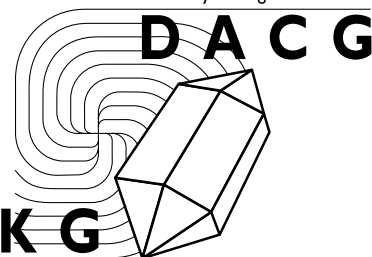


FACET

dutch association for crystal growth



i n f o r m a t i e b l a d v a n d e

NVKG

nederlandse vereniging voor kristalgroei

25 april 2005

nummer 1

FACET

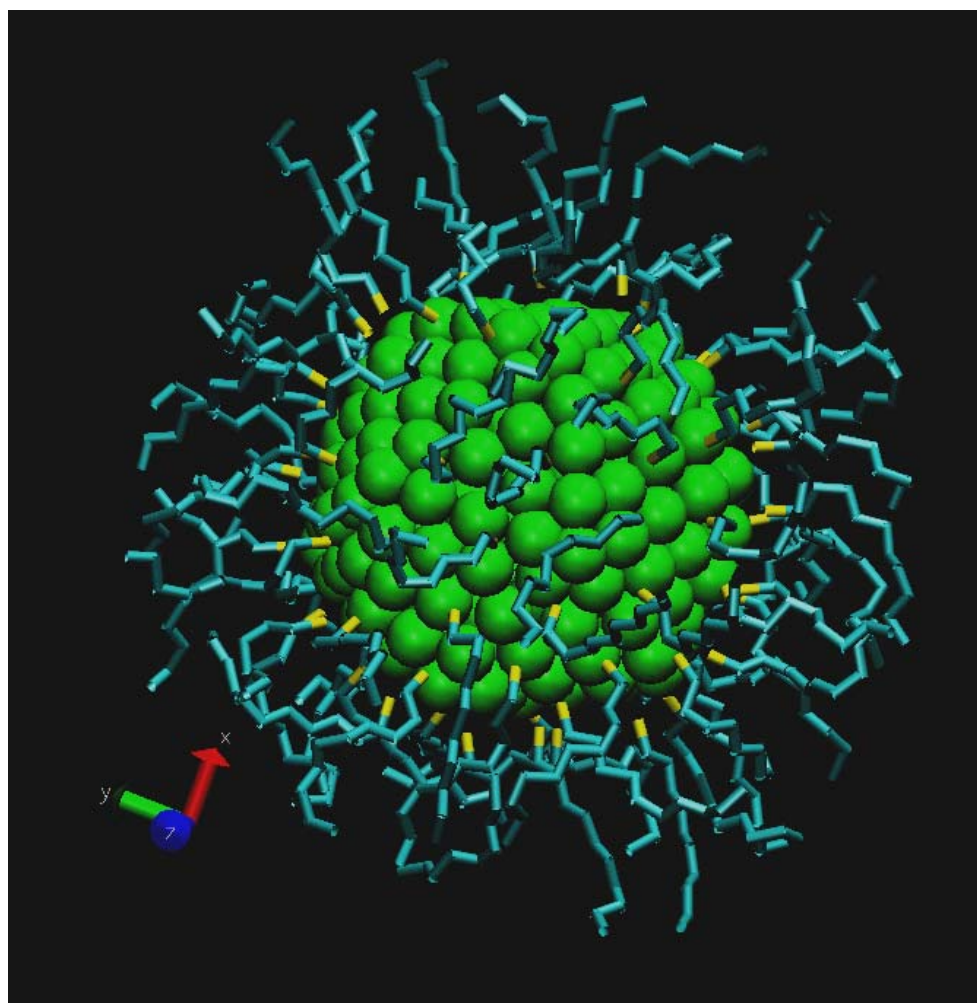
informatieblad van de NVKG
sectie van de KNCV en de NNV

redactie

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inhoud

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prof.dr. E. Vlieg	lid
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dr. G. Bögels	lid

Mededeling NVKG-bestuur

Het bestuur heeft n.a.v. de voordracht van Raoul van Gastel (UT) en Lianne van Oord (DSM) bij de algemene ledenvergadering 2004, binnen de daarvoor gestelde termijn geen schriftelijk bezwaar ontvangen op hun benoeming als bestuurslid. Zij zijn beiden inmiddels bij de meest recente bestuursvergadering formeel geïnstalleerd.

Omslagfoto/Cover

Computer simulation of a gold nanocrystal (NC). Its core consists of 309 gold atoms (shown as green spheres), in an icosahedral equilibrium structure. The core is capped with 80 thiol molecules ($\text{HS}-(\text{CH}_2)_9-\text{CH}_3$), the sulfur atoms are colored yellow. The reasons of capping a NC are (1) to control the interactions between NCs, (2) to control the growth during colloidal synthesis, and (3) to passivate dangling bonds to prevent nonradiative recombination of electrons and holes at the surface. Computer simulations are used to investigate the influence of the capping layer on the interactions between NCs and on their self-assembling properties. Figure provided by [Thijs Vlugt](#) and [Jan van der Eerden](#) of the [Universiteit Utrecht](#).

