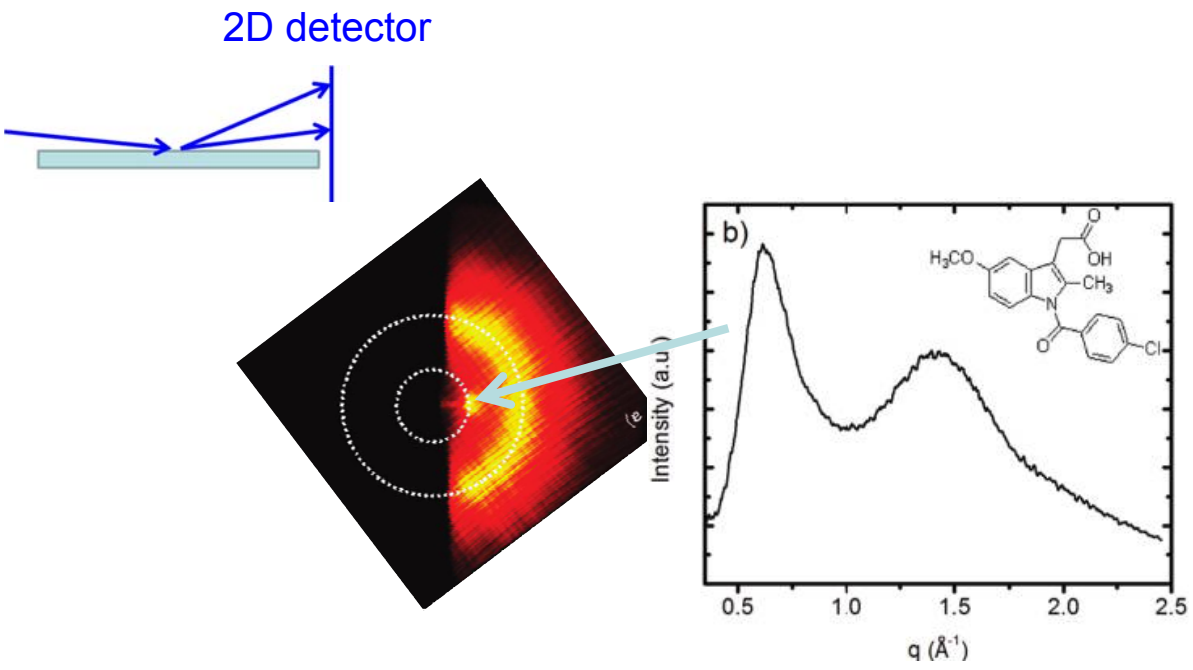


Simon, B.; George Z.; Engers, D.; Morris, K.; Crowley, K.; Newman, A. *Pharm. Res.* 2006, 23, 2333

FIG. 5. Pair static distribution functions at $T = 300$ K calculated on atoms (A), ring centers of mass (B), and molecular centers of mass (C); full lines represent the total contribution of both intramolecular and intermolecular distances, dashed lines only the intermolecular contribution.

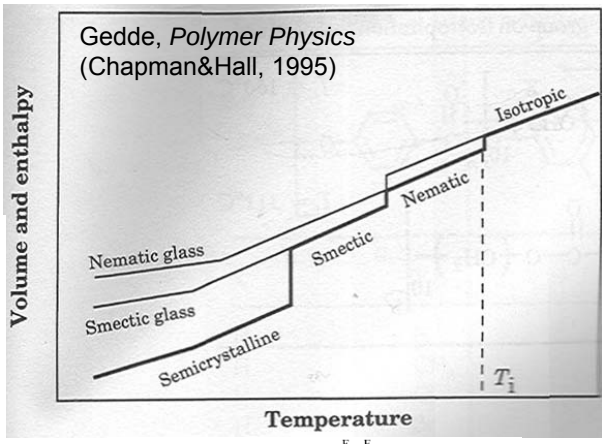
Mossa et al. *Phys. ReV. E* **2000**, *62*, 612

