

Summer School on Crystal Nucleation

Prof. Joop H. ter Horst







Please Turn off Your Mobile Phones

Fire Exit







European Federation of Chemical Engineering EFCE working party on crystallization



Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation





Strathclyde Institute of Pharmacy & Biomedical Sciences

British Association for Crystal Growth



Organizing Committee



Joop ter Horst Rene Steendam Andrew Dunn Olayinka Olalere Maria Briuglia



Objectives



- Bring together experts in the field of crystal nucleation
 - Small organic compounds (pharmaceuticals)
 - Proteins
 - Biominerals
- Lecture the state of the art on Crystal Nucleation to early stage and advanced researchers
 - Current crystal nucleation theories
 - Measurement methods and characterization tools
 - Fundamentals & applications

Lecturers

Joop ter Horst

• CMAC, University of Strathclyde

Peter Vekilov

• University of Houston

Roger Davey

• University of Manchester

Denis Gebauer

• University of Konstanz

Jan Sefcik

• CMAC, University of Strathclyde



Participant Background



Program

	Мо	Tue	Wed	Thu	Fri			
	20 June 2016	21 June 2016	22 June 2016	23 June 2016	24 June 2016			
00:00 10:00		L4: RD	L7: PV	L13: RD	L12: PV			
09.00 - 10.00	Registration & Coffee	Solution Chemistry and structure	Classical and non-classical nucleation mechanisms	Molecular routes to nucleation control	Classical and non-classical nucleation mechanisms			
10:00 - 11:00	-	Coffee	Coffee	Coffee	Coffee			
	L1: JtH	L5: JS	L8: DG	L11: DG	L10: JS			
11:00 - 12:00	Classical nucleation - History & Theory	Secondary nucleation	Mesocrystals and non- classical crystallization	Biomineralization and	Shear and laser induced			
12:00 - 13:00	a meory		clussical crystallization	bioininetics	Closuro			
13:00 - 14:00	lunch	lunch	lunch	•	closure			
14:00 - 15:00	L2: PV Thermodynamics of	L6: JtH Crystal nucleation	L9: RD Molecular Packing &					
15:00 - 16:00	Crystallization	measurements	Nucleation					
	Coffee			Excursion				
16:00 - 17:00	L3: DG The pre-nucleation cluster	Poster session / Lab tour	Poster session					
17:00 - 18:00	pathway							
Evening	Evening event							
Lunch w	ill be provided	Go out for lunch (see program booklet)		Packed lunch included				

Program

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		Coffee	Coffee	Coffee	Coffee				
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12:00 - 13:00	& Theory	Secondary nucleation	classical crystallization	biomimetics	Nucleation				
					Closure				
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14:00 - 15:00	L2: PV	L6: JtH	L9: RD						
	Thermodynamics of	Crystal nucleation	Molecular Packing &						
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	The pre-nucleation cluster	Poster session / Lab tour	Poster session						
17:00 - 18:00	pathway								
		T	T						
Evening	 Evening event 								
		<u> </u>							
Drygate Brewery Bar Poster session Posters & drinks Poster prize									
& CMAC Labtour & info on Excursion									

Program: Excursion













Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation

University of Strathclyde

Classical Nucleation Theory

Prof. Joop H. ter Horst





A Crystalline Product



- Crystal Form
- Crystal Size Distribution
- Crystal Purity
- Crystal Shape





Product properties

Industrial Suspension Crystallization









EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation

> Towards Continuous Manufacturing

J.H. ter Horst et al., Fundamentals of Industrial Crystallization, In: Nishinaga T, Rudolph P, editors, Handbook of Crystal Growth, Vol. II., Elsevier, 2015, pp. 1317–49.



Primary Crystal Nucleation



- Start of crystallization process
- Large impact on product quality aspects like Crystal Size Distribution, polymorphs







My Lecture:

Arrive at the expression for the nucleation rate using Classical Nucleation Theory

Classical Nucleation Theory

- → Nucleation is an Activated Process
 - Solubility & Supersaturation
 - Crystal Nucleation
 - Nucleation Work

Nucleation





Crystal Nucleation H₂O





Crystallization Characteristics



Clear point - Upon heating there is a temperature that a suspension turns into a clear solution

Cloud point - Upon cooling a solution there is a temperature that crystals will be detected

Metastable Zone Width - The difference between the saturation temperature (Clear point) and cloud point





Why is there a difference between clear and cloud point?

