Teton, Wyoming

Phase Behavior of Model Block Copolymers in Near Critical Solutions: Toward Self-Assembled Nanoparticles For Drug Delivery

Maciej Radosz, Winoto Winoto, Zachary Tyrrell, Jade Green, Youqing Shen

Soft Materials Laboratory, University of Wyoming

Jimmy Mays, Kunlun Hong, CNMS, ORNL

2010 User Meeting

Center for Nanophase Materials Sciences

Oak Ridge National Laboratory, 09-14-2010

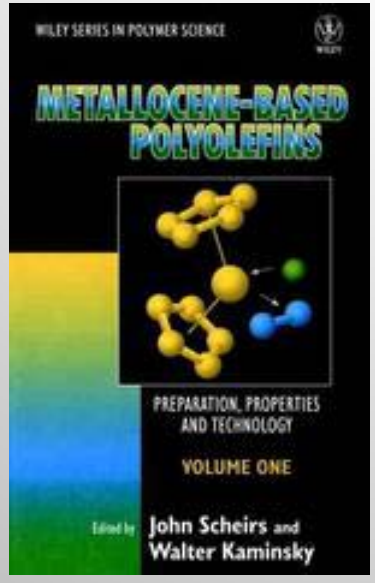
Outline

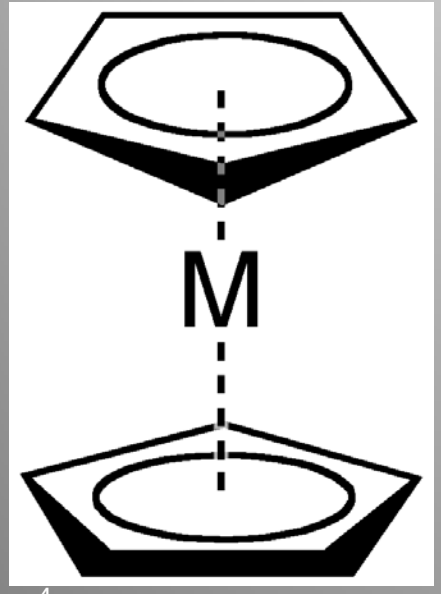
- ***m*-Homopolymers, *m*-copolymers**
- **Drug-delivery example → NUCLEAR delivery… drug loading a challenge**
- **Physics of block copolymer micellization**
- **Compressible solvents a new frontier**
  - **How to measure, calculate micellization?**
  - **How to account for crystallizability?**
  - **How about morphology?**
  - **Can nanoparticles be dispersed in water?**

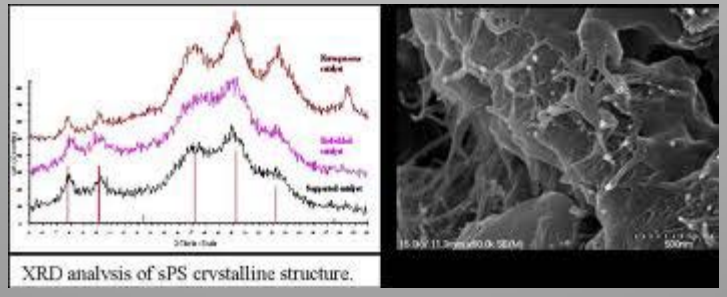
- ***CNMS User Project with Prof. Mays key***

The Metallocene Story (Catalysis Innovation)

Walter Kaminsky
Hamburg 1980



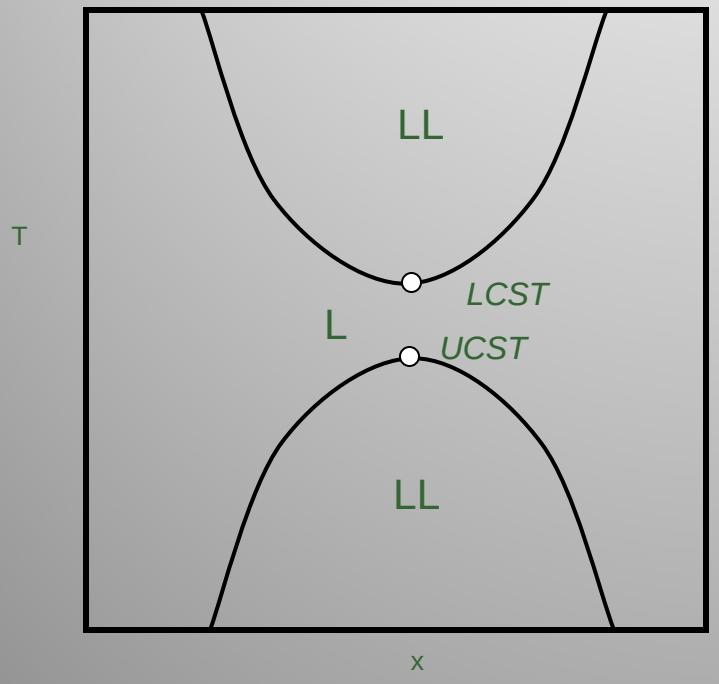



XRD analysis of sPS crystalline structure.

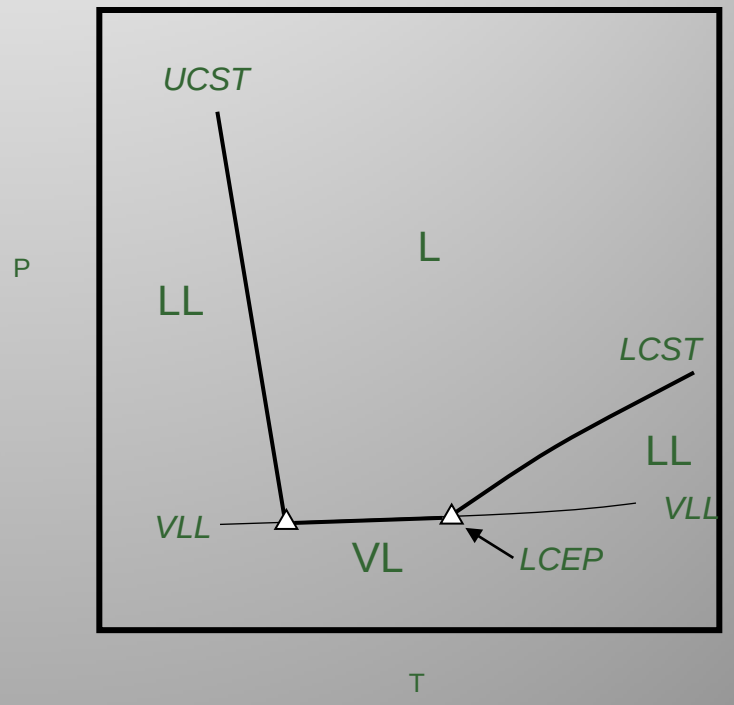
PE? No: mPE!

Phase diagrams:
amorphous polymer + solvent/monomer

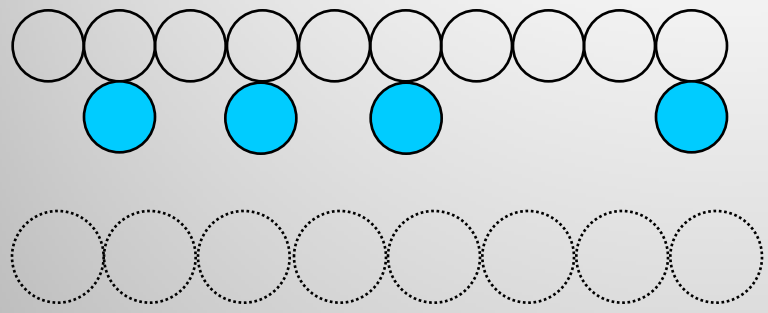
P constant



X constant



Homopolymer SAFT Approximation



PEP Copolymer

Effective Homopolymer

A chain of equisized spherical segments

Homopolymer chain term (SAFT)

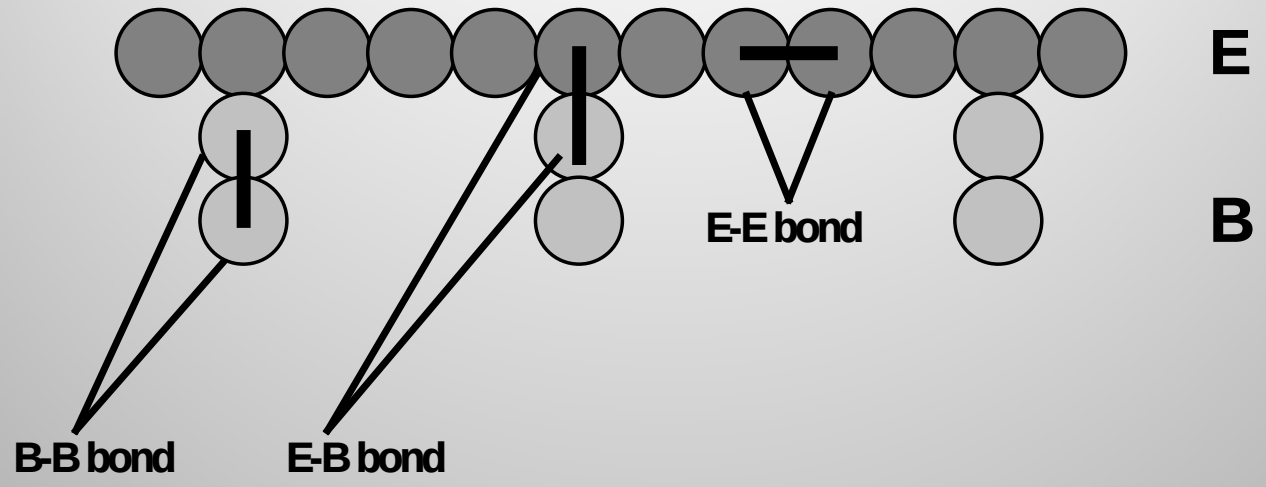
$$\frac{P-P_R}{k_B T \rho_c} = \sum_{i=1}^{r} X_i (1-m_i)\left[1+\rho\frac{\partial}{\partial\rho}\ln g_R(L_i)\right]$$

Huang and Radosz, 1990, 1991

Microstructure characteristics buried in parameters:

- SEGMENT VOLUME
- SEGMENT ENERGY

Copolymer SAFT Approximation

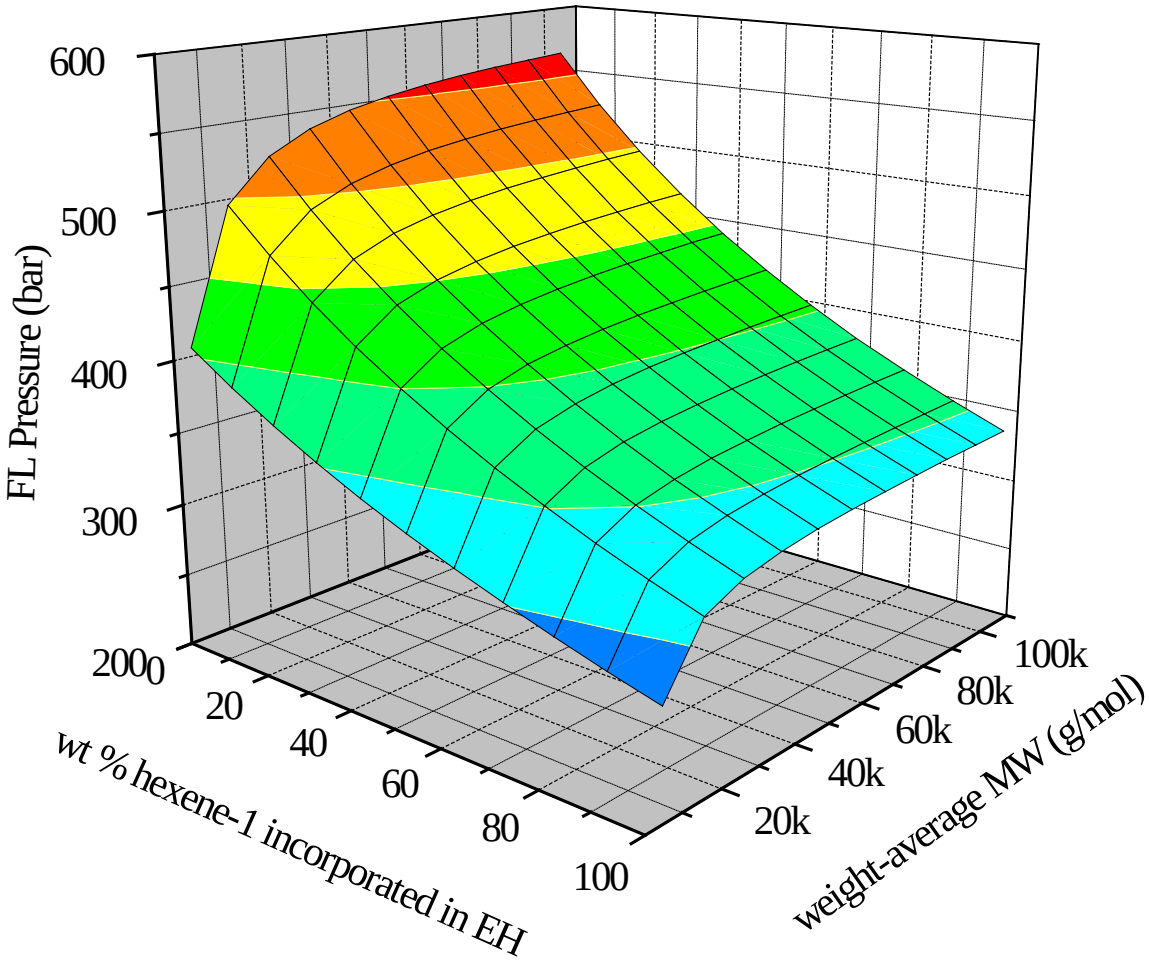


***Copolymer* chain term (Copolymer SAFT)**

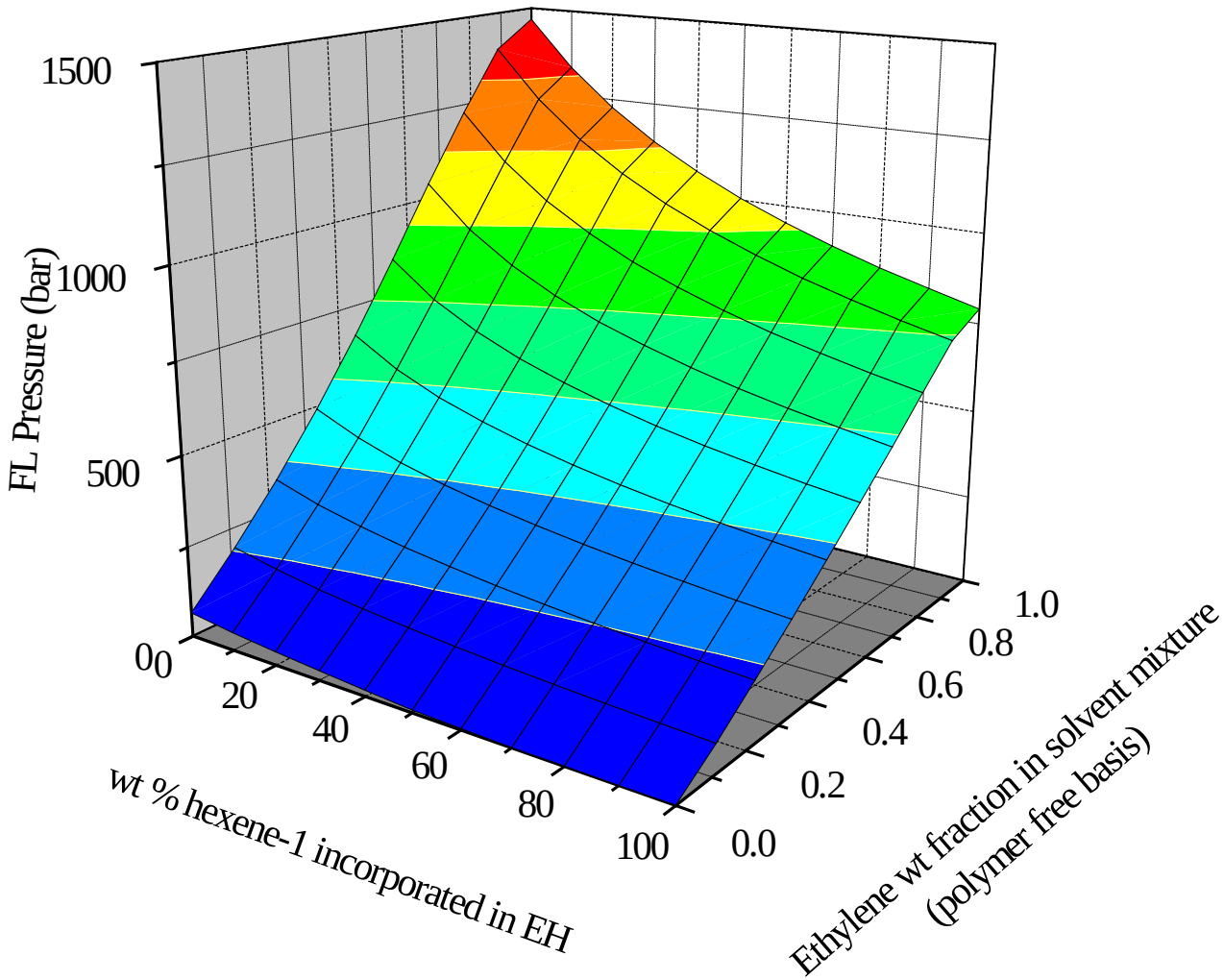
$$\frac{P-P_R}{k_B T \rho_c} = \sum_{i=1}^{r} X_i (1-m_i) \left[1 + \sum_{\kappa_i=1}^{K_i} \phi_{\kappa_i}^{i} \rho \frac{\partial}{\partial \rho} \ln g_R^{\kappa_i}(L_{\kappa_i}) \right]$$

