J|A|C|S ARTICLES

Published on Web 07/29/2010

Amorphous Precursors in the Nucleation of Clathrate Hydrates

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Abstract: The nucleation and growth of clathrate hydrates of a hydrophobic guest comparable to methane or carbon dioxide are studied by molecular dynamics simulations of two-phase systems. The crystallization proceeds in two steps: First, the guest molecules concentrate in “blobs”, amorphous clusters involving multiple guest molecules in water-mediated configurations. These blobs are in dynamic equilibrium with the dilute solution and give birth to the clathrate cages that eventually transform it into an amorphous clathrate nucleus. In a second step, the amorphous clathrate transforms into crystalline clathrate. At low temperatures, the system can be arrested in the metastable amorphous clathrate phase for times sufficiently long for it to appear as an intermediate in the crystallization of clathrates. The “blob mechanism” unveiled in this work synthesizes elements of the labile cluster and local structuring hypotheses of clathrate nucleation and bears strong analogies to the two-step mechanisms of crystallization of proteins and colloids.

Introduction

Clathrate hydrates are crystalline inclusion compounds in which small guest molecules are contained within cages formed by a network of water molecules.[1] In clathrate hydrates, as in ice, each water molecule is hydrogen-bonded to four water neighbors. A difference, however, is the predominance of pentagonal rings in the hydrates that results in the formation of an open frame of polyhedral water cages. Although the guest-free water clathrates are metastable with respect to ice,[2] the clathrate crystal is stabilized by the interaction of water with guest molecules, even hydrophobic molecules that present very low solubility in water (e.g., methane and carbon dioxide). Methane, for example, forms clathrates with a ratio of methane to water that is about 2 orders of magnitude larger than that in the solution from which they grow. This poses the question, how do clathrates of hydrophobic guests form from aqueous solutions? Answering this question and identifying the structure of the clathrate critical nuclei are crucial for the development of strategies to inhibit and promote clathrate formation.

Different hypotheses have been proposed to explain the microscopic mechanism of nucleation of clathrate hydrates. Most of the evidence in support of and against these hypotheses arises from molecular simulations, as the crystal nuclei are usually too small for a direct experimental determination of their structure and mechanism of formation.[3] The first hypothesis for clathrate nucleation was proposed by Sloan and co-workers;[4,5] their labile cluster hypothesis (LCH) suggests that cage-like water clusters corresponding to the polyhedral cages of clathrates form around guests in solution, and these combine in the liquid to form the unit cell of the crystal. Since then, molecular simulations have shown that isolated empty or guest-filled clathrate cages in solution are rare and — when they form — have a flickering existence,of a few picoseconds.[6] Radhakrishnan and Trout computed the barrier for agglomeration of CO_2-filled cages in simulations and concluded that disintegration of the cages was more favorable than their agglomeration to grow a crystal nucleus.[7] Guo et al. searched for polyhedral cages in 60 million hydration shells of methane using molecular simulations.[8] They found that closed polyhedral shells only form in concentrated methane solutions, with probability 10^{-6}. In another study, they demonstrated that methane molecules adsorb to a dodecahedral cage and that the lifetime of the cage increases exponentially with the number of solute molecules that surround it.[9] On the basis of these results, we conjecture that, *if there is any viability for the labile cluster hypothesis, the labile clusters may not be bare cages but agglomerates that involve several guest molecules.*

The most recent mechanism proposed for clathrate nucleation is the local structuring hypothesis (LSH) of Radhakrishnan and Trout,[7] which states that the limiting step in the nucleation pathway is a concentration fluctuation that arranges a group of guest molecules in a configuration similar to that of the clathrate crystal. The water molecules, according to this hypothesis, follow the ordering of the guest molecules, building the cages that constitute the clathrate nucleus. The LSH was derived from umbrella sampling Monte Carlo simulations of aqueous solutions of CO_2, constraining the systems to sample the phase space along a series of predetermined order parameters that measure

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the difference in structure between water in the liquid and in a perfect clathrate crystal.

