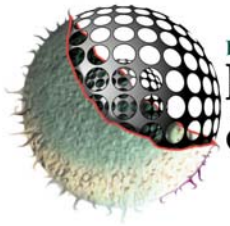

Predicting Particle Shape and Impurity Segregation for Molecular Solids

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Batch Crystallisation

- Often the final step in the synthesis of speciality materials and fine chemicals.
- Method can deliver purification of solute in solid is comparison to solute in solution in energy efficient process however…
- …very sensitive to process conditions as manifested through variations in polymorphic and pseudo-polymorphic form and solid phase purity.
- Combination of experimental in-process analytical techniques and molecular modelling can be used to begin to address these issues.

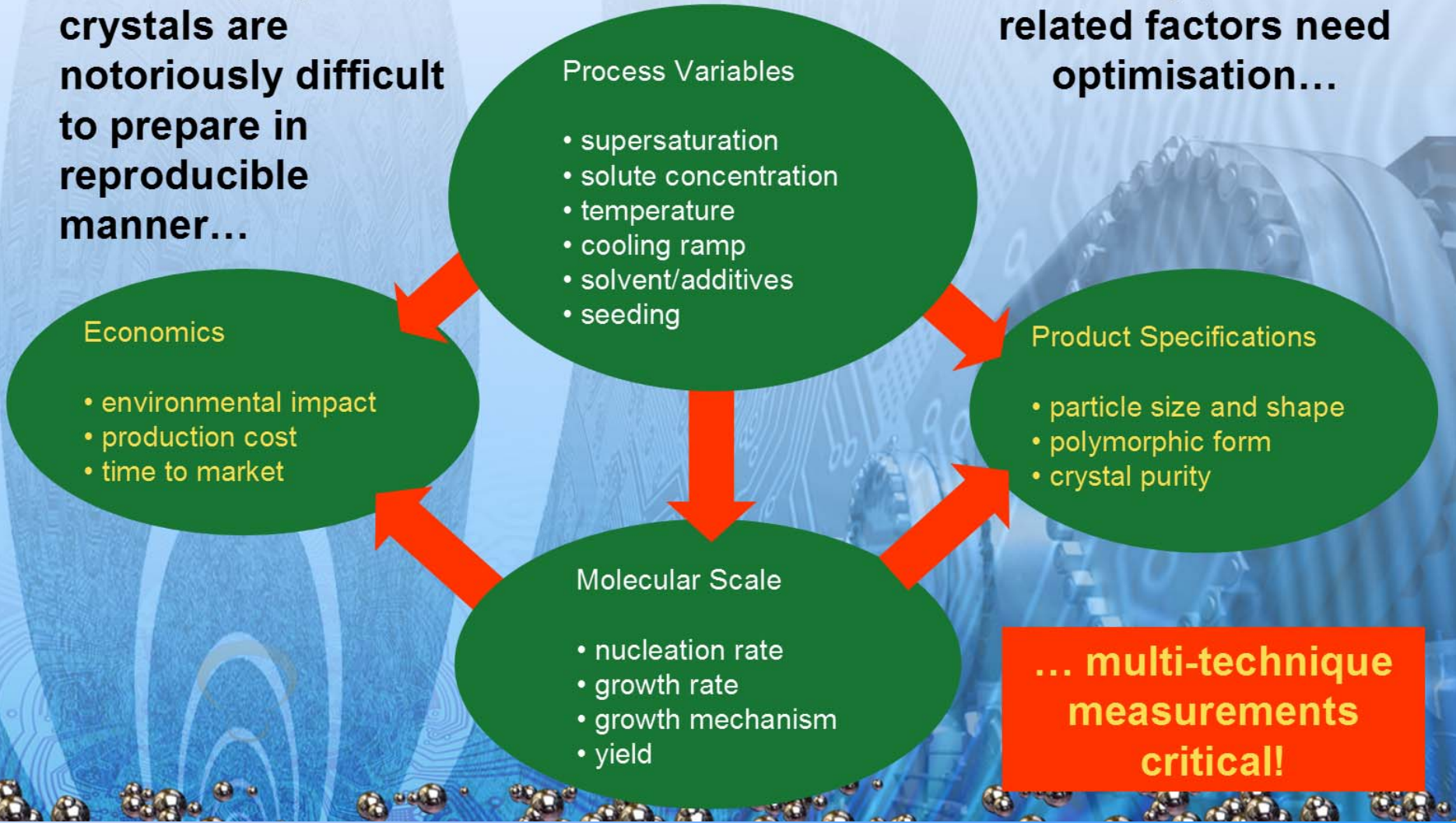
Crystallisation: Process Engineering

- Batch crystallisation from solution phase
  - Separation/purification of solid drug compound from reaction mother liquor
- Process involves product molecular recognition at growing solid/liquid interface
  - Differentiating between host compound & any (reaction) hetero impurities
- Crystallisation process involves two stages
  - 3-D nucleation-assembly of molecular clusters on nm scale
  - Simultaneous 2-D crystal growth on all (atomically smooth) particle surfaces (hkl)