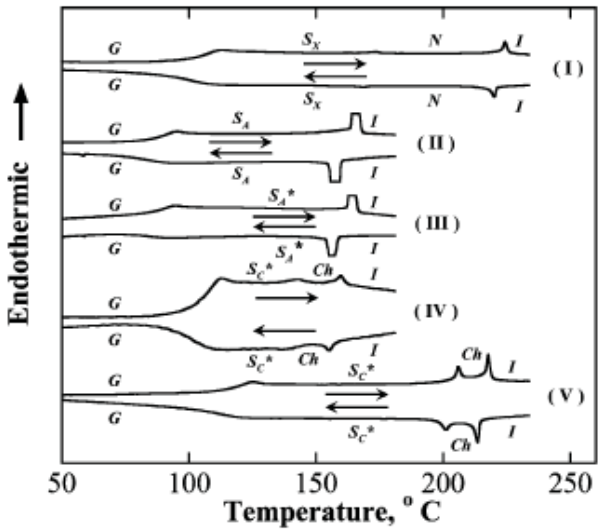
Anisotropic glasses by vapor deposition



Dawson et al. *PNAS* **2009** ; *J. Phys. Chem. B* **2011**

Anisotropic glasses by cooling liquid crystals





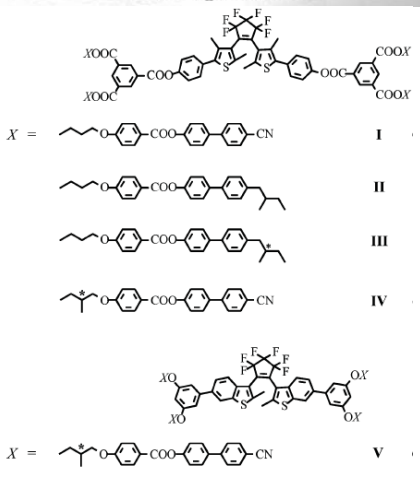


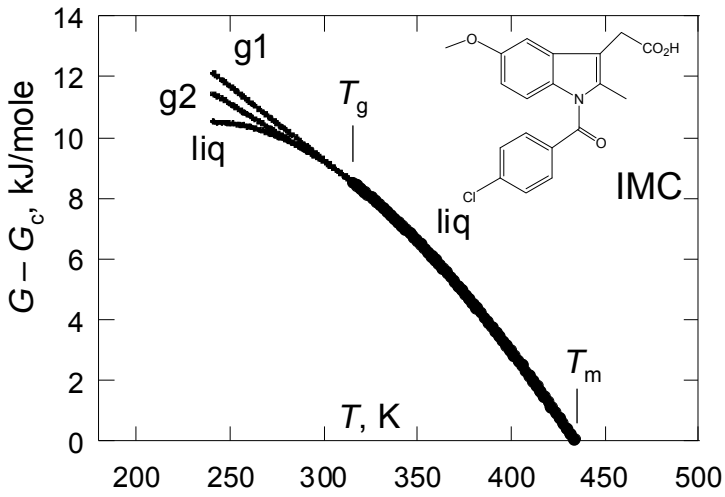
Fig. 1 Differential scanning calorimetric heating and cooling scans of I–V at 20 °C/min of samples preheated above their clearing points followed by cooling to −30 °C. Symbols: *G*, glassy; S_A, smectic A; S_A*, chiral smectic A; S_C*, chiral smectic C; S_X, unidentified smectic; *Ch*, cholesteric; *I*, isotropic. Kim et al. *J. Mater. Chem*. **2008**, *18*, 5592

How much more soluble are amorphous solids than the corresponding crystals?

Solubility enhancement can be calculated from the free-energy difference

$\Delta G = G_{amorphous} - G_{crystal}$

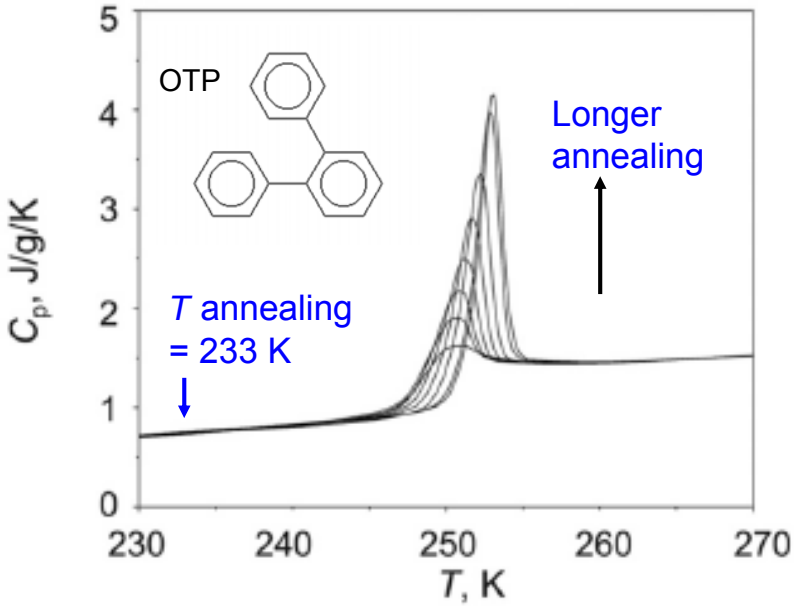
$\ln (x_a/x_c) = \Delta G/RT$



At 298 K in water, x_a/x_c = 38 (predicted), 4.9 (measured)
Murdande et al. (2010) attribute the difference to