Copolymer SAFT: Banaszak et al., 1996
SAFT1: Adidharma, Radosz, 1999

Fluid-liquid surface for 0.15 EH-x-y in Propane at T = 180 °C



Fluid-liquid surface for 0.15 EH-x-80k in Ethylene + 1-Hexene at T = 180 °C



SAFT design tools enabled these plants…

Grass roots and revamp…

Plastics

$1-5/kg

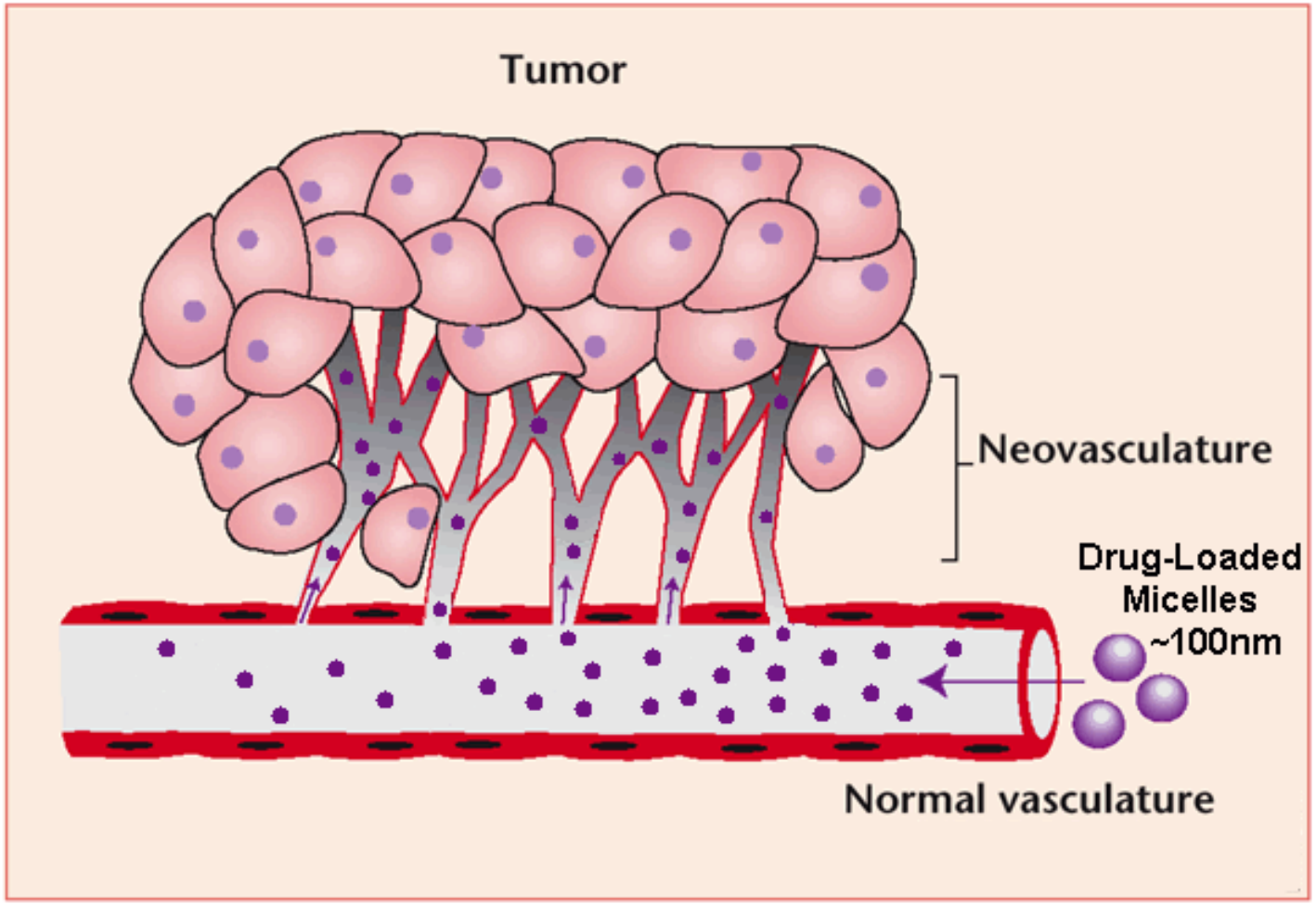
(Oil $0.3/kg)

Cancer drugs

$1-5/mg *(Paclitaxel)*

$1-5,000,000/kg

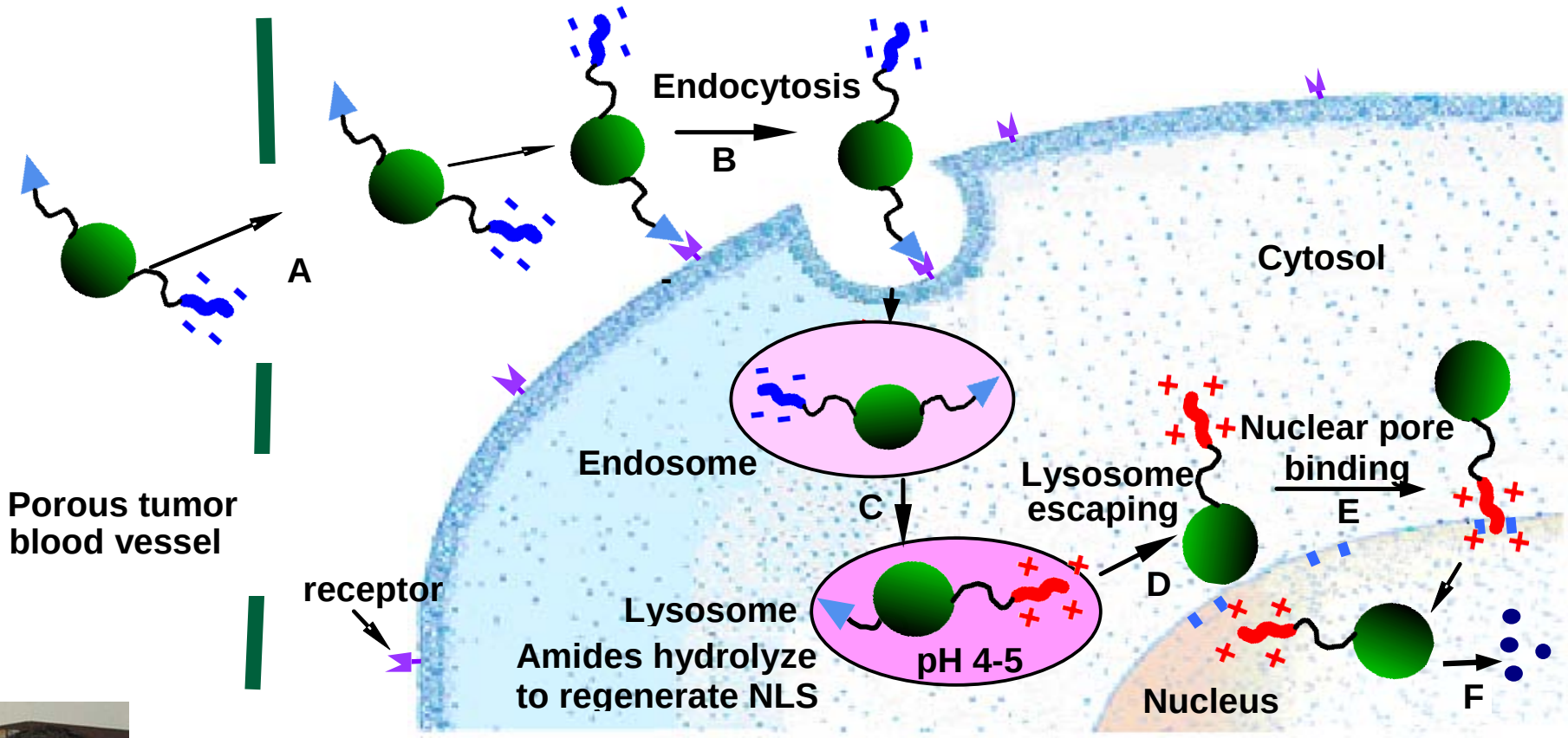
Drug-Loaded Block-Copolymer Micelles:
Enhanced Permeability and Retention (EPR)



Cancer-Drug Delivery

Torchillin 2001

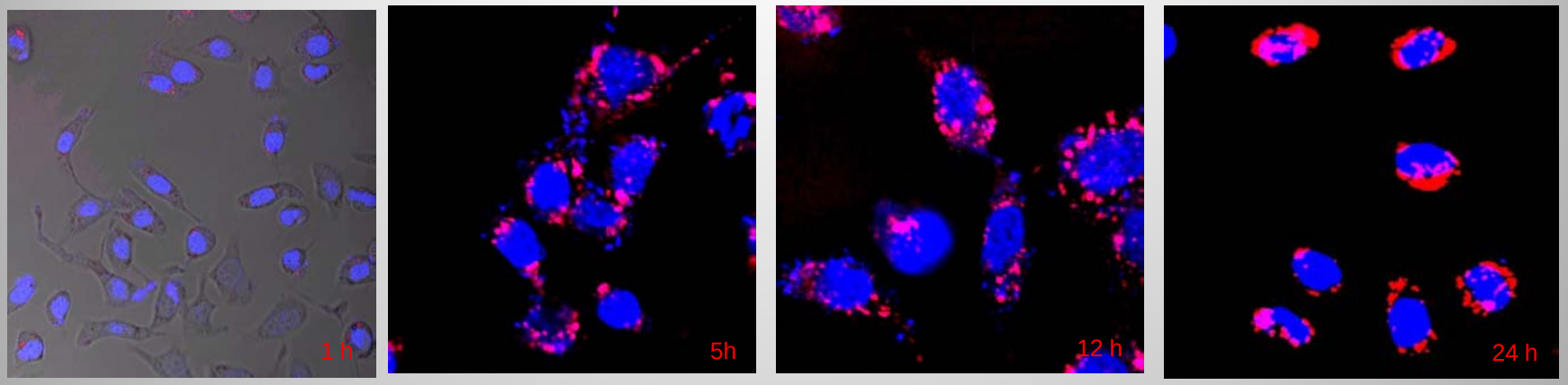
Adaptable Nuclear-Localizing Nanoparticles (ANLN)

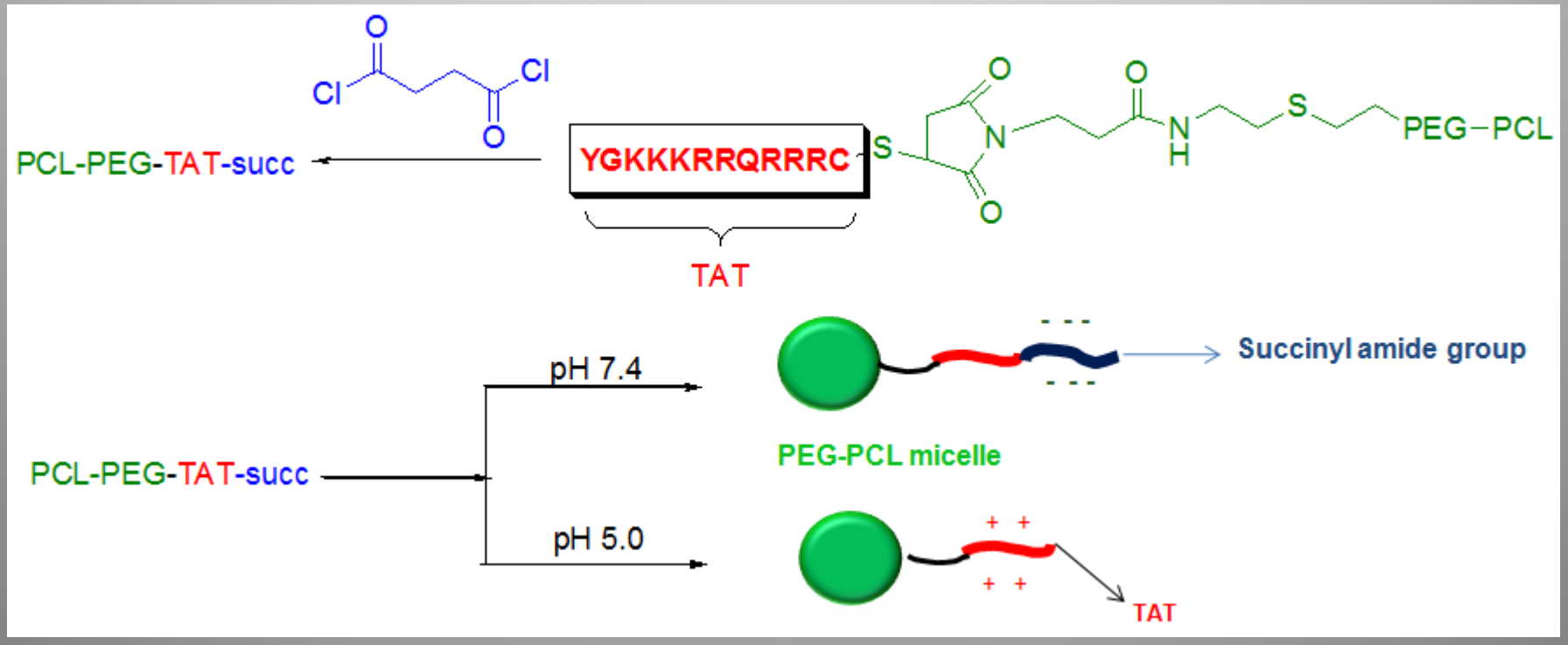


Zhou, Shen, Tang, Fan, Van Kirk, Murdoch, Radosz ***Advanced Functional Materials*** 2009, *19*, 3580

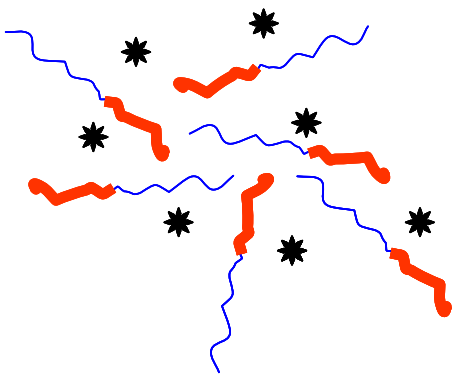
Xu, Van Kirk, Zhan, Murdoch, Radosz ,Shen ***Angewandte Chemie, International Edition*** 2007, 46, 4999

ANLN Example: Cellular Uptake of PCL-PEG-TAT-succ (15%)

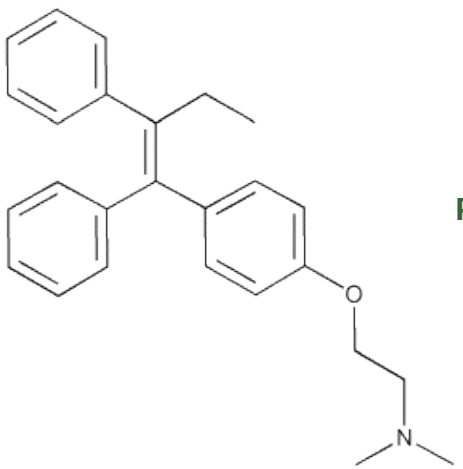




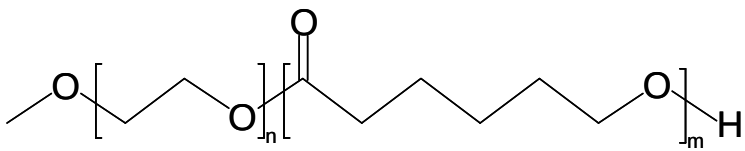
How to maximize micelle drug content?



