CHAPTER 3

Nucleation and Co-Operativity in Supramolecular Polymers

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Contents

1. INTRODUCTION

Supramolecular polymers are polymeric objects that spontaneously arise in solutions or melts from one or more types of molecular building block that can range from the chemically simple to the very complex (Ciferri, 2005). Depending on the shape of these molecules, such self-assembled polymers can have different geometries but invariably are the result of a process usually called *micro phase separation* (Cohen Stuart, 2008; Safran, 1994) although strictly speaking *nano phase separation* would be a more appropriate term. Micro (or nano) phase separation is the spontaneous ordering of molecules on a local (molecular) scale but not on a global (macroscopic) scale; however, the assemblies so formed may themselves self-assemble hierarchically into structures on much larger scales (Cates and Fielding, 2006; Ciferri, 2005). For example, self-assembled helical tapes of specifically designed β-sheet-forming oligopeptides form bundles of various sort, including ribbons, fibrils, and fibers, which at sufficiently high concentrations collectively align and self-assemble into a macroscopic nematic phase (Aggeli, 2001). (see Figure 1).

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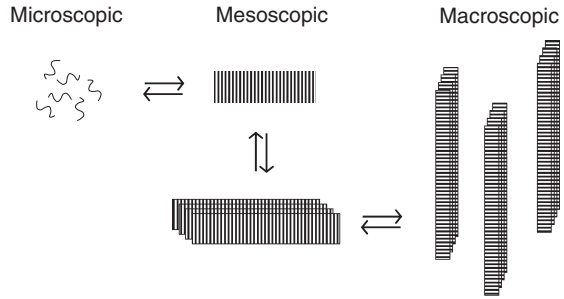

Figure 1 Schematic representation of an example of hierarchical self-assembly at microscopic, mesoscopic, and macroscopic levels. At the microscopic level, molecules assemble into supramolecular polymer-like assemblies. This involves conformational changes to the monomer units that themselves are complex molecules. The polymers assemble into bundles at mesoscopic levels that under appropriate conditions spontaneously align macroscopically along some preferred direction to form a uniaxial nematic liquid–crystalline phase (after Aggeli et al., 2001).

Historically, micro phase separation is understood to give rise to micelles in aqueous surfactant solutions but also to highly regular structures in block copolymer melts (Cohen Stuart, 2008; Gelbart et al., 1994; Safran, 1994). Micro phase separation results from a compromise between antagonistic physical (i.e. noncovalent) interactions between different moieties on the molecular building blocks that as a rule combine parts of different polarity. In surfactant molecules, for instance, highly polar or charged groups are covalently linked to apolar aliphatic moieties. Dissolved in water, the aliphatic groups drive the molecules together in order to shield themselves from contact with the solvent, in this case water, whilst still allowing for the polar or charged parts of the molecules to be solvated by the solvent. The term nano phase separation is quite appropriate as only the solvent-phobic parts of the molecules are guarded from it and the solvent-phylic parts still interact with the solvent.

The molecules that form supramolecular polymers tend to be much more complex than surfactants or block copolymers and are usually designed for the purpose of forming a structure with a predestined geometry, and to perform a certain function (Binder, 2005; Brunsveld et al., 2001; ten Cate and Sijbesma, 2002; Dankers and Meijer, 2007; van Gorp et al., 2002; Vriezema et al., 2005). The ultimate supramolecular polymer formers are, of course, proteins, molecules of which the structure and function are intimately connected. In biology, supramolecular polymerization is a strategy followed when large-scale structures are to be constructed at minimal cost of genetic encoding (Caspar, 1980; Chiu et al., 1997; Kushner, 1969; Lauffer, 1975; Oosawa and Asakura, 1975). A case in point are viruses that package their

genome in highly regular (and typically icosahedral or helical) structures, constructed from very many copies of one or a few kinds of the so-called 'coat proteins'. Because infectious viruses can be assembled in vitro by simply mixing the constituents under appropriate physicochemical conditions, virus assembly is considered a thermodynamic process and viruses a kind of supramolecular polymer (Bruinsma et al., 2003; Kegel and van der Schoot, 2004; McPherson, 2005).