Redactioneel

Voor u ligt de eerste FACET van het jaar 2005 en tevens de eerste FACET van uw nieuwe redactie. In deze FACET vindt u o.a. een

uitnodiging voor het NVKG kristalgroei-symposium 2005, alsmede het voorlopige programma van deze voorjaarsbijeenkomst, die dit jaar georganiseerd wordt bij de Universiteit Twente te Enschede, op 27 mei 2005.

Zoals gebruikelijk doet de redactie op deze plaats een oproep naar input. Wat kunt u bijdragen?

- Aankondigingen van lezingen, symposia en congressen (niet alleen de activiteiten die u zelf organiseert, maar ook activiteiten waarover u langs andere weg bent geïnformeerd)
- Verslagen van (kristalgroei)-conferenties
- Artikelen (mag ook heel kort zijn!) over een opmerkelijke ontdekking
- Advertenties: bijvoorbeeld i.v.m. vacature
- Omslagfoto's (met toelichting). Telkens zal de beste ingezonden foto op de omslag van de FACET worden afgedrukt samen met een korte toelichting aan de binnenzijde van het blad. Bovendien zullen de foto's op de fotogalerij van onze webstek worden gepost.

De drempel voor uw bijdragen is *zeer laag*: aanleveren kan per brief, fax, [e-mail](#), of telefoon. En we staan natuurlijk open voor alle direct of indirect met de NVKG verwante onderwerpen. De deadline voor kopij voor de volgende FACET is vrijdag 14 oktober 2005.

[Raoul van Gastel](#)

Elektronische FACET

Bij voorkeur sturen wij u de FACET op in de vorm van een PDF-file, die als attachment wordt toegevoegd aan een e-mail bericht. Voor de "digibeten" onder ons: een PDF-file kan probleemloos op *elke computer* worden gelezen. Hiervoor hebt u het programma Acrobat Reader nodig, dat *gratis* op uw computer wordt gezet vanaf de website van de firma Adobe: klik op het logo, of surf naar <http://www.adobe.com>.

Staat u nog niet op onze elektronische verzendlijst, geef uw e-mail adres dan a.u.b. even aan [ons](#) door!

Net zoals de vorige elektronische FACETten, bevat ook dit exemplaar weer handige, automatische links voor web en e-mail.

NVKG Kristalgroeisymposium 2005

Datum: Vrijdag, 27 Mei 2005
Plaats: Universiteit Twente, Enschede (zie routebeschrijving pagina 4)
Aanmelding: Via de NVKG-website, uiterlijk 22 mei 2005 i.v.m. catering.
Bijdragen en posters aanmelden middels een mailtje aan [Raoul van Gastel](#) tot 13 mei 2005.

PROGRAMMA (zie de [NVKG-website](#) voor het definitieve programma)

10:00	ONVANGST en KOFFIE in HO-3136	
10:30	WELKOMSTWOORD	Dr. Raoul van Gastel (UT)
10:35	<i>PEEM studies of the growth of pentacene thin films</i>	Dr. F. Meyer zu Heringdorf (Universiteit Essen-Duisburg)
11:30	<i>Steering induced patterning during growth of Cu/Cu(001)</i>	Ir. F. Rabbering (UT)
11:50	<i>Title not yet known</i>	Prof. D. Kashchiev (Bulgarian Academy of Science)
12:10	LUNCH en POSTERS	
13:30	<i>Effect of supersaturation and mixed solvent composition on anti-solvent crystallisation of L-Histidine</i>	S. Jiang (TUD)
13:50	<i>Presentation</i>	
14:10	<i>Presentation</i>	
14:30	<i>Presentation</i>	
14:50	Koffie/thee	
15:15	Rondleiding MESA+ cleanroom	H. Teeuwen (MESA+)
16:00	BORREL en AFSLUITING	

Route

Met de auto: komend vanaf de A1 neemt U vanaf de A35 de afslag **Enschede-West/Universiteit**. Hierna volgt U de borden **Universiteit**, zie het routekaartje hieronder. Het symposium wordt gehouden op de UT campus in gebouw 45, Hogekamp, zie de campuskaart op de volgende pagina.