- water sorption by the solid, which lowers ΔG
- ionization of IMC: RCOOH → $RCOO^-$ + H^+, which introduces charged species not included in the prediction

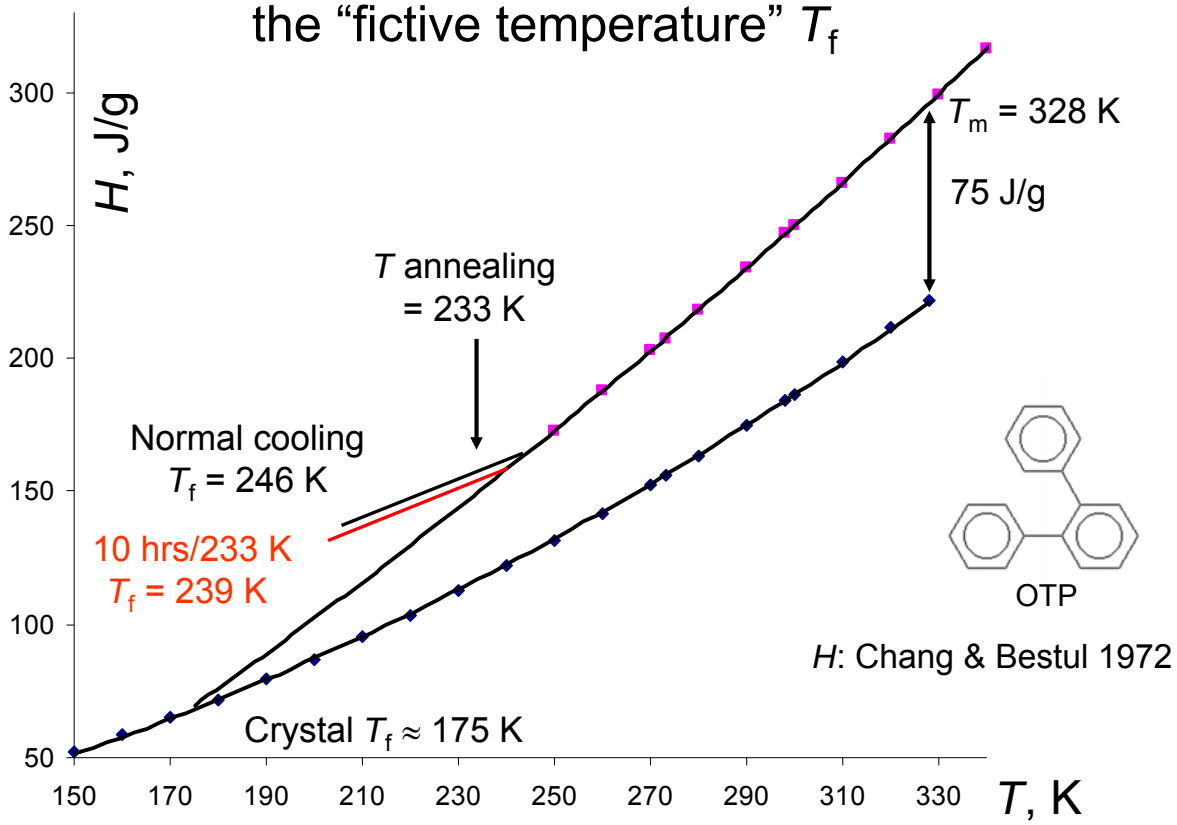
Glasses can relax over time to lower-energy states