Despite large differences in the primary structure, that is, the amino acid sequence, the tertiary or three-dimensional structure of the viral coat proteins of very many viruses, is similar and (usually but not exclusively) characterized by the so-called jelly-roll structure (Chiu et al., 1997). Despite their apparent similarity in structure, these proteins still produce assemblies that can be very different in size and/or shape depending also on the solution conditions. One of the great challenges is to understand the relation between molecular and supramolecular structure, not just in structural and molecular biology but also in the context of supramolecular chemistry. In fact, the field of supramolecular polymers has proven highly successful in constructing complex structures with predestined functionalities utilizing relatively simple molecular building blocks (Bouteiller, 2007; Hagerink et al., 2001; Kato et al., 2006; Lehn, 1990; Moore, 1999; Percec, 1996; Weiss and Terech, 2006; Whitesides and Boncheva, 2002). Not surprisingly, supramolecular chemists are often inspired by examples taken from biology (Binder, 2005; Ciferri, 2002; Moore, 1999).

There are in fact good reasons for the biomimetic design of supramolecular polymers, quite irrespective of the desired topology and/or functionality. Nature has found ways to control the relatively blunt and insensitive instrument provided by the *law of mass action*, a principle that regulates the balance between the assembled and disassembled states of molecules (Ciferri, 2005; Gelbart et al., 1994; Safran, 1994). The mass action of pertinent variable is $X = \phi K$, a measure of the probability that a molecule will attach to an assembly. Here, ϕ denotes a dimensionless concentration (e.g. a mole fraction) and K a dimensionless equilibrium constant. The constant K is temperature dependent and can be associated with the Boltzmann weight of a *free energy of binding*, g, of a single monomer through $K = \exp[-\beta g]$, where $\beta = 1/k_B T$ and $k_B T$ denotes the thermal energy with k_B is Boltzmann's constant and T the absolute temperature.

The mass action variable X is the product of the a priori probability ϕ of a molecule being near the growing assembly and the enhancement K of this probability by the gain of free energy by actually attaching to it (Ciferri, 2005). Unless the supramolecular assembly is highly co-operative, the fraction of bound molecules and their mean aggregation number is a fairly weak function of this variable because it is regulated by a simple Boltzmann distribution between the assembled and free species (Cates and

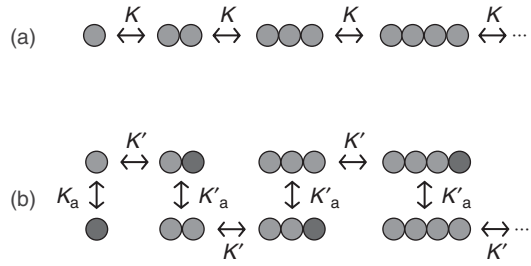

Figure 2 Chemical reaction models for (a) isodesmic and (b) nucleated supramolecular assembly. $K \gg 1$ and $K' \gg 1$ are equilibrium constants for the elongation reactions, and $K_a \ll 1$ and K'_a those for the conversion between assembly active and inactive forms of the monomer units. If $K'_a \gg K_a$, then the nucleated assembly is self-catalyzed ("autosteric") and if $K'_a = K_a$ this is not so.

Candau, 1990; Safran, 1994). For the ideal case of supramolecular assemblies in which each monomer gains a fixed free energy of binding irrespective of the size of the aggregate, schematically depicted in Figure 2a, the polymerized fraction of material, f, obeys the simple relation (Ciferri, 2005)

$$f = 1 - \overline{N}^{-2} \tag{1}$$

where $\overline{N}$ denotes the mean aggregation number. The latter is a simple function of the mass action variable,

$$\overline{N} = \frac{1}{2} + \frac{1}{2}\sqrt{1 + 4X} \tag{2}$$

and enters the *mass* or *molecular weight distribution* that within the model can be shown to be exponential (Cates and Candau, 1990; Ciferri, 2005). The *weight distribution* over the molecular weights, however, is peaked around $\overline{N}$.

This model, termed the *isodesmic assembly*, *multistage open association*, or *ladder model* (Brunsveld et al., 2001; Ciferri, 2002, 2005), is often applied to quasi one-dimensional, *linear* assemblies and found to be quite accurate all the way from the dilute to the very concentrated solutions and even in the melt state, irrespective of whether the chains are rigid or flexible (Ciferri, 2005). Interactions within the chains or between chains modify the predictions only very mildly and can be ignored for most practical applications (Cates and Candau, 1990), except in liquid–crystalline phases where a strong coupling between alignment and growth has been predicted theoretically (Cates and Fielding, 2006; Lü and Kindt, 2006; van der Schoot, 1996; Taylor and Herzfeld, 1993). Also, rings do not form in appreciable

quantities if the chains are sufficiently rigid on the scale of the size of the monomer units (Cates and Candau, 1990; Ciferri, 2005; Porte, 1983).