Batch Crystallisation Process Science

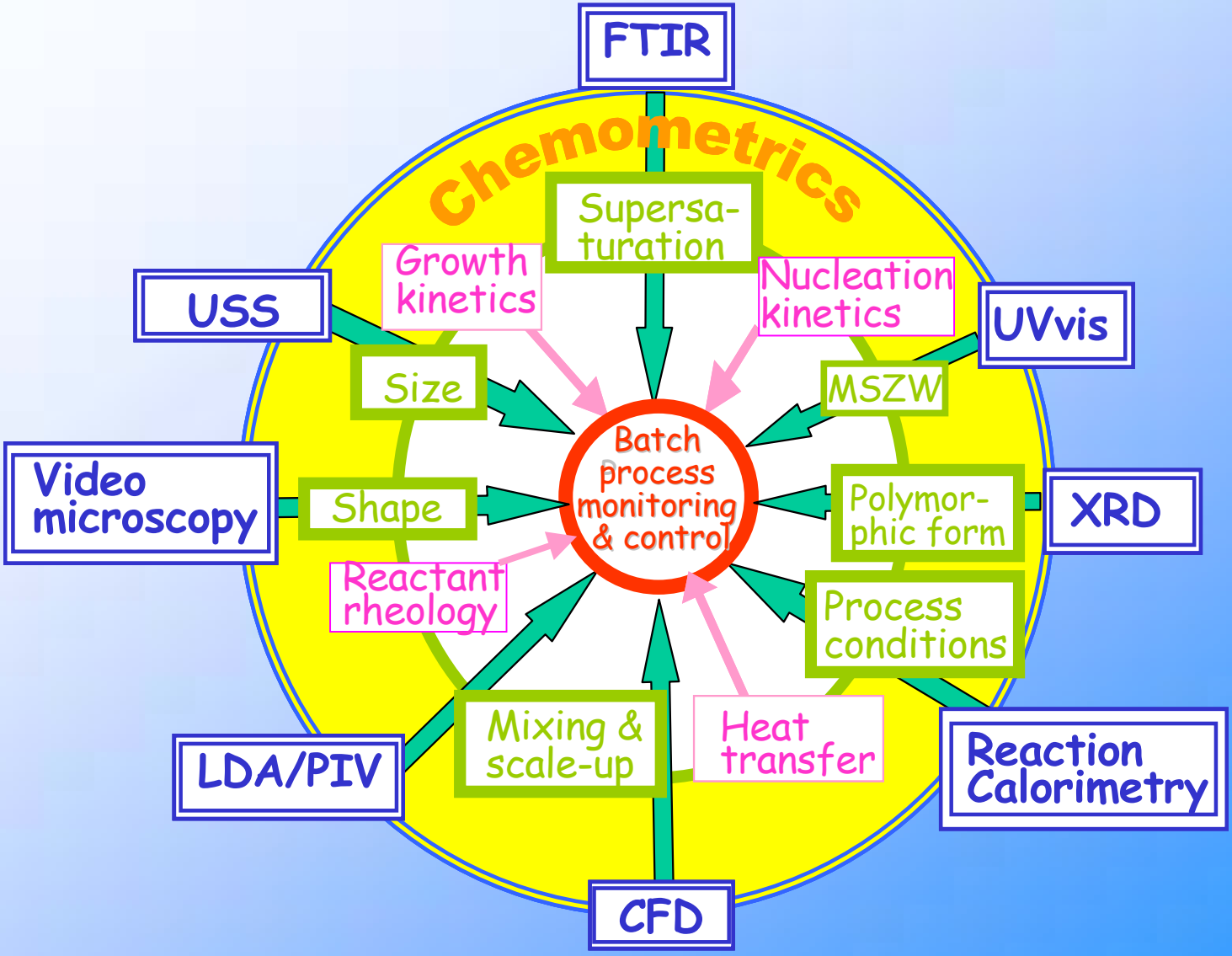
… batch prepared crystals are notoriously difficult to prepare in reproducible manner…

… many process related factors need optimisation…



… multi-technique measurements critical!

CBB Programme: Integrated In-Process Analytics



Motivation for Research

Why do we use molecular modelling?

- To enable us to exploit, optimally, ***all*** information inherent in experimental data; currently data readily obtained but insufficiently utilised.
  (e.g. crystal structure elucidation from powders)

- To achieve a truly ‘molecule-up’ approach for reliable *ab initio* prediction of particulate properties. Smallest scale in ‘across the length scales’ approach.

What Sort of Problems can be Addressed?

Formation of particles by crystallisation from solution:

- Particle phase (polymorphism)
- Particle size (related to solution supersaturation)
- Particle shape (growth rate dispersion)
- Particle purity (molecular specificity of surface vs bulk)
- Particle mechanical properties and surface energies