Slide 24

Activated process



1889

An **energy barrier** must be overcome before two molecules will react.

The Arrhenius equation gives a relation between the activation energy *W** and the reaction rate *J*.

$$J = A \exp\left(-\frac{W^*}{kT}\right)$$



Svante August Arrhenius 1859 –1927

Crystal Nucleation Rate



- Crystal Nucleation is an activated process
- There is an energy barrier for nucleation to occur: the nucleation work W^*
- The nucleation rate is the speed of formation of supernuclei per unit of time and volume
- This can be described by the Arrhenius equation

$$J = A \exp\left(-\frac{W^*}{kT}\right) \qquad [m^{-3}s^{-1}]$$

Crystal Nucleation Rate



This Lecture:

Arrive at the expression for the nucleation rate using Classical Nucleation Theory

$$J = A \exp\left(-\frac{W^*}{kT}\right)$$

It is not the destination, but the journey that matters

Understand how Classical Nucleation Theory is constructed

Classical Nucleation Theory

- Nucleation is an Activated Process
- ----- Solubility & Supersaturation
 - Crystal Nucleation
 - Nucleation Work

Solubility and Supersaturation



Find an expression for

The **driving force** for crystal nucleation

Crystallization methods



- To provoke crystallization the state of a solution is shifted from (under)saturated to supersaturated by an external action
- The nature of the external action determines the crystallization method
 - Crystallization from solution
 - Evaporative crystallization
 - Cooling crystallization
 - Anti-solvent crystallization
 - Precipitation
 - Melt crystallization



Crystal Solubility Binary Systems



Phenanthrene



Benzene

in

Intermolecular interactions between solute and benzene are essentially **identical** But **solubility is hugely different**

*x**=0.81 mol%

 $x^* = 20.7 \text{ mol}\%$

Anthracene

University of Strathclyde Science

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Crystal Solubility Binary Systems



Phenanthrene



*x**=20.7 mol% *T*_m=100°C

in

Intermolecular interactions in Anthracene crystal are much larger than in Phenanthrene crystal:

Benzene

Anthracene prefers the solid phase

*x**=0.81 mol%

*T*_m=217°C



Anthracene

Crystal Solubility Binary Systems



Phenanthrene



Benzene

Solubility is determined by intermolecular interactions in both

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solution and solid



Anthracene

Solubility and Supersaturation



Find an expression for

The **driving force** for crystal nucleation

Which is

The **chemical potential difference** between the new phase and the old supersaturated phase

Solubility Diagram

Of isonicotinamide (INA) in Ethanol




Solubility



Solubility ideal system:



Fitting the solubility data of a real system:

$$\ln x^* = \frac{A}{T} + B$$

Van 't Hoff-plot

Of isonicotinamide (INA) in Ethanol





Fitting equation:

 $\ln x^* = \frac{A}{T} + B$

Convenient and accurate to extrapolate

Van 't Hoff-plot

Of isonicotinamide (INA) in Ethanol





Why is there a difference between ideal and real solubility?

Solubility



Ideal system

$$\ln x^* = -\frac{\Delta H}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right)$$

Real system

$$\ln a^* = -\frac{\Delta H}{R} \left(\frac{1}{T} - \frac{1}{T_m} \right)$$

The activity coefficient y describes non-ideality

$$a = \gamma x$$

Of isonicotinamide (INA) in Ethanol





Of isonicotinamide (INA) in Ethanol





Of isonicotinamide (INA) in Ethanol







$$\Delta \mu = kT \ln \frac{a}{a_{eq}} = kT \ln S$$



Of isonicotinamide (INA) in Ethanol





The formation of a bulk new phase is associated with an energy release of 2.45 kJ/mol Slide 45





Supersaturated Bulk old phase Bulk new phase

The free energy difference between the more stable new phase and the supersaturated old phase:

 $\Delta \mu = RT \ln S$

Ostwald Rule of Stages

1897

In general it is not the most stable but the least stable polymorph that crystallizes first



Temperature

W. Ostwald,

Studien über die Bildung und Umwandlung fester Körper. 1. Abhandlung: Übersättigung und Überkaltung, *Zeitschrift für Physikalische Chemie* 22 (1897) 289–330.