The mass action variable X can be rendered into an experimentally more meaningful form. To do this, let X_* be a reference value for given values of the concentration ϕ_* and temperature T_*. Then, by a linear Taylor expansion of the dimensionless free energy βg around the reference temperature T_*, we have

$$X/X_* \sim (\phi/\phi_*)\exp[h_*(T/T_* - 1)/k_B T_*] \tag{3}$$

with h_* the binding *enthalpy* at the temperature $T = T_*$. For instance, we may choose to set $X_* = (2(1 - f_*)^{-1/2} - 1)/4$ by the fraction polymerized material under the arbitrary reference conditions, f_*, often taken to be half-way point for which $f_* = 1/2$. This is done in Figures 3 and 4, representing the fraction polymerized material and the mean aggregation number as a function of X/X_*, showing their relatively weak sensitivity to the value of this parameter.

According to Equation (3), the mass action variable X/X_* depends strongly, that is, exponentially, on the temperature. Depending on whether the assembly is endo or exothermic, that is, whether $h_* \gtrless 0$,

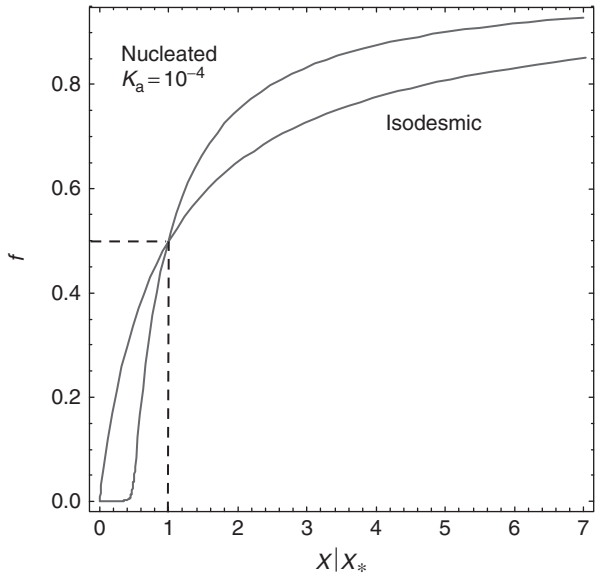

Figure 3 Fraction of material in the polymerized state, f, as a function of the mass action variable X relative to its value X_* at the half-way point $f = 1/2$. Indicated are predictions for the isodesmic and the self-catalyzed nucleated polymerization models. Activation constant of the nucleated polymerization $K_a = 10^{-4}$.

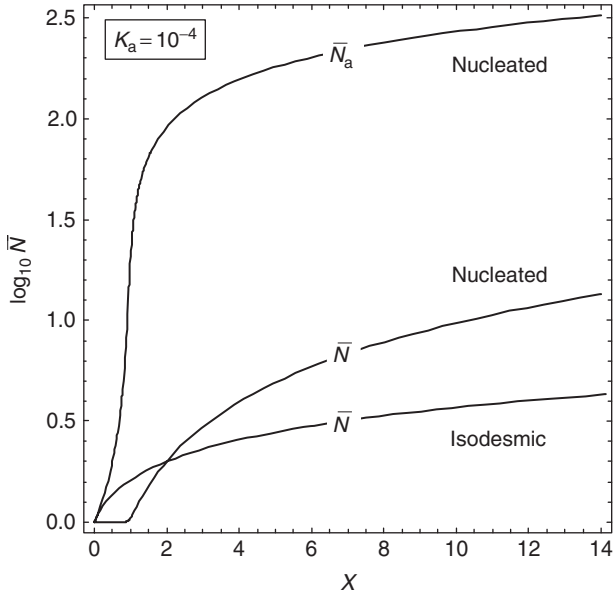

Figure 4 Mean degree of polymerization as a function of the mass action variable X for the isodesmic and the self-catalyzed nucleated polymerization models. $\overline{N}$ is the value averaged over all the monomers in the solution, $\overline{N}_a$ that averaged over the active material only. Activation constant of the nucleated polymerization: $K_a = 10^{-4}$.

the aggregates grow or shrink with increasing temperature. However, unless $|h_*/k_B T_*|$ is very large, the crossover from monomer- to the polymer-dominated temperatures occurs over many tens of degrees on the Kelvin scale. Typical values for $|h_*/k_B T_*|$ range from 25 to $75\, k_B T_*$, in themselves not large enough to produce a sharp crossover to the polymerized state (Würthner et al., 2004).