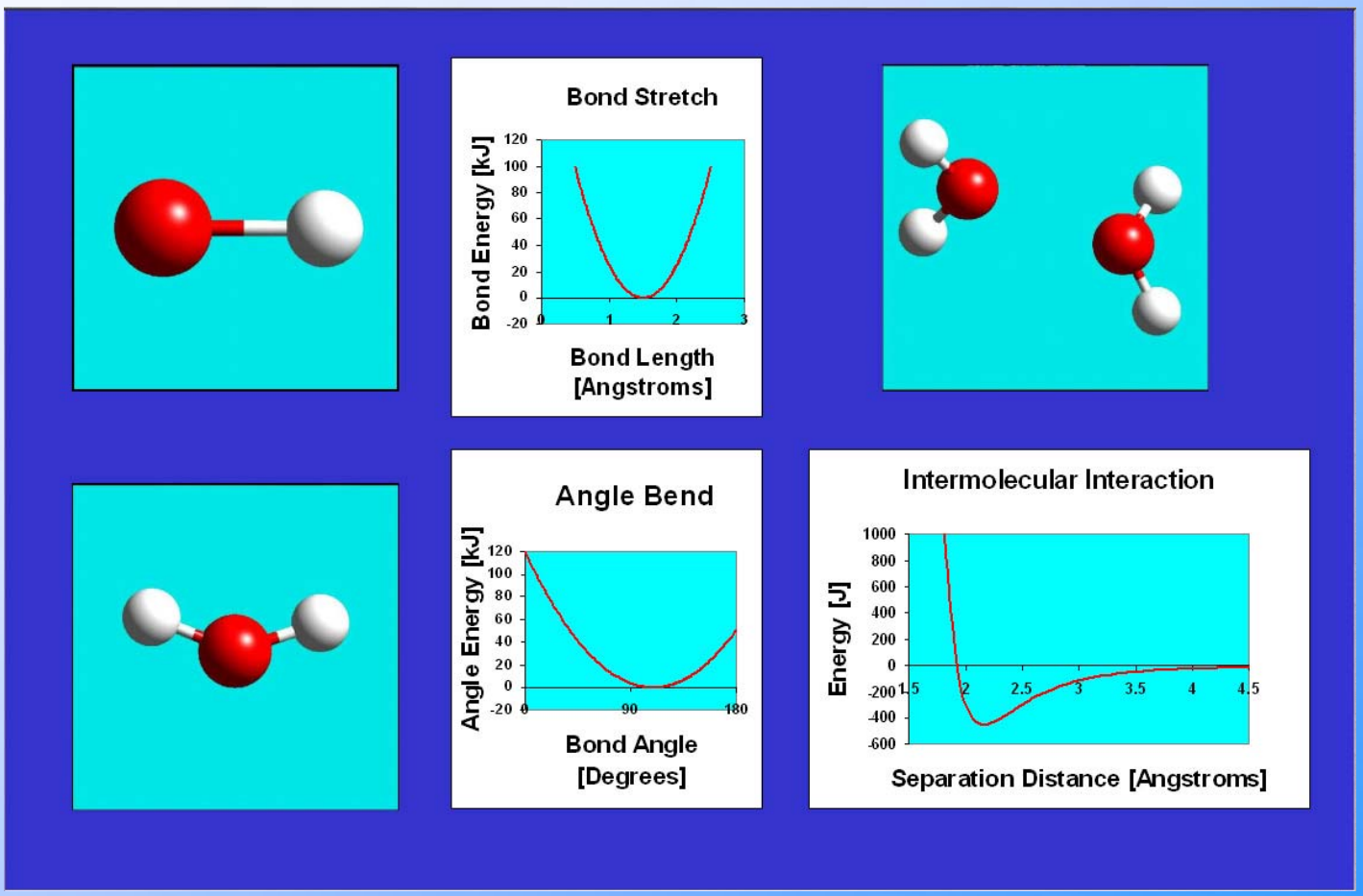
Key is to combine molecular modelling with experimental techniques.

Understanding Molecular Structure…

… we can model forces between atoms using Newtonian mechanics.

… bonds act like springs, atoms act like billiard balls…

… as atoms move from equilibrium, energy goes up…



Atom-atom Force Fields

- Utilise a Molecular Mechanics (MM) approach.
- Consist of intra-molecular energy terms: bond energy, bond angle energy, torsion angle energy etc...

$$U_{bond} = \tfrac{1}{2}k(l - l_0)^2 \qquad U_{angle} = \tfrac{1}{2}k(\theta - \theta_0)^2$$

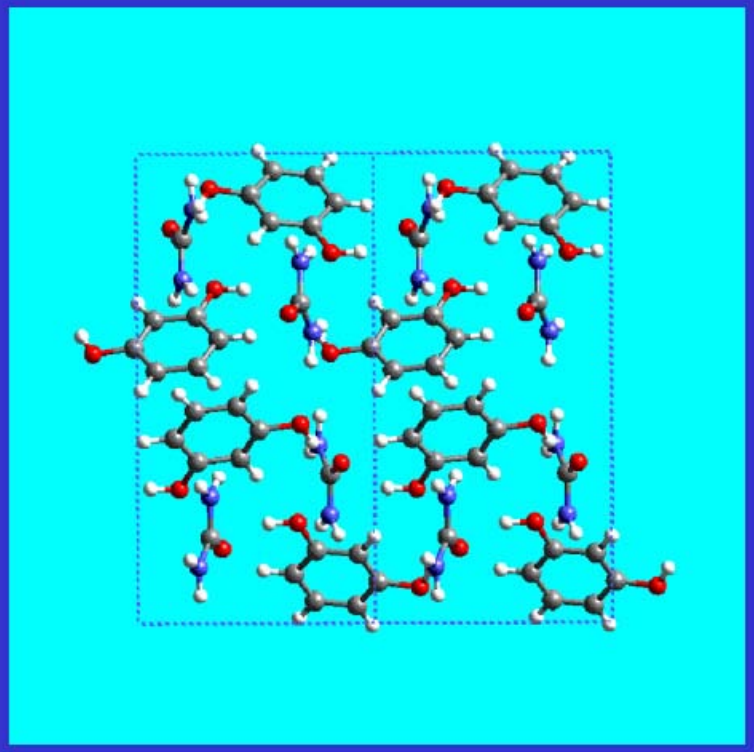
$$U_{torsion} = \sum_{all\ pairs\ i,j} \frac{V_{ij}}{2}\left[1 + \cos(n\omega - \omega_0)\right]$$

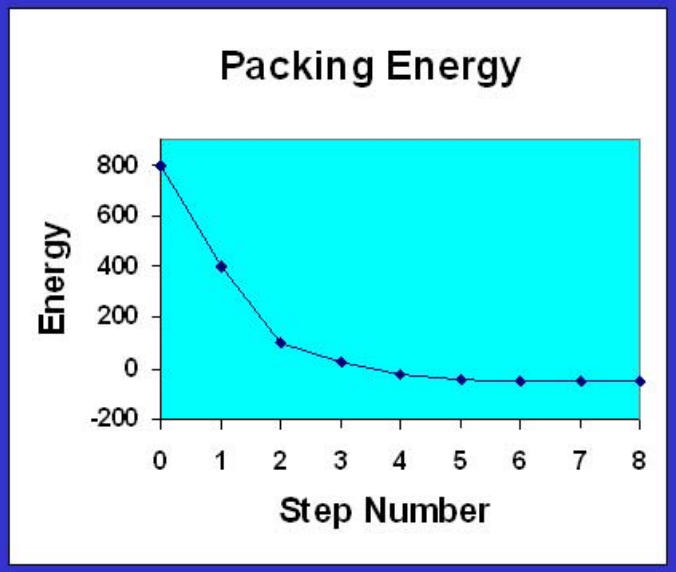
- ..and inter-molecular energy terms e.g.