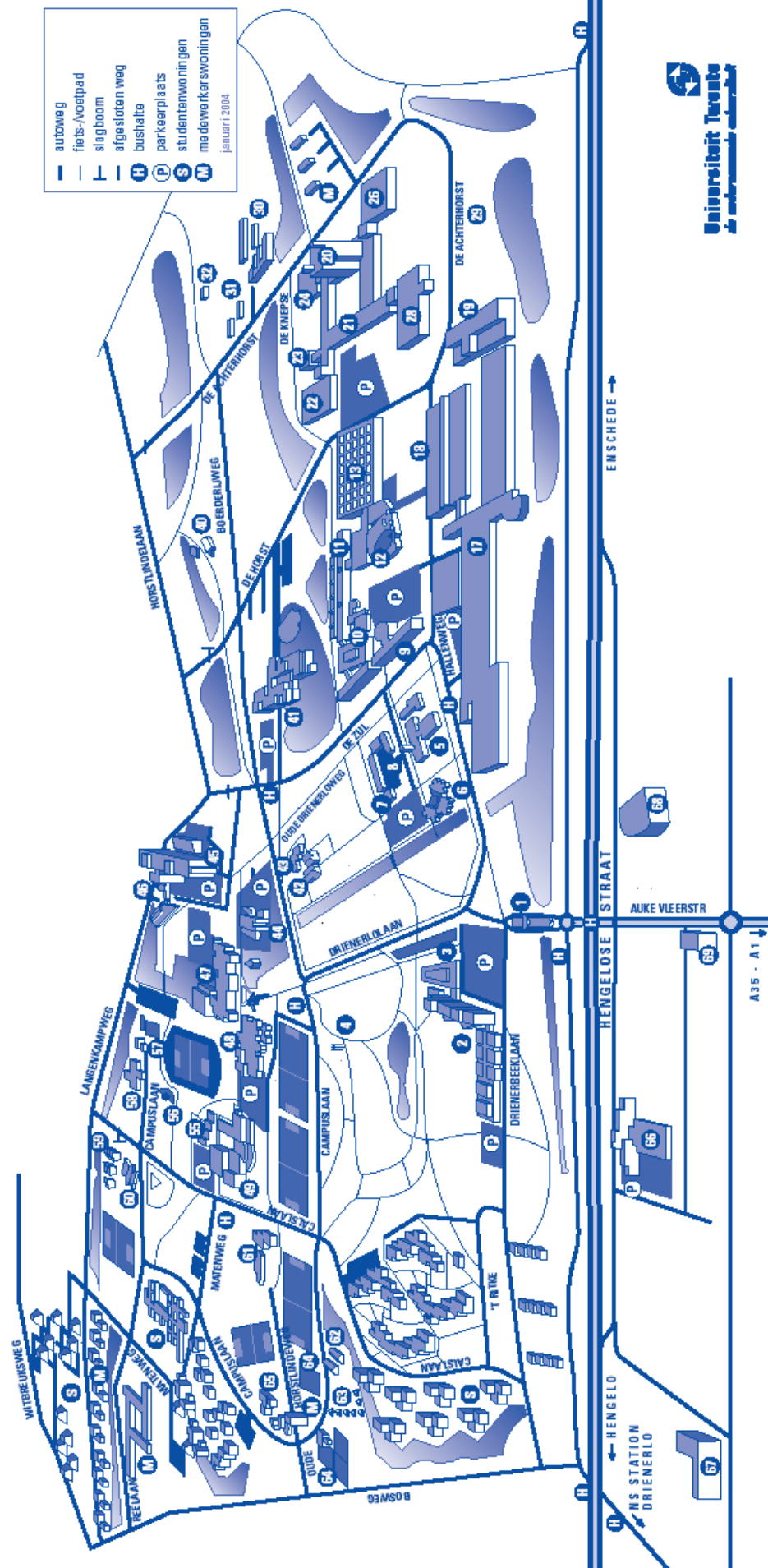
Met openbaar vervoer, met de intercity of stoptrein: uitstappen op station Enschede of Enschede Drienerlo. Van hieruit vertrekken er regelmatig bussen richting Universiteit (buslijn 1).



Met de bus vanuit Enschede of Hengelo: vanaf station Enschede met buslijn 1 richting Universiteit en vanaf station Hengelo met buslijn 3 richting Enschede/Glanerbrug/Gronau (uitstappen bij de halte UT viaduct).

De bijeenkomst zal plaatsvinden in gebouw 45, Hogekamp, zaal 3136.

- | | | | | | | | | | | | |
|---|-------------|----|------------|----|-----------------------|----|---------------|----|-----------------|----|---------------------|
| 1 | Charlie | 10 | Rave lijn | 22 | Westhorst | 40 | Erve Holzik | 49 | Sportcentrum | 63 | blokhutten |
| 2 | Spiegel | 11 | Zilverling | 23 | Kleinhorst | 41 | Cubicus | 55 | winkelcentrum | 64 | tennispark |
| 3 | Vleugel | 12 | Waaijer | 24 | Noordhorst | 42 | Faculty Club | 56 | amfitheater | 65 | Logica |
| 4 | carillon | 13 | Matrix | 26 | Oosthorst | 43 | Schuur | 57 | zwembad | 66 | BTC |
| 5 | hogedruklab | 17 | Langezijds | 28 | Zuidhorst | 44 | Drienerburght | 58 | Sleutel | 67 | Capitool 15 |
| 6 | Paviljoen | 18 | AKI | 29 | pinetum | 45 | Hogekamp | 59 | Mondriaan | 68 | Hengelosestraat 583 |
| 7 | Seinhuis | 19 | Temp | 30 | afvalstofdepot | 46 | cleanrooms | 60 | Vlinder | 69 | Institutenweg 1 |
| 8 | Garage | 20 | Horsttoren | 31 | windpark | 47 | Vrijhof | 61 | medisch centrum | | |
| 9 | Citadel | 21 | Horstring | 32 | biomagnetisch centrum | 48 | Bastille | 62 | Boerderij Bosch | | |



NL GUTS
Group of Users of Technology for Separation in the Netherlands

Agenda voor de bijeenkomst van de gebruikersgroep scheidingstechnologie NL GUTS.

