

Equilibrium polymerization models of re-entrant self-assembly

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As is well known, liquid-liquid phase separation can occur either upon heating or cooling, corresponding to lower and upper critical solution phase boundaries, respectively. Likewise, self-assembly transitions from a monomeric state to an organized polymeric state can proceed either upon increasing or decreasing temperature, and the concentration dependent ordering temperature is correspondingly called the “floor” or “ceiling” temperature. Motivated by the fact that some phase separating systems exhibit closed loop phase boundaries with two critical points, the present paper analyzes self-assembly analogs of re-entrant phase separation, i.e., re-entrant self-assembly. In particular, re-entrant self-assembly transitions are demonstrated to arise in thermally activated equilibrium self-assembling systems, when thermal activation is more favorable than chain propagation, and in equilibrium self-assembly near an adsorbing boundary where strong competition exists between adsorption and self-assembly. Apparently, the competition between interactions or equilibria generally underlies re-entrant behavior in both liquid-liquid phase separation and self-assembly transitions. © 2009 American Institute of Physics.

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I. INTRODUCTION

Self-assembly is an ubiquitous phenomenon in which molecules or particles reversibly assemble at equilibrium into structures with well defined sizes and shapes. Although a dynamic equilibrium exists between the associated species and unassociated “monomers” in self-assembling systems, the free energy of these systems exhibits a *single* minimum, so that the fluids do not ultimately stratify into spatially separated coexisting phases as in phase separating mixtures. This essential difference in the thermodynamic nature of the transitions associated with self-assembly and phase separation implies that the self-assembly transition lines (the polymerization transition temperature as a function of the system’s composition) and the phase separation boundaries are quite distinct. While the latter are roughly parabolic in shape [see Fig. 1(a)], the former tend to vary monotonically with the concentration of the associating species [see Fig. 1(b)].

Both types of thermodynamic transition may involve ordering (phase separation or self-assembly) either upon heating or cooling [see Figs. 1(a) and 1(b)]. Upper and lower critical solution phase boundaries correspond to phase separation upon cooling and heating [see Fig. 1(a)], respectively, whereas the temperatures at which self-assembly proceeds upon cooling and heating (at a fixed concentration of the associated species) are termed, respectively, “ceiling” and “floor” temperatures^{1,2} [see Fig. 1(b)]. Both phase separation and self-assembly occur simultaneously in many systems.³ The general patterns of the transition lines, such as those in Figs. 1(a) and 1(b), can be described qualitatively by mean

field theories, such as Flory–Huggins (FH) theory. The theory must be augmented, however, by inclusion of a temperature independent contribution χ_s to the effective interaction parameter χ in order to describe the lower critical solution phase separation.⁴ (Generally, this “entropic portion” in χ arises from the disparity in the shape and size of the monomer structures between the two components of the mixture.⁴ Extensions of FH theory that incorporate details of molecular structure greatly complicate the calculations,^{4,5} and therefore χ_s is normally treated as a phenomenological parameter.)

Another common pattern of thermodynamic phase stability involves re-entrant phase separation in which the phase boundaries form a closed loop with *two* critical points [see Fig. 2(a)], so that disordering (i.e., phase mixing) can occur either upon heating or cooling. A similar re-entrant phenomenon has been observed for self-assembly, where disassem-

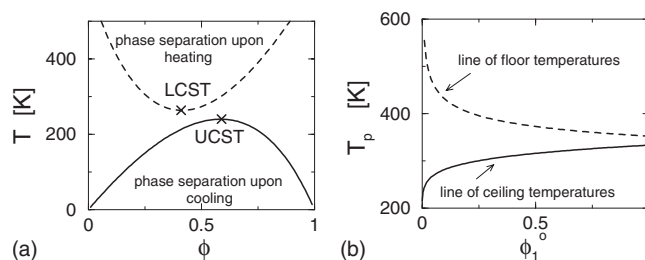


FIG. 1. (a) Typical phase separation boundaries (coexistence curves) for binary mixtures that phase separate upon cooling (bottom UCST curve) or upon heating (top LCST curve). T is the absolute temperature, and ϕ is the volume fraction of one component. Critical points are denoted by crosses. (b) Typical self-assembly transition lines $T_p(\phi_1)$ for self-assembly on cooling (bottom curve) and on heating (top curve). T_p is the polymerization temperature, and ϕ_1 is the initial volume fraction of the assembling species. The nonassembling solvent is a second component.

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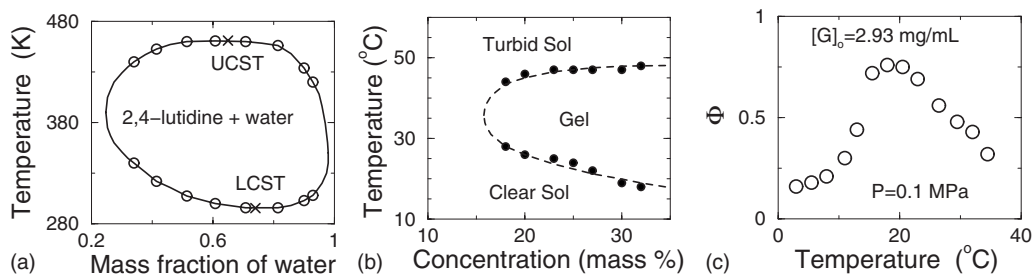


FIG. 2. (a) Representative closed loop phase boundary (coexistence curve) for a 2,4-lutidine-water binary mixture. The coexistence curve supports two critical points, which are indicated by crosses. Data taken from Wang *et al.* (Ref. 30). The original source of these data is Ref. 31. (b) Transition lines for thermally reversible gelation of aqueous solutions of diblock copolymers. Data taken from Bae *et al.* (Ref. 10). (c) The extent of assembly Φ as a function of temperature T for actin in a H_2O buffer at a fixed initial concentration of G-actin and of KCl (16 nM). Experimental data are taken from Matthews *et al.* (Ref. 8).