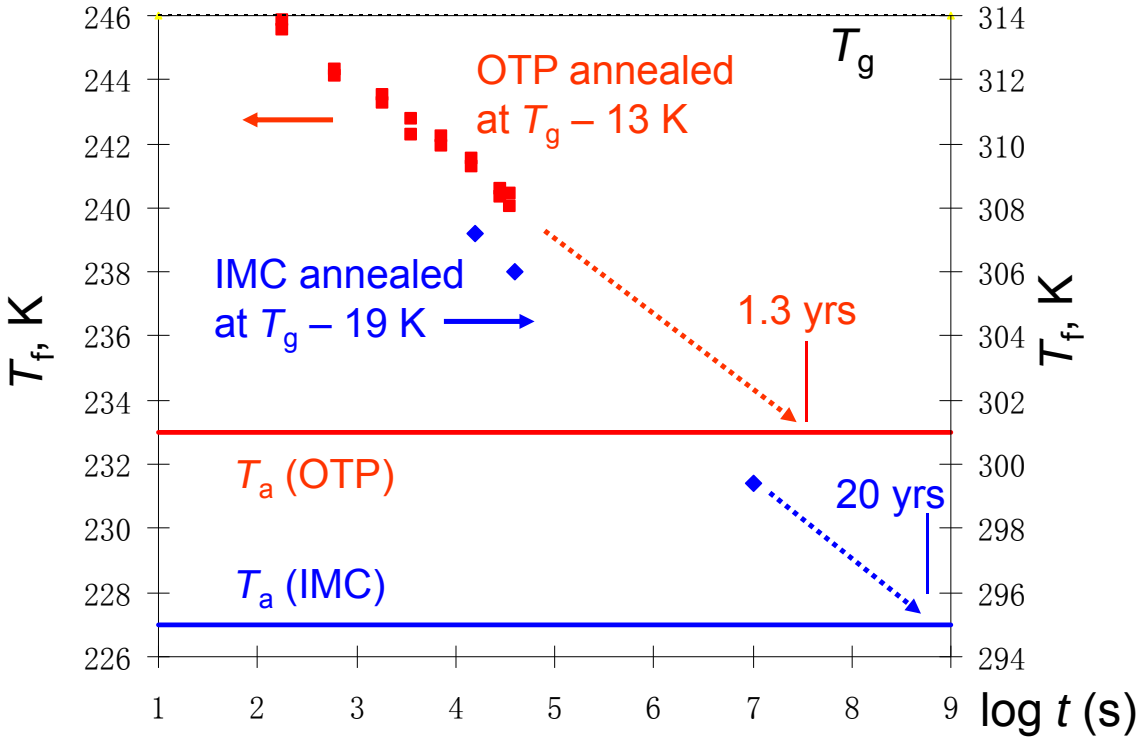
Heat capacity of OTP glass annealed for up to 10 hrs at 233 K (T_g – 13 K). Longer annealing leads to lower energy and higher "heat of melting".

Xi, H.; Sun, Y.; Yu, L. *J. Chem. Phys.* **2009**, *130*, 094508.

Progress of glass aging is often tracked with the "fictive temperature" T_f

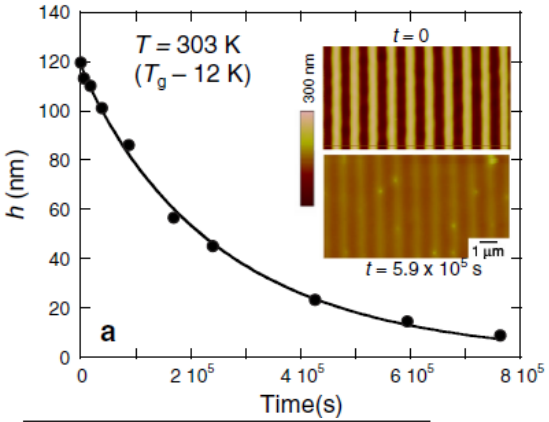


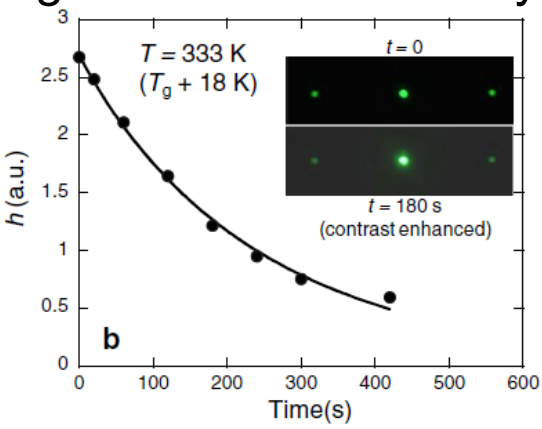
Aging a glass to equilibrium could be slow

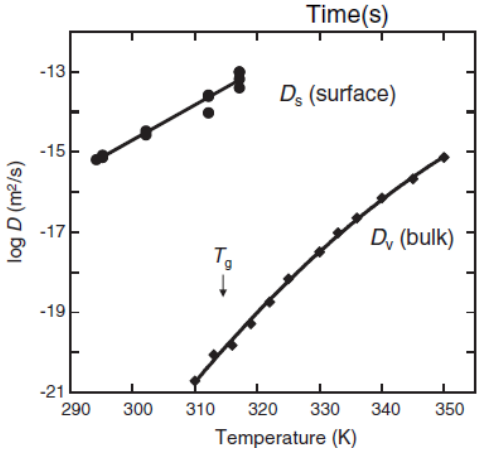


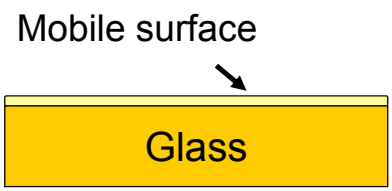
IMC data: Kearns et al. *J. Phys. Chem. B* **2008**, *112*, 4934