$$U_{non-bonded} = \tfrac{1}{2}\sum_{i=1}^{n1}\sum_{j=1}^{n2}\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}} + \frac{q_i q_j}{Dr_{ij}}$$

Simulating Solid-State Structure…

We can optimise the way molecules pack in a periodic structure…





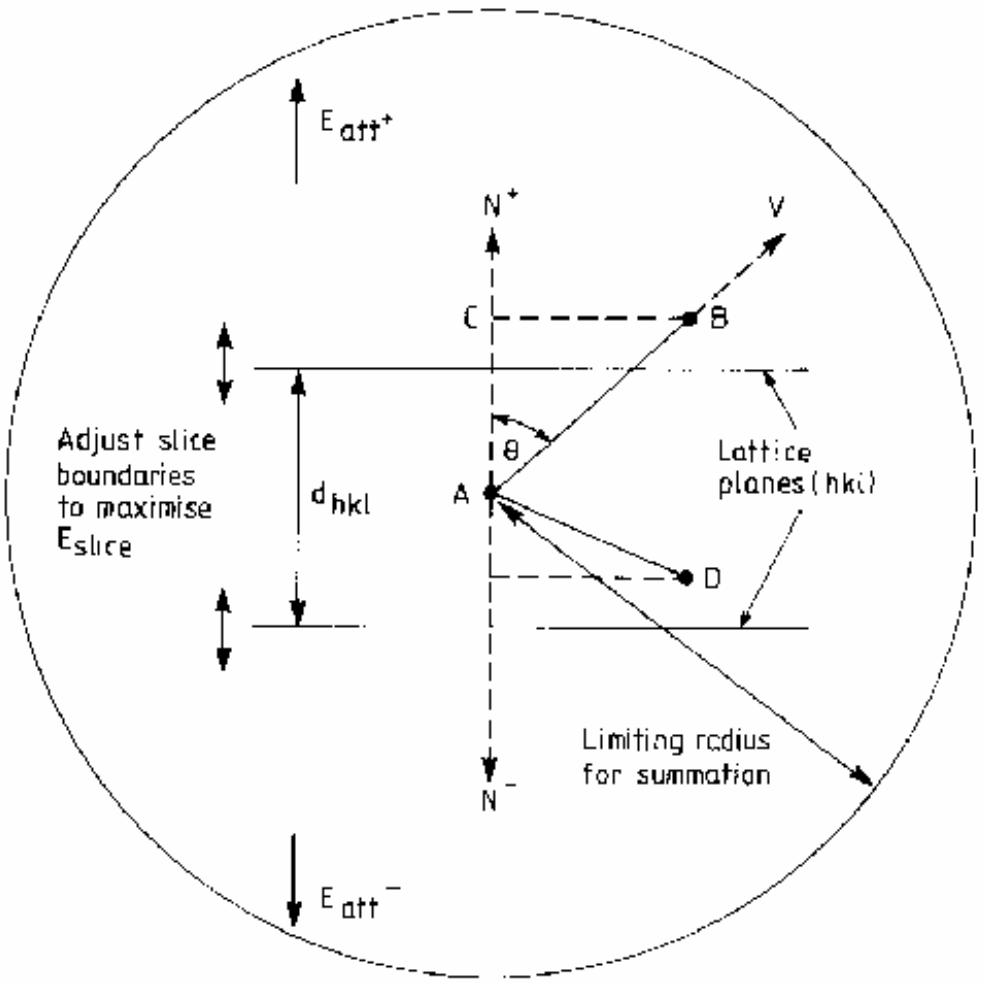


Fig. 1. Basic approach for calculation of intermolecular interactions using atom-atom method showing how the lattice energy is partitioned between the slice and attachment energies within a limiting sphere. A is the central molecule, B is a molecule outside the slice, D is a molecule inside the slice.