For the polymerization of the protein *g-actin* into *f-actin* fibers, to name but one example, the transition occurs at a sharp, well-defined temperature and does not seem to follow isodesmic polymerization (Greer, 2002; Hofrichter et al., 1974; Lomakin et al., 1996; Niranjan et al., 2003; Oosawa and Asakura, 1975; Šiber and Podgornik, 2007). In fact, isodesmic assembly cannot explain the huge aggregation numbers nor the highly co-operative and nucleated assembly often seen in supra-molecular polymers from biological origin, including actin, tubulin, and flagellin (Oosawa and Asakura, 1975) but also in biomimetic ones, such as those shown in Figure 6.

Indeed, to get very large aggregation numbers in the tens or hundreds of thousands requires very high free energies g of binding not much below 1 eV, being equivalent to approximately $40\, k_B T$. This, of course, is quite

difficult to justify if the interactions between the monomers in an assembly are of physical origin, and typical values seem to be in the range 10–20 k_BT (Cates and Candau, 1990; Ciferri, 2005). Higher values are possible, for example, if multiple hydrogen bonds are involved in the binding of each monomer, such as is the case in β-sheet fibril forming oligopeptides (real or synthetic) (Aggeli et al., 2001). We come back to the issue of how to interpret or even predict the quantity g below, a quantity that is of *microscopic* origin, that is, it depends on the chemical structure of the molecules involved as well as that of the solvent, and the way the solvent and the supramolecular polymer formers interact.

In the remainder of this brief overview, several mechanisms are discussed that (i) significantly enhance aggregation numbers and (ii) provide sensitive control over assembled and disassembled states of the supramolecular polymers. As we shall see, co-operativity is required but not sufficient for this purpose. Models at different levels of coarse-grained description shall be presented and a case is made for studying supramolecular assembly both as a function of concentration of molecular building blocks as of the ambient temperature. The latter methodology seems the more practical in distinguishing isodesmic from nucleated assembly. The relation between reversible polymerization in biological and supramolecular chemistry contexts shall be stressed and also their relation with phase transitions in condensed matter physics (Wheeler and Pfeuty, 1981).

2. NUCLEATED ASSEMBLY

Almost 30 years ago, Caspar suggested that switching between conformational states of molecules exerts self-control in the structure and action of protein assemblies in vivo (Caspar, 1980). In practice, this means that a protein molecule can exist in two (or more) conformational states, one of them *assembly inactive* and the other(s) *assembly active*. These conformers are in thermodynamic equilibrium, meaning that they can in principle interconvert. However, if the balance between them is very much in favor of the inactive state, a free energy has to be invested in order to form the assemblies. This free energy is gained by the interactions between the molecules that drive the assembly, part of which is lost to convert these molecules to their active state. If the free-energy cost of producing an active monomer is very high, then their self-assembly into supramolecular aggregates becomes highly co-operative and nucleated, that is, the transition between assembled and disassembled states is sharp and resembles a thermodynamic phase transition (Jahn and Radford, 2008; Scott, 1965; Tobolsky and Eisenberg, 1960; Wheeler and Pfeuty, 1981; Zhao and Moore, 2003).

We can distinguish between two extremes of nucleated assembly, one where the addition of each monomer to the growing assembly is associated with a free-energy cost, $g_a > 0$, of the conversion from the inactive to the active state, and one where only the conversion of the first one costs free energy but the subsequent ones do not (or not as much as the first one) (see also Figure 2b.). The latter kind of binding can be called self-catalyzed or *autosteric* because the conversion of the first molecule catalyzes the conversion of the next one bound to it and so on (Caspar, 1980). [Recent calculations show that allosteric and therefore also autosteric enhancement of binding may result from the coupling of internal fluctuations of the molecules involved in the binding (Hawkins and McLeish, 2006).] It is not so easy to distinguish between the two scenarios of nucleated assembly in practical situations. Both types have been discussed in various kinds of context, most notably the polymerization of a wide variety of proteins (Douglas et al., 2008; Edelstein-Keshet and Ermentrout, 1998; Erickson and Pantaloni, 1981; Goldstein and Stryer, 1986; Greer, 2002; Martin, 1996; Oosawa and Asakura, 1975), so we only outline the predictions of the simplest of coarse-grained models put forward.