bly proceeds either upon increasing or decreasing temperature. For instance, a nonmonotonic ordering with temperature has clearly been demonstrated for the polymerization of actin^{6–8} and for thermally reversible gelation in aqueous solutions of block copolymers.^{9–14} A more complete mapping of the order-disorder transition lines associated with re-entrant self-assembly is available for block copolymers in solution, where self-assembly transition lines also appear to have a parabolic shape as in phase separation. However, this transition line is rotated by 90° relative to the usual orientation of boundaries for phase separation (see Fig. 1), displaying a strange *sideway orientation* [see Fig. 2(b)]. Moreover, the interior region is roughly parabolic, corresponding in the block copolymer system to thermally reversible gelation. The interior region can be displaced up or down in temperature by varying the molecular mass of the polymer blocks and their chemical composition.^{9–14} Tuning the location of the self-assembly transition line in this way has proven to be useful in developing thermally reversible gels for drug delivery^{13,14} and in other applications in which ordering (gelation) is desired within a particular temperature window.

No theoretical explanation has been given for the physical mechanism responsible for re-entrant self-assembly and for the unusually shaped transition lines mentioned above. On the other hand, we have encountered this phenomenon in previous modeling of equilibrium self-assembly of actin in aqueous solutions^{6,7} and of the competition between self-assembly and monomer adsorption.¹⁵ However, these previous studies did not analyze the concentration dependence of the self-assembly transition temperature, which is the focus of the present paper. These two models of self-assembly are reviewed in Sec. II, while our illustrative calculations of transition curves for re-entrant self-assembly are discussed in Sec. III. Our model systems exhibit re-entrant self-assembly transitions with many features in common with experimental observations of re-entrant self-assembly.

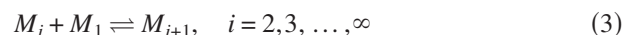
II. THEORETICAL BACKGROUND

A. Activated equilibrium self-assembly

Thermal activation is often an essential step in initiating a self-assembly process, and this activation can dramatically alter the free energy landscape for self-assembly, so that thermal activation regulates the cooperativity and thermodynamics of the self-assembly transition.¹⁶ More generally, self-

assembly often involves the formation of some protocluster, which “seeds” or “nucleates” the subsequent assembly process. (Basically, this process is an analog of nucleation in crystal growth.) Initiation of self-assembly through thermally reversible activation of a particular species (e.g., a conformational transition in a protein assembly or the rupture of a ring of sulfur atoms in sulfur polymerization) is the simplest type of “nucleated” self-assembly. Because the thermodynamics of thermally activated self-assembly is quite similar to that of nucleated self-assembly, the simpler activated self-assembly model is adopted for our illustrative calculations and discussion.

The basic activated equilibrium polymerization model is described by the minimal reaction scheme,³



in which the activated species M_1^* reacts only with non-activated monomers M_1 to form dimers, but does not participate in successive chain propagation stages. The corresponding equilibrium constants for these processes,

$$K_a = \exp[-(\Delta h_a - T\Delta s_a)/(k_B T)], \quad (4)$$

$$K_p^{(2)} = \exp[-(\Delta h_p^{(2)} - T\Delta s_p^{(2)})/(k_B T)], \quad (5)$$

$$K_p^{(i)} = \exp[-(\Delta h_p^{(i)} - T\Delta s_p^{(i)})/(k_B T)], \quad (6)$$

are defined in terms of the enthalpy Δh_a and entropy Δs_a of activation, the enthalpy $\Delta h_p^{(2)}$ and entropy $\Delta s_p^{(2)}$ of dimerization, and the enthalpy $\Delta h_p^{(i)}$ and entropy $\Delta s_p^{(i)}$ of chain propagation, respectively. The symbol k_B in Eqs. (4)–(6) denotes Boltzmann’s constant. In order to minimize the number of adjustable parameters, the free energy parameters for reactions (2) and (3) are taken as identical, i.e., $\Delta h_p^{(2)} = \Delta h_p^{(i)} \equiv \Delta h_p$ and $\Delta s_p^{(2)} = \Delta s_p^{(i)} \equiv \Delta s_p$, which, in turn, implies that these two processes are governed by the common equilibrium constant $K_p = \exp[-(\Delta h_p - T\Delta s_p)/(k_B T)]$ for self-assembly.

Because the FH-type theory for activated equilibrium polymerization systems has been extensively discussed in our previous papers,^{3,16–18} only a brief description of this approach is provided. Before self-assembly, the system com-

prises n_1^o molecules of the associating species M and n_s solvent molecules that are all assumed to occupy single lattice sites. At equilibrium, the system contains clusters of all possible sizes $\{i\}$, including activated and nonactivated, unpolymerized monomers with the volume fractions ϕ_1^* and ϕ_1 , respectively, as well as solvent molecules. Excluded volume constraints preclude any two species from occupying a common lattice site. Due to the assumption of the system's incompressibility that is intrinsic to classic FH theory, the composition of the system is uniquely determined by the volume fraction $\phi_1^o \equiv n_1^o/(n_1^o + n_s)$, so the combination of ϕ_1^o with the temperature T and the free energy parameters Δh_a , Δh_p , Δs_a , and Δs_p constitutes the set of relevant thermodynamic variables. Basic thermodynamic properties of activated equilibrium self-assembly in solution, such as the extent of polymerization Φ , the average cluster size L (also called the average degree of polymerization), the cluster size distribution $\phi_1^*, \{\phi_i\}$, specific heat C_V , the polymerization temperature T_p , etc., are functions only of these variables.³ The insensitivity of these basic properties to the strength of the effective cluster-solvent van der Waals interaction parameter χ is due to the simplifying assumption that unpolymerized and polymerized monomers have identical energetic parameters χ_{ij} .³

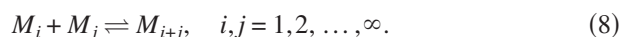
B. Competition between adsorption and self-assembly

Self-assembly often occurs in the presence of physical boundaries. Adsorption of the assembling species onto the surface can greatly affect the assembly process in solution and can lead to a new assembly process on the boundary.¹⁹ Our recent theory¹⁵ describes the essential aspects of this competition between self-assembly (equilibrium polymerization) and monomer adsorption, so only basic characteristics of the underlying Langmuir-type model are summarized here.