Surface mobility can be higher than bulk mobility









Lei Zhu et al. *Phys. Rev. Lett.* **2011**, *106*, 256103

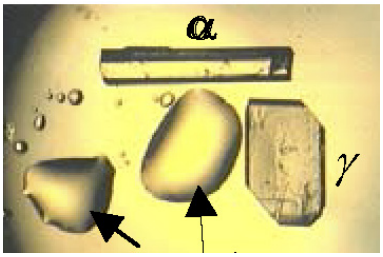
Glass Doesn't Flow and Doesn't Crystallize and It Isn't a Liquid

Stephen J. Hawkes

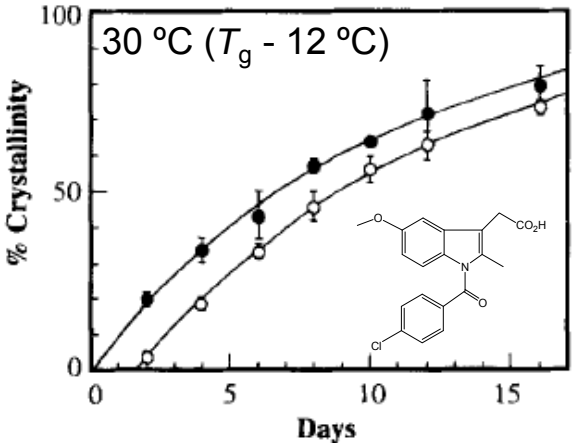
J. Chem. Educ. 2000, 77, 846

But glasses do crystallize!

Amorphous indomethacin crystallizes in days →

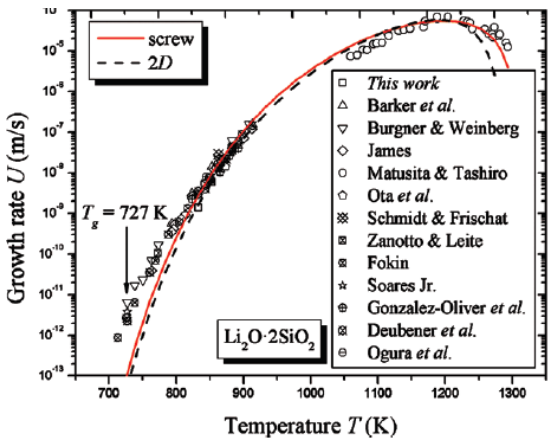


Yoshioka et al. *J. Pharm. Sci.* **1994**, *83*, 1700



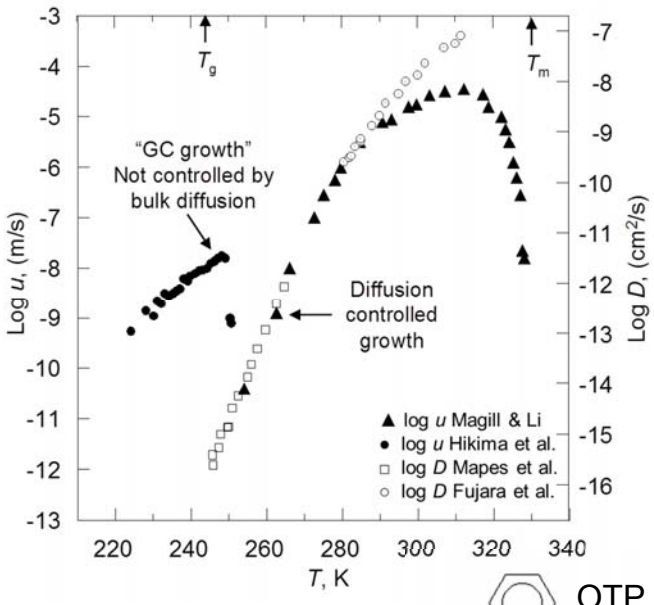
Organic glasses show fast modes of crystal growth unknown for non-organic glasses

Typical silicates



Nascimento & Zanotto *J. Chem. Phys.* 2010, **133**, 1

o-terphenyl (OTP)