Rodger and co-workers[10−12] and, more recently, Walsh et al.[13] were able to produce spontaneous methane hydrate nucleation in unconstrained atomistic molecular dynamics (MD) simulations of water−methane systems under conditions of high driving force. They found that a large number of methane molecules surrounded a new water cage when it formed, in agreement with the LSH. The structure of the growing nucleus in the simulations, however, was not crystalline as the LSH proposed, but an amorphous agglomerate of 5^{12} and $5^{12}6^n$ cages, with $n = 2$, 3, and 4, that were not organized nor followed the proportions found in clathrate crystals. Crystallization through an intermediate amorphous phase is not unheard of and has been demonstrated for proteins, colloids, and $CaCO_3$.[14−17] Although there is no direct experimental evidence of an amorphous phase in the pathway of methane hydrate crystallization, spectroscopic data of cage occupancy in Xe, CO_2, and CH_4 clathrates indicate that, at the beginning of the growth process, the ratio of small and large cages does not correspond to the stoichiometry of the stable sI crystal (one 5^{12} cage every three $5^{12}6^2$ cages) or to the sII crystal (two 5^{12} to one $5^{12}6^4$), but it is close to 1.[18−22] These results suggest that either an amorphous phase or a mixture of well-defined sI and sII crystals forms at initial stages of growth. The actual process has not yet been elucidated. Methane, carbon dioxide and xenon clathrates belong to the same class of hydrates: those of hydrophobic guests small enough to occupy the 5^{12} cages and for which sI is the stable polymorph. For this class, the metastable sII crystal has a free energy very close to that of sI: the melting temperature of sII is within a few degrees of that of the sI stable crystal.[23] Here we use molecular simulations to investigate the mechanism of nucleation of this class of hydrates and − in particular − elucidate the structure of the clathrate nuclei and whether there are amorphous microscopic precursors or amorphous metastable phases in the crystallization pathway of clathrate hydrates from aqueous solutions.

Amorphous precursors in the pathway to crystallization have been reported for colloids and proteins.[14−16] Crystal nucleation of these systems occurs in two steps: first, a sufficiently sized cluster of solute (protein, colloid) forms from the solution, and then that concentrated cluster reorganizes into an ordered structure. The common feature to these two quite different systems is the presence of very short-ranged attractive potentials between the crystallizing particles. In very recent work, Matsumoto computed the multibody potentials of mean force (pmf's) between four methane molecules in water.[24] He reported that although two isolated methanes in water prefer to adopt contact pair (CP) over solvent-separated pair (SSP) configurations, when four methane molecules are within distances comparable to the first methane−methane shell in clathrates, the SS configuration becomes the most stable. The stability is attained through rings of water between pairs of methane that "glue" the cluster of methanes. This results in a water-mediated methane−methane effective interaction that is attractive and very short-ranged.[24] By analogy with the phase diagram of other systems with short-ranged attractive potentials, the water-mediated interactions could stabilize relatively large clusters of water-mediated methane molecules that could assist the nucleation of the clathrate. This is the mechanism of clathrate nucleation we report in the present study.

Models and Methods

Nucleation of a new phase is a rare event, and it is computationally expensive to produce in direct atomistic simulations. We address this challenge through the use of a coarse-grained model that is 2−3 orders of magnitude more efficient than atomistic models,[23] allowing for an efficient sampling of multiple independent nucleation trajectories encompassing several microseconds of simulations. Water is described with the mW model that represents each molecule as a single particle that interacts through anisotropic short-ranged potentials that encourage "hydrogen-bonded" configurations.[25] It is important to note that although the mW model does not have explicit hydrogen atoms, it is able to reproduce the structure of liquid water, low-density amorphous ice, clathrates, and ice and has been successfully used to elucidate the nucleation and growth of ice in bulk and confinement.[2,23,25−30]

The guest M is also represented as a single particle and has properties intermediate between those of CH_4 and CO_2. The water−guest and guest−guest interactions are those of the [$\sigma_{WM} = 4.05$ Å; $\varepsilon_{WM} = 0.24$ kcal/mol] guest model developed in ref 23. At 313 and 178 K, the solubility (in molar fraction) is 0.0023 for CH_4, 0.024 for CO_2, and 0.0038 for M.[23] The melting temperatures of the polymorphs at $p = 500$ atm are, for sI and sII, respectively, 307 ± 2 and 303 ± 1 K for M, 299.2 and 293.9 K for CH_4, and 287.1 and 277.3 K for CO_2. The T_m of the model was computed following the protocols of ref 23, and the T_m values for CO_2 and CH_4 were computed using the CSM-Gem program.[31]