Before adsorption and self-assembly, the surface contains N_l^* lattice sites that are entirely covered by solvent molecules, while the N_l lattice sites in the bulk ($N_l \gg N_l^*$) are occupied by n_s^o solvent molecules and n_1^o monomers M_1 of the self-assembling species M . Under thermodynamically favorable circumstances, the monomers M_1 adsorb and desorb from the surface at equilibrium, as schematically represented by the equilibrium reaction,

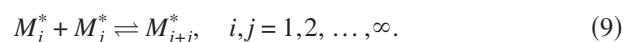


This reaction is formally equivalent¹⁵ to the thermal activation step in equilibrium self-assembly theory.³ The assumed incompressibility of the system implies that an adsorbed M_1^* species must displace solvent molecules from the surface into the bulk. The monomers M_1 may also assemble in solution, and the assembly process is assumed to proceed in the absence of additional constraint, i.e., as in the free association model,³



The adsorbed species M_1^* may also self-assemble on the surface where they are likewise assumed to organize by free

association,



The three processes in Eqs. (7)–(9) proceed in equilibrium with the corresponding equilibrium constants (K_{ad} , K_p , K_p^*),

$$K_{ad} = \exp[-(\Delta h_{ad} - T\Delta s_{ad})/(k_B T)], \quad (10)$$

$$K_p = \exp[-(\Delta h_p - T\Delta s_p)/(k_B T)], \quad (11)$$

and

$$K_p^* = \exp[-(\Delta h_p^* - T\Delta s_p^*)/(k_B T)], \quad (12)$$

where $(\Delta h_{ad}, \Delta s_{ad})$, $(\Delta h_p, \Delta s_p)$, and $(\Delta h_p^*, \Delta s_p^*)$ are the enthalpies and entropies of monomer adsorption and self-assembly in solution and on the surface, respectively.

Both solvent molecules and monomers of the self-associating species M are taken to occupy single lattice sites (in solution and on the surface), whereas a cluster M_i (or M_i^*) extends over i lattice sites. Excluded volume constraints imply that a given lattice site can be occupied only by a single monomer or solvent molecule. As before, unassociated monomers M_1 and those involved in clusters in solution are treated as energetically indistinguishable, and additionally the effective cluster-solvent van der Waals interaction parameters in solution (χ) and on the surface (χ^*) are set to zero ($\chi = \chi^* = 0$). The initial volume fraction $\phi_1^o \equiv n_1^o/(N_l + N_l^*) \approx n_1^o/N_l$ refers to the overall system, while equilibrium volume fractions are defined separately for the solution and the surface. Consequently, the basic solution thermodynamic quantities, such as extent of polymerization Φ , average cluster size L , the polymerization temperature T_Φ , etc., differ from those (Φ_s, L_s, T_{Φ_s}) on the surface.¹⁵ While the former depend (for the given assumptions) on the initial monomer concentration ϕ_1^o , temperature T , and the free energy parameter Δh_p and Δs_p , the latter are functions of ϕ_1^o , T , and the enthalpies and entropies of both monomer adsorption and self-assembly on the surface (Δh_{ad} , Δs_{ad} , Δh_p^* , and Δs_p^*).

III. RESULTS

Illustrative calculations are performed for a model of activated equilibrium self-assembly and for a model in which equilibrium self-assembly competes with adsorption of the monomers on the surface and with their subsequent self-assembly. Both activation and self-assembly in solution are assumed to proceed either upon cooling (i.e., $\Delta h_a < 0$, $\Delta s_a < 0$, $\Delta h_p < 0$, $\Delta s_p < 0$) or heating (i.e., $\Delta h_a > 0$, $\Delta s_a > 0$, $\Delta h_p > 0$, $\Delta s_p > 0$) for the first model. In the second model, monomer adsorption occurs upon cooling (i.e., $\Delta h_{ad} < 0$, $\Delta s_{ad} < 0$; the normal physical situation), while self-assembly in solution and on the surface are both taken as occurring upon heating (i.e., $\Delta h_p > 0$, $\Delta s_p > 0$, $\Delta h_p^* > 0$, $\Delta s_p^* > 0$). Our previous studies^{6,7,15} indicate the existence of re-entrant self-assembly, but no systematic analysis of this phenomenon was considered at the time (e.g., even the transition curve has not been determined). For simplicity, the self-assembled polymeric clusters are treated in these illustrative calculations as stiff structures, but qualitatively similar trends are obtained for the self-assembly of flexible polymers. The