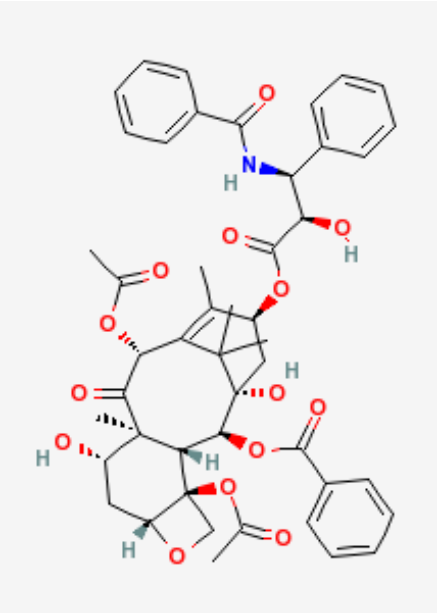
Organic Solvent



Tamoxifen

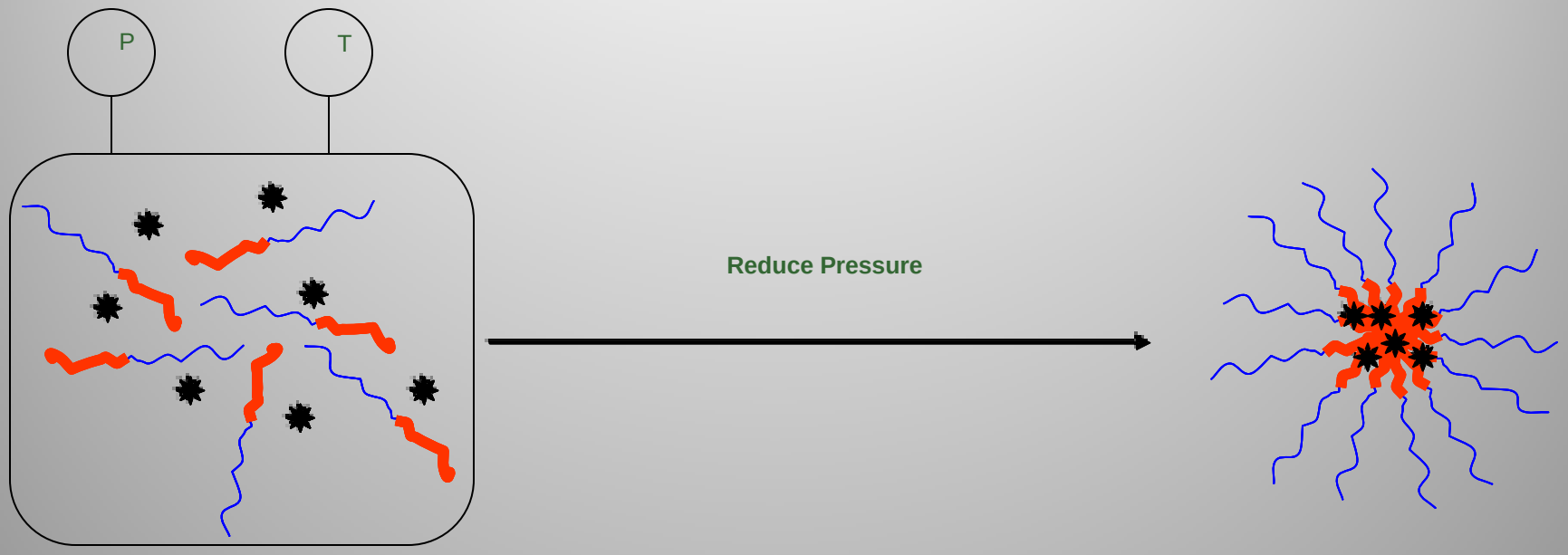


Poly(ethylene glycol)-*block*-Poly(ε-caprolactone)
PEG-*b*-PCL



Paclitaxel

Micelle Preparation in Compressible Solvent



Dissolve Polymer and Drug in

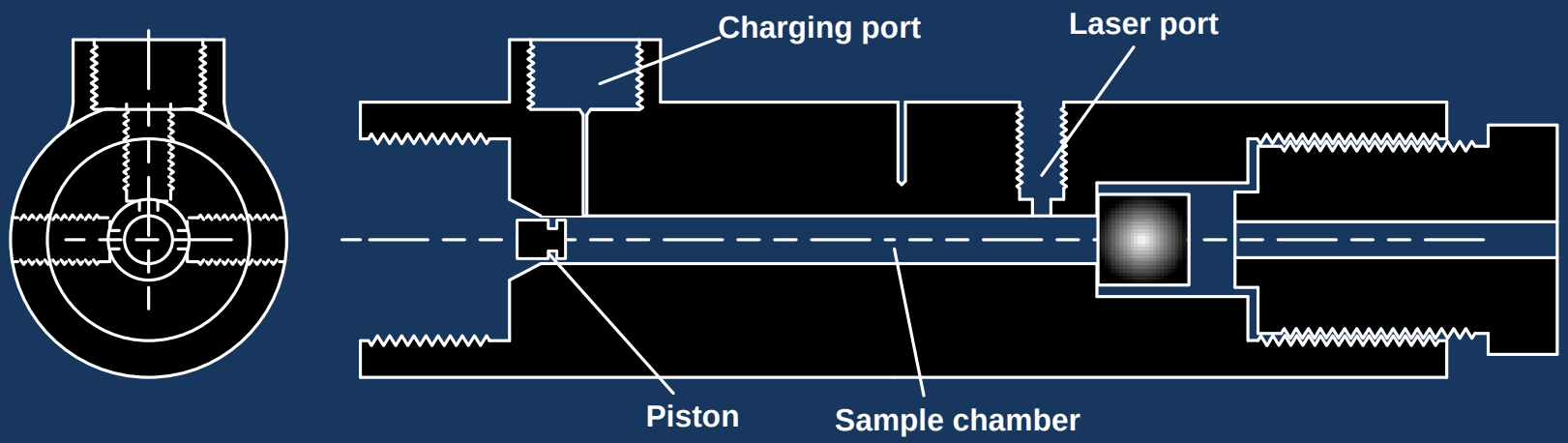
Sub- or Supercritical Fluid

… OR in a liquid solvent and pressurize with a Supercritical AntiSolvent (SAS)