Calculation of Lattice Energy, Attachment Energy and Slice Energy

$$E_{cr} = E_{sl}^{hkl} + E_{att}^{hkl}$$

Prediction of Crystal Morphology

$$R_{growth} \ \alpha \ E_{att}^{hkl}$$

Impact of Impurity or Additive Molecules on Crystal Growth Process

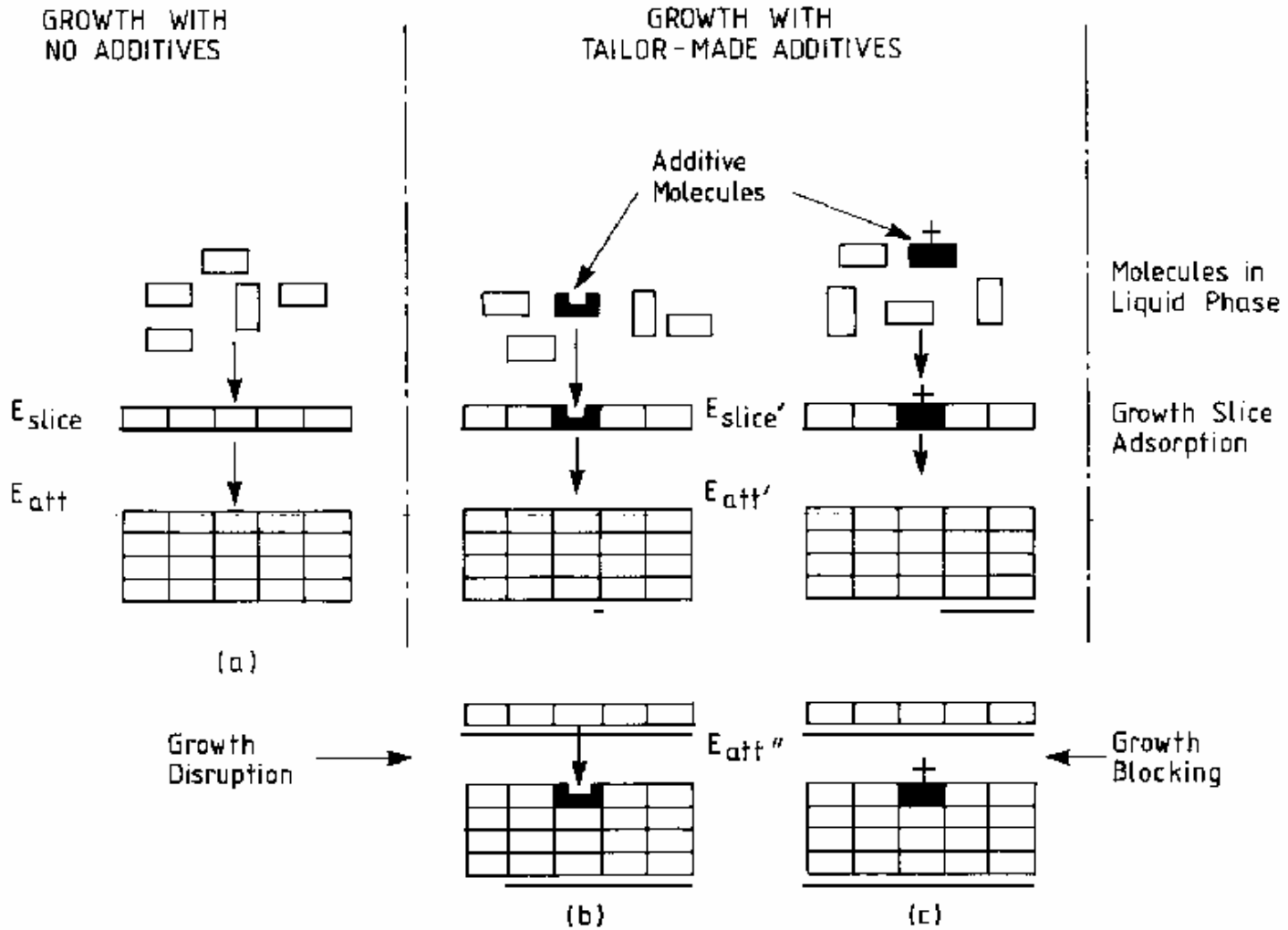
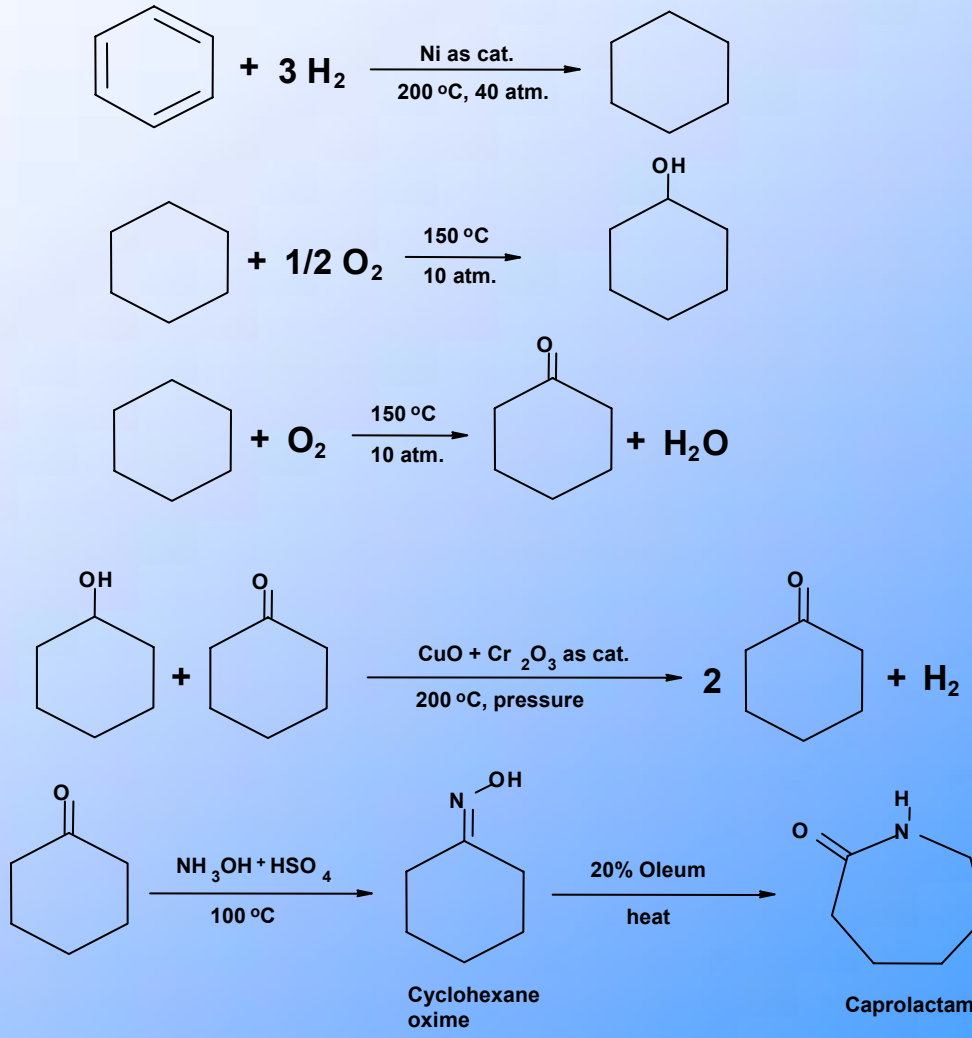


Fig. 2. Schematic showing the definition of the energy terms E_{att}, E'_{att}, E''_{att}, E_{sl} and E'_{sl} used in morphological modelling for (a) pure systems and systems having (b) disruptive-type and (c) blocker-type tailor-made additives.