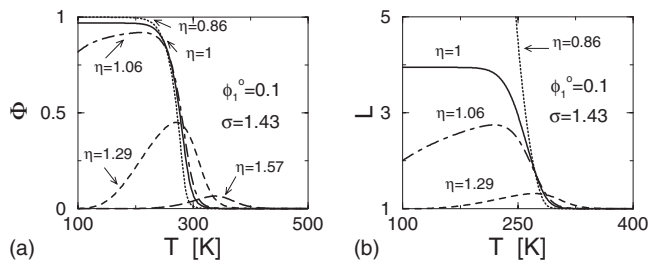


FIG. 3. The extent of assembly Φ [Fig. 3(a)] and the average degree of polymerization L [Fig. 3(b)] as a function of temperature T for the model activated equilibrium assembly system in which activation and self-assembly are both promoted by *cooling*. All curves correspond to fixed initial monomer concentration $\phi_1^o = 0.1$, constant enthalpy of assembly $\Delta h_p = -35$ kJ/mol, fixed entropies of activation and assembly ($\Delta s_a = -150$ J/mol K, $\Delta s_p = -105$ J/mol K, i.e., $\sigma \equiv \Delta s_a / \Delta s_p \approx 1.43$), but a different enthalpy of activation Δh_a , i.e., different ratios $\eta \equiv \Delta h_a / \Delta h_p$.

lattice coordination number z is chosen as $z=6$ and $z=4$, respectively, for self-assembly in solution and on a surface, as appropriate for simple cubic and simple square lattices.

A. Activated equilibrium self-assembly

The activated self-assembly model is specified by four free energy parameters, the enthalpies and entropies of activation (Δh_a and Δs_a) and self-assembly (Δh_p and Δs_p). As discussed previously,³ disparities between the enthalpies Δh_a and Δh_p may produce serious thermodynamic consequences. More specifically, the extent of self-assembly $\Phi(T, \phi_1^o = \text{const})$ and the average cluster size $L(T, \phi_1^o = \text{const})$ become nonmonotonic functions of temperatures when $|\Delta h_a| > |\Delta h_p|$. (Other situations, not discussed here, correspond to the situations where the derivative $(\partial\Phi/\partial T)|_{\phi_1^o}$ vanishes because Δh_a and Δh_p have different signs.)

1. Activation and assembly upon cooling

Following our previous papers,^{3,16,18} the energetic parameters of the self-assembly model, $\Delta h_p = -35$ kJ/mol and $\Delta s_p = -105$ J/mol K, are taken to be representative of a system self-assembling upon cooling [such as poly(α -methylstyrene) in solution¹]. Figures 3(a) and 3(b) illustrate the temperature variation of Φ and L , respectively, for a fixed initial monomer concentration $\phi_1^o = 0.1$ and for a fixed ratio σ of the entropies of activation and assembly ($\sigma \equiv \Delta s_a / \Delta s_p \approx 1.43$). The curves in these figures refer to different ratios η of the enthalpies of activation and polymerization ($\eta \equiv \Delta h_a / \Delta h_p$). Inspection of Figs. 3(a) and 3(b) reveals that both $\Phi(T, \phi_1^o = \text{const})$ and $L(T, \phi_1^o = \text{const})$ exhibit maxima when $\eta > 1$, and these properties approach a plateau at low T when $\eta = 1$. The magnitude of this maximum diminishes with increasing η , while the height of the plateau increases with σ . (The progressive increase in σ , however, cannot elevate Φ above the limiting value of 1.) If the enthalpy ratio η is less than 1, i.e., if the enthalpy of assembly Δh_p is more favorable than the enthalpy of activation Δh_a , the extent of self-assembly $\Phi(T, \phi_1^o = \text{const})$ saturates to unity at low temperatures, while the average cluster size $L(T, \phi_1^o = \text{const})$ diverges as $T \rightarrow 0$. Figures 4(a) and 4(b) [compare to Figs. 3(a) and 3(b)] illustrate how the magnitudes of the peaks in $\Phi(T, \phi_1^o = \text{const})$ and $L(T, \phi_1^o = \text{const})$ vary with σ

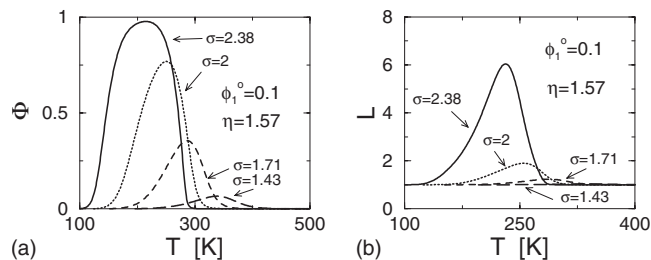


FIG. 4. The order parameter Φ for self-assembly [Fig. 4(a)] and the average cluster size L [Fig. 4(b)] as a function of temperature T for the model activated equilibrium assembly system for which activation and assembly both proceed upon *cooling*. All curves correspond to specified initial concentration $\phi_1^o = 0.1$, entropy of assembly $\Delta s_p = -105$ J/mol K, enthalpies of activation and assembly ($\Delta h_a = -55$ kJ/mol, $\Delta h_p = -35$ kJ/mol, i.e., $\eta \equiv \Delta h_a / \Delta h_p \approx 1.57$), but variable entropy of activation Δs_a , i.e., different ratios $\sigma \equiv \Delta s_a / \Delta s_p$.

when η exceeds unity. Larger σ , i.e., a more negative entropy of activation Δs_a , leads for fixed $\eta > 1$ and Δs_p to more advanced cluster growth (i.e., to higher Φ and L). The maxima of $\Phi(T, \phi_1^o = \text{const})$ and $L(T, \phi_1^o = \text{const})$ then correspondingly shift to lower temperatures. The presence of a maximum in $\Phi(T, \phi_1^o = \text{const})$ [see Figs. 3(a) and 4(a)] combines with the observation that each branch of the parabolic curve $\Phi(T, \phi_1^o = \text{const})$ exhibits an inflection point, to indicate the presence of *two* polymerization temperatures $T_\Phi \equiv \partial^2\Phi/\partial T^2|_{\phi_1^o}$ for a given initial monomer concentration ϕ_1^o . The self-assembly transition is thus *re-entrant* with variation of temperature.