Drug-Loaded Micelles

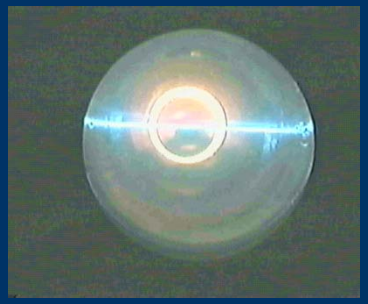
Patent Pending

High Pressure Cell

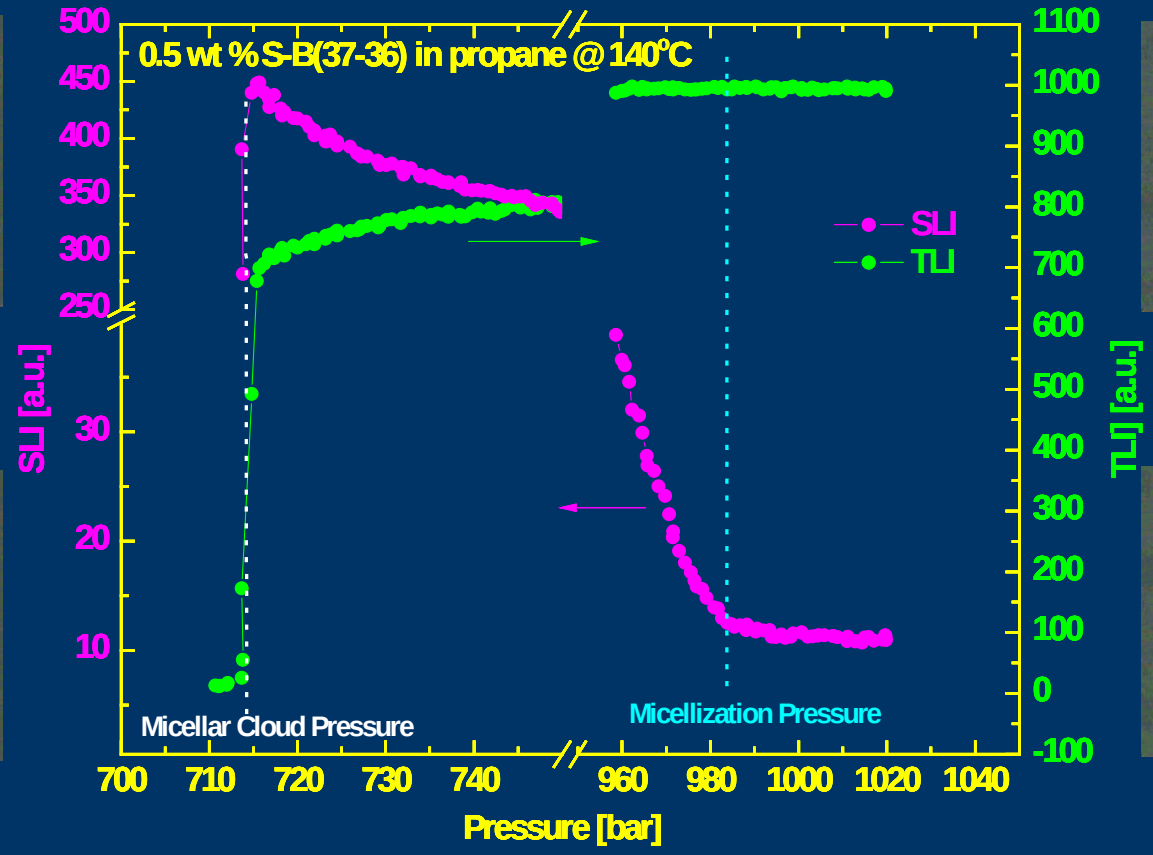


Transmitted and Scattered Light Intensities

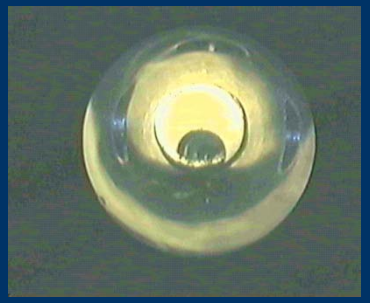
Micellar



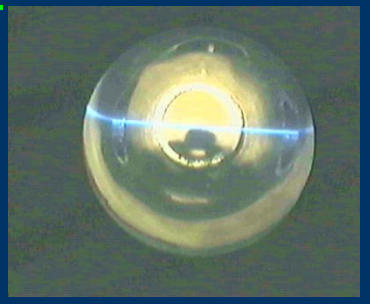
Two-Phase



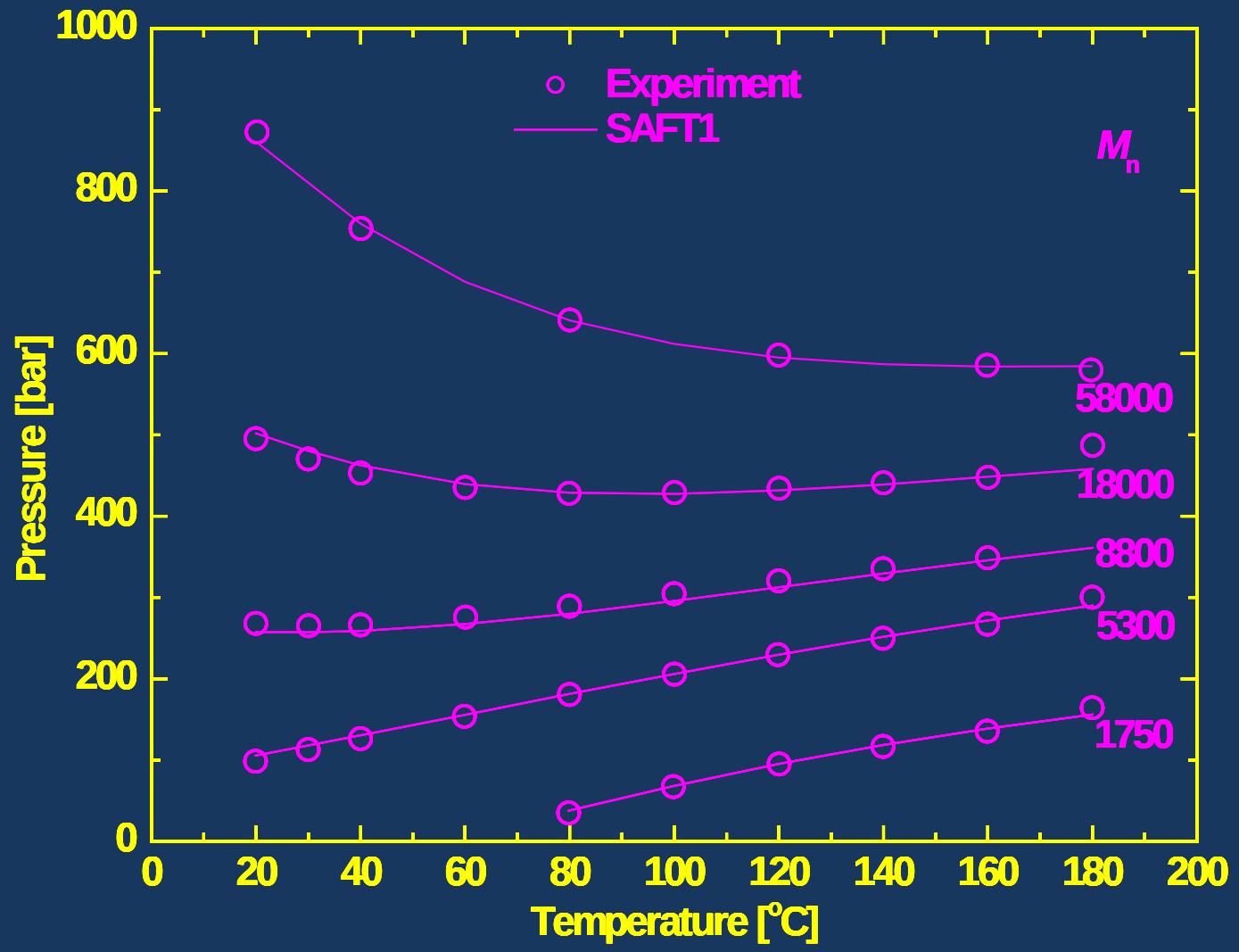
Random



Micellar

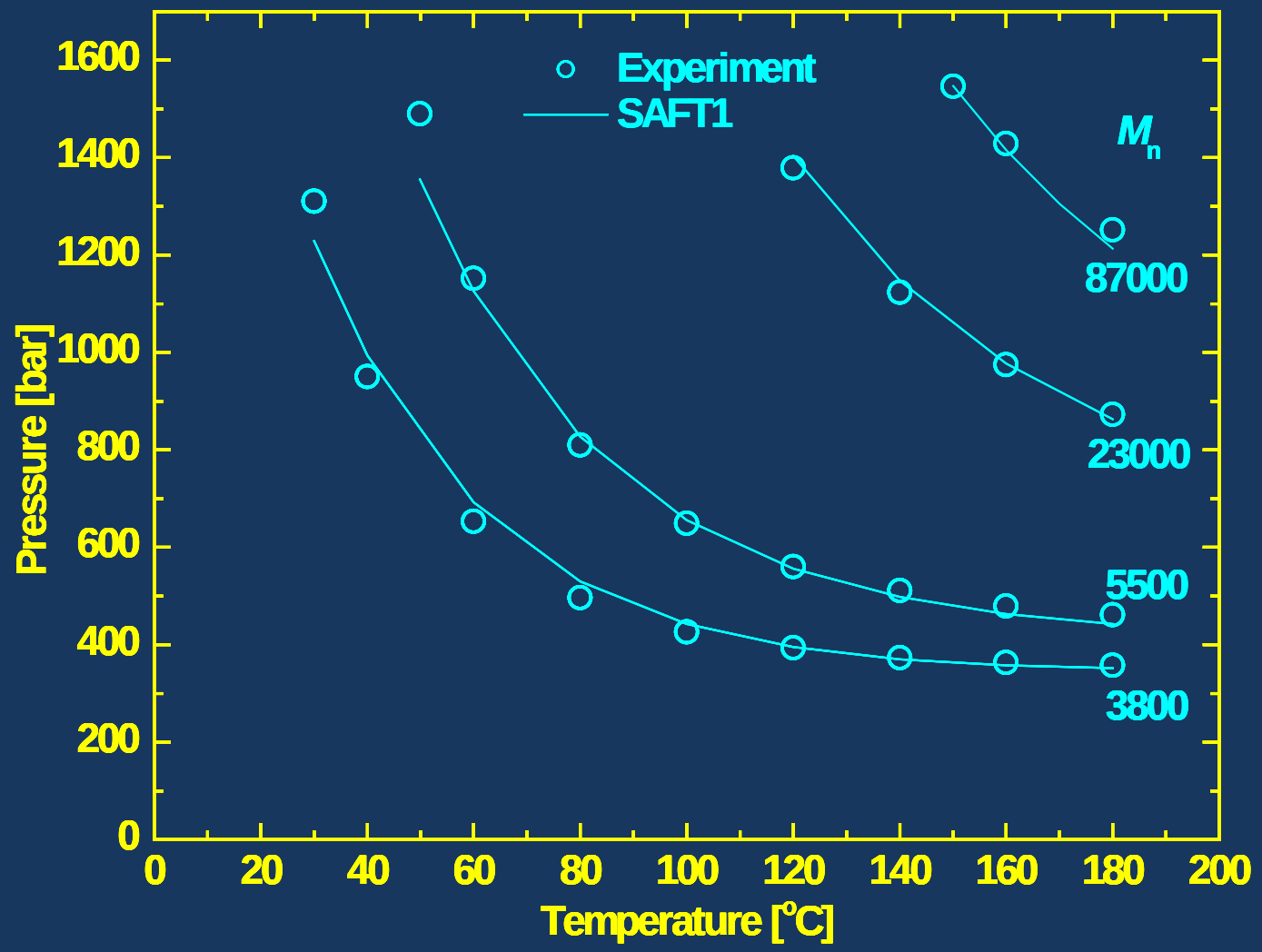


Polybutadiene



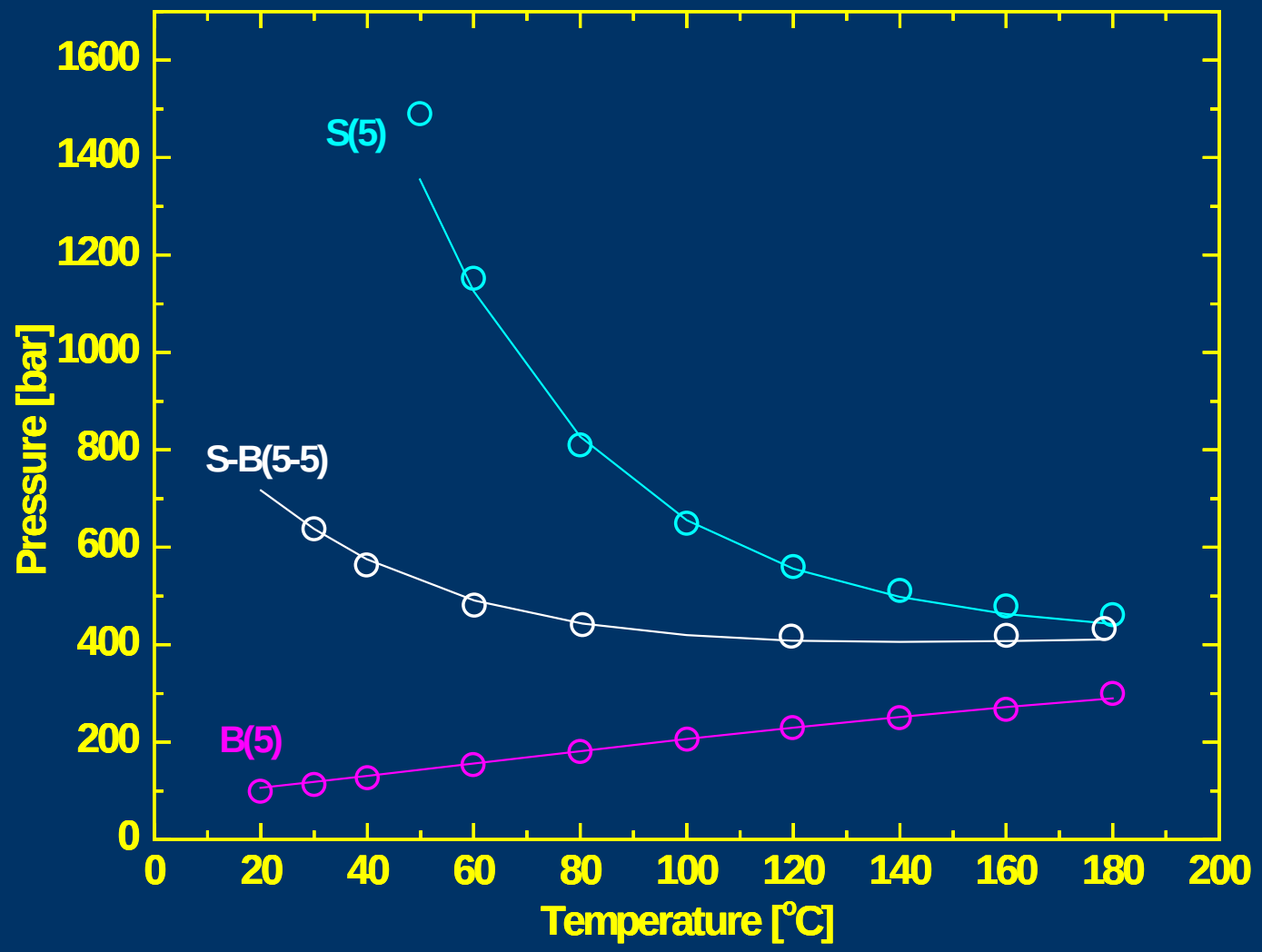
J. Phys. Chem. C 2007, 111, 15752-15758.

Polystyrene



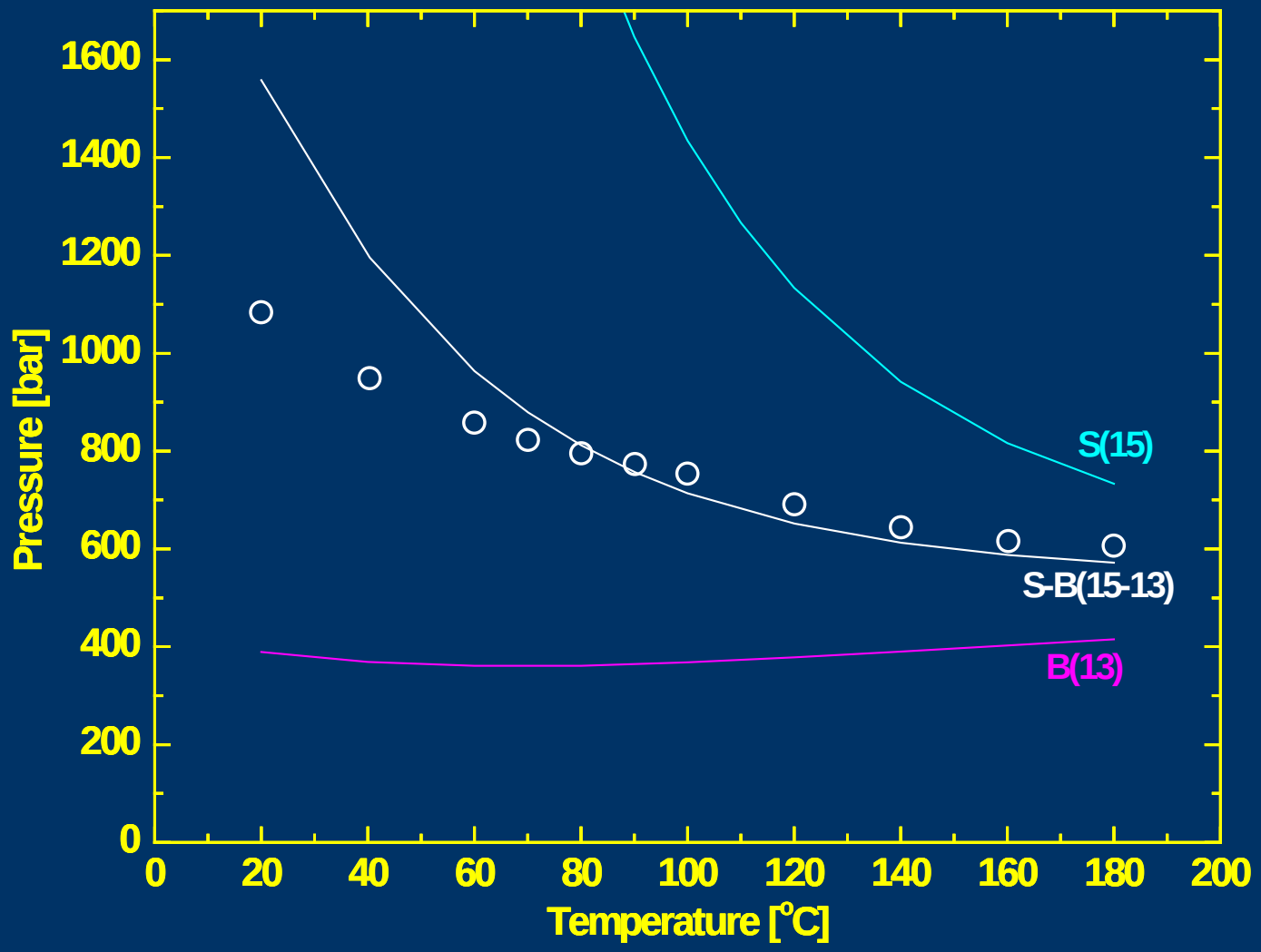
Fluid Phase Equilib. 2004, 226, 189-194.

S-B(5-5)



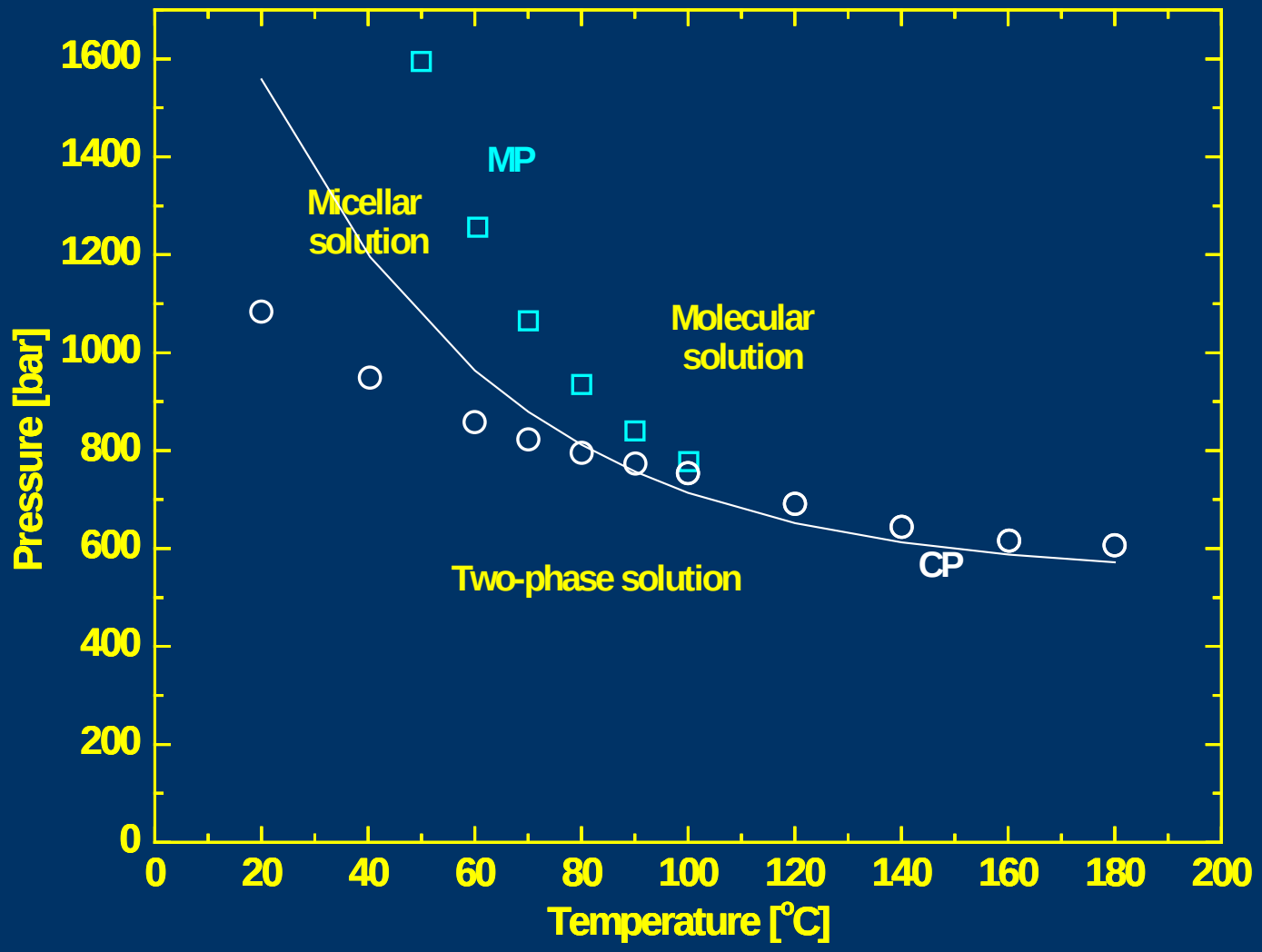
J. Phys. Chem. C 2007, 111, 15752-15758.