MD simulations were carried out using LAMMPS.[32] The velocity Verlet algorithm was used to integrate the equations of motion using a time step of 10 fs.[23] Simulations were performed in the NpT ensemble using a Nosé−Hoover thermostat and barostat with damping constants of 5 and 25 ps, respectively. Periodic boundary conditions were used in all directions. Twelve independent crystallization trajectories were collected at $p = 500$ atm and $T = 210$ K $= 0.7\ T_m$ from an equilibrated two-phase (aqueous solution and M fluid) system containing 8000 molecules (6847 water molecules

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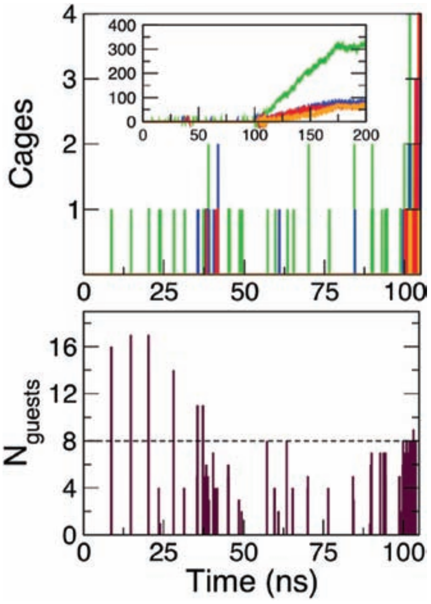

Figure 1. Upper panel: Number of cages versus time for subcritical nuclei during a typical nucleation trajectory. Green represents the 5^{12} cages, blue $5^{12}6^2$, red $5^{12}6^3$, and orange $5^{12}6^4$. The complete crystallization is shown in the inset. Lower panel: Number of guests within the first shell (8 Å) of the center of mass of the cage for frames with one cage present. The cages with more that nine surrounding guests formed at the guest−water interface.

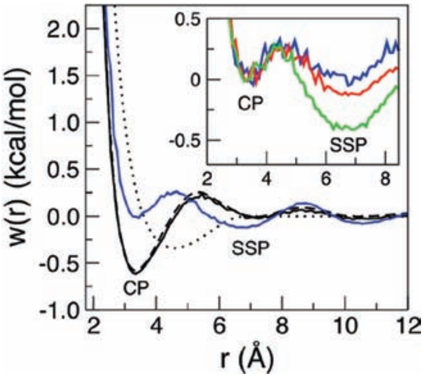

Figure 2. Potential of mean force $w(r)$ of the guest in water at 100 atm and 300 K (black dashed and solid lines) and at 500 atm and 210 K (blue line). Dashed lines indicate $w(r)$ determined from integrating constraint forces. Solid lines indicate $w(r)$ calculated from the guest−guest radial distribution function, $g(r)$, as $w(r) = -RT \ln g(r)$. The dotted line indicates the direct guest−guest interaction potential. CP indicates the contact pair configurations and SSP the solvent-separated ones. The inset shows $-RT \ln g(r)$ averaged over the induction period of the 12 crystallizing trajectories for blobs containing N guests (a cluster is defined as a group of “connected” guest molecules in the water phase, where connected means that pairs are within 8.5 Å of each other). The blue line indicates averages over clusters of $N = 2$ guests, red over clusters of 3−7 guests, and green over clusters with 8 or more guests. The curves in the inset were displaced such that the contact pair rests at 0 kcal/mol.

and 1153 guest molecules). The simulations were then run for 250 ns or until nucleation and complete crystallization occurred.