Figure 3 does not provide insight, however, into the dependence of the maximum in $\Phi(T, \phi_1^o = \text{const})$ on the initial monomer concentration ϕ_1^o . This issue is crucial for the determination of the self-assembly transition lines and is addressed in Figs. 5 and 6 for the model system considered in Figs. 3 and 4 and specified by $\eta \approx 1.57$ and $\sigma = 2$. The various curves in Figs. 5 and 6 correspond to a range of ϕ_1^o . Both the extent of assembly $\Phi(T, \phi_1^o = \text{const})$ and the average cluster size $L(T, \phi_1^o = \text{const})$ exhibit a maximum as a function of temperature T , regardless of the magnitude of ϕ_1^o . A single maximum also appears in the specific heat $C_V(T, \phi_1^o = \text{const})$ for an arbitrary concentration $0 < \phi_1^o < 1$ [see Fig. 6(a)], while two maxima in $C_V(T, \phi_1^o = \text{const})$ are found only for concentrations $\phi_1^o > (\phi_1^o)^*$, where the critical value $(\phi_1^o)^*$ depends on η , σ , Δh_p , and Δs_p . The absence of two maxima in C_V over a certain range of ϕ_1^o indicates the absence of a correspondence between the temperature T_{C_V} at which the

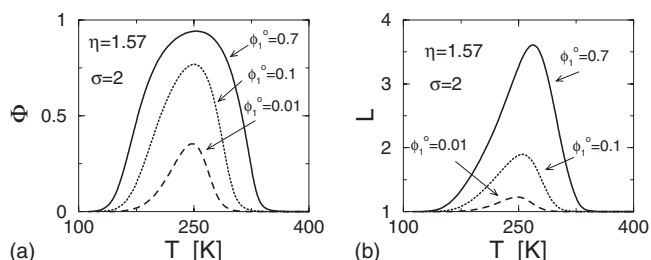


FIG. 5. The temperature variation of the extent of self-assembly Φ [Fig. 5(a)] and the average cluster size L [Fig. 5(b)] for one of the model systems considered in Figs. 4(a) and 4(b) ($\eta \approx 1.57$, and $\sigma = 2$). Curves are labeled by the initial monomer concentration ϕ_1^o .

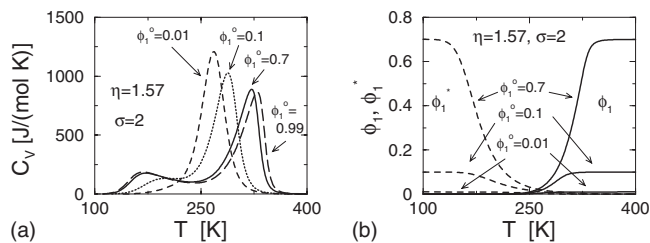


FIG. 6. The specific heat C_V [Fig. 6(a)] and the concentration of activated (ϕ_1^*) and non-activated (ϕ_1) monomers [Fig. 6(b)] as functions of temperature for one of the model systems considered in Figs. 4(a) and 4(b) ($\eta \approx 1.57$, and $\sigma=2$). Curves are labeled by the initial monomer concentration ϕ_1^o .

specific heat C_V is maximum and the temperature T_Φ at which the extent of assembly Φ exhibits an inflection point. Moreover, the temperatures T_Φ and T_{C_V} are clearly distinct, in contrast to cases of activated self-assembly where re-entrant behavior is absent so that $T_\Phi = T_{C_V}$.³

The origin of the maximum in $\Phi(T, \phi_1^o = \text{const})$ can be understood from a consideration of the temperature variation of the equilibrium concentrations $\phi_1(T, \phi_1^o = \text{const})$ and $\phi_1^*(T, \phi_1^o = \text{const})$ of nonactivated and activated monomers, respectively [see Fig. 6(b)]. At low temperatures, ϕ_1^* approaches ϕ_1^o , while ϕ_1 saturates to zero, and the opposite occurs at high temperatures. This behavior arises because the free energy parameters [$\eta \equiv \Delta h_a / \Delta h_p \approx 1.57$, $\sigma \equiv \Delta s_a / \Delta s_p = 2$, $\Delta h_p = -35$ kJ/mol, $\Delta s_p = -105$ J/mol K] favor activation over chain propagation at lower temperatures, so that practically all monomers become activated. However, no self-assembly appears due to the lack of nonactivated species. At high temperatures, almost all of the monomers remain nonactivated, and the lack of activated entities prohibits cluster growth. At intermediate temperatures, the overall monomer concentration $\phi_1(T, \phi_1^o = \text{const}) + \phi_1^*(T, \phi_1^o = \text{const})$ displays a minimum which, in turn, is directly responsible for the appearance of a maximum in the extent of self-assembly $\Phi(T, \phi_1^o = \text{const})$. Specifically, the maximum arises from the definition of the order parameter Φ ,³

$$\Phi = 1 - \frac{\phi_1 + \phi_1^*}{\phi_1^o}. \quad (13)$$

Figure 7 summarizes the self-assembly temperature T_Φ as a function of the initial monomer concentration ϕ_1^o . The tran-

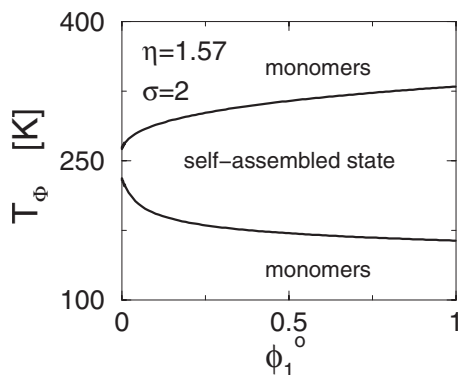


FIG. 7. The self-assembly transition temperature T_Φ as a function of ϕ_1^o for the model system from Figs. 5 and 6 ($\eta \approx 1.57$, and $\sigma=2$).