S-B(15-13)



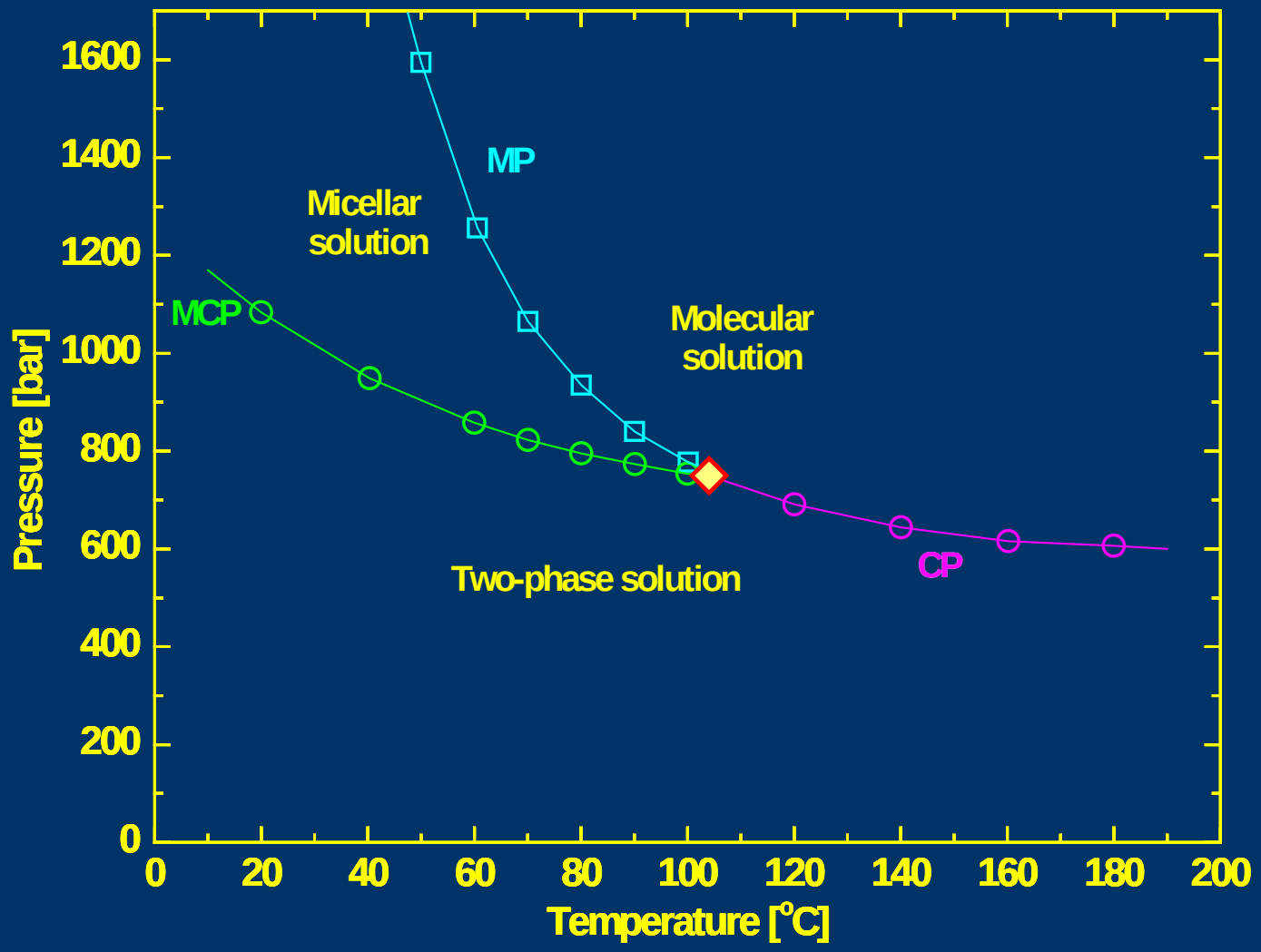
Macromolecules 2009, 42, 3823–3826.

S-B(15-13) – CP Reduction



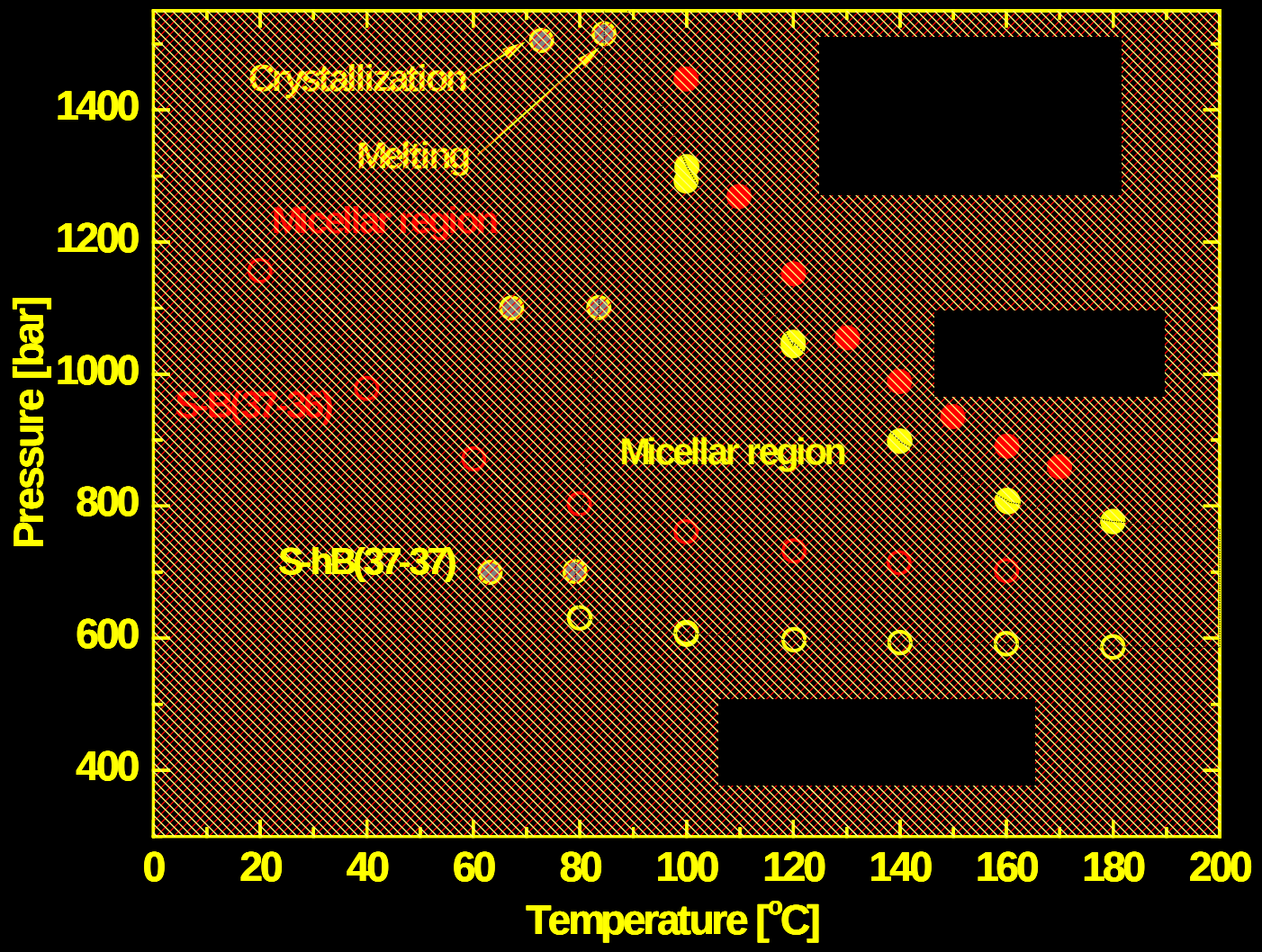
Macromolecules 2009, 42, 3823–3826.

S-B(15-13) – MEP



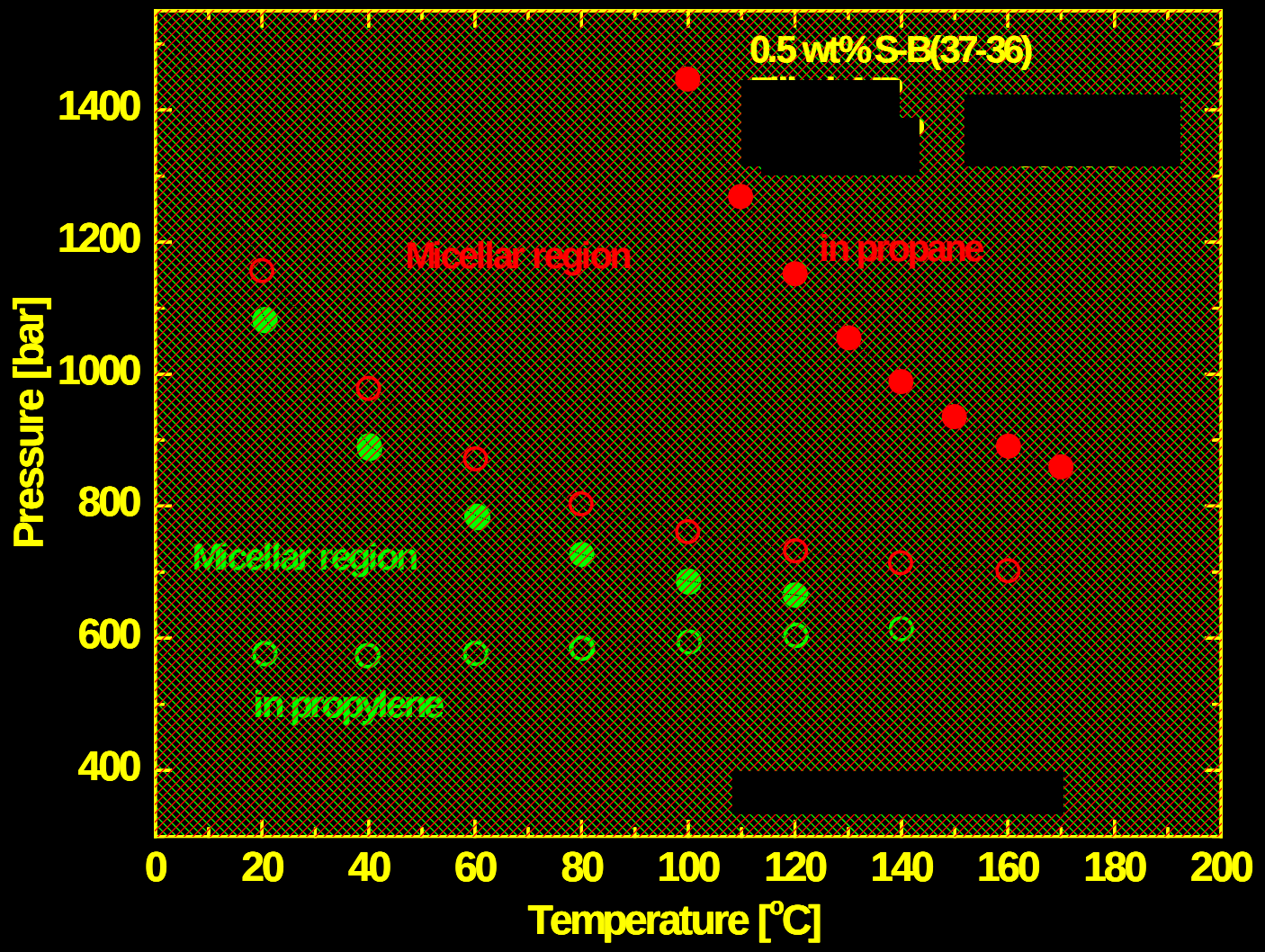
Macromolecules 2009, 42, 3823–3826.

Hydrogenation of Copolymer



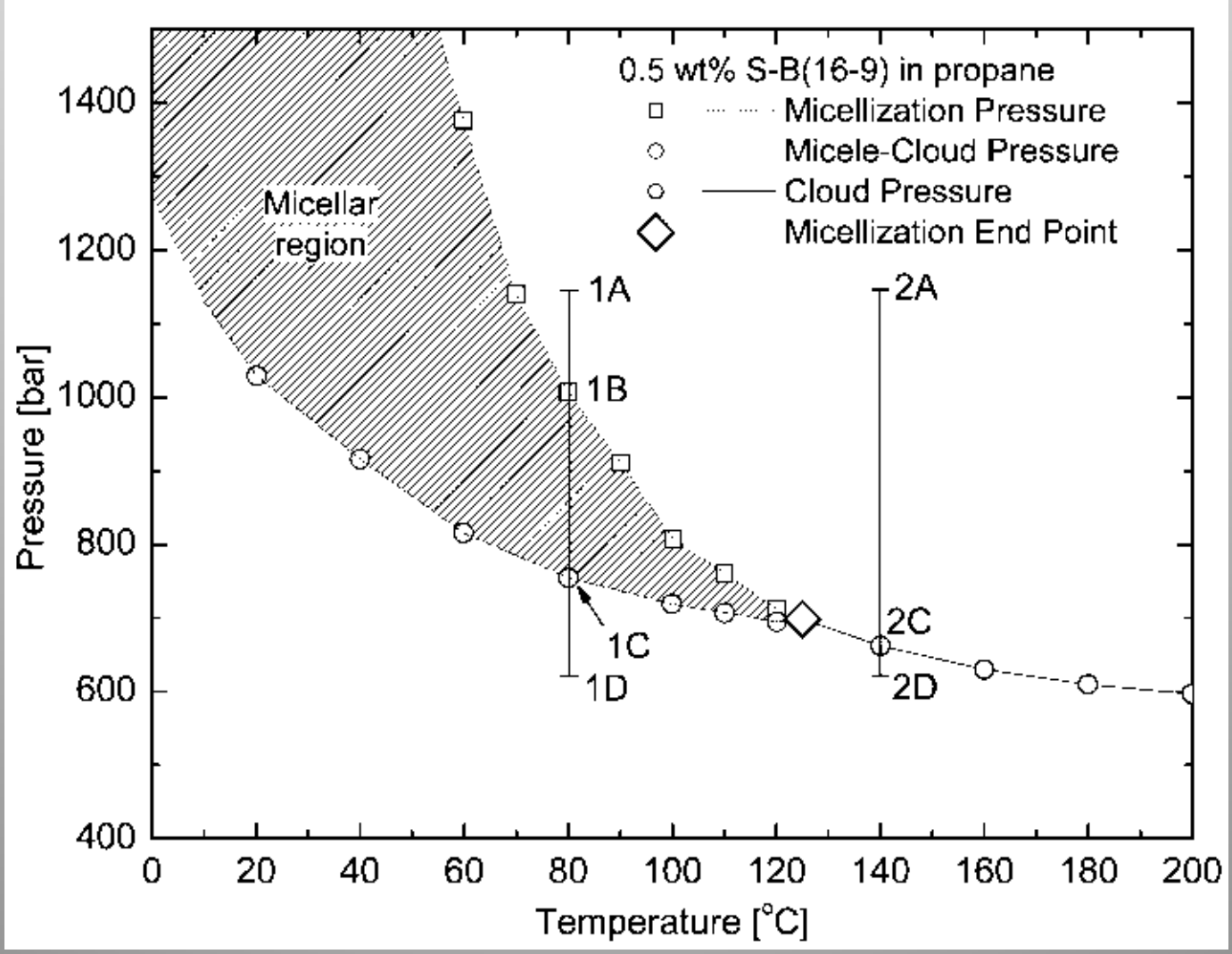
J. Non-Cryst. Solids 2009, 355 (24–27), 1393–1399.

Solvent Type



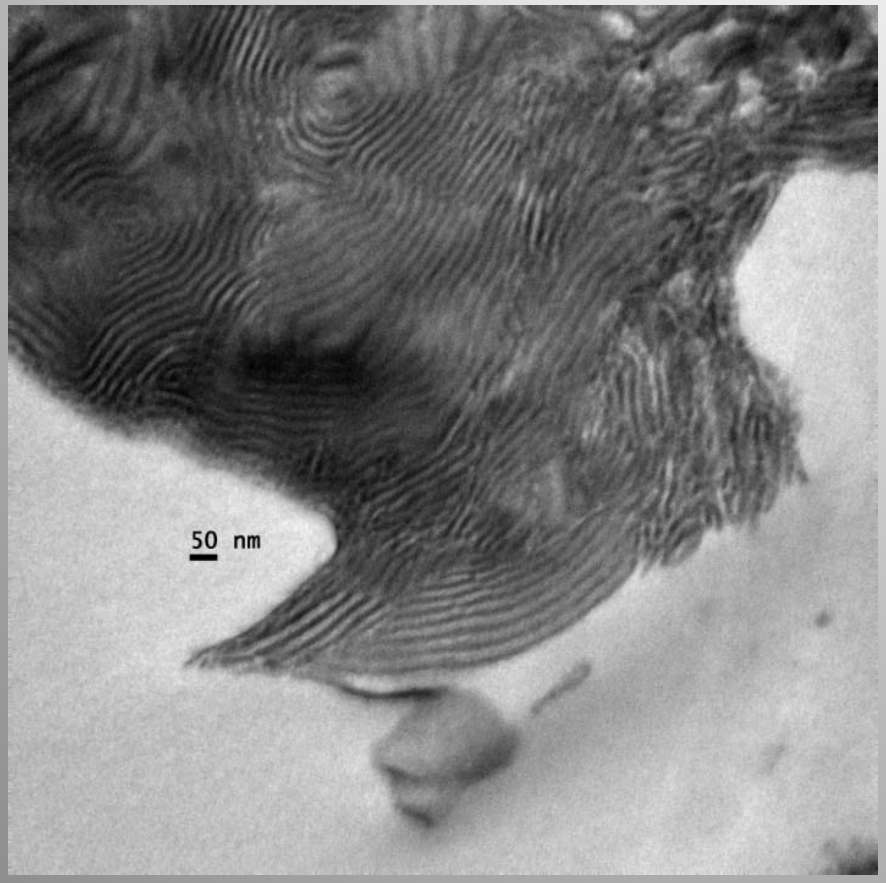
J. Non-Cryst. Solids 2009, 355 (24–27), 1393–1399.