Datum/tijd: **woensdag 27 april 2005**, ontvangst 10.00 uur.
Plaats: **DSM Research, Geleen**
(zie *routebeschrijving op de volgende pagina*)
Gastheer: Geert Ekkelenkamp, t. 046 4761030,
e-mail : Geert.Ekkelenkamp@dsm.com

AGENDA

- 10.00 uur: **Ontvangst**
10.30 uur: **1. Opening, Welkom** en vaststelling agenda.
2. Presentatie: "Polymorphism in precipitation processes"
door Mark Roelands, TUD/API
3. Presentatie: "Eutectisch vriezen; technologie en economie",
door Daniela Trambitas en Robert Gaertner, TUD/API
4. Presentatie: "Segregation of granular material",
door Christiaan Zeilstra, UT-PK/FAP
- 12.45 uur: **Lunch**
- 13.30 uur: **5. Mededelingen:**
nieuwe opzet NL GUTS 2005 e.v.
stand van zaken mbt "Roadmap scheidingstechnologie"
6. Mogelijkheden voor projecten:
verkennende projecten met starters/MKB
projectsuggestie TNO-MEP
7. Verdere NL GUTS activiteiten/ thema's (onderwerpen):
planning 2005
- 14.15 uur: **8. Presentatie:** "Metastable zone determination,
how small can you go?",
door Danny Stam, Avantium Technologies BV
- 15.00 uur: **9. Introductie** DSM Research/Particle Technology,
door Geert Ekkelenkamp (DSM)
- 15.30 uur: **10. Rondvraag**
15.30-16.30 uur **11. Rondleiding** Laboratoria
16.30 uur (ca.): **12. Sluiting** bijeenkomst.



NVKG Kristalgroei prijs 2005

Dit jaar zal opnieuw de twee-jaarlijkse NVKG prijs voor kristalgroei, bestaande uit een oorkonde en een geldbedrag van € 1000, worden toegekend aan een jonge onderzoeker voor hoogstaand wetenschappelijk onderzoek op het gebied van de kristalgroei. De prijs is bedoeld voor de auteur van het beste proefschrift of van een daarmee gelijkwaardige serie wetenschappelijke publicaties (bijvoorbeeld opgesteld in een industriële context). Het proefschrift dient na 1 januari 2003 met succes te zijn verdedigd aan een Nederlandse universiteit. Voor de toekenning van de prijs komen Nederlanders in aanmerking en niet-Nederlanders die hun onderzoek in Nederland hebben verricht.

De kandidaat, met een leeftijd van maximaal 35 jaar tijdens de uitreiking, moet hebben getoond te beschikken over grote bekwaamheden als onderzoeker alsmede over wetenschappelijke originaliteit en productiviteit. Bovendien moet de kandidaat een goed inzicht hebben in de problemen op het vakgebied van de kristalgroei. De toekenning van de prijs geschiedt door het bestuur van de NVKG op basis van een aanbeveling door een selectiecommissie van drie deskundigen. De uitreiking van de prijs zal plaatsvinden tijdens de NVKG jaarvergadering, die in november 2005 gehouden zal worden op een nog nader bekend te maken locatie.

Het bestuur van de NVKG geeft aan iedereen de gelegenheid om geschikte kandidaten schriftelijk voor te dragen. Een voordracht, met daarin de naam van de kandidaat, een korte argumentatie waarom de betrokkene in aanmerking komt, een kort curriculum vitae en drie exemplaren van het proefschrift of de serie van publicaties, dient **uiterlijk 30 september 2005** toegezonden te worden aan de voorzitter van de selectiecommissie: Prof.dr. Elias Vlieg, IMM afdeling Vaste Stof Chemie, Toernooiveld 1, 6525 ED Nijmegen (email: e.vlieg@science.ru.nl).

De kandidaatstelling dient vertrouwelijk te worden behandeld.

JANE-2006

In 2006 zal opnieuw een Japans-Nederlandse bijeenkomst georganiseerd worden op het terrein van kristalgroei, waarbij het format vergelijkbaar zal zijn met dat van twee eerdere JANE bijeenkomsten in 1999 (Nederland) en 2002 (Japan). Jane-2006 zal in Nederland worden gehouden van 13-18 maart 2006 (onder voorbehoud). Er zullen ca. 40 deelnemers zijn die het hele bereik van kristalgroei, d.w.z. van fundamenteel tot industrieel, zullen bespreken. Er wordt veel ruimte voor discussie overgelaten. De bijeenkomst wordt gesponsord door JSPS en NWO. Meer informatie bij de Nederlandse voorzitter: [Elias Vlieg](#).

Recente proefschriften

Maarten Voncken

“The Epitaxial Lift-Off Process; Parameter Studies and Solar Cell Application”

Promotor: Prof. Dr. P. Larsen

Co-promotor: Dr.Ir. J.J Schermer

Radboud University Nijmegen

Verdedigd op: 08-09-2004

The epitaxial lift-off (ELO) process is a technique that allows the separation of a single crystalline film from the substrate it was deposited on via the etching of an intermediate AIAs release layer. For this purpose, the extreme selectivity of hydrofluoric acid (HF) for AIAs over GaAs is employed. The technique has a large potential for optoelectronic applications, because it can lead to several benefits. Among these are cost reduction via a substrate reuse, increased power output of devices because of better cooling capabilities and the integration of III/V based devices with silicon circuitry. ELO, however, can only be implemented on an industrial scale in device processing if the rate at which substrate and epilayers are separated is sufficiently high. The lateral etch rate of the process has therefore been under serious investigation during the last years. A starting point in this research is a model, originally developed in 1987 by Yablonovitch *et al.* This model derives a theoretical maximum value for the lateral etch rate, based on the assumption that hydrogen is

formed in the etching of AIAs with HF, and that the out-diffusion of this hydrogen through the narrow crevice between substrate and epilayers is the limiting factor of the process. A maximum etch rate of 3 $\mu\text{m/hr}$ is predicted, whereas experiments show etch rates that exceed this value by a factor of 10000. This gave reason to believe that the model contains some serious flaws and that a structural investigation of both the relevant process parameters and the assumptions, made in the model, was necessary.