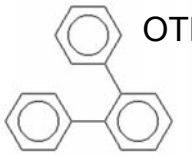
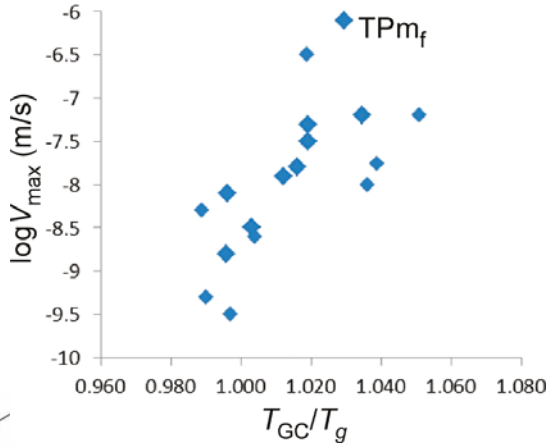
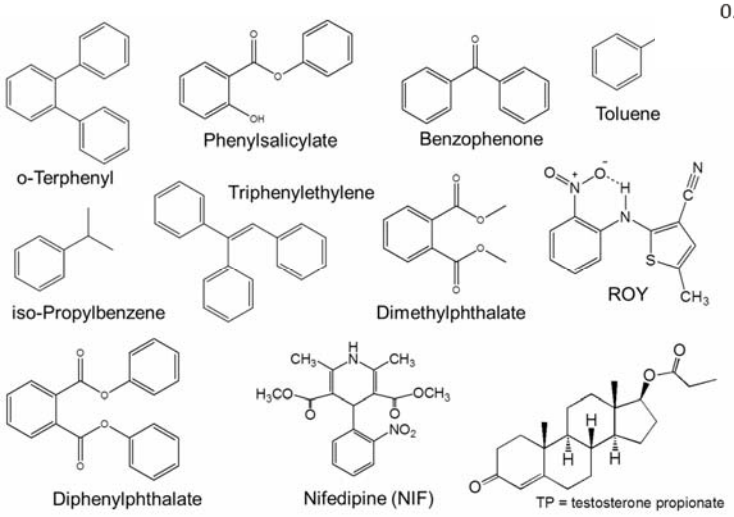


Figure: Y. Sun et al. *J. Phys. Chem. B* **2008**, *112*, 661

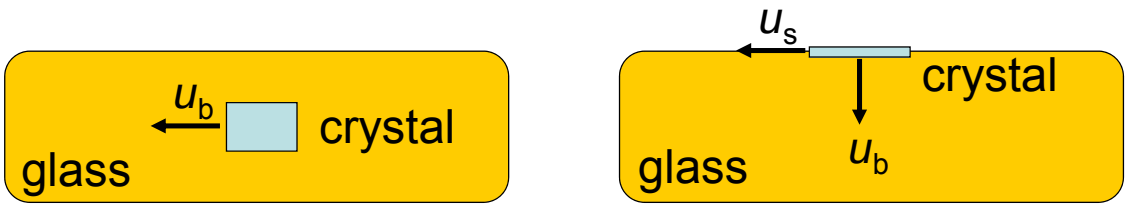
Many organic liquids show emergence of GC growth near T_g





Shtukenberg, A.; Freundenthal, J.; Gunn, E.; Yu, L.; Kahr, B. *Crystal Growth & Design* **2011**, *11*, 4458