Let us start with the nucleated assembly that is *not* self-catalyzed. It turns out useful to distinguish between the mean aggregation number of all the material in the solution, $\overline{N}$, from that in which only the activated species is considered and that we denote by $\overline{N}_a$. If we define the equilibrium constant $K = \exp[-\beta g]$ with g as the binding free energy, and introduce the nucleation constant $K_a = \exp[-\beta g_a]$, then under conditions of thermodynamic equilibrium, mass action gives (Aggeli, 2001; Ciferri, 2005; Nyrkova et al., 2000; Tobolsky and Eisenberg, 1960)

$$f = K_a \overline{N}_a^2 / (1 + K_a \overline{N}_a^2) \tag{4}$$

for the fraction active material in terms of the mean aggregation number, $\overline{N}_a$, of active (polymerized) material that obeys the relation

$$XK_a = 1 - \overline{N}_a^{-1} + K_a(\overline{N}_a - 1)\overline{N}_a \tag{5}$$

We furthermore have the identity

$$\overline{N}^{-1} = 1 - f + f\overline{N}_a^{-1} \tag{6}$$

The smaller the value of the activation constant, K_a, the sharper the transition from the monomer- to the polymer-dominated regime (Douglas et al., 2008; van Jaarsveld and van der Schoot, 2007; Scott, 1965; Tobolsky and

Eisenberg, 1960; Wheeler and Pfeuty, 1981). The distribution of the sizes of the assemblies is bimodal over the inactive and active states of the material, where the latter is an exponential function of the aggregation number. The weight distribution is also bimodal and has peaks centered at the aggregation numbers of unity and $\overline{N}_a$ (Zhao and Moore, 2003).

If we take the formal limit $K_a \to 0$, which in practice implies the less restrictive conditions that $K_a \ll 1$ and that the polymerization is highly co-operative, we find that $f \sim 1 - (K_a X)^{-1}$ and $\overline{N}_a \sim \sqrt{(K_a X - 1)/K_a}$ for $K_a X > 1$, and $f \sim 0$ with $\overline{N}_a \sim 1$ for $K_a X < 1$. We can define a critical polymerization concentration $\phi_p = \phi_p(T) \equiv 1/K_a K$ at fixed temperature T such that $f \sim 1 - \phi_p/\phi$ and $\overline{N}_a \sim \sqrt{(\phi - \phi_p)K}$ for $\phi > \phi_p$. This has to be compared with the predictions for the isodesmic model that gives $\overline{N} \sim \sqrt{\phi K}$ for $X = \phi K \gg 1$. So, for both kinds of equilibrium polymerization, we find the functional dependence of the length of the polymers on the equilibrium constant K and on the concentration ϕ obey the same asymptotic relation deeply in the polymerized regime, that is, at very high concentrations $\phi \gg \phi_p$.

If $K_a \ll 1$, we are able to define a sharp polymerization temperature $T_p = T_p(\phi)$ that is a function of the concentration ϕ, such that

$$f \sim 1 - \exp[-h_p/k_B T_p (T/T_p - 1)] \tag{7}$$

for $T > T_p$ if the enthalpy $h_p > 0$ or $T < T_p$ if $h_p < 0$, and $f \sim 0$ otherwise. Note that (i) the enthalpy here is defined as the sum of the activation and elongation steps and (ii) T_p is not to be confused with the temperature at the half-way point T_*. A more accurate estimate for the degree of polymerization valid near the polymerization temperature $T = T_p$ is presented at the end of this section. Because the transition can be very sharp indeed, sufficiently many data points have to be taken to be able to tell the difference between isodesmic and nucleated assembly. This is obviously more practical in the temperature than in the concentration domain because the former type of measurement can be automated.

If the nucleated assembly is self-catalyzed, then this modifies only the role of the equilibrium constant K in the non-self-catalyzed model and has to be replaced by the ratio K/K_a. This means that we again obtain for the fraction polymerized material $f = K_a \overline{N}_a^2/(1 + K_a \overline{N}_a^2)$ but that the degree of polymerization averaged over the active material only now obeys (Ciferri, 2005)

$$X = 1 - \overline{N}_a^{-1} + K_a(\overline{N}_a - 1)\overline{N}_a \tag{8}$$

So, if we again take the limit $K_a \to 0$ to make the polymerization highly co-operative, we find that $f \sim 1 - X^{-1}$ and $\overline{N}_a \sim \sqrt{(X-1)/K_a}$ for $X > 1$, and $f \sim 0$ with $\overline{N}_a \sim 1$ for $X < 1$. In this case, the activation step enhances the growth of the assemblies by a factor $1/\sqrt{K_a}$ for large $X \gg 1$ and reduces

the critical concentration by a factor K_a to $\phi_p \equiv 1/K$. We have plotted the fraction active material and the degree of polymerization in Figures 3 and 4 as a function of the value of X relative to the half-way point X_*, showing the strongly enhanced growth of nucleated supramolecular polymerization when compared to that of the isodesmic mode of aggregation.