Study of Impurity Segregation in Solid Caprolactam

- Caprolactam precursor in production of nylon-6.
- Polymerization process influenced by presence of impurities.
- Melt crystallization is possible purification route for caprolactam.
- Incorporation of impurity molecules into host solid can be studied by molecular modelling.

Synthesis of Caprolactam: Source of Impurities



Methodology

- Construct models of impurity molecules.
- Use geometrical fitting to superimpose impurity on host molecule in context of host lattice.
- Relax impurity molecule w.r.t rigid body rotations and translations to optimise calculated lattice energy.
- Use grid of different starting positions for minimisations to check global minimum in energy found.

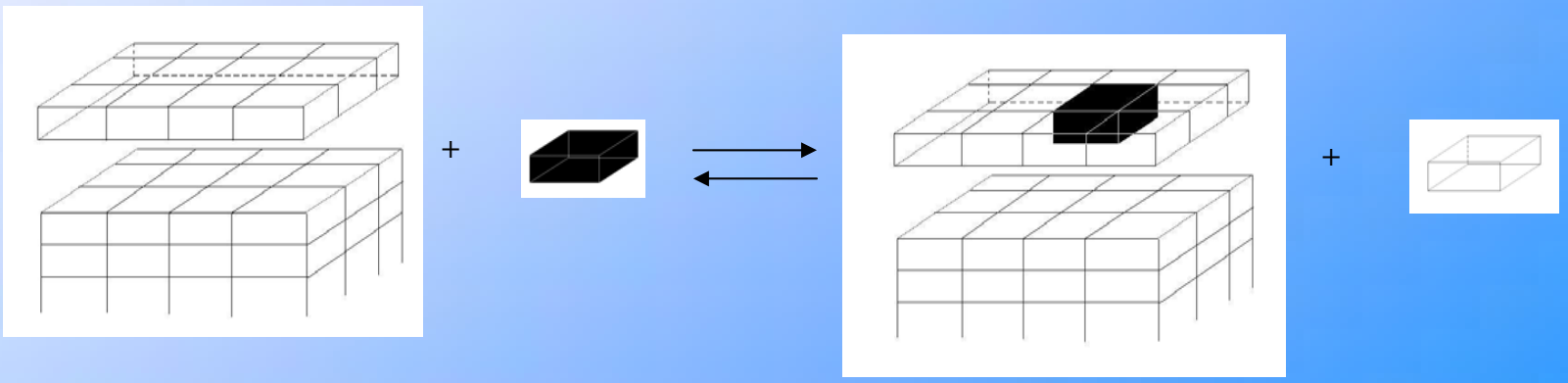
Incorporation of Impurity Molecule into Host Crystal Lattice

$$E_{cr} = E_{sl}^{hkl} + E_{att}^{hkl}$$

Cohesive energy of crystal lattice sum of slice and attachment energies for every surface (hkl).

$$\Delta b = E'_{sl} - E_{sl} - \Delta E_{att}^{UVWZ}$$

Differential binding energy for impurity vs host molecule on surface (hkl).



Segregation Coefficient

$$K_p = \frac{[X]_S}{[X]_L}$$

K_p segregation coefficient $[X]_S$ and $[X]_L$ impurity concentrations in solid & liquid phase respectively.

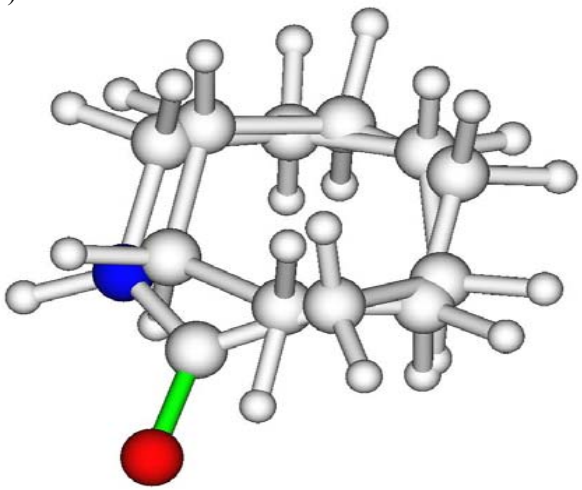
$$K = \frac{z_B}{z_A}\exp\left(\frac{-\Delta\varepsilon_0}{\kappa T}\right)$$

K, equilibrium constant A↔B, z_A, z_B partition functions, $\Delta\varepsilon_0$ difference in ground state energy, κ Boltzmann constant T absolute temperature.

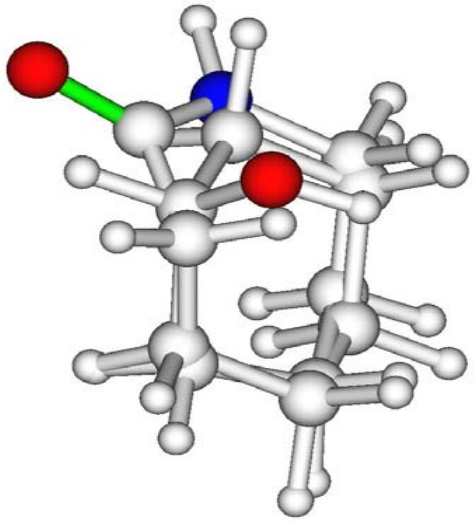
$$K_p \approx \exp\left(\frac{-\Delta b}{RT}\right)$$

Approximate expression relating equilibrium segregation coefficient to calculated differential binding energy.