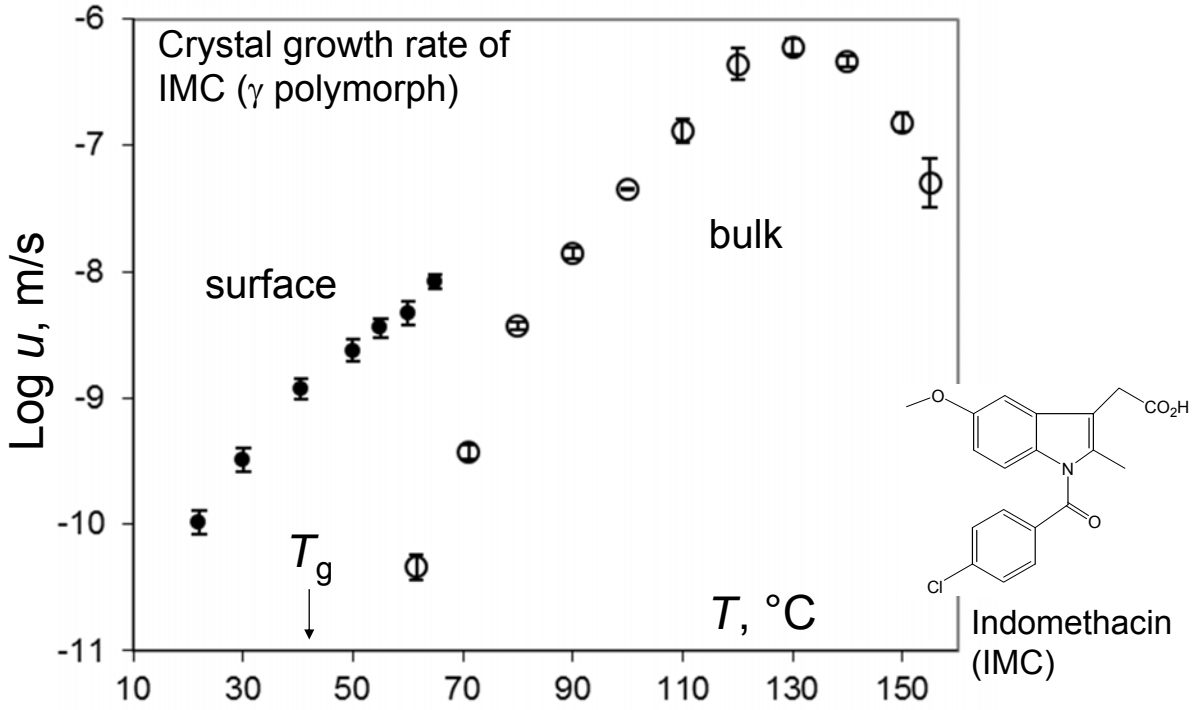
Crystal growth in bulk and at free surface



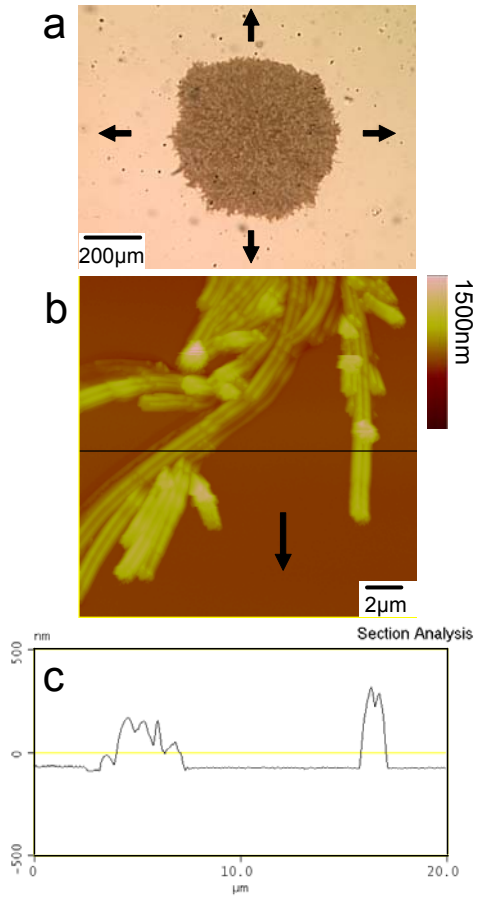
"Whereas in many metallic glasses nucleation has been observed to be enhanced at the surface, growth rates are usually quite comparable with those in the bulk." U. Koster (*Mat. Sci. & Eng.* 1988, *97*, 233)

[For silicate glasses,] "The crystal growth velocities of crystals in the volume and of the surface layer in the glass volume, as well as of isolated crystals on the glass surface are equal." Diaz-Mora et al. (*J. Non-Crystalline Solids* 2000, *273*, 81)

Organic glasses can grow crystals faster at the surface than in the bulk



Wu, T.; Yu, L. *J. Phys. Chem. B* **2006,** *100*, 15694**;** *Pharm. Res.* **2006**, *23*, 2350



What do surface crystals look like?