In chapters 3 and 4 the three relevant process parameters, namely release layer thickness, temperature, and applied radius of curvature, are under investigation. For this purpose a weight-induced ELO (WI-ELO) setup is employed in which a plastic foil is mounted on the epilayer and a weight is used to provide the necessary curvature. It was found that the relations between release layer thickness and etch rate and between temperature and etch rate show a trend, as predicted by the model. The relation between applied radius of curvature and etch rate, however, was found to consist of a constant and a curvature-dependant part, thereby contradicting the predicted trend. Quantitatively, a large discrepancy was found between model and experiments, because etch rates up to 30 mm/hr were encountered in practice. The constant part, further on referred to as intrinsic etch rate, was investigated in chapter 5 through a multi-release layer approach, a setup in which 5 different release layers are introduced in one sample. By the variation of a release layer property over the 5 release layers, the influence of this parameter on the intrinsic etch rate was revealed. It was shown that a variation of the Al-fraction in the AlGaAs release layer has the largest effect on the etch rate, while n-type doping and release layer thickness showed no effect, provided that the release layer thickness exceeded 10 nm. Doping with zinc (p-type) showed a small positive influence on the etch rate. In chapter 4, it was already shown that etching through a narrow crevice in the WI-ELO setup results in etch rates that exceed those obtained for etching planar AIAs layer. In chapter 6 it is shown that this is most likely caused by the fact that the AIAs in the WI-ELO setup

experiences a massive tensile strain, which can be as large as 5 %. By combining the results from this chapter with those from chapter 4, a better microscopic description of the etch front is obtained, showing that the force exerted by the weight is projected on an area, defined by the sample width and a distance of $\sim 5 \mu\text{m}$.

Chapter 7 shows that the main assumption of the model, namely the production of 3 moles of hydrogen per mole of AIAs etched, proves to be wrong. By a structured investigation of solid, solution and gaseous reaction products, it is shown that AlF_3 is formed, both solid and in the solution. Furthermore, it is shown that the main gaseous reaction product is arsine, while it is proven that no hydrogen is formed. Experiments carried out in a controlled atmosphere showed that oxygen plays a significant role in maintaining the reaction. The precise mechanism, however, is still unclear.

In chapter 8 the results obtained on solar cells, produced with the WI-ELO process are given. It is shown that the quality of the released ELO layers is of excellent quality, because the solar cells, produced from these layers show efficiencies that equal or sometimes even exceed those of comparable cells, processed on the substrate they were deposited on. This clearly shows that ELO is a viable technique for intrinsically large area applications like solar cells.

Based on the research, described in this thesis, it can be concluded that many components of the ELO-etching process have been elucidated. However, some points are still unclear. In chapter 9, several recommendations for further research are given. On the area of the chemistry of the ELO process, further research on the exact reaction mechanism, especially on the role of oxygen on the etch process, still has to be done. The removal of the reaction products through the narrow etch crevice, possibly by the formation of bubbles and a theoretical model describing the effect of strain in the layers on the etch rate form two of the interesting physical aspects, worthy of further investigation. In the technical part of the process, better mounting procedures and a new setup for releasing complete 2-inch wafers are presently under investigation

Herma Cuppen

“Theory and simulations of crystal growth; Fundamental steps in morphology predictions”

Promotor: Prof. Dr. E. Vlieg

Copromotores: Dr. H.L.M. Meekes and Dr. W.J.P. van Enckevort

Radboud Universiteit Nijmegen

Verdedigd op: 15-02-2005

The morphology or outer shape of a crystal is an important property and has as such received much attention in the literature. The aim of the present thesis is to contribute to the study of crystal morphology by integrating the methods of three sub-disciplines within the field of crystal growth to come to a better understanding of the underlying mechanisms that determine the morphology. These are the study of atomistic models, continuum descriptions of growth mechanisms and morphology prediction methods. The thesis can be divided into two parts. The first part discusses classical microscopic models in detail to arrive at a better fundamental understanding of the crystal growth mechanisms. The second part studies "real" crystal structures. The first five chapters study crystal growth on an atomic level. Fluctuations in growth steps on crystal surfaces are considered using a statistical mechanical approach. We start by studying kink and step kinetics of the simple cubic or Kossel crystal in Chapters 2 and 3. For this very simple one-particle crystal model we were able to obtain analytical expressions which are in close agreement with Monte Carlo simulation results, for both the kink density and the step propagation velocity. For a slightly more complicated two particle crystal, referred to as a non-Kossel model, it is however not possible to obtain a general expression for these quantities as is shown in Chapter 4. For each step different kinetics apply which are determined by the local structure and interactions between the growth units. Based on this knowledge of kink kinetics, the phenomenon of kinetic roughening is studied. For the Kossel crystal, an expression for the step free