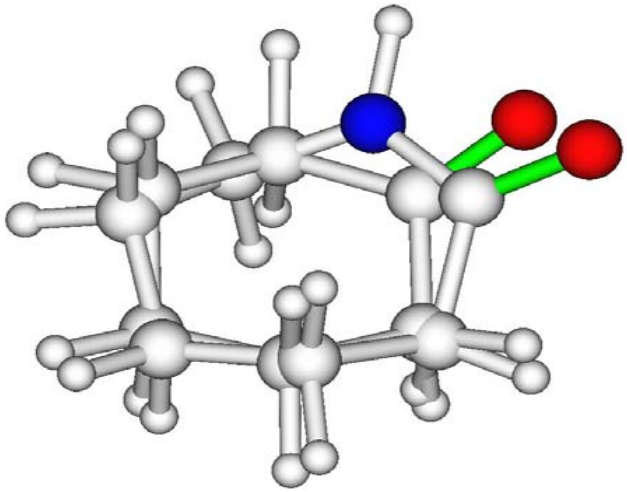
a)



b)



c)



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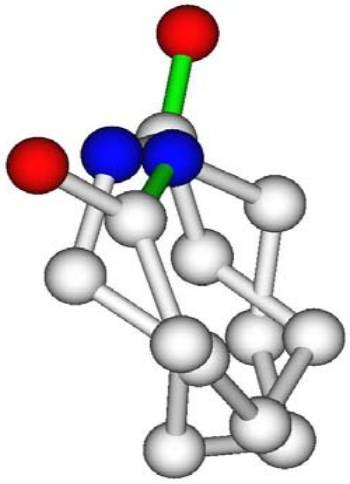


Impurity molecules overlaid with host molecules in context of host crystal lattice. a) cyclohexane, b) cyclohexanol, c) cyclohexanone, d) caprolactim.

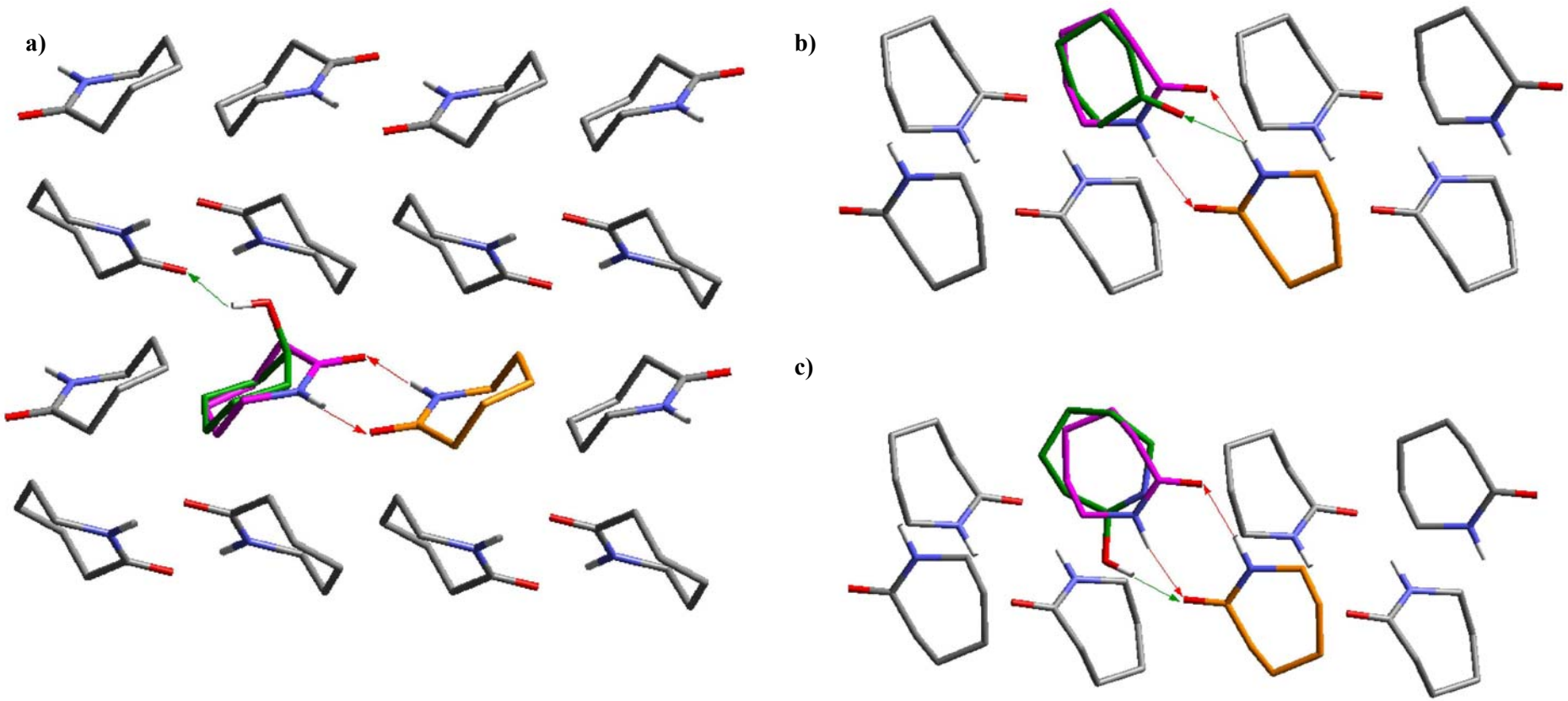
Summary of Lattice Energy Calculations

Lattice Energy Component [kcal/mol]	Cyclohexane			Cyclohexanol			Cyclohexanone			Caprolactim		
	Initial	Initial Optimised	Global Optimum	Initial	Initial Optimised	Global Optimum	Initial	Initial Optimised	Global Optimum	Initial	Initial Optimised	Global Optimum
Total	-2.30	-9.84	-9.84	12.12	-8.51	-12.73	-11.13	-12.47	-12.47	760.26	-8.68	-12.35
van der Waals r^{-6}	-19.28	-18.17	-18.17	-21.90	-20.81	-20.33	-19.79	-19.51	-19.51	-32.53	-23.09	-23.50
van der Waals r^{-12}	16.94	8.33	8.33	34.28	11.88	10.91	9.90	8.51	8.51	793.17	14.54	14.94
HB van der Waals r^{-10}	n/a	n/a	n/a	-0.29	-0.093	-12.15	-3.54	-4.06	-4.06	-3.98	-0.13	-14.20
HB van der Waals r^{-12}	n/a	n/a	n/a	0.12	0.031	9.34	2.98	3.53	3.53	3.00	0.051	11.24
coulombic	0.034	0.000	0.000	-0.09	0.48	-0.51	-0.68	-0.93	-0.93	0.59	-0.039	-0.83