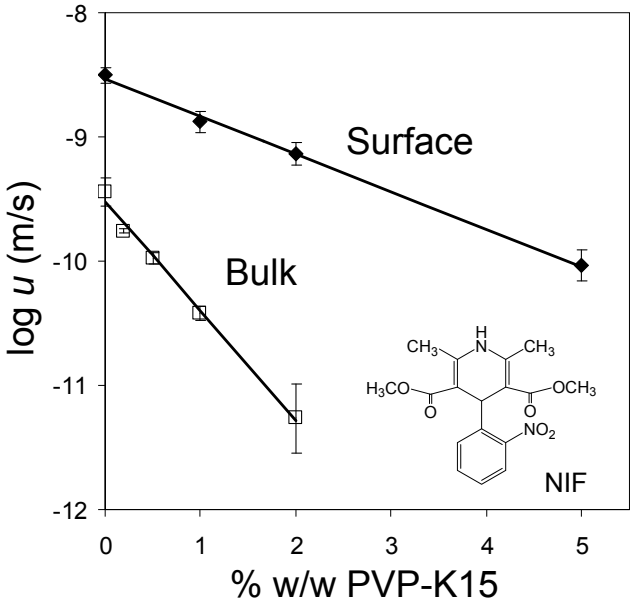
α IMC crystals at T_g – 2°C

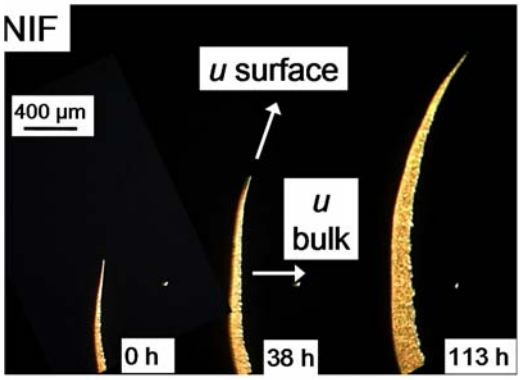
Surface crystals rise above glass surface by 100 – 1000 nm, as they grow laterally

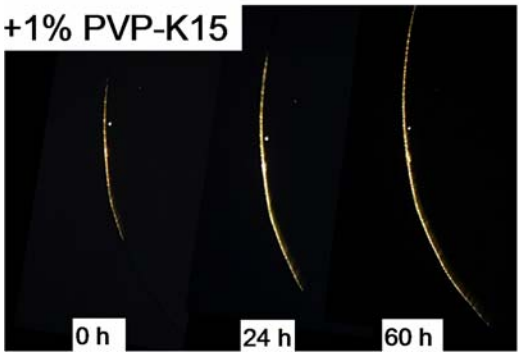
Ye Sun et al. *PNAS* **2011**, *108*, 5990

Polymer dopants can strongly inhibit bulk crystal growth, but their effect on surface growth is less

Crystal growth in NIF glass at T_g – 12 °C

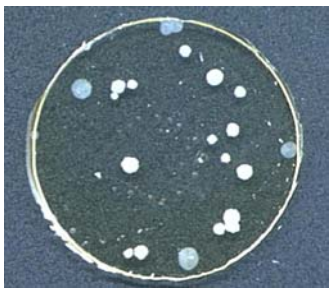






Ting Cai et al. *Pharm. Res.* 2011, *28*, 2458

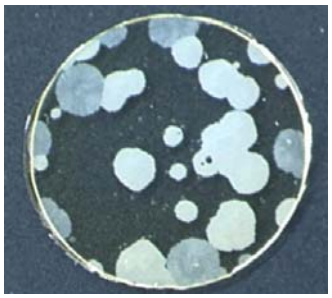
Surface crystallization can be inhibited with a nanocoating

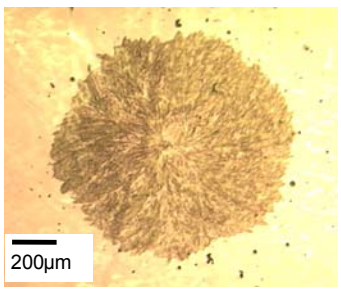


15 mm

Uncoated IMC glass

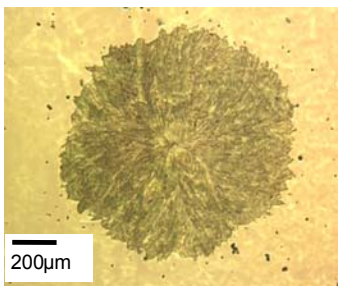
7 d at 40 ºC



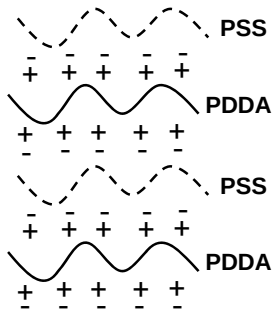


Coated with 10 nm gold or 2–30 nm polymer

7 d at 40 ºC



Layer-by-layer coating



IMC glass

Wu, Sun, Li, de Villiers, and Yu. *Langmuir* **2007**, *23*, 5148

Summary

- Organic glasses are useful for pharmaceutical and electronic applications
- Besides cooling liquids, there are other ways to make glasses (amorphous solids)
- Solidity does not mean no mobility. Glasses relax, and mobility at surfaces can be high
- Fast modes of crystal growth can emerge as organic liquids become glasses, both in the bulk and at surfaces
- Crystal growth in organic glasses can be inhibited by polymer additives and coatings