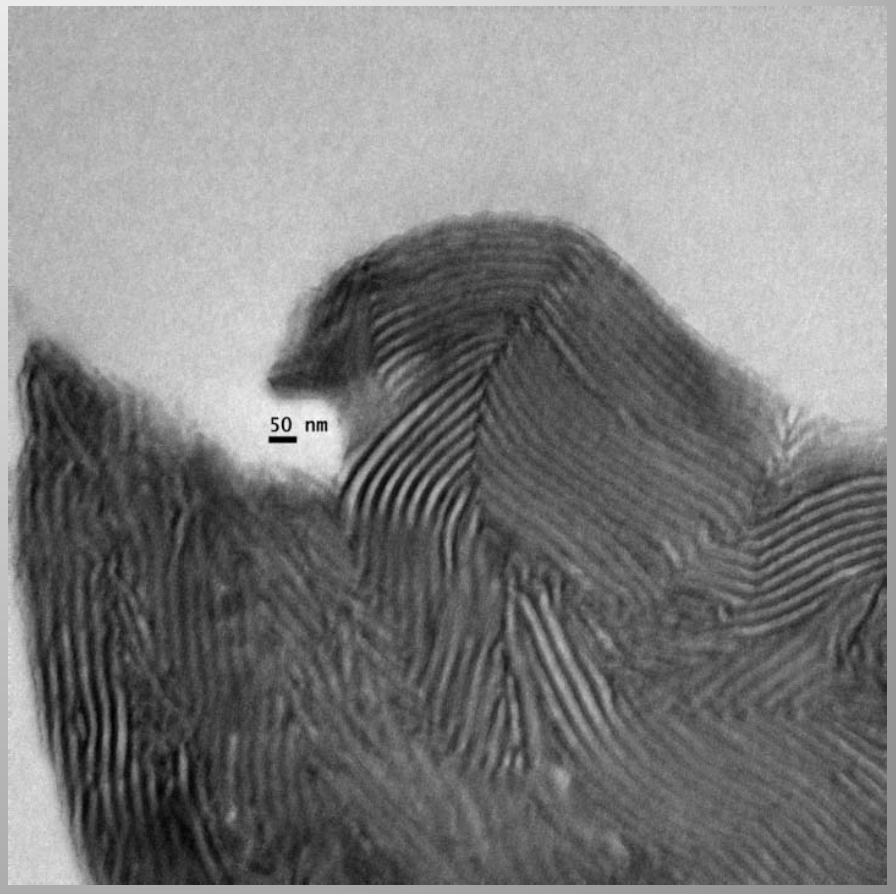
Decompression Paths



(Phase Diagram from Winoto 2008)

TEM: Micellar vs Molecular

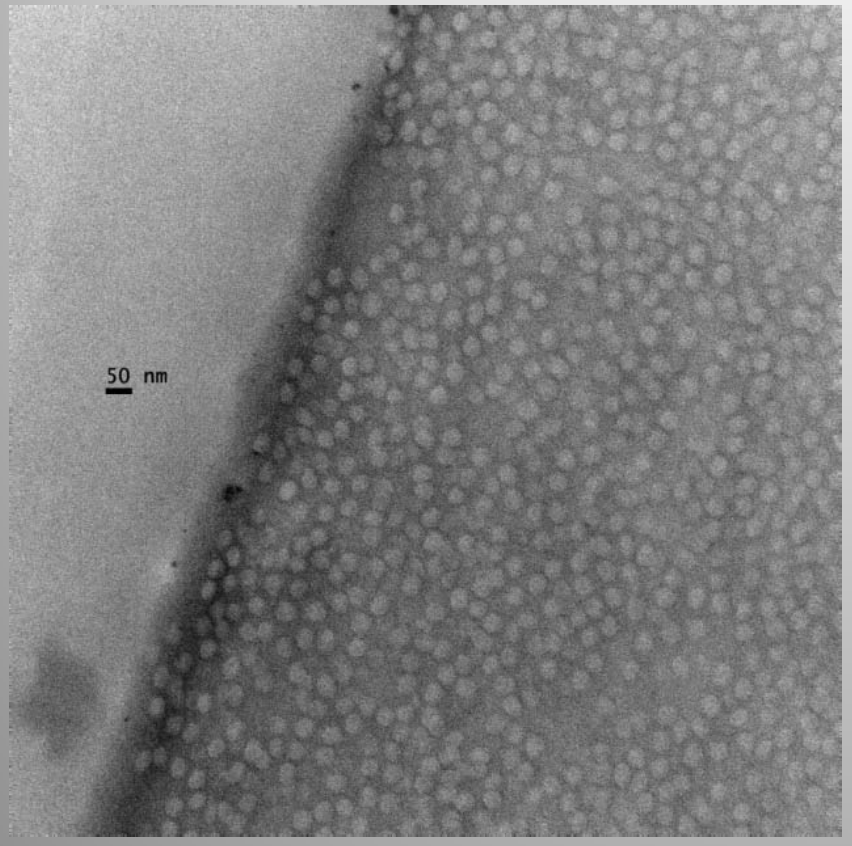




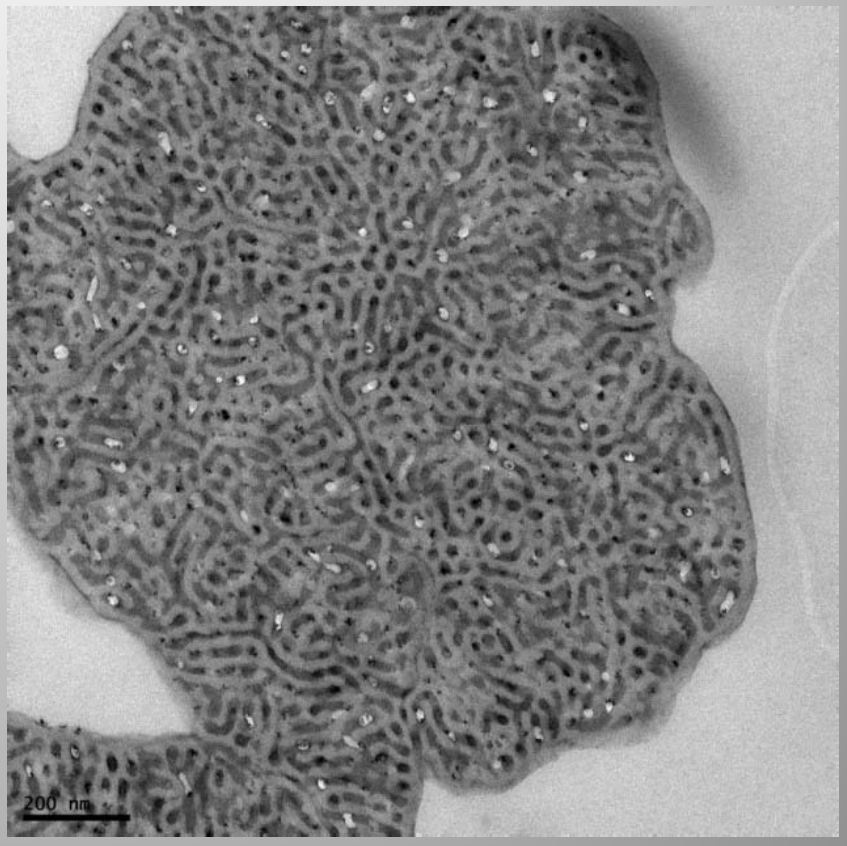
S-B(16-9)

Jade Green 2010

Rapid decompression of asymmetric blocks



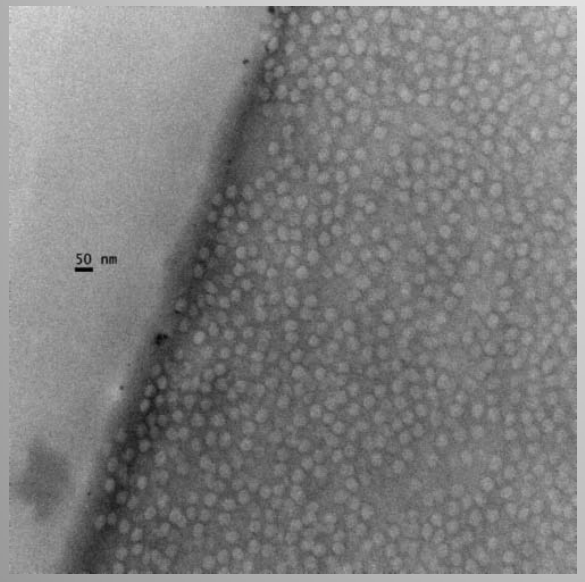
S-B (38-113)



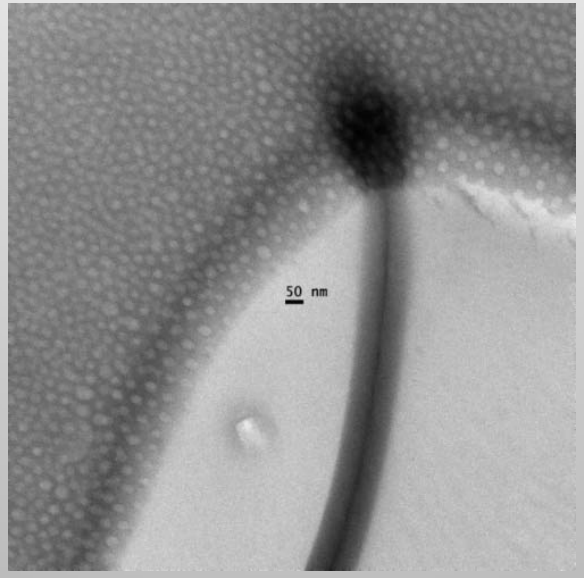
S-B (37-13)

Jade Green 2010

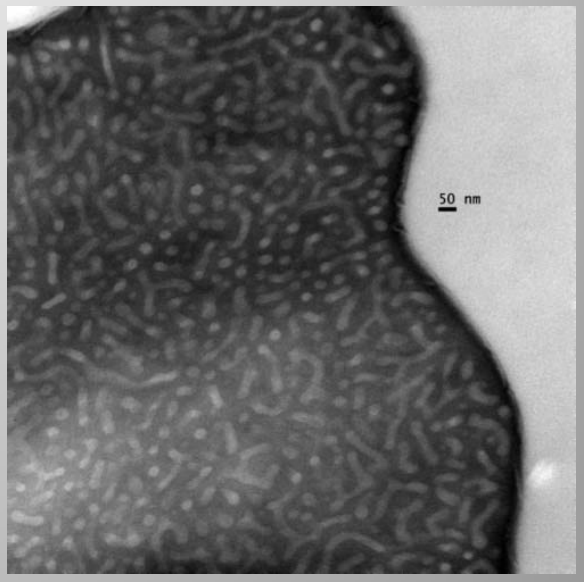
Decompression rate effects



Rapid



Slow

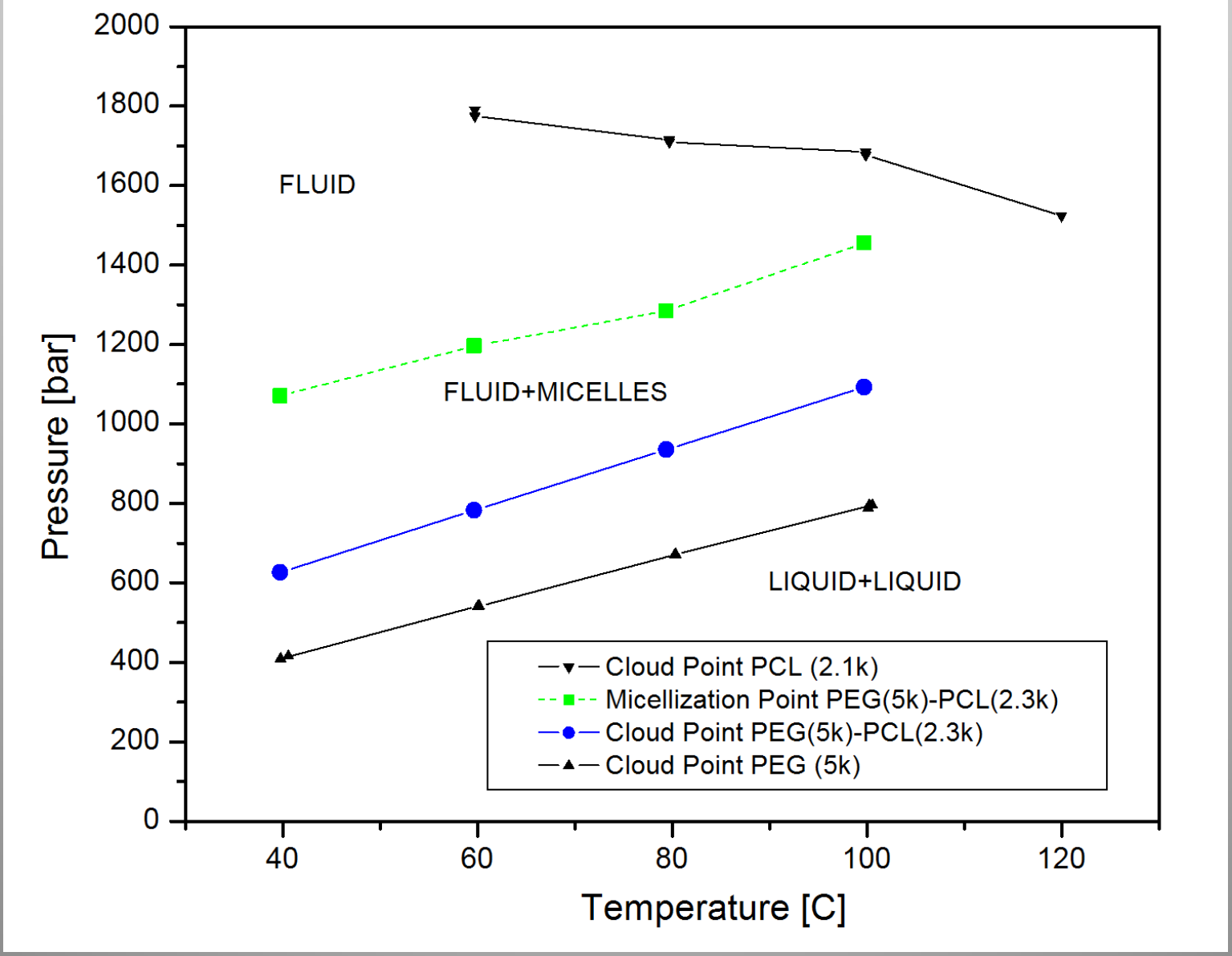


Virgin Polymer

S-B (38-113)

