Crystal Engineering

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Mode of Action and Design Rules for Additives That Modulate Crystal Nucleation

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There is considerable interest, both fundamental and technological, in understanding how additives and impurities influence crystal nucleation, and in the modulation of nucleation in a predictable way by using designer additives. An appropriate additive can promote, retard, or inhibit crystal nucleation and growth, assist in the selective crystallization of a particular enantiomer or polymorphic form, or enable crystals of a desired habit to be obtained.[1–3] Applications involving additives include the control of the nucleation of proteins,[4] the inhibition of urinary-stone formation[5] and of ice formation in living tissues during cryoprotection,[6] their use as antifreeze agents in Antarctic fish,[7,8] the prevention of blockages in oil and gas pipelines as a result of wax precipitation[9] and gas-hydrate formation,[10] crystal-twin formation,[11] and as a possible basis for the antimalarial activity of some drugs.[12] We report herein the mode of action and explicit (apparently intuitive) rules for designing additive molecules for the modulation of crystal nucleation. The mode of action and the design features have been derived from molecular-dynamics simulations involving simple models.[13] These findings will help to rationalize how known nucleation inhibitors and modulators exert their effect and aid in the identification or design of new additives for the inhibition or promotion of nucleation in specific systems.

Although the mode of action of additives that modulate crystal nucleation and growth has been investigated extensively,[1–3] much of this research has focused on the action of additives on crystal growth. Whether a given additive affects the nucleation stage (rather than crystal growth) can be ascertained by measurement of the width of the metastable zone, which is widened by nucleation inhibitors.[9,14] However, how these additives exert their effect is still largely a mystery, partly because the molecular-level processes involved are inaccessible to experiment.

Molecular simulations provide the required molecular-level resolution and indeed have been employed to investigate the effects of additives on crystal nucleation. However, these studies have generally followed a crystal-growth-type protocol and explored the interaction of the additive with crystal surfaces.[10,14–16] The technical difficulty from a simulation perspective is that the nucleation process is a rare event in a limited volume (the simulation cell is typically of the order of 10 nm^3), and hence cannot be simulated explicitly for realistic molecular systems by using molecular dynamics.[17] However, the process can be simulated for simple model or atomistic (ionic) systems.[13,18–20] A particularly relevant study, which forms the basis for the current investigations, involved the explicit simulation of crystal nucleation from a solvent by using the Lennard-Jones (LJ) model.[13] In the present context, the LJ solute and solvent particles are perceived as simple coarse-grained molecules, which makes our findings generic. The LJ parameters for the reference system, that is, the solute–solvent system without additives, are given in Table 1.

Table 1: Lennard-Jones parameters for the solute and solvent particles.

Interaction	ε [kJ mol^{-1}]	σ [Å]
solute–solute	8.314	4.48
solvent–solvent	2.494	3.00
solute–solvent	1.000	3.74

We have systematically investigated the effects of additive molecules on crystal nucleation by using the LJ model system, with a view to identifying key features of effective additives. The additive designs investigated include single particles and dimers of varying effective size and variable solute and solvent affinity (Figure 1). For the single-particle additive, three variables were investigated: its size relative to that of a solute particle (the size was varied in terms of the LJ σ parameter) and its relative affinity (the respective LJ ε parameter) for the solute and for the solvent, thus making the

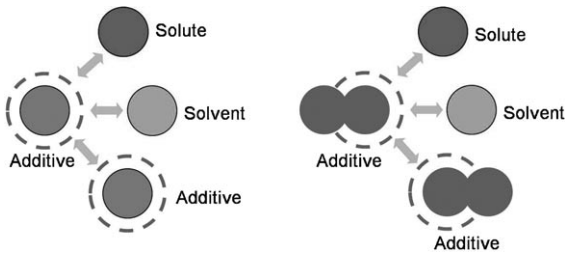

Figure 1. The various interactions considered as variables for the single-particle (left) and dimer (right) additive molecules. The arrows refer to the interaction energy, and the broken circumference outlines refer to variation in particle size.

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additive either "solute-philic" or amphiphilic (affinity for both solute and solvent). The dimer additive consisted of a solute particle linked to another atom whose effective size and relative affinity for the solute and the solvent were varied. The variation in the relative affinities for the solute and solvent characterized the dimer molecule as either "solute-philic", amphiphilic (one particle has solute character, whereas the other is solventlike), or weakly amphiphilic (the second particle has affinity for both the solute and the solvent). The actual values of the interaction parameters are given in the Supporting Information.