Results and Discussion

The crystallization was monitored through the time evolution of the polyhedral cages that make up the clathrate lattices.[2] The cage types were identified by the number of pentagonal and hexagonal rings. All the cages in the sI and sII polymorphs, and the faults they form while growing, have 12 pentagonal rings and $n = 0, 2, 3$, or 4 hexagonal rings. These cages are commonly denoted as $5^{12}6^n$. The upper panel of Figure 1 shows the number of cages for each type versus time for a representative crystallization trajectory. All trajectories display the same characteristics: an induction period of stochastic duration during, which isolated clathrate cages form and dissolve, followed by a rapid growth in the number of cages. The final product displays small (5^{12}) and large (the sum of all $5^{12}6^n$, with $n > 0$) water cages in a ratio 1.48 ± 0.14, a ratio closer to that in sII (2) than in sI (0.33). The resulting clathrate has elements of the sI and sII structures but no long-range crystalline order. Movie 1 in the Supporting Information displays the four cage types as clathrates cages nucleate and grow to encompass all the aqueous phase. The amorphous nature of the clathrate phase obtained could be ascribed to the large driving force for the formation of both sI and sII at $0.7T_m$. We note, however, that deeply supercooled pure water can crystallize as hexagonal (Ih) and cubic (Ic) ices that have a stability gap smaller than those of the sI and sII clathrate polymorphs, in spite of which simulations of water crystallization at $0.66T_m$ yield well-defined crystallites with cubic and hexagonal stacking layers.[27,28,30] A main difference between ice and clathrates resides in the almost isotropic interaction of the clathrate cages and their versatility to fill the space, even when not forming long-ranged structures. The formation of $5^{12}6^3$ cages (Figure 1, Movie 1), not native to sI or sII but known to form at the interface between the two polymorphs,[2,33] allows for a seamless space-filling amorphous growth of clathrate cages. The lack of well-defined crystalline order and the agreement in the ratio between small and large cages in our simulations and the experiments[18,22] suggest that, under conditions of high supercooling, the amorphous solid clathrate could be an intermediate in the crystallization pathway toward crystalline clathrate hydrates.

How do clathrates nucleate? Guest M is hydrophobic, like methane: at room temperature the pmf between two M molecules in water (Figure 2) displays a clear preference for CP over SSP. Note that the direct M−M interaction is repulsive for the CP and almost null for the SSP. This shows that water−guest and, mostly, water−water interactions dominate the structure of methane in water. The cooperative multibody effect in the hydrophobic association of methane reported in ref 24 is also observed for M in water. Figure 2 shows that the SSPs are favored at low temperature: at 210 K isolated pairs of M already show a small preference for SSP over CP. Most significant for the nucleation of clathrates, we find that *the more M molecules there are in a cluster, the more the solvent-separated configurations are stabilized (inset of Figure 2)*, resulting in persistent clusters of guests separated by water (Figure 3). The multiguest clusters of M and its cementing water molecules behave like droplets of viscous liquids, i.e. *blobs*. Persistent clusters of guest molecules have been observed in other MD studies of nucleation of methane hydrate.[10,13,34] The water that separates the hydrophobic guests favors configurations of clathrate half-cages,[2] “cups” made of pentagonal and hexagonal planar rings of water molecules. These water rings were also observed between the SS methane molecules of refs 10, 13, 24, and 34.

Figure 3 displays the clathrate half-cages, the complete clathrate cages, and the guest molecules for snapshots along a

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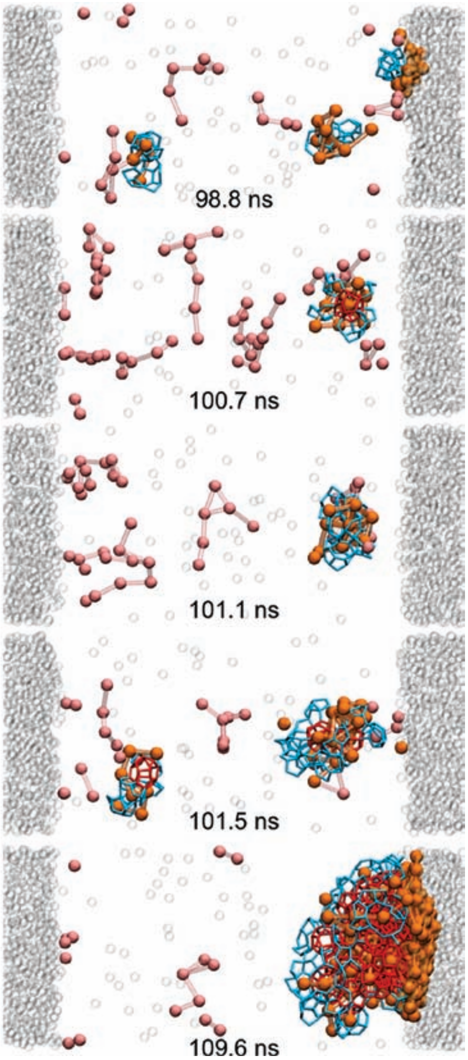