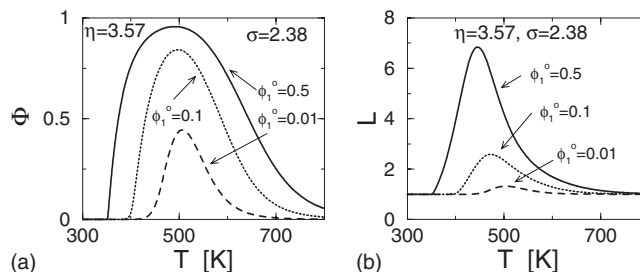


FIG. 8. The order parameters Φ for assembly [Fig. 8(a)] and the average cluster size L [Fig. 8(b)] as a function of temperature T for the model activated equilibrium self-associating system for which both activation and assembly are both promoted by heating ($\Delta h_a = 125$ kJ/mol, $\Delta h_p = 35$ kJ/mol, $\eta \equiv \Delta h_a / \Delta h_p \approx 3.57$, $\Delta s_a = 250$ J/mol K, $\Delta s_p = 105$ J/mol K, $\sigma \equiv \Delta s_a / \Delta s_p \approx 2.38$). Curves are labeled by the initial monomer concentrations ϕ_1^o .

sition lines $T_\Phi(\phi_1^o)$ in Fig. 7 have distinct upper and lower branches, delineating the roughly parabolic thermodynamic regime in which self-assembly is developed.

2. Activation and self-assembly upon heating

The absolute magnitudes of the enthalpy and entropy of assembly are assumed, for simplicity, to be identical to those chosen when activation and polymerization proceed upon cooling, i.e., $\Delta h_p = 35$ kJ/mol and $\Delta s_p = 105$ J/mol K, while the free energy parameters for the activation process are selected as $\Delta h_a = 125$ kJ/mol and $\Delta s_a = 250$ J/mol K. This choice ensures that the extent of self-assembly $\Phi(T, \phi_1^o = \text{const})$ is appreciable over the whole composition range and that the temperatures, corresponding to the inflection points of $\Phi(T, \phi_1^o = \text{const})$, lie in a physically accessible temperature regime [see Fig. 8(a)].

Figures 8(a), 8(b), 9(a), and 9(b), respectively, present the extent of assembly Φ , the average cluster size L , the specific heat C_V , and the equilibrium monomer volume fractions ϕ_1 and ϕ_1^* as a function of temperature T for a few fixed initial monomer concentrations ϕ_1^o . Figures 8 and 9 thus serve as counterparts to Figs. 5(a), 5(b), 6(a), and 6(b) which refer to systems in which activation and assembly both occur upon cooling. Comparison of Figs. 5 and 6 with Figs. 8 and 9 demonstrates that switching the signs of the enthalpies and entropies of the activation and association processes leaves the qualitative behavior of Φ , L , and C_V unaltered. The comparison reinforces our previous finding concerning the inequality and lack of correspondence between of the temperatures at which the derivatives

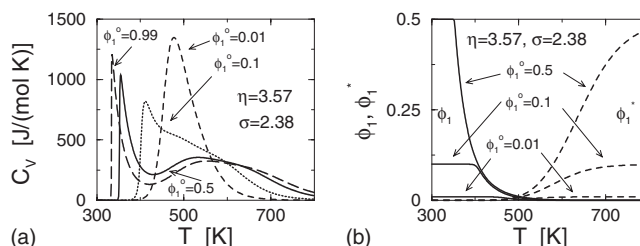


FIG. 9. The specific heat C_V [Fig. 9(a)] and the concentration of activated (ϕ_1^*) and non-activated (ϕ_1) monomers [Fig. 9(b)] as a function of temperature T for the model system analyzed in Figs. 8(a) and 8(b). Initial monomer concentrations ϕ_1^o are specified for each curve.

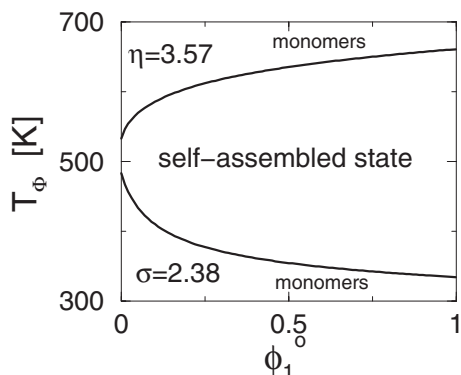


FIG. 10. The self-assembly transition temperature T_Φ as a function of ϕ_1^o for the model system described in Figs. 8 and 9.

$(\partial C_V / \partial T)|_{\phi_1^o}$ and $(\partial^2 \Phi / \partial T^2)|_{\phi_1^o}$ vanish. In fact, the only relevant change is exhibited by the equilibrium monomer volume fractions $\phi_1(T, \phi_1^o = \text{const})$ and $\phi_1^*(T, \phi_1^o = \text{const})$ that, respectively, decrease and increase with temperature, thereby exchanging their roles with ϕ_1^* and ϕ_1 from Fig. 6(b). Consistent with this relationship, the re-entrant self-assembly transition line $T_\Phi = T_\Phi(\phi_1^o)$ in Fig. 10 has a similar shape to that in Fig. 7.