energy of an infinitely long step is derived in Chapter 5 based on the previously found expression for the kink density. The non-equilibrium step free energy vanishes beyond a critical value of the driving force. We propose to define the onset of the kinetic roughening regime by this point, which is found to agree with earlier phenomenological criteria for this transition. However, since the kink density is the basis of the step free energy, this method cannot easily be applied to more complicated structures like the non-Kossel model. Chapter 6 therefore uses an alternative method based on an analysis by Leamy and Gilmer to estimate the onset of the kinetic roughening regime without prior knowledge of the structure. This is done by determining the vanishing point of the step energy, which is roughly defined as the difference in surface energy between faces with a zero and non-zero misorientation angle. The estimate found in this way for the Kossel model is very close to the onset previously found and the method is therefore also applied to two steps in the non-Kossel model. Both steps are found to show very different growth behaviour as compared to the Kossel step. Chapter 7 has a topic which in a sense bridges the atomistic approach of the previous chapters and the more continuum approach of the next chapters. It discusses the influence of the size of 2D nuclei on the edge (free) energy of the nucleus. The edge free energy is a variable often used in continuum expression for birth-and-spread growth as is discussed in Chapter 8 and is usually considered to be independent of the nucleus size and the driving force. Chapter 7 tests this assumption. It is found that the step free energy is a function of both quantities, but that the step free energy of a critical nucleus is approximately constant given a constant bond strength. These findings are used in Chapter 8 to derive a birth-and-spread model for an anisotropic crystal and fit it to growth data obtained from Monte Carlo simulations of an isotropic and anisotropic Kossel surface and a non-Kossel surface. Besides the 2D nucleation mechanism spiral growth is an as important

phenomenon in crystal growth. Chapter 9 studies the interaction between spiral growth, 2D nucleation and step flow for a wide range of driving forces by means of Monte Carlo simulation. The last chapter of the first part, Chapter 10, deals with crystal structures with orientations that have connected nets, but nevertheless have zero step energies in at least one direction which makes them grow rough.

Part II consists of five chapters that study some particular phenomena encountered in the growth of real crystals. These are studied using Monte Carlo simulations based on crystal graphs as models for these real crystals. Chapter 11 studies the influence of the force field on the morphology prediction using Monte Carlo simulations. Monoclinic paracetamol is used as a model structure. Small differences in interaction energies are found to give huge differences in the simulation results. Chapter 12 studies the morphology of polycenes like naphthalene, anthracene and tetracene both experimentally and by computer simulations. The results show that at moderate conditions crystals of these compounds growing with a 2D nucleation mechanism would be extremely thin platelets. Only crystals with screw dislocations on the basal faces can be formed. Chapter 13 discusses the polar morphology of crystals growing in spacegroups without inversion symmetry. It shows that the morphology of a polar crystal can be polar as a result of differences in kinetic pathways for opposite faces. This results from bulk interactions instead of external factors like the solvent or impurities. Finally, Chapters 14 and 15 explain the needle-like morphology of aspartame forms II-A and I-A, respectively. The extreme aspect ratios of these crystals stems from the unexpectedly small edge energy for steps on the fast growing top faces as compared to those of the side faces.

Robert S. Gärtner

“Mixed solvent reactive recrystallisation of sodium carbonate”

Promotor: prof.dr.ir. G.J. Witkamp
Technical University of Delft

The basic concept of antisolvent crystallization and mixed solvent crystallization are quite similar. The decisive difference is that in antisolvent crystallization (or in most cases rather: precipitation), the antisolvent is added during the process to induce crystallization by dramatically decreasing the solubility of the product compound.

The strategy of mixed solvent crystallization is to employ a miscible co-solvent to modify the crystallization behavior of a system. By the use of a ‘tailor-made’ mixed solvent, the morphology, the growth rate, the metastable zone width, the solubility and even the stability of a solid phase can be modified. Thereby, this method offers significant potential to fundamentally improve crystallization processes, especially since it also has the potential of significant savings in energy consumption and operation costs as energy intensive evaporative crystallization steps can be avoided.

The technical challenge for this method is its application to the crystallization of chemical bulk products. While in the production of high-added-value products like pharmaceuticals, the replacement / recycling of the solvent might be a minor cost factor, it is of vital importance for bulk products, where the price of a ton of co-solvent can be higher than the price of the same amount of product. This cost factor has to be countered by an increased added value of the product, significant savings in production costs and efficient recycling of the solvent.

Oosterhof et al. [1-4] have successfully applied mixed solvent (re)crystallization in the densification of soda, employing a mixed solvent composed of ethylene glycol and water. They succeeded in developing a process for the production of soda of higher purity, mechanical stability and bulk density,

a.k.a. *super dense soda*, at lower production costs than the currently employed industrial process.

The process of Oosterhof et al. [1-4] is limited to increasing the value of common light soda ash by a downstream densification. *The aim of this work was to develop complete, novel process routes based on the concept of mixed solvent recrystallization for the production of super dense soda from all of the principal sources of sodium carbonate*, i.e. to provide concepts to replace the current, energy-consumptive production routes.