Now, for both kinds of catalyzed and non-catalyzed nucleated assembly we can write $f \sim 1 - \phi_p/\phi$ and $\overline{N}_a \sim \sqrt{(\phi/\phi_p - 1)/K_a}$ if $\phi > \phi_p$, and $f \sim 0$ and $\overline{N}_a \sim 1$ if $\phi < \phi_p$ in the limit $K_a \to 0$, implying that it is indeed impossible to distinguish between the self-catalyzed and non-self-catalyzed models. Both models predict an actual phase transition in the limit $K_a \to 0$, with a heat capacity that jumps at $\phi = \phi_p$ or, equivalently, at the polymerization temperature $T = T_p$. The jump is typical for mean field theories (Chaikin and Lubensky, 1995). In reality, K_a is not vanishingly small and the polymerization transition not infinitely sharp albeit that it should still be accompanied by a significant peak in the heat capacity (Douglas et al., 2008; Greer, 2002; van Jaarsveld and van der Schoot, 2007).

For small $K_a \ll 1$, the fraction polymerized material can in the vicinity of the polymerization temperature be described by the approximate expression (Jonkheijm et al., 2006)

$$f \sim K_a^{1/3} \exp\left[\frac{2}{3} K_a^{-1/3} h_p (T/T_p - 1)/k_B T_p\right] \tag{9}$$

where $|T/T_p - 1| \ll 1$, allowing for the determination of K_a provided h_p and T_p are fixed by fitting the asymptotic relation $f \sim 1 - \exp[-h_p(T/T_p - 1)/k_B T_p]$ valid more deeply in the polymerized regime (see Figure 5). The same

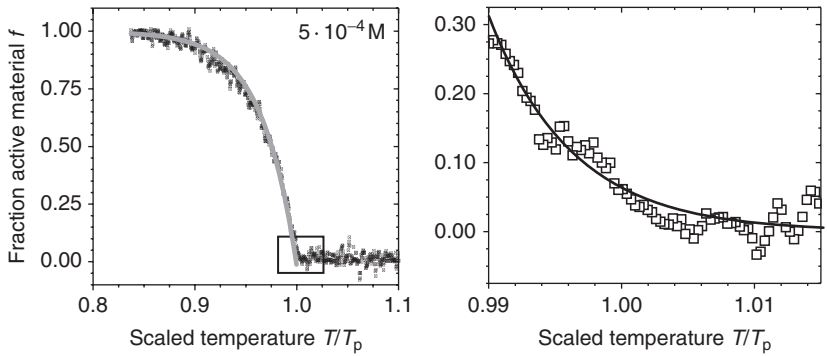

Figure 5 Left: determination of the polymerization temperature T_p by fitting the approximate relation Equation (7) indicated with the drawn line to the experimental data points for $T < T_p$ obtained for an oligo(phenylene vinylene) similar to compound 2 of Figure 6 in dodecane (Jonkheijm et al., 2006). Around T_p, the more accurate expression Equation (9) can be used to obtain the value of $K_a \approx 10^{-4}$ at $T = T_p$.

quantities can be determined isothermally by varying the concentration although this is more cumbersome as already noted above. In that case, one could invoke the expression

$$f \sim K_a^{1/3} \exp\left[\frac{2}{3} K_a^{-1/3}(\phi/\phi_p - 1)\right] \tag{10}$$

for $|\phi/\phi_p - 1| \ll 1$ and fix ϕ_p by fitting the expression $f \sim 1 - \phi_p/\phi$ that applies more deeply in the polymerized regime.

The self-catalyzed model is a simplification of the actin polymerization model of Oosawa and Kasai (1962) [and more recent elaborations of it (Niranjan et al., 2003)], and both equilibrium constants K and K_a, and hence the free energies g and g_a can in principle be obtained by fitting the theory to assembly experiments. Typical values of g for, for example, actin vary between -10 and $-20\,k_BT$ and g_a between $+2$ and $+3\,k_BT$ (Oosawa and Asakura, 1975; Oosawa and Kasai, 1962). For the biomimetic compound oligo(phenylene vinylene) similar to compound 2 shown in Figure 6, dissolved in alkane solvents, similar values were found for g but much larger ones for g_a of $+8$ to $+10\,k_BT$, making the supramolecular polymerization of this compound an extremely highly co-operative process (Jonkheijm et al., 2006).