Figure 3. Time evolution of the blobs in the trajectory of Figure 1 as the system ends the nucleation period and starts forming the amorphous clathrate. Clathrate cages are colored red, and half-cages are colored cyan. Guest molecules within 5 Å of cages or half-cages are shown in orange, and guest clusters more than 5 Å away from cages or half-cages are pink. Otherwise, guest molecules are shown as translucent spheres. Images are labeled by the time elapsed from the beginning of the simulation. At 98.8 ns, multiple small clusters are present. At 100.7 ns, a transient polyhedral cage is present in the blob. At 101.1 ns, the blob remains but does not contain any polyhedral cages; it has only half-cages comprised of pentagonal and hexagonal rings. At 101.5 ns, the blob continues to grow, now with two cages. Also present is a subcritical blob to the left that dissolves. At 109.6 ns, the clathrate nucleus now has a core of polyhedral cages with half-cages on the periphery. The nucleus then continues to grow (not shown). This sequence is also shown in Movie 2 in the Supporting Information.

crystallization trajectory. The time evolution is better appreciated in Movie 2 in the Supporting Information. The figure and movie show the formation and dissolution of blobs. Small blobs persist for times shorter than larger blobs (compactness of the M clusters also matters: threads of solvent-separated M molecules are much shorter lived than a compact blob). The water and guest molecules of the blob exchange slowly with the solution, producing fluctuations in blob size and structure; nevertheless "large" compact blobs (with more than about 15 guest molecules) persist at $0.7T_m$ for times longer than the characteristic diffusion time of the components. The blobs themselves are not stationary but slowly diffuse in solution. In this respect, the *blobs are large analogues of the labile clusters* proposed by Sloan and co-workers.[4,5]

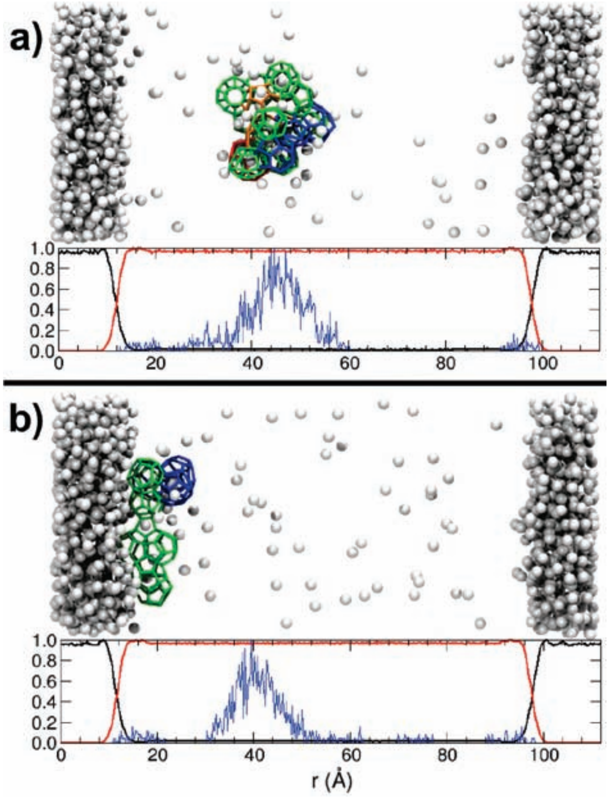

Figure 4. The locus of formation of clathrate cages is tied to the presence of blobs. Each panel shows the cages present in the nucleus immediately prior to crystallization and the density profile of the guest (black), water (red), and the polyhedral clathrate cages (blue) during the latent period that precedes it. The density profiles are scaled such that the maximum density is 1. We note that the density of cages in a region is not sufficient to predict the locus of nucleation of the clathrate. Panel (b) corresponds to a trajectory for which the higher density of cages occurred in a blob located in the bulk of the aqueous phase; nevertheless, the nucleus that successfully crystallized the system formed at the two-phase boundary.