To obtain fundamental understanding of these new processes, the conversion mechanisms were studied, and thermodynamic and kinetic models developed, to not only allow proper control of the processes, but also their predictive modeling for optimization and scale-up. Also the incorporation of common impurities during the mixed solvent crystallization steps was studied as well as different process steps for the in-line removal of these impurities from the mixed solvent to allow its efficient and continuous recycling.

The most common industrial sources of sodium carbonate are sodium bicarbonate ($\text{NaHCO}_3(\text{s})$), produced by the Solvay process [5], and trona ($\text{Na}_2\text{CO}_3 \cdot \text{NaHCO}_3 \cdot 2\text{H}_2\text{O}(\text{s})$), which occurs as a natural ore at locations on all continents [6]. Both sources contain bicarbonate, which has to be converted to carbonate, to obtain pure soda. It was found in this work, that bicarbonate could be converted by thermal decomposition in the mixed solvent simultaneously to the mixed solvent recrystallization.

The reaction mechanisms and kinetics of the thermal decomposition of pure solid and dissolved bicarbonate in mixed solvent solution were investigated. It was found, that bicarbonate decomposes preferentially in the dissolved state according to a first order mechanism that matched the one found in literature for aqueous solution. The solvent mediated decomposition results also

in the recrystallization of solid sodium bicarbonate. As the bicarbonate decomposition in solution is a reversible process, it results in an equilibrium between dissolved bicarbonate and carbonate. Above a temperature of ca. 90°C , this results in the formation of trona as the stable solid phase in contact with aqueous solution, while sodium carbonate anhydrate (soda) is formed in mixed solvent solution. Interestingly, the limiting temperature of 90°C for the stability of solid sodium bicarbonate in solution was found to be independent of solvent composition. Additionally, the decomposition rate in mixed solvent solution is slower than in aqueous solution, which allowed good control of the carbonate supersaturation, created by the decomposition reaction, and the growth of the soda crystals.

The study of the conversion of trona revealed, that its recrystallization was driven by two separate effects: The instability of the crystal water and the bicarbonate decomposition. Both effects increased with temperature. While at low driving forces the trona recrystallized solution mediated, higher driving forces resulted in a pseudo solid-state conversion. The product of the pseudo solid-state conversion consisted of pseudomorphs, i.e. agglomerates of fine soda crystallites in the shape of the original trona crystal. These pseudomorphs are undesirable products, as they retain solvent and impurities and yield a low bulk density. The kinetics of the conversion mechanisms were determined and 3 different mixed solvent process routes were developed to avoid pseudomorph formation while balancing short process times with controlled crystal growth and high product bulk densities.

The recrystallization of solid sodium bicarbonate and trona to soda in the mixed solvent was only possible due to the significantly increased stability of the anhydrous soda compared to the aqueous system. The stabilities and solubilities of all occurring solid phases were determined for a range of temperatures and mixed solvent

compositions. It was found, that not only the stability range of soda increased with increasing ethylene glycol content, but also the one of wegscheiderite ($\text{Na}_2\text{CO}_3 \cdot 3\text{NaHCO}_3(\text{s})$), while the stability ranges of all hydrates including trona strongly decreased.

The study of the impurity incorporation during the mixed solvent recrystallization steps showed that chloride, fluoride and borate were excluded from the monohydrate and anhydrate crystals. Sulfate was incorporated to a high degree, which even resulted in morphological changes of the formed monohydrate and anhydrate. Interestingly, mixed solid phases of carbonate and sulfate, which were observed in the aqueous system, did not appear in the mixed solvent system.

Reactive extraction, ion exchange and electro dialysis were evaluated as possible methods for the in-line extraction of impurities from the mixed solvent recycle.

The application of reactive extraction was not promising for the in-line removal: For all of the tested reactive extraction systems, ethylene glycol was taken up into the extractant and vice versa. Therefore only the results of another reactive extraction study are given, as reactive extraction is an attractive option for similar applications.

The application of ion exchange was more successful. Chloride and sulfate were extracted with a decent degree of selectivity from the trona-saturated mixed solvent. The extraction was apparently enhanced by a partitioning ('salting out') effect between the mixed solvent bulk and the pore solution of the ion exchangers.

Also by electro dialysis, chloride and sulfate were extracted from the carbonate saturated mixed solvent, but here it was found, that the selectivity was reduced compared to the aqueous system. The electrical resistance for electro dialysis in the mixed solvent was increased by a factor of 8, due to the increased resistance of the

more apolar mixed solvent solution. Still, electro dialysis offers a viable option for the desalting of a mixed solvent, due to the good retention of the ethylene glycol.

An economical evaluation of different mixed solvent (reactive) recrystallization process alternatives was done. Comparison to processes currently employed in industry, revealed that the mixed solvent processes offer the possibility for significant savings in investment capital and operation costs – in the Solvay process [5] as well as in the processing of solution-mined trona [6]. Savings in operation costs of 10 to 15 M€ for a 500.000t/a soda plant were estimated, resulting in payback times of 3 to 4 years. These savings mainly resulted from savings of 55 to 70% in energy-consumption, namely heating utilities.