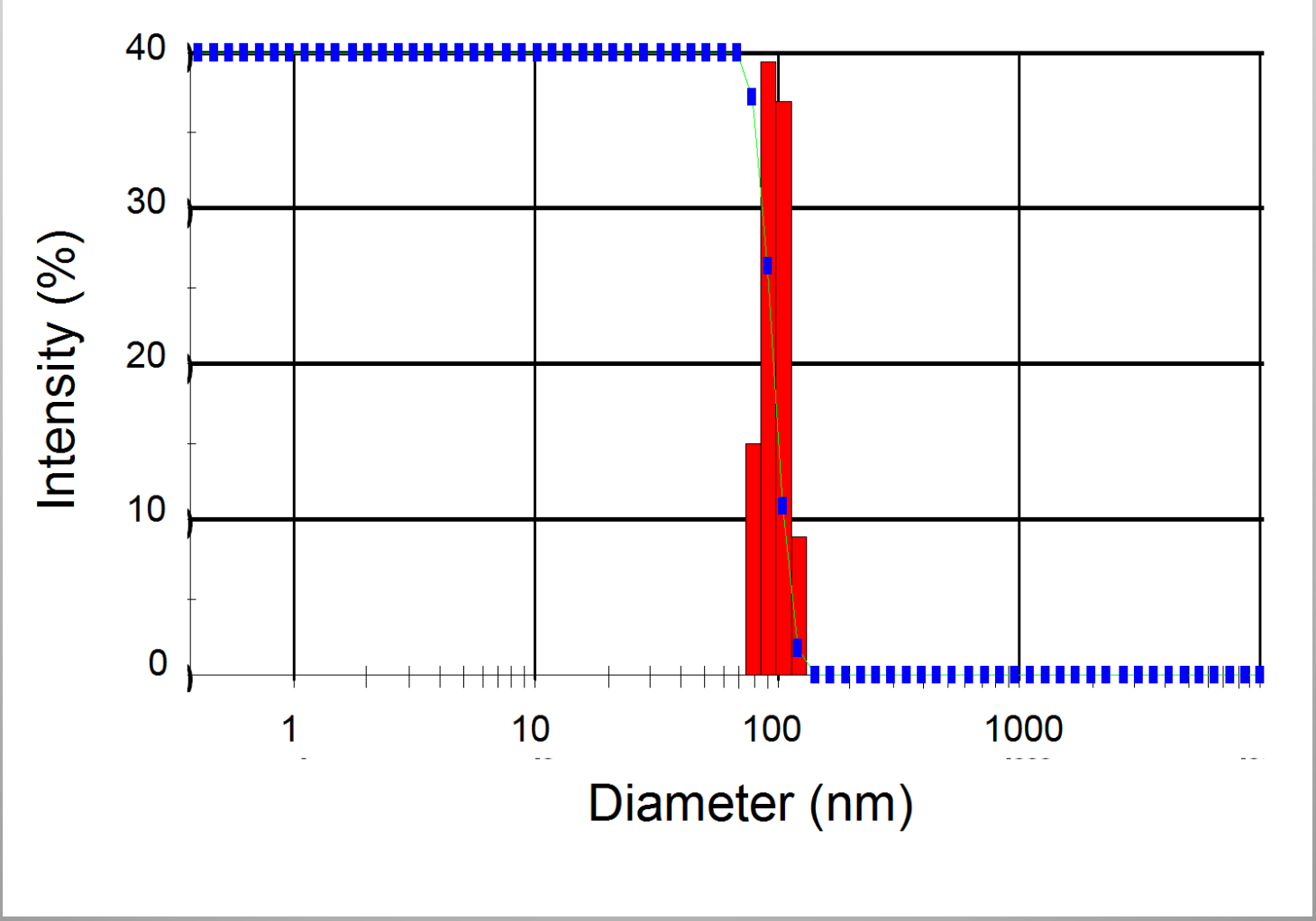
Jade Green 2010

Practical Example: PCL, PEG, PEG-b-PCL in CHF_3



Tyrrell, Winoto, Shen, Radosz 2008

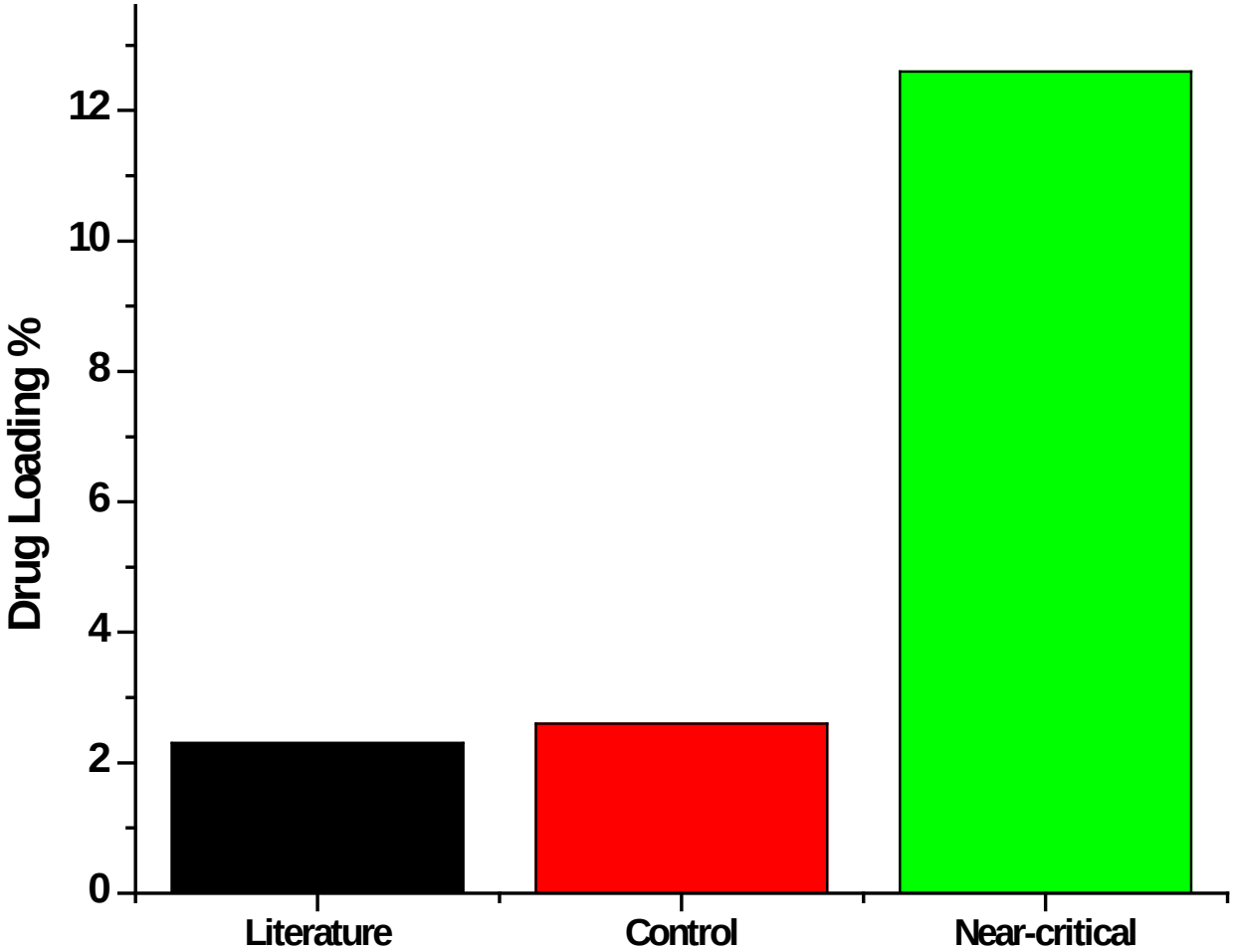
Micelles Recovered in Aqueous Solution



- PEG(5k)-b-PCL(2.3k) micelles in CHF_3 (40°C, 600 bar)
- Redissolved in cold water
- Virgin polymer in water - peak at 5000+ nm
- Demonstrates supercritical fluid route…

Tyrrell
Winoto
Shen
Radosz
2008

Compressible Solvent: Higher Drug Loading



Paclitaxel
Shuai et al. 2004

Paclitaxel
Solvent Evaporation

Paclitaxel
DME/HCF_3

All in PEG-b-PCL

Conclusion

- **NUCLEAR delivery works** (long way to go)
- **Block copolymer micellization key**
- **Compressible solvents a new frontier**
  - **Micellization characterized, predicted**
  - **Crystallizability imposes low-T limit**
  - **Nanostructure block- and path-dependent**
  - **Decompressed nanoparticles dispersable in water**
  - **High-drug loadings feasible**
  - **How to scale it up, say from mg to gram?**

CNMS User Outcomes – Direct:

Winoto, W.; Adidharma, H.; Mays, J. W.; Shen, Y.; Radosz, M., Micellization Temperature and Pressure for Polystyrene-block-Polyisoprene in Subcritical and Supercritical Propane. ***Macromolecules***, 2006, 39, 8140-8144.

Winoto, W.; Radosz, M.; Hong, K.; Mays, J., Amorphous Polystyrene-block-Polybutadiene and Crystallizable Polystyrene-block-(Hydrogenated Polybutadiene) Solutions in Compressible Near Critical Propane and Propylene - Hydrogenation Effects. ***Journal of Non-Crystalline Solids*** (2009) 355 1393-1399.

Winoto, W.; Shen, Y.; Radosz, M.; Hong, K.; Mays, J., Deuteration Impact on Micellization Pressure and Cloud Pressure of Polystyrene-block-polybutadiene and Polystyrene-block-polyisoprene in Compressible Propane. ***J. Phys. Chem.*** (2009) *113*(46) 15156-15161.

Winoto, W.; Tan, S. P.; Shen, Y.; Radosz, M.; Hong, K.; Mays, J., High-Pressure Micellar Solutions of Polystyrene-block-Polybutadiene and Polystyrene-block-Polyisoprene Solutions in Propane Exhibit Cloud-Pressure Reduction and Distinct Micellization End Points. ***Macromolecules*** (2009) *42* 3823-3826.

Winoto, W.; Tan, S. P.; Shen, Y.; Radosz, M.; Hong, K.; Mays, J., High-Pressure Micellar Solutions of Symmetric and Asymmetric Styrene-Diene Diblocks in Compressible Near-Critical Solvents: Micellization Pressures and Cloud Pressures Respond but Micellar Cloud Pressures Insensitive To Copolymer Molecular Weight, Concentration, and Block Ratio Changes. ***Macromolecules*** (2009) *42*(18) 7155-7163.

+ three manuscripts in the pipeline…

CNMS User Outcomes – Indirect:

Tan, S.P.; W. Winoto; M. Radosz, Statistical Associating Fluid Theory of Homopolymers and Block Copolymers in Compressible Solutions: Polystyrene, Polybutadiene, Polyisoprene, Polystyrene-block-Polybutadiene, and Polystyrene-block-Polyisoprene in Propane. ***The Journal of Physical Chemistry C, 2007***, 111, (43), 15752-15758.

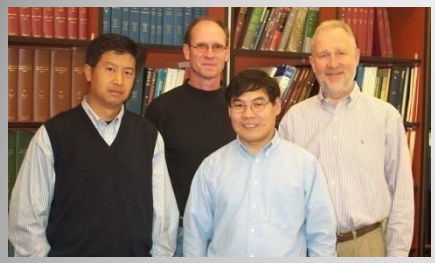
Jenczyk, J.; Makrocka-Rydzyk, M.; Wypycha, A.; Głowinkowski, S.; Jurga, S.; Radosz, M., The Phase Structure and Molecular Dynamics in Poly(styrene-b-isoprene) Diblock Copolymer (NMR study). ***Journal of Non-crystalline Solids*** (2010) *356* (11-17) 582-588

Tyrrell, Z.; Winoto, W.; Shen, Y.; Radosz, M., Block Copolymer Micelles Formed in Supercritical Fluid Can Become Water-dispensable Nanoparticles: Poly(ethylene glycol)-block-Poly(ε-caprolactone) in Trifluoromethane. ***Ind. Eng. Chem. Res.*** (2009) *48*(4) 1928-1932.

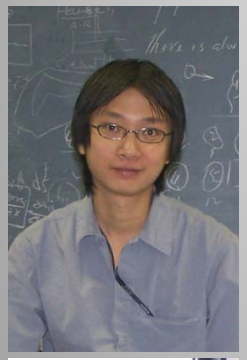
Tyrrell, Z.; Shen, Y.; Radosz, M., Fabrication of micellar nanoparticles for drug delivery through the self-assembly of block copolymers (Review). ***Progress in Polymer Science*** (2010) *35* (27) 1128-1143 (Impact Factor 24)

…examples, out of 60 since 2006

Major Contributors



- Youqing Shen, Synthesis
- William Murdoch, Animal Science
- Jun Ren, Pharmacy
- Jimmy Mays, Kunlun Hong, ORNL→



W. Winoto (DLS, phase behavior)

Zachary Tyrrell (drug delivery nanoparticles)

Jade Green (drug delivery nanoparticles)

Jianbin Tang (synthesis, sorption)

George Hu (membranes)→

←Sugata Tan (SAFT)

Hertanto Adidharma (SAFT)

←Sebastian Woloszczuk (Physics, MC simulations)

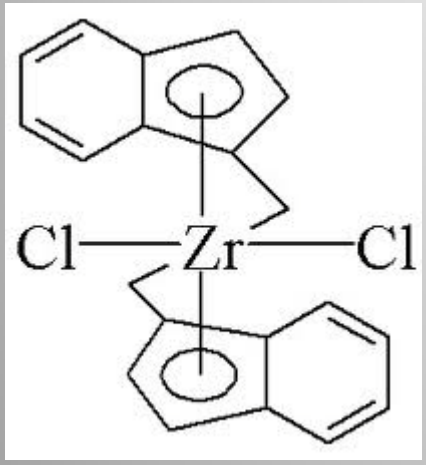
Michal Banaszak (MC simulations)→

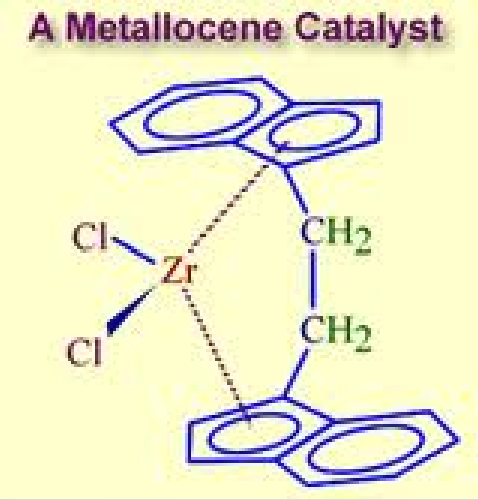
Funding: NSF, State, ORNL , NIH, DoD

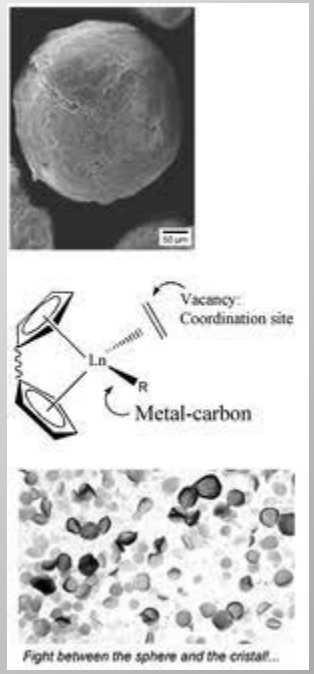
Teton Flowers by Margret Paul

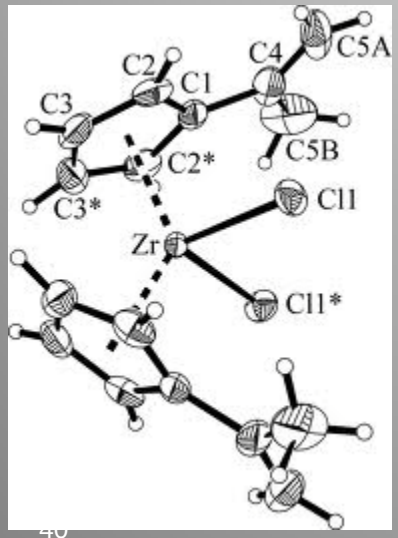
SOFT MATERIALS LABORATORY

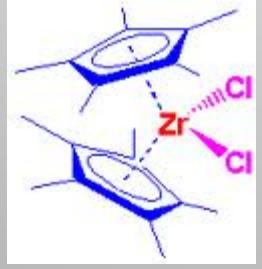
* BIOMATERIALS * ENERGY MATERIALS

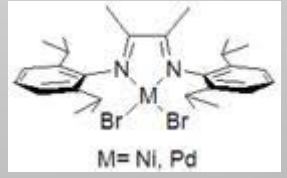

Cl
Zr
Cl

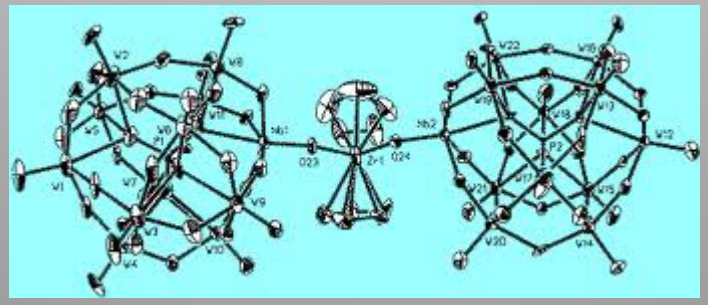

A Metallocene Catalyst
Cl
Zr
Cl
CH2
CH2

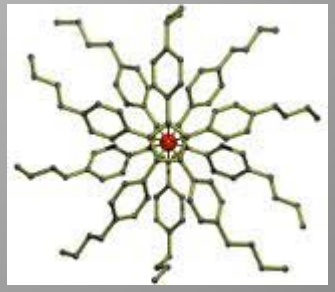

Vacancy:
Coordination site
Ln
R
Metal-carbon
Fight between the sphere and the cristall...