For comparison the values [kcal/mol] for the host lattice are Total -16.46, van der Waals r^{-6} -22.28, van der Waals r^{-12} 9.41, HB van der Waals r^{-10} -9.15, van der Waals r^{-12} 8.02, Coulombic -2.46. (HB ≡ Hydrogen Bonding)

Ranked energy minima (energy < 0.0 kcal/mol) found for impurity molecules in host lattice

Rank of cluster	Cyclohexane		Cyclohexanol		Cyclohexanone		Caprolactim	
	Cluster Energy [kcal/mol]	Number of starting positions in cluster	Cluster Energy [kcal/mol]	Number of starting positions in cluster	Cluster Energy [kcal/mol]	Number of starting positions in cluster	Cluster Energy [kcal/mol]	Number of starting positions in cluster
1	-9.84	42	-12.73	6	-12.47	6	-12.35	12
2	-9.33	22	-12.03	6	-11.61	7	-12.01	6
3	-9.18	23	-10.72	13	-11.35	10	-11.42	2
4	-4.90	3	-10.43	8	-11.08	4	-10.57	3
5	-2.36	2	-10.37	3	-10.96	11	-9.42	12
6	-2.16	2	-9.96	4	-10.78	7	-8.68	7
7	-0.70	6	-9.70	6	-10.43	2	-8.27	5
8			-9.67	10	-10.33	5	-8.20	4
9			-8.88	9	-10.14	13	-8.19	4
10			-8.51	5	-9.89	7	-7.80	4



Optimal position of impurity molecules (a) cyclohexanol, (b) cyclohexanone & (c) caprolactim in ε-caprolactam host lattice, carbon atoms of impurity molecule coloured green, of substituted caprolactam molecule magenta and of caprolactam molecule for which hydrogen-bonded interactions are missing orange. Hydrogen bonds that are broken on substitution of an impurity molecule for a host molecule are indicated by red arrows that formed by a green arrow.

Growth Face	Differential Binding Energy Δb [kcal/mol]		AE for Host onto Impurity Containing Slice E''_{att} [kcal/mol]		AE for Host on Pure-Host Slice E_{att} [kcal/mol]	Relative Growth Rates Scaled on AE of (200) Face		
	Fitted	Optimised	Fitted	Optimised		Fitted	Optimised	Pure Host
(200)	4.34	3.07	-2.94	-3.12	-4.01	1.00	1.00	1.00
(110)	4.31	3.25	-4.25	-4.63	-5.33	1.45	1.48	1.33
$(11\bar{1})$	4.04	3.12	-5.32	-5.84	-6.68	1.81	1.87	1.67
(111)	2.50	1.82	-6.40	-7.15	-9.30	2.18	2.29	2.32
$(31\bar{1})$	3.70	2.77	-6.19	-6.70	-7.88	2.11	2.15	1.97
$(20\bar{2})$	2.21	1.62	-7.95	-8.81	-11.21	2.70	2.82	2.80
(310)	2.37	1.81	-6.64	-7.52	-9.67	2.26	2.41	2.41
(002)	1.15	0.76	-7.15	-8.21	-11.46	2.43	2.63	2.86
$(11\bar{2})$	1.11	0.73	-7.91	-8.96	-12.19	2.69	2.87	3.04
$(40\bar{2})$	3.41	2.57	-9.02	-9.62	-11.07	3.07	3.08	2.76

Differential binding energies, attachment energies and relative growth rates calculated for the impurity cyclohexanone on crystallographically most important faces of ε-caprolactam. Values are given for the initial, geometrically fitted position and the position of global minimum in lattice energy.

Cyclohexanone in Melt [mol%]	Supersaturation x 10^3 $\frac{\Delta H_m(T_m - T)}{RT_m^2}$	Segregation Coefficient for {110} Form x 10^2	Segregation Coefficient for {11 $\bar{1}$ } Form x 10^2
0.10	1.7	1.4	6.5
	3.3	1.4	4.9
	5.0	7.3	9.0
5.0	3.3	0.70	2.0
	4.1	1.1	3.2
	5.8	1.1	4.4
15.0	3.5*	3.7	3.9
	3.5*	4.9	2.9
	4.4	4.6	3.1
30.0	4.7	0.77	1.1
	5.6	1.3	1.0

Experimentally determined segregation coefficients for the {110} and {11$\bar{1}$} forms of caprolactam crystals grown from melts containing cyclohexanone taken from. van den Berg, E. P. G.; Bögels, G.; Arkenbout, G.J. *J. Cryst. Growth* **1998,** *191*, 169-177 (ΔH_m is heat of fusion, T_m melting temperature, T temperature, R ideal gas constant).

Segregation-coefficient calculated for {110} form at 342K (the melting point of pure ε-caprolactam) is 8.4 x 10^{-3} and for {11-1} form at 342K 1.0 x 10^{-2}.

Conclusions

- A procedure has been developed for identifying the most energetically favourable location and orientation of impurity molecules in host crystals.

- A grid searching approach has been employed for identifying minima in the calculated lattice energy in an attempt to ensure that the position of the global minimum in lattice energy is located.

- Using the optimal configurations identified differential binding energies & modified attachment energies are calculated for important growth forms, values enable equilibrium segregation-coefficients to be calculated for each form.