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"Production of controlled drug delivery microparticles using supercritical CO₂"

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Micro- and nanoparticles consisting of a drug dispersed in a polymeric matrix are desirable in the pharmaceutical industry for drug targeting, controlled delivery and drug stabilisation and protection. Conventional methods to produce such microparticles are often limited by the use of high temperatures, the difficulties to control particle size, morphology and particle size distribution, and the use of toxic organic solvents.

During the last decades, new techniques based on the use of supercritical fluids have been studied extensively as promising alternatives for the production of controlled drug delivery microparticles. One of the most attractive properties of supercritical technology is the possibility of tuning system properties (i.e. solubilities, viscosities, densities, phase behaviour) by changing operating variables such as pressure and temperature. Separation between the processed microparticles and the supercritical fluid is easily achieved by depressurization, which yields a dried solvent-free product. Using low critical temperature supercritical fluids (such as CO₂), the process can be performed at low temperatures, avoiding thermal and chemical degradation of the processed materials. Due to its beneficial properties for the processing of pharmaceutical compounds (inexpensiveness, non-toxicity, non-flammability and non-reactivity), CO₂ is usually used as supercritical fluid in these processes.

This thesis assesses the feasibility of supercritical technology to produce controlled drug delivery microparticles, focusing on the development of new equipment and methods. Research is also oriented to a better understanding of the underlying mechanisms involved in the particle formation process.

Chapter 1 provides the background information about the importance of controlled drug delivery microparticles and the description of the different supercritical techniques that can be used to produce them. The Precipitation with a Compressed Antisolvent (PCA) process is introduced as the supercritical technique applicable to the widest range of drugs and polymers, which explains that this thesis is mainly focused on the PCA process.

Chapter 2 is a state of the art overview of the production of controlled drug delivery microparticles using the PCA process. The gaps in knowledge and the research and development challenges are identified in this chapter. It emphasizes that two different operating regions have to be considered when processing diluted drug/polymer solutions with the PCA process. Below the mixture critical pressure of the solvent-CO₂ system, droplets are formed due to the existence of an interface between the solvent and the CO₂. Above the mixture critical pressure, solvent and carbon dioxide are miscible in the entire composition range and no droplet formation by atomisation is possible. In order to understand the mechanism of particle formation, thermodynamics, hydrodynamics, mass transfer, and precipitation kinetics need to be considered jointly.

Chapter 3 deals with measurements of the phase behavior of the system dextran-DMSO-CO₂, which was used in this thesis as a model system to study the micronisation of polymers using the PCA process. An easy and reliable method to measure polymer-solvent-CO₂ diagrams at constant pressure and temperature conditions is presented in this chapter. The

phase behaviour measurements show that a liquid-liquid phase split is induced in the dextran solution as it gets into contact with the CO₂. This observation shed some light on the mechanism of particle formation.

Chapter 4 investigates the two-way mass transfer between a dichloromethane droplet and carbon dioxide at conditions below their mixture critical pressure. A finite-difference approximation of the Maxwell-Stefan equations was used to simulate the effect of the different operating variables (i.e. pressure, temperature, droplet diameter, solution to CO₂ flow ratio) on the droplet lifetime. Simulations show the variation with time of the droplet composition, the fluxes through the droplet-supercritical fluid interface, and the droplet diameter and provide a good insight to understand the two-way mass transfer process.

Chapter 5 presents an improved PCA process that eliminates the problems with agglomeration and reproducibility observed when precipitating dextran using the conventional PCA process at conditions above the mixture critical pressure of the system DMSO-CO₂. In contrast to other authors who tried to control the PCA process by influencing fluid dynamics or mass transfer, the approach in this chapter is based on slowing down the kinetics of the precipitation process. This improved PCA process makes it possible to control the product properties by separating the different physical phenomena involved in the PCA process: mixing of solution and CO₂, liquid-liquid phase split and stripping of the solvent. The particle size can be easily manipulated over a size range from several nanometers to tens of microns by changing the operating conditions.

Chapter 6 shows experimental evidence of the existence of two different operating regions (above and below the critical pressure of the solvent-CO₂ mixture) to perform the PCA process. In addition, results support that droplets can be formed by two different mechanisms: hydraulic atomisation in the nozzle (at conditions

below the critical pressure of the solvent-CO₂ mixture) or by liquid-liquid phase split (either below or above the mixture critical pressure). The possibility of encapsulation of cholesterol in poly(L-lactic acid) was also demonstrated in this chapter.

Chapter 7 presents an innovative approach to precipitate proteins and polar polymers from DMSO using CO₂ as antisolvent. It was found that the addition of water to the DMSO solution displaces the mixture critical pressure of the solution-CO₂ system to higher pressures and creates a new operating region in which the PCA process can be carried out. Following this approach it was possible to develop a process to produce 1-10 µm particles of N-trimethyl chitosan chloride (TMC) suitable for inhalation.

Finally, **Chapter 8** explores the feasibility of the different supercritical antisolvent techniques (conventional PCA, improved PCA, double improved PCA and vapour-liquid PCA) to coprecipitate lysozyme and dextran. Controlled coprecipitation of both compounds is achieved when the precipitation process is spatially confined to the droplets produced by atomization in the nozzle.

Results on the production of solvent-free polymer/drug microparticles using other supercritical techniques such as PGSS (Particle from Gas Saturated Solutions) and RESS (Rapid Expansion of Supercritical Solutions) are presented in **Appendix II and III**.

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