B. Self-assembly competing with adsorption

Illustrative calculations have been performed by assuming that the absolute enthalpies and entropies of monomer adsorption and of assembly in solution and on the surface are equal to our “standard” free energies, i.e., $-\Delta h_{\text{ad}} = \Delta h_p = \Delta h_p^* = 35$ kJ/mol and $-\Delta s_{\text{ad}} = \Delta s_p = \Delta s_p^* = 105$ J/mol K. The extent of polymerization on the surface Φ_s plays the role of the order parameter for surface self-assembly and has the same physical meaning as the extent of polymerization in solution Φ . However, Φ_s is a parabolic function¹⁵ of temperature at fixed initial monomer concentration ϕ_1^o . Similar to $\Phi(T, \phi_1^o = \text{const})$ in Figs. 3(a), 5(a), and 8(a), the order parameter curve $\Phi_s(T, \phi_1^o = \text{const})$ displays *two* inflection points (see Fig. 11) and, thus, two characteristic temperatures T_{Φ_s} that are determined from the mathematical condition

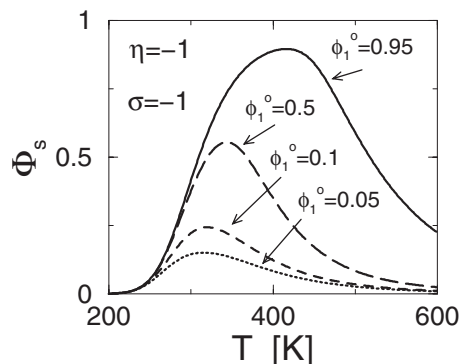


FIG. 11. The extent of self-assembly on the surface (Φ_s) as a function of temperature T for the model self-assembling system in which monomer adsorption is promoted by *cooling* ($\Delta h_{\text{ad}} = -35$ kJ/mol, $\Delta s_{\text{ad}} = -105$ J/mol K) and self-assembly (on the surface and in solution) is enhanced by *heating* [$\Delta h_p^* = \Delta h_p = -\Delta h_{\text{ad}} = 35$ kJ/mol, $\Delta s_p^* = \Delta s_p = -\Delta s_{\text{ad}} = 105$ J/mol K, $\eta \equiv \Delta h_{\text{ad}} / \Delta h_p = -1$, $\sigma \equiv \Delta s_{\text{ad}} / \Delta s_p = -1$]. Initial monomer concentration ϕ_1^o is designated for each curve.

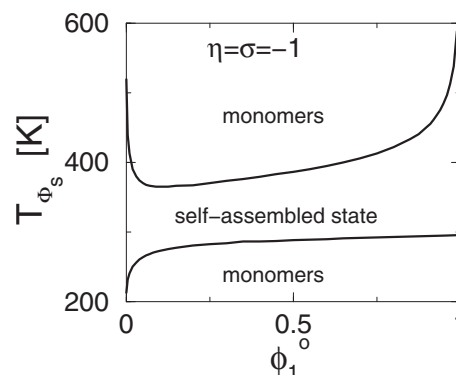


FIG. 12. The self-assembly temperature T_{Φ_s} as a function of ϕ_1^o for the model system analyzed in Fig. 11.

$(\partial^2 \Phi_s / \partial T^2)|_{\phi_1^o} = 0$. The surface self-assembly transition lines $T_{\Phi_s} = T_{\Phi_s}(\phi_1^o)$ are displayed in Fig. 12. The self-assembly line of the upper transition in Fig. 12 is, however, a nonmonotonic function of the solution composition ϕ_1^o and thereby resembles a phase boundary rather than a standard self-assembly line. Despite appearances, the free energy has a unique, distinct minimum at each composition of the associating species, so that no coexisting phases exist.

IV. DISCUSSION

Ordering processes exhibiting re-entrant behavior characteristically reflect some form of “frustration” associated with competitive interactions or equilibria. For example, closed loop phase boundaries naturally appear in fluid mixtures in which van der Waals interactions favor phase separation upon cooling, while directional associative interactions promote self-assembly upon heating, or vice versa.²⁰ In the present paper, we consider two models of equilibrium self-assembly that exhibit re-entrancy, namely, a model where there is competition between growth of activated (or “nucleated”) monomers and growth of self-assembled structures as well as a model of a system with competition between surface adsorption and self-assembly in solution. This re-entrant phenomenon is expected to be widely present in self-assembling systems and is examined here based on a simple equilibrium polymerization theory^{15,3} that ignores the details of the molecular structure of the monomers and solvent.^{4,5}

The existence of thermal activation in reversible self-assembly is insufficient by itself to produce re-entrant self-assembly. As demonstrated by the illustrative calculations in Figs. 3–10, this re-entrant phenomenon arises only if the enthalpy Δh_a of monomer activation is more favorable than the enthalpy of self-assembly Δh_p , i.e.,

$$|\Delta h_a| > |\Delta h_p|,$$

for physical situations where both activation and chain propagation processes proceed either upon cooling or heating. In the opposite case (i.e., if $|\Delta h_p|$ is greater than $|\Delta h_a|$), the average cluster size L for the activated equilibrium self-association model varies monotonically with temperature, and L then diverges as T approaches zero or infinity, depending on whether the system exhibits a ceiling or floor tem-

perature, respectively. For the special case where the enthalpies of activation and self-assembly are equal, the average cluster size L saturates to a constant plateau value at low or high T . We do not discuss combinations of negative Δh_a and Δs_a and positive Δh_p and Δs_p or vice versa since self-assembly is absent in these cases. However, these cases are important since varying solution conditions, such as pH, may alter the energetic parameters and switch the system from assembling to nonassembling.