Individual polyhedral clathrate cages, on the other hand, are very short-lived, and — most significant for the mechanism of clathrate nucleation — they originate within the blobs. We note that a single blob can give birth to several clathrate cages before extinguishing by dissolution or succeeding in forming a critical nucleus. The clathrate cages produced by a single blob are of different types ($5^{12}6^n$, with $n = 0$, 2, 3, and 4) and their location within the blob also changes. Multiple events of cage formation in the latent period before crystallization are shown in the trajectory of Figure 1. As these cages originate in a few persistent blobs, the spatial location of the cages is not random through the aqueous phase but on the spots where the blobs were. This is evident in Figure 4, which presents a normalized density profile for the guest molecules, all water molecules, and the water in clathrate cages along a direction perpendicular to the aqueous/guest-fluid interface, averaged over the latent period before crystallization. The cages formed in well-defined regions that correspond to the blobs. We conclude that *the blob is a guest-rich amorphous precursor in the nucleation pathway of clathrate hydrates of small hydrophobic guests.* The liquid blobs produce the clathrate cages which grow into an amorphous solid clathrate nucleus that would subsequently evolve — in a time scale exceeding those of the present simulations[18,22] — into a crystalline clathrate. Annealing of the amorphous clathrates at 240 K ($0.8T_m$) leads to development of nanocrystalline sI *and* sII domains within 20 ns. We expect crystallinity to develop also at 210 K, although at a lower rate. The formation at low temperatures of amorphous nuclei or an amorphous metastable phase that matures to a polycrystalline state is consistent with the evolving ratio of small to large cages in the experimental studies of clathrate formation under conditions of high driving force.[18,20,22]

The LSH proposes that the number of guests around a central guest molecule is the order parameter for the advance of the clathrate crystallization. This would suggest that blobs located at the interface are more successful in leading to the formation of critical nuclei. The lower panel of Figure 1 displays the time evolution of the number of guests within the first cloaking shell of the clathrate cages (all types considered) until the onset of clathrate formation. The figure evidences that the number of guests alone is not a sufficient indicator of the success of the nucleation: the large number of guest molecules that a cage acquires by being at the fluid M/aqueous interface does not ensure the formation of a critical nucleus. The reason is probably the dense CP structure of the guest at the interface while the guest molecules in the clathrate, as in the blobs, are in SS configurations (Figure 2).

Experiments demonstrate that clathrates form close to the interface.[1,35,36] The simulations allow for a distinction between *close to* and *at* the interface: the latter would originate in a blob that rests on the fluid phase (e.g., Movie 1). We observe blobs that succeed in nucleating at the interface although they originated in the bulk, and vice versa. Of the 12 trajectories of this study, about half nucleated *at* the water−guest interface; we do not find a marked preference for nucleation at the interface.

Conclusions and Outlook

In this work we presented an analysis of a set of molecular simulations of nucleation and growth of clathrates of a hydrophobic guest with clathrate-forming properties similar to methane and carbon dioxide. The mechanism of clathrate nucleation that emerges from this study involves a first reversible step of formation of *blobs*, long-lived aggregates of guests separated by water molecules, wherein the clathrate cages repeatedly nucleate and dissolve until a cluster of cages reaches a critical size (about five cages at $0.7T_m$ supercooling) that prompts the space-filling growth of face-sharing clathrate cages. The amorphous clathrate that results from this process is a metastable intermediate toward the formation of crystalline clathrate.

The multistep process of clathrate crystallization supported by this study is *solution* $\rightleftarrows$ *blob* → *amorphous clathrate* → *crystalline clathrate*, where we have made a distinction between *blobs*, in which the water is not yet locked into clathrate cages, and *amorphous clathrate*, for which the positions of the guest molecules are not so distinct from the blob but the water has organized in hydrogen-bonded polyhedral cages that cement the structure. At low temperatures, the system can be arrested in the metastable amorphous clathrate state for times sufficiently long to appear as an intermediate phase. Ripening of the amorphous phase produces nanocrystals of the stable sI and metastable sII clathrates seamlessly connected through $5^{12}6^3$ cages.

The most relevant cases of clathrate crystallization involve relatively low supercooling. Is the distinction between blob and amorphous clathrate still valid when clathrates form at higher temperatures? A preliminary answer is obtained by warming amorphous clathrates to 280 K and following their dissolution. The cages in the water structure are first lost at the periphery and then at the very center of the amorphous clathrate as it dissolves. We conclude that large clusters of water-mediated guest molecules always contain a core of clathrate cages. Thus large-enough blobs are "amorphous clathrate blobs" (large clusters of guests mediated by *ordered* water). These blobs with an amorphous clathrate core, we hypothesize, are the precursors of clathrate crystallization at low driving forces.