In fact, studies on oligo(phenylene vinylene)s have exposed an unexpected role of *solvent* in nucleated assembly. Usually, the solvent is thought to be in some sense passive and hence in effect ignored in theoretical studies by absorbing the influence of the solvent in the free energies of binding. However, by (i) using the fact that exactly at the polymerization point, $X = 1$, the average degree of polymerization of the activated species obeys $\overline{N}_a \sim K_a^{-1/3}$ for $K_a \ll 1$, and (ii) comparing values of $\overline{N}_a$ obtained by fitting the activation constant $K_a \approx 10^{-4}$ to assembly experiments for a homologous series of alkanes, Jonkheijm and collaborators found an odd–even effect in the aggregate size at the transition point with increasing length of the solvent molecules (Jonkheijm et al., 2006).

Odd–even effects are usually only encountered in the large scale, that is, *macroscopic* ordering of molecules, for example, in liquid crystals (Chandrasekhar, 1992). This suggests that solvent molecules must not only actively participate in the co-operative formation of the helical assemblies but somehow physically be part of the ordered assembly. The connection between solvent size and the stability of assemblies was also pointed out by Bouteiller and collaborators (2007).

3. KINETICS OF NUCLEATED ASSEMBLY

A tell-tale sign of nucleated assembly is the existence of a critical concentration below which assemblies do not form in measurable quantities. Another is the observation of hysteresis in assembly and disassembly experiments

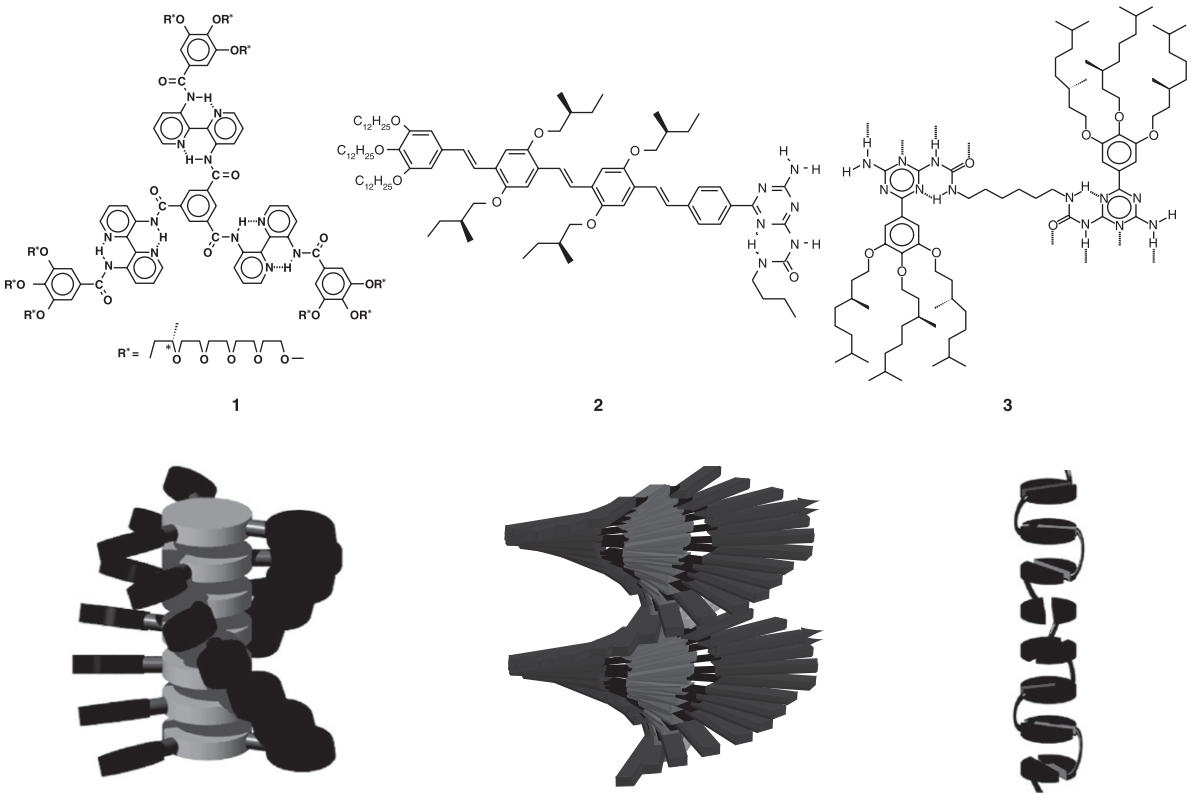

Figure 6 Examples of compounds that in selective solvents produce biomimetic supramolecular polymers that depending on the conditions exhibit a co-operature intramolecular ordering transition from random to highly ordered helical stacks or a nucleated polymerization transition from oligomeric prenuclei to very long, helical polymeric objects (ten Cate and Sijbesma, 2002; Dankers and Meijer, 2007; van Gorp et al., 2002; Brunsveld, 2001; Jonkheijm, 2005; Hirschberg, 2001).

and of *sigmoidal kinetics*, that is, the existence of what can be viewed as a lag time before assembly actually sets in. Kinetic experiments are interesting in their own right because they provide insight in reaction pathways and therefore in the free energy landscape of the system at hand (Auer et al., 2007). Unfortunately, quite often kinetic studies are performed without a clear view of, or reference to, the underlying "phase diagram" of monomer- and polymer-dominated regimes, making the interpretation of experimental observations not so straightforward.