As the behavior of the reference solute/solvent system has been discussed previously,[17] we outline herein only the salient features. At the outset, the solute atoms begin to form clusters, which tend to come together to form, typically, a single large cluster. At this stage, the formed cluster is structurally amorphous. A few picoseconds later, the amorphous cluster undergoes one or more nucleation events and starts to form either a single crystal or a polycrystalline face-centered cubic (fcc) structure. This entire process takes about 100 ps to reach completion, after which the nucleus undergoes annealing to finally yield a structure with rudimentary facets. The appearance of an amorphous phase, which then nucleates, has been observed experimentally for both small molecules[21] and proteins.[22]

The structural progress of the emerging nuclei was monitored by radial distribution functions (RDFs) of the solute particles as a function of time, with each time point averaged over 4 ps (Figure 2). Initially, the RDFs indicate a diffuse structure, which later develops into a crystalline fcc structure. The kinetics of the nucleation process were followed by monitoring the height of the peak at 8.5 Å in the RDF and characterized by the following parameters: 1) time for the onset of nucleation τ_{nuc}, 2) first-order rate constant k_{nuc}, and 3) the maximum attained peak height g_{max}, which gives an indication of the extent of crystallinity of the final structure. The first-order kinetic model took the form $g(t) = g_0[1-\exp(-k_{nuc}t)]$, in which $g(t)$ is the peak height at time t, and g_0 is the peak height for the unnucleated cluster (typically about 3.8).

The overall effects of the single-particle additives on the nucleation process are tabulated in Table 2 (detailed data are given in the Supporting Information). The results indicate that, for the solute-philic additive molecule, the effect is always inhibitory, that is, nucleation is either inhibited altogether (over the simulation period) or retarded. In contrast, the amphiphilic additive is only able to retard nucleation.

For the solute-philic additive, the largest effect appears to be due to its size: An additive that is larger or smaller than the solute atom inhibits or retards nucleation, unless its affinity for the solute is low, in which case nucleation is enabled, albeit slowly. When the additive has a low affinity for the solute, irrespective of its size, the additive particles are excluded from the interior of the solute cluster (Figure 3a) and at best only retard nucleation. Additives that are larger or smaller than the solute molecules but have a high affinity for the solute cause the solute molecules to structure around them in a way that conflicts with the emerging solute lattice and hence cause inhibition (Figure 3b). Large additives cause complete inhibition, whereas small additives are only able to retard nucleation as they become incorporated within the solute lattice. The inability of the amphiphilic additive to completely inhibit nucleation arises from its failure to be incorporated into the solute cluster. In contrast to the solute-philic additive (which resides within the emerging cluster), the amphiphilic

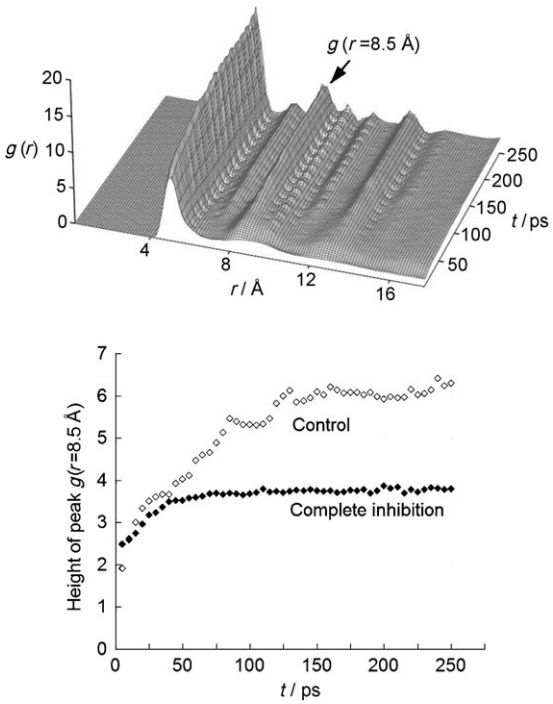

Figure 2. Top: RDF of the solute particles as a function of simulation time for the reference system without additive molecules. Each RDF is averaged over 4 ps. With increasing simulation time, the RDF takes the characteristic form (well-defined peaks) for a crystal. Bottom: Kinetics of the nucleation process as characterized by the height of the peak at $r = 8.5$ Å in the solute–solute radial distribution function for the reference system and a system that retains nucleation in the presence of additive molecules. In the early stages of the experiment (0–40 ps), the curves characterize phase separation of the solute phase.

Table 2: Rates of nucleation for the single-particle additive as a function of its effective size and its affinity for the solute particles.