The transition temperature T_p can be defined as the temperature T_Φ at which the extent of self-assembly $\Phi(T, \phi_1^o = \text{const})$ yields an inflection point, but the polymerization temperature is often also identified^{1,2} with the temperature T_{C_V} at which the constant pressure specific heat $C_p(T, \phi_1^o = \text{const})$ achieves a maximum. (A change of slope in the temperature dependence of the solution density is sometimes used to identify the polymerization temperature,²¹ as in the determination of the glass transition temperature in supercooled liquids.) The analysis of the temperature variation of $C_V(T, \phi_1^o = \text{const})$ in Figs. 6(a) and 9(a) indicates that the self-assembly transition curves $T_{C_V}(\phi_1^o)$ also display re-entrant behavior. The re-entrant character of the $T_{C_V}(\Phi^o)$ curves does not necessarily extend over the whole composition range and may be limited to a certain span of compositions that depends on the free energy parameters Δh_a , Δs_a , Δh_p , and Δs_p used in calculations. Mapping out the transition lines is evidently a more complicated problem for re-entrant self-assembling systems.

Re-entrant self-assembly transitions in aqueous solutions probably represent a rather common phenomenon due to the frequent occurrence of cooperative nucleation processes that initiate self-assembly. Systematic experimental studies of these entropically driven (i.e., occurring upon heating) processes are, however, limited. Re-entrant self-assembly has been clearly observed in equilibrium polymerization of actin under *in vitro* conditions [see Fig. 2(c)] and in the thermally reversible gelation of aqueous solutions of block copolymers [see Fig. 2(b)]. Most experimental estimates of the actin polymerization curve are restricted to the low temperature branch¹ because it was thought that actin would degrade at elevated temperatures.²² Latter studies established the existence of re-entrancy in actin^{6,7,23} by showing that the upper branch (the “depolymerization temperature”) could also be determined⁸ [see Fig. 2(c)]. Re-entrant self-assembly has also been observed²⁴ in a mixture of α -cyclodextrin in water in the presence of 4-methylpyridine, although the form of the assembled structures is largely uncharacterized. We expect that this system might provide a convenient synthetic analog of actin and other biological macromolecules that display re-entrant self-assembly.

The re-entrant thermoreversible gelation transition in block copolymer systems is perhaps the most qualitatively studied example of re-entrant self-assembly due to its applications to the controlled release of drugs.^{9–14} In particular, the assembling species in these systems first assemble into spherical micelles that themselves associate to form the thermally reversible gel or branched polymer²⁵ self-assembly. Moreover, the “transition line” is determined from the simple condition that the solution ceases to flow on a reasonable

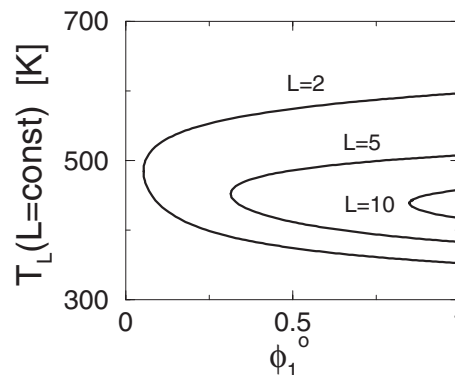


FIG. 13. The temperature $T_L(\phi_1^o)$ for which the average cluster size $L(T, \phi_1^o)$ is constant as a function of ϕ_1^o for the activated assembly systems described in Figs. 8–10. Curves are labeled by the value of L .

timescale upon inverting the container with the solution. In the context of equilibrium self-assembly, this condition implies the presence of large clusters, i.e., long chain polymers, and its thermodynamic implications are addressed in Fig. 13 which presents the temperature $T_L(\phi_1^o)$ corresponding to a fixed cluster size $L(T, \phi_1^o)$ as a function of the initial monomer concentration ϕ_1^o for the activated self-assembly model that exhibits both activation and propagation upon heating. The “gelation curves” in Fig. 13 are shifted from the temperature axis and thus better resemble those determined experimentally for diblock copolymer systems [see Fig. 2(b)]. Gelation in aqueous solutions of block copolymers is also observed as re-entrant when varying pH (Ref. 26) and pressure,^{27,28} which suggests that the variation of other thermodynamic parameters can also drive these phenomena.

In addition to re-entrant self-assembly processes in bulk solutions and polymer melts, re-entrant self-assembly may arise from competition from surface segregation and self-assembly. Thus, we consider the situation where adsorption of the associating species competes with linear chain assembly in solution and entropy driven assembly on the substrate (i.e., which occurs upon heating as often found in many aqueous systems¹⁵). Evidence for this re-entrant phenomenon is described in Ref. 15, which focuses on the nature of adsorption-induced assembly rather than on the analysis of re-entrancy. The general pattern of self-assembly in Fig. 12 shares common features of activated equilibrium self-assembly, where thermal activation plays a role analogous to that of the adsorption-desorption equilibrium. On the other hand, the upper polymerization curve in Fig. 12 departs from the simple parabolic shape found for activated self-assembly, indicating that re-entrant adsorption-induced assembly appears to have unique characteristics.

Adsorption-induced self-assembly is particularly important in biology and is implicated in the pathological assembly of protein fibers associated with numerous diseases (see Ref. 15). Moreover, we have suggested that this process also serves a constructive role in regulating biological self-assembly processes essential for cell functions.¹⁵ The folding of proteins often follows a re-entrant pattern as a function of temperature,²⁹ pressure, and other thermodynamic variables. This ubiquitous phenomenon is of obvious importance in the preservation of protein drugs by cooling.

Our theoretical analysis describes the thermodynamics for this new class of self-assembling systems and is expected to stimulate further efforts toward improved characterization of these systems. Because of the slow responses of some systems, phase separation is often assigned despite the lack of observation of macroscopic phase separation. The many parallels between phase boundaries and self-assembly transition curves suggest that some of these cases involve self-assembly rather than phase separation, and the present theory should aid in distinguishing between them. Since competing interactions as in our model calculations are no doubt widespread in real self-assembling systems, we expect that our framework will be useful in characterizing a wide range of self-assembly systems utilized in material fabrication and in understanding a wide variety of biological processes.

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