Friedrich Wilhelm Ostwald 1853 –1932

Ostwald Rule of Stages

1897

In general it is not the most stable but the least stable polymorph that crystallizes first

The form obtained is a balance between **driving force** (thermo) and **Rate of barrier crossing** (kinetics)

W. Ostwald,Studien über die Bildung und Umwandlung fester Körper.1. Abhandlung: Übersättigung und Überkaltung,*Zeitschrift für Physikalische Chemie* 22 (1897) 289–330.

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Friedrich Wilhelm Ostwald 1853 –1932

Solubility and Supersaturation

Find an expression for

The **driving force** for crystal nucleation

Which is

The **chemical potential difference** between the new phase and the old supersaturated phase





 $\Delta \mu = RT \ln S$

Classical Nucleation Theory

- Nucleation is an activated process
- Solubility & Supersaturation
- → Crystal Nucleation
 - Nucleation work





Understand the interplay between **Driving force** and **Interface**

Nucleation is the start of a phase transition





Density Fluctuations



Swarm of birds



Density Fluctuations

cause locally different and temporally fluctuating numbers of variously sized molecular clusters



In a **supersaturated** old phase, if the fluctuations are sufficiently large, a stable new phase can form.



Molecule



1878

Thermodynamic description of the condensation of supersaturated vapours into liquid droplets.

- **1. Density fluctuations** lead to new phase clusters
- New and old phase are separated by an **interface** region with intermediate structure and properties





Josiah Willard Gibbs 1839 – 1903



Bonding in the interface region is less strong than that in the bulk of the new phase cluster.

Molecules in the interface region have higher free energy compared to those in the bulk new phase.

The interface is associated with an **excess free energy**.





Josiah Willard Gibbs 1839 – 1903



- There is a thermodynamic driving force in the old phase to create **the new phase cluster of size** *n* $\Delta \mu = kT \ln S$ Free energy gain per cluster molecule
- The driving force is counterbalanced by the energy cost of creating the **interface**





 There is a thermodynamic driving force in the old phase to create the new phase cluster of size n

 $-n\Delta\mu$ contribution of cluster volume to free energy

 The driving force is counterbalanced by the energy cost of creating the interface

*G*_{excess} = f(cluster surface area, specific **interfacial energy**)



Density Fluctuation in a Supersaturated Old Phase





Molecule

CNT Assumption:

The interfacial energy of a cluster is equal to that of an infinitely flat surface.

Classical Nucleation Theory

- Nucleation is an activated process
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- → Nucleation work





Find an expression for

The nucleation work W*,

the energy barrier for crystal nucleation,

As a function of the **supersaturation ratio S**



п



 ΔG_{c} *W** **n*** W(n) ΔG_{v} Cluster size

п

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J.J. Thomson

1856 - 1940



Heterogeneous Nucleation of CO2 bubbles on a Mentos in Diet Coke











Effective interfacial energy γ_{ef} $\gamma_{\rm ef} = \Psi \gamma$ With activity factor $0 < \psi < 1$

 $\gamma_{\rm ef} = \psi \gamma$ with $\psi = 1$

V
Heterogeneous Nucleation





The heterogeneous particle provides a surface for nucleation

The nucleation work is much **lower** compared to homogeneous nucleation

The nucleation rate drastically increases



Nucleus size



Nucleus size $1 < n^* < 1000$ molecules

Nucleation work





The nucleation work (the energy barrier) is always smaller for Heterogeneous nucleation

Metastable zone width





Why is there a difference between clear and cloud point?

Because supersaturation is needed to overcome **the nucleation work** *W**

Cooling crystallization: Seeding





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Classical Nucleation Theory

- Nucleation is an activated process
- Solubility & Supersaturation
- Crystal Nucleation
- Nucleation work
- → Nucleation kinetics
 - Crystal Nucleation Rate Measurements