	Effective size	Rate of nucleation[a]		
		low affinity[b]	medium affinity[c]	high affinity[d]
solute-philic	< solute[e]	slow	no nucl.	slow
	= solute[f]	fast	fast	fast
	> solute[g]	slow	no nucl.	no nucl.
amphiphilic	< solute[e]	fast	slow	slow
	= solute[f]	fast	slow	very fast

[a] Slow: $\tau_{nuc} = 40$–250 ps, $k_{nuc} = 0.001$–0.03 ps^{-1}, $g_{max} = 4.4$–5.7; fast: $\tau_{nuc} = 40$–80 ps, $k_{nuc} = 0.03$–0.08 ps^{-1}, $g_{max} = 5.9$–7.1; very fast: $\tau_{nuc} = 30$–55 ps, $k_{nuc} = 0.06$–0.11 ps^{-1}, $g_{max} = 6.2$–7.1. [b] $\varepsilon_{add-solute} = 4.55$ kJ mol^{-1}; $\varepsilon_{add-add} = 2.49$ kJ mol^{-1}. [c] $\varepsilon_{add-solute} = 8.31$ kJ mol^{-1}; $\varepsilon_{add-add} = 8.31$ kJ mol^{-1}. [d] $\varepsilon_{add-solute} = 10.18$ kJ mol^{-1}; $\varepsilon_{add-add} = 12.47$ kJ mol^{-1}. [e] $\sigma_{add-add} = 3.0$ Å. [f] $\sigma_{add-add} = 4.48$ Å. [g] $\sigma_{add-add} = 6.72$ Å.

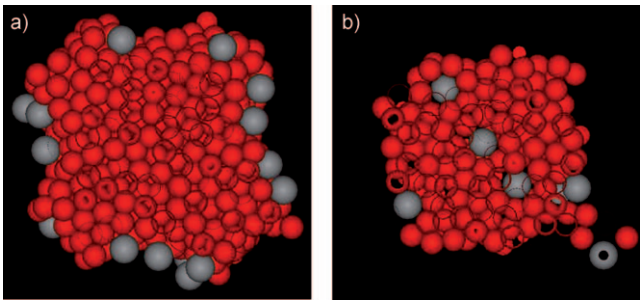

Figure 3. a) Slice through an emerging nucleus for the single-particle additive with a low affinity for the solute and an effective size greater than that of a solute molecule: All such additive molecules are excluded from the interior of the nucleus because of their low affinity for the solute. b) Slice through the solute aggregate for the single-particle additive with a high affinity for the solute and an effective size greater than that of a solute molecule: The solute molecules form a structured shell around the additive molecules. The structuring, which is induced by the high affinity of the additive for the solute molecules, is at odds with the solute–solute packing and hence causes inhibition of nucleation.

additive tends to reside at the solute/solvent interface, where its influence is limited.

The effect of the dimer additive on the nucleation process is summarized in Table 3. Not only can the dimer additives inhibit nucleation, but they can also promote nucleation (and in a remarkable manner), depending on their characteristics. The solute-philic dimer acts essentially as an inhibitor. The inhibitory effect is strong when the size of the second particle of the dimer is either equivalent to or greater than the size of the solute. The effect of variation in the affinity of the dimer for the solute is secondary, whereby higher affinity causes inhibition.

The weakly amphiphilic dimers are able to both inhibit and promote nucleation as a direct consequence of how they are distributed. Whereas the solute-philic dimer molecules tend to reside within the solute clusters, the weakly amphiphilic dimers are mostly found at the solute/solvent interface (often aligned parallel to the interface, see Figure 4a), where their effect is limited in terms of disruption of the packing or even beneficial as a result of a decrease in the solute/solvent interfacial free energy. When the second particle of the dimer additive is larger than a solute particle, we observe inhibition; when it is equal in size to the solute, the kinetics are similar to the reference system; when it is smaller than a solvent particle, we observe a rapid nucleation event. The nucleation process, however, slows down significantly as the affinity of the additive for the solute particles is increased.

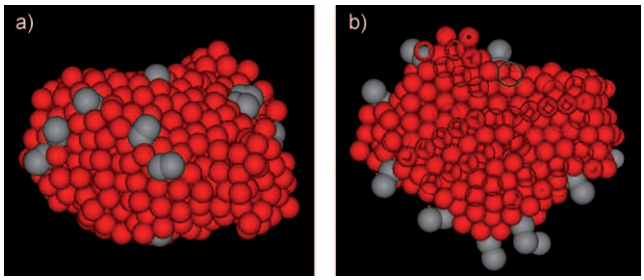

Figure 4. a) Snapshot of the solute aggregate for the weakly amphiphilic dimer additive: The additive molecules tend to be oriented parallel to the surface. b) Slice of the emerging nucleus for the amphiphilic dimer additive: The additive molecules are mostly oriented perpendicular to the surface.