We note that the multistep mechanism for clathrate crystallization proposed here is nonclassical, in the sense that it does not follow the tenets of classical nucleation theory which postulates that the critical nuclei form from the reactants through addition of individual "monomers" (e.g., clathrate cages) to a structure that already has the symmetry of the final phase (the clathrate crystal). The crystallization mechanism unveiled in this study evolves sequentially along three main order parameters: first, densification of the dilute solution to produce the blobs; second, ordering of the water to form the clathrate cages; and third, ordering of the guest molecules in a structure consistent with crystalline clathrates. Growth of a macroscopic crystalline clathrate phase may occur directly from amorphous nuclei or from crystalline clusters obtained through maturation of the amorphous nuclei. Studies are needed to assess the relative stability of small amorphous and crystalline clathrate clusters.

The mechanism of crystallization of clathrates bears strong analogies with the one for proteins, colloids, and nanoparticles: a first step that includes the self-assembly of denser domains from a dilute phase, followed by ordering of these domains to grow the crystal.[37,38] In these systems, nucleation is assisted by the presence in the supercooled region of their phase diagrams of a metastable fluid−fluid equilibrium involving a dilute and a concentrated liquid.[15] Our work suggests that the amorphous clathrate is the "dense fluid" and the aqueous solution of guest the "dilute fluid". It has been recently shown that the dense fluid can be an intermediate in the crystallization of proteins, even under conditions under which this dense amorphous phase is *unstable*.[16] This supports our conjecture that blobs of amorphous clathrate assist in the crystallization under conditions of low driving force. Strategies to prevent nucleation of clathrates should destabilize the formation of the blobs or their growth.

The "blob mechanism" of clathrate crystallization synthesizes elements of both the labile cluster and local structuring hypotheses. The local ordering of the guests drives the nucleation of clathrates, as suggested by LSH. The ordering, however, is not necessarily the one of the clathrate crystals. The clusters of water-mediated guests survive for times long enough to diffuse in solution, as the LCH proposes. The labile clusters, however, are not bare clathrate cages but large aggregates that may contain multiple clathrate cages. Our

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simulations indicate that the lifetime of the blobs increases with their size (probably controlled by the degree of water-mediated M−M connectivity). Large blobs of amorphous clathrates could survive in solution, without enough driving force to grow but too slow to dissolve even close to the melting point. A recent neutron and laser reflectivity study of the water−methane interface under conditions of clathrate formation close to equilibrium evidence surface roughening during the induction period, before crystallization sets it. Koga et al. propose that this is due to the presence of embryos, precursors of the crystalline clathrate phase.[35] In light of the present study, we interpret these embryos to be blobs or clathrate nuclei residing at the interface. The persistence of the roughening detected by Koga et al. during the 180 min latent period before crystallization does not imply that each of these blobs survive such a long time, nor that they remain in the amorphous state. Lehmkühler et al. used X-ray diffraction and reflectivity to study the water−carbon dioxide interface under conditions of hydrate formation.[36] They detected the formation of freely moving clathrate crystallites of size about 20 nm that nevertheless did not lead to macroscopic crystallization during the long times of the experiment. How long do blobs survive as a function of their size? What is their role in the so-called memory effect?[1] How do they develop into crystalline structures? These important questions deserve further study.

The guest M of this study has properties (solubility, hydration number, relative stability of sI and sII, T_m of sI and sII, width of the water−guest interface[23]) that make it comparable to methane and carbon dioxide. In future communications we will address the role of the size of the guest molecule (how do clathrates form if the guests cannot occupy the small cages?) and hydrophilicity (do soluble guests also form long-lived water-mediated blobs?) in the nucleation pathway of clathrate hydrates.

Acknowledgment. We gratefully acknowledge support by the Beckman Foundation through a Young Investigator Award to V.M. and the National Science Foundation through award CHE-1012651. We thank the Center of High Performance Computing at the University of Utah for allocation of computing time.

Supporting Information Available: Two movies showing the microscopic crystallization of clathrates. This material is available free of charge via the Internet at http://pubs.acs.org.

JA1051445