C2
C1
C4
C5A
C3
C2*
C5B
C3*
Cl1
Zr
Cl1*

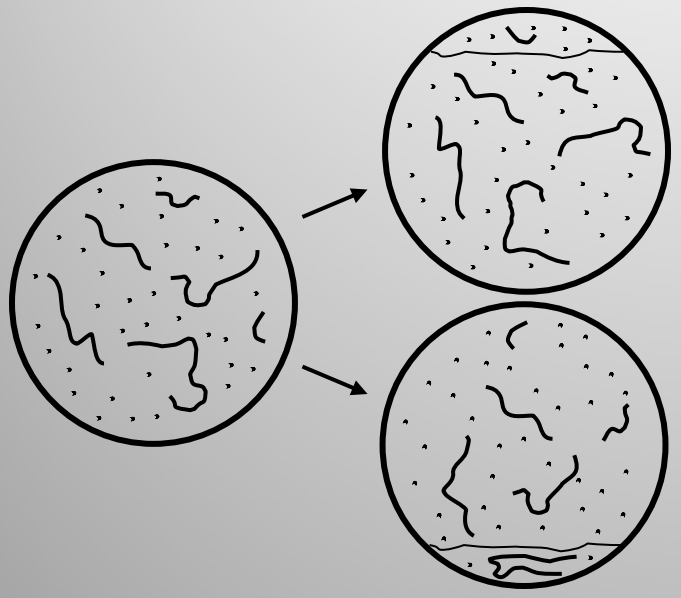

Zr
Cl
Cl


N
N
M
Br
Br
M= Ni, Pd





Liquid → Fluid-Liquid Phase Separation



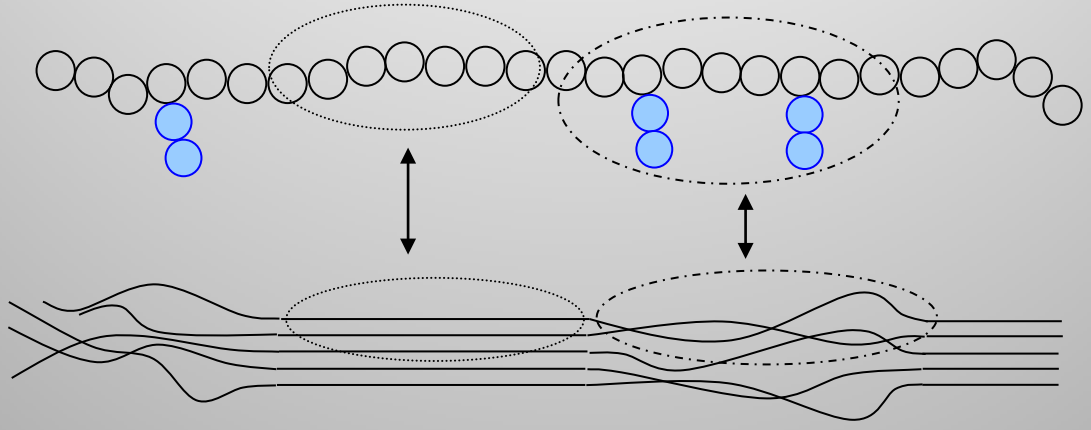
BUBBLE-POINT-LIKE
(High Polymer Concentration)

DEW-POINT-LIKE
(Low Polymer Concentration)

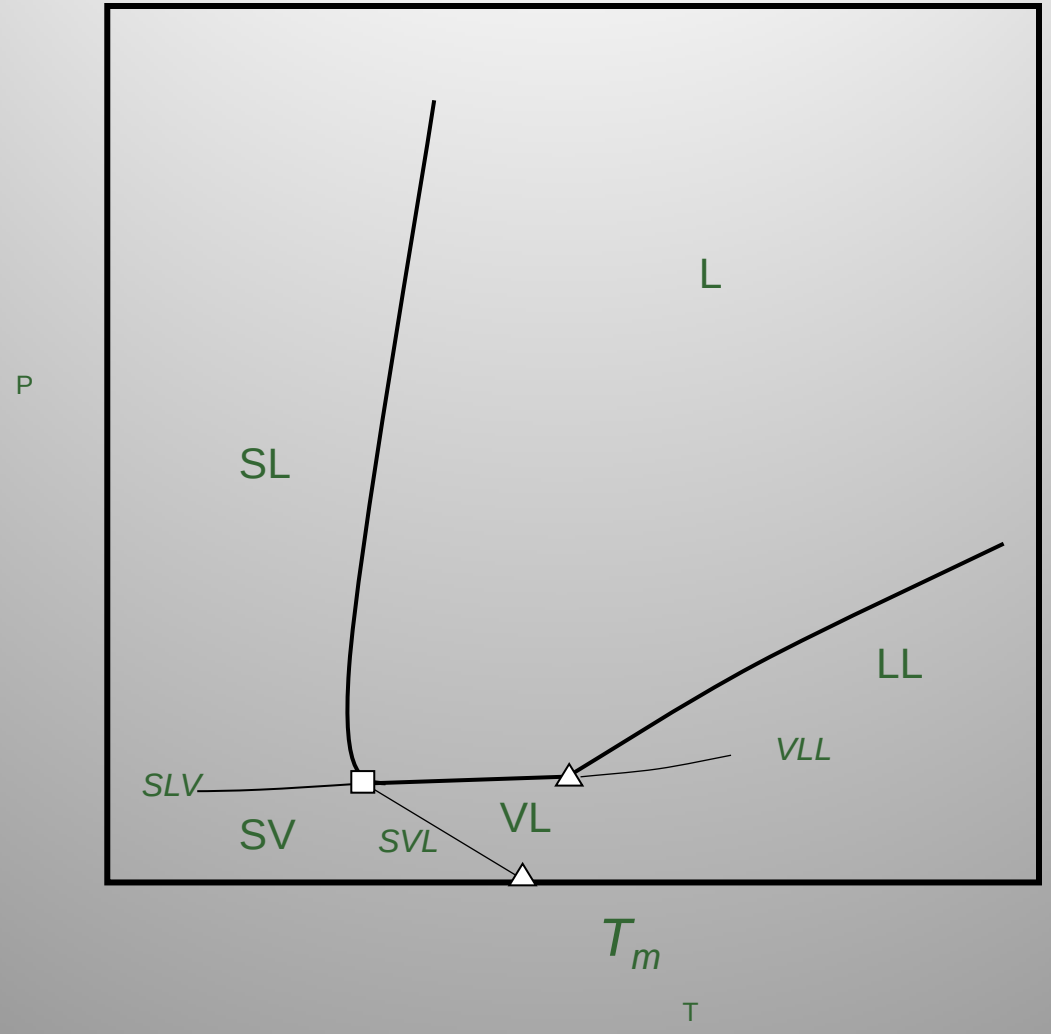
PROBLEM: **Given composition, estimate the onset P or T, or partitioning**

APPLICATIONS: **Homogeneous reactor → Monomer/solvent recovery in high-pressure and solution processes**

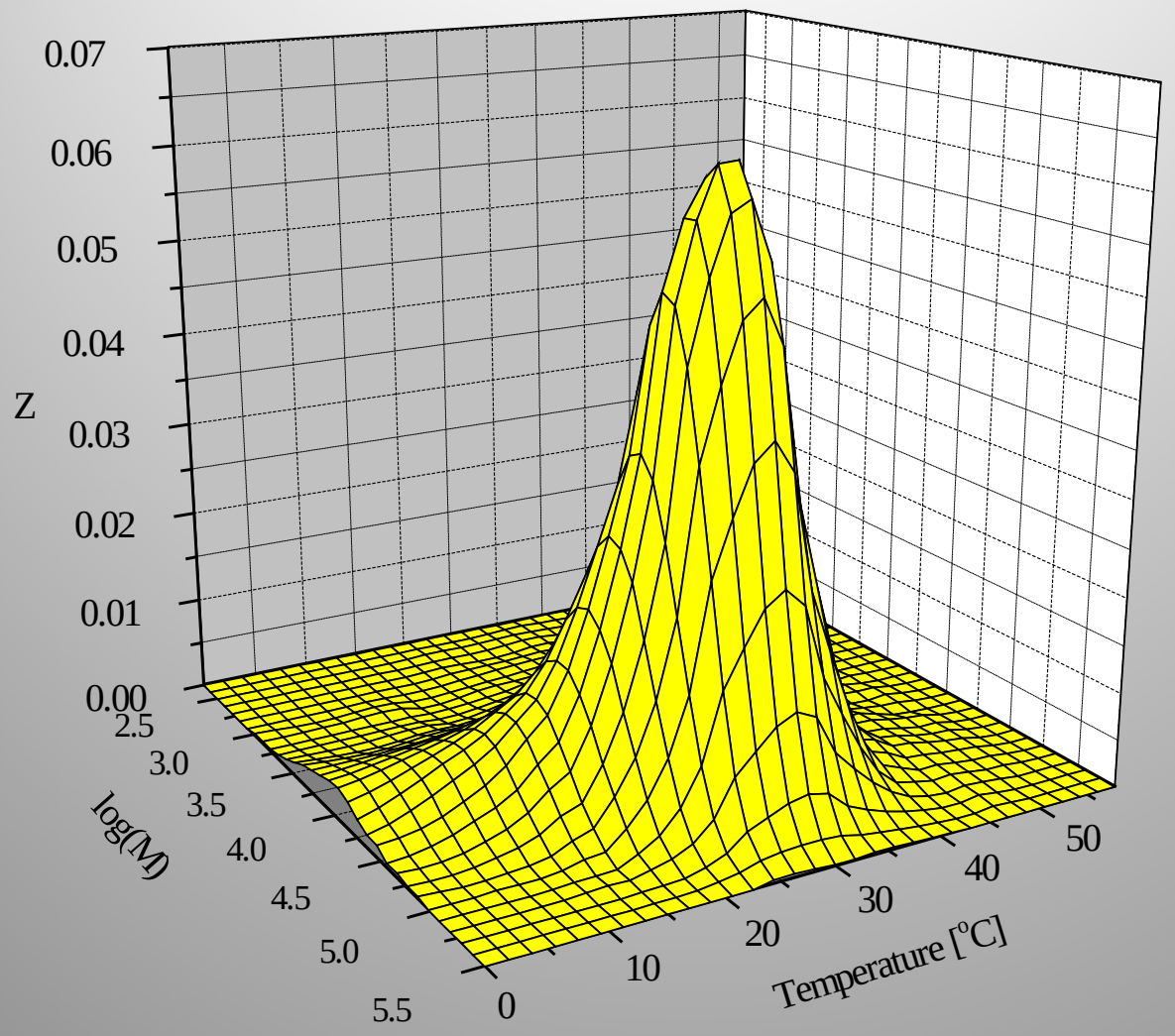
Crystallizability: a function of branch density



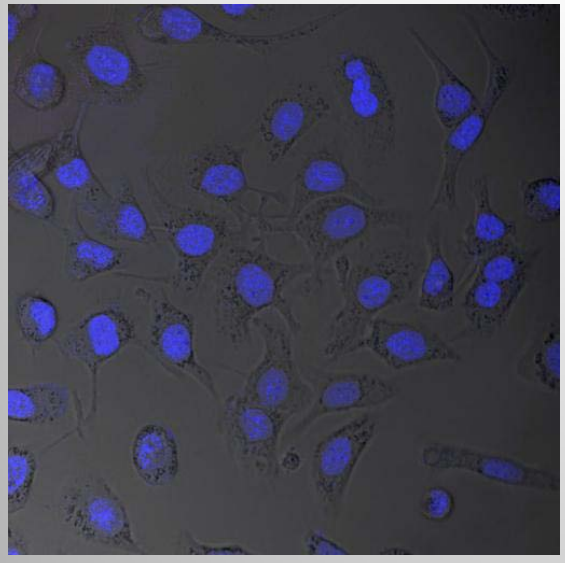
Crystallizable monodisperse polymer + solvent/monomer



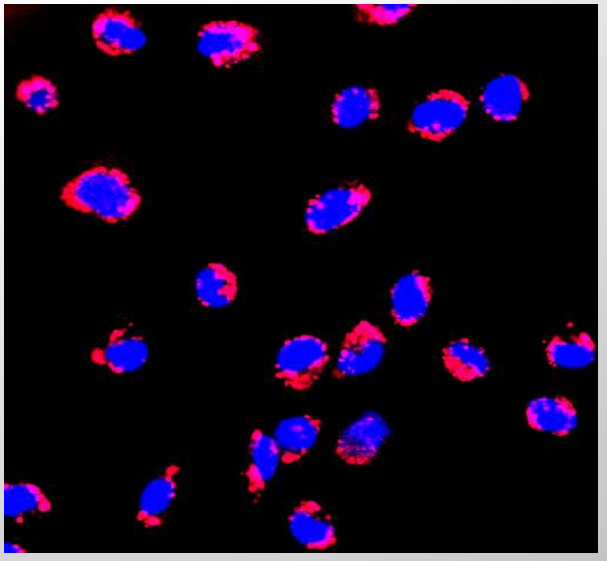
Molecular Weight and Crystallizability Distribution



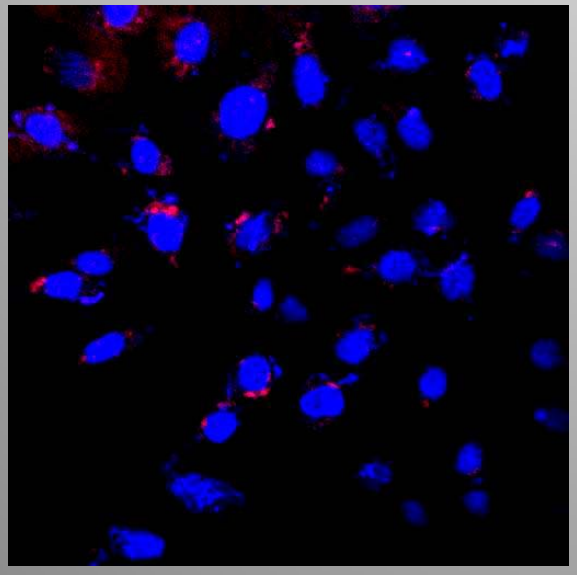
HA, 1999



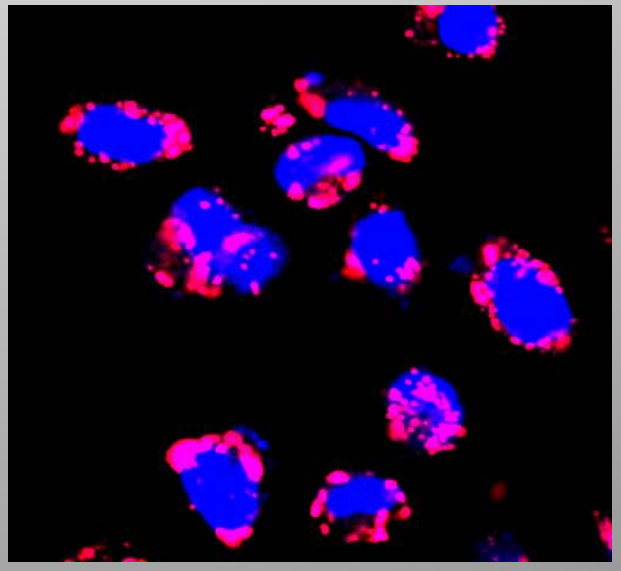
PEG-PCL /nile red 1h



PCL-PEG-TAT /nile red 1h



PEG-PCL /nile red 5h



PCL-PEG-TAT /nile red 5h