The amphiphilic dimers confine themselves entirely to the interface (generally oriented perpendicular to the interface, see Figure 4b) and are able to promote nucleation but not inhibit the process; at best they only retard nucleation. When the size of the second particle is large, we observe a retardation of the nucleation process but not inhibition. For the other two size variations, the additive promotes rapid nucleation that surpasses the rate of nucleation of the reference system in a spectacular manner (Figure 5).

Simulations of the additive molecules with high self-affinity were also carried out and revealed a tendency towards clustering (Figure 6), which made the additives less effective.

Overall, the results reveal a number of generic features of how additives and impurities can affect crystal nucleation. An effective nucleation inhibitor should interact strongly with the solute and have a structure that is able to disrupt the periodicity that characterizes the emerging nucleus. A strong affinity for the solute (relative to that for the solvent and itself) not only ensures that the additive molecules end up within the emerging solute aggregates, but also leads to

Table 3: Rate of nucleation for the dimer additive as a function of the effective size and affinity for the solute and solvent particles of one of the particles that make up the dimer.

	Effective size	Rate of nucleation[a]		
		low affinity[b]	medium affinity[c]	high affinity[d]
solute-philic	< solute[e]	very fast	slow.	slow
	= solute[f]		no nucl.	
	> solute[g]	slow	no nucl.	no nucl.
weakly amphiphilic	< solute[e]	very fast	fast	slow
	= solute[f]		very fast	
	> solute[g]	slow	no nucl.	no nucl.
amphiphiliic	< solute[e]	slow	very fast	slow
	= solute[f]		very fast	
	> solute[g]	slow	very fast[h]	very fast[h]

[a] Slow: $\tau_{nuc}=40$–250 ps, $k_{nuc}=0.001$–0.03 ps^{-1}, $g_{max}=4.4$–5.7; fast: $\tau_{nuc}=40$–80 ps, $k_{nuc}=0.03$–0.08 ps^{-1}, $g_{max}=5.9$–7.1; very fast: $\tau_{nuc}=30$–55 ps, $k_{nuc}=0.06$–0.11 ps^{-1}, $g_{max}=6.2$–7.1. [b] For solute-philic ($\varepsilon_{add\text{–}solvent}=1.0$ kJ mol^{-1}) and weakly amphiphilic additives ($\varepsilon_{add\text{–}solvent}$ determined by Lorentz–Berthelot (LB) rules): $\varepsilon_{add\text{–}solute}=4.55$ kJ mol^{-1}, $\varepsilon_{add\text{–}add}=2.49$ kJ mol^{-1}; for amphiphilic additives ($\varepsilon_{add\text{–}solute}=1.0$ kJ mol^{-1}): $\varepsilon_{add\text{–}solvent}=2.49$ kJ mol^{-1}, $\varepsilon_{add\text{–}add}=2.49$ kJ mol^{-1}. [c] For solute-philic ($\varepsilon_{add\text{–}solvent}=1.0$ kJ mol^{-1}) and weakly amphiphilic additives ($\varepsilon_{add\text{–}solvent}$ determined by LB rules): $\varepsilon_{add\text{–}solute}=8.31$ kJ mol^{-1}, $\varepsilon_{add\text{–}add}=8.31$ kJ mol^{-1}; for amphiphilic additives ($\varepsilon_{add\text{–}solute}=1.0$ kJ mol^{-1}): $\varepsilon_{add\text{–}solvent}=4.55$ kJ mol^{-1}, $\varepsilon_{add\text{–}add}=8.31$ kJ mol^{-1}. [d] For solute-philic ($\varepsilon_{add\text{–}solvent}=1.0$ kJ mol^{-1}) and weakly amphiphilic additives ($\varepsilon_{add\text{–}solvent}$ determined by LB rules): $\varepsilon_{add\text{–}solute}=10.18$ kJ mol^{-1}, $\varepsilon_{add\text{–}add}=12.47$ kJ mol^{-1}; for amphiphilic additives ($\varepsilon_{add\text{–}solute}=1.0$ kJ mol^{-1}): $\varepsilon_{add\text{–}solvent}=5.58$ kJ mol^{-1}, $\varepsilon_{add\text{–}add}=12.47$ kJ mol^{-1}. [e] $\sigma_{add\text{–}add}=3.0$ Å. [f] $\sigma_{add\text{–}add}=4.48$ Å. [g] $\sigma_{add\text{–}add}=6.72$ Å. [h] Incomplete nucleation.

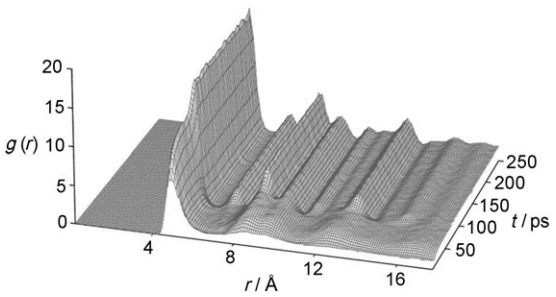

Figure 5. RDF of the solute particles as a function of simulation time for the system containing amphiphilic dimer additives. The RDFs show the remarkably rapid nucleation event induced by the amphiphiles: Both the peak-evolution rate and the heights of the peaks formed surpass those observed for the reference system without additives (Figure 2a).

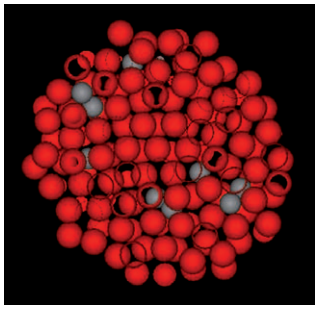

Figure 6. Slice through an emerging nucleus for the single-particle additive with high self-affinity: The additive molecules tend to aggregate, which makes them less effective.

disruption of the packing, as the solute particles are forced to align themselves around the additive at the expense of solute–solute interactions and packing. In the laboratory, these affinities are reflected in the respective solubilities. More generally, disruption can be caused by steric effects resulting from structural differences between the additive and solute molecules or extensive degrees of freedom in the additive (the latter point was not examined directly in the study but is inferred). These prerequisites of a strong affinity for the solute and a disruptive ability are quite different from those required for the inhibition of crystal growth.

Additive molecules that have an amphiphilic character end up at the solute/solvent interface and can inhibit, retard, or promote nucleation depending on their specific structure, their interactions with the solute and solvent, and the given supersaturation. The inhibitory/retardation effect occurs when the solute–additive interaction is relatively strong and the additive molecules are still able to influence the packing of the emerging structure, despite being confined to the surface. Promotion of nucleation appears to occur when the additive is able to reduce the solute/solvent interfacial energy. This promotion effect need not lead to rapid crystal growth; such additives could in fact serve to inhibit crystal growth, particularly if the additive–solute interaction is strong, because of competition between the surface active molecules and the solute for the solute sites on the developing crystal. Whether inhibition or promotion of crystal growth is likely to be observed will also depend on the driving force. At low levels of supersaturation, the decrease in interfacial free energy is likely to promote crystal growth (by aiding the required 2D nucleation on the crystal-growth surface), whereas at higher levels of supersaturation, one would expect inhibition as the detachment of the surface-active molecules becomes the rate-limiting step.

Finally, the simulations highlight the importance of the affinity of the additive for itself relative to its affinity for the solute. Strong additive–additive interactions encourage the additive molecules to self-associate (Figure 6), which minimizes their interaction with the solute molecules and thus decreases their impact on solute nucleation.

In conclusion, the study suggests that, other than the ability of an additive molecule to serve as a template, the key factors that determine the ability of an additive to modulate crystal nucleation are 1) the strength of its interaction with the solute, 2) its disruptive ability (which may be based on steric, entropic or energetic effects), 3) interfacial properties, and 4) the degree of self-association.

Experimental Section

Molecular-dynamics simulations of the LJ systems were carried out in an NPT (Nosé–Hoover[23,24] thermostat) ensemble with isotropic periodic boundary conditions by using the computer program DLPOLY.[25] The time step was 5 fs, and the mass for all atoms in the system was set to 5 g mol^{-1}. The cutoff for the atom interactions was 3.5σ. The maximum LJ σ parameter in the system was varied from 15.5 to 23.5 Å. For all simulations, the solute particles were initially interdispersed within the solvent. The additive particles were then introduced by randomly replacing solute and/or solvent particles. Typically, the systems contained about 700 solute particles (ca. 15%), 4000 solvent particles, and 27 additive molecules (ca. 5% solute basis). The simulations were carried out for a period of 250 ps, which was sufficient to induce nucleation in the reference (pure) solute–solvent system. The relatively small system sizes and low simulation times (with respect to current standards) are justified, since a wide, multifactorial parameter space was explored, and numerous simulations were involved. The force-field interaction parameters that characterize the solute, solvent, and additive molecules are given in Tables 1–3 and detailed in the Supporting Information.

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