There is a large body of theoretical literature on the kinetics of reversible linear supramolecular polymerization, in particular on the isodesmic assembly of linear surfactant micelles (Cates and Fielding, 2006; O'Shaughnessy and Vauylonis, 2003; O'Shaughnessy and Yu, 1995; Padding and Boek, 2004). These works focus on different kinetic mechanisms known as *reversible scission/recombination*, *end interchange*, and *end association/evaporation* (Dubbeldam and van der Schoot, 2005; Marques et al., 1993; Marquesa et al., 1994). Nucleated linear assembly has attracted quite a bit of attention too, albeit mostly in the context of the polymerization of proteins (Attri et al., 1991; Edelstein-Keshet and Ermentrout, 1998; Goldstein and Stryer, 1986; Hiragi et al., 1990; Lomakin et al., 1996; Oosawa, 1970; Oosawa and Asakura, 1975; Oosawa and Kasai, 1962; Powers and Powers, 2006; Sept and McCammon, 2001). Almost all theoretical studies available in this field focus on *end association/evaporation* kinetics, where single monomers attach and detach from the chains, but *reversible scission/recombination* kinetics, involving chain breakage and fusion, has also very recently been investigated (Nyrkova and Semenov, 2007).

The starting point of the kinetic models are seemingly simple reaction rate equations that deal with addition and/or shedding of material from polymers, but it so happens that these equations are (i) nonlinear and (ii) there are in principle infinitely many of them. (There is no obvious upper limit to their size other than that set by the system size.) This makes the analysis non-trivial, notwithstanding that in some cases useful analytical results can be obtained, exact or approximate (Dubbeldam and van der Schoot, 2005; Nyrkova and Semenov, 2007; Oosawa and Kasai, 1962; O'Shaughnessy and Yu, 1995; Powers and Powers, 2006; van der Linden and Venema, 2007; Wentzel, 2006). Here, we do not wish to indulge in the often times highly technical kinetic analysis but instead focus on the prevalent physics at hand. As mentioned already, nucleated assembly resembles a thermodynamic phase transition. It makes sense, then, to make use of this fact and apply the phenomenological theory of phase transitions to describe the assembly and disassembly kinetics in this kind of system (Chaikin and Lubensky, 1955; Hohenberg and Halperin, 1977; van der Schoot and Zandi, 2007).

In the phenomenological theory of phase transitions, it is customary to attribute order parameters to the relevant thermodynamic quantities associated with the macroscopic transition of the state of the material. In our case,

we are dealing with monomers that self-assembly to form polymer-like objects. There is inactive material and active material, separated by a conversion reaction. It seems sensible, therefore, to define two order parameters, not one, and both are nonconserved. This means that they do not obey any balance equation or sum rule, such as the law of conservation of mass.

Let the order parameter S_1 be associated with the fraction active material, and be defined as $S_1^2 \equiv f$. For the second order parameter we choose $S_2 \equiv \overline{N}_a(\overline{N}_a - 1)K_a/X$ as a measure of the degree of polymerization of the active material and presume that the polymerization is highly co-operative, so $K_a \to 0$. The *macroscopic* Landau free-energy density F that describes the nucleated assembly now reads

$$\beta F = -(1 - X^{-1})S_1^2 + S_1^4 + \frac{1}{2} S_2^2 - S_1^2 S_2 \tag{11}$$

It is easy to verify that in equilibrium, that is, under condition where $\partial f / \partial S_1 = \partial f / \partial S_2 = 0$, $f = 0$ for $X \leq 1$ and $f = 1 - X^{-1}$ for $X \geq 1$. Furthermore, in that case $S_2 = S_1^2$, so under conditions of equilibrium $f = \overline{N}_a(\overline{N}_a - 1)K_a/X$ as expected from the theory of Section 2.

The obvious ("model A") set of relaxational kinetic equations are (Hohenberg and Halperin, 1977)

$$\frac{\partial S_1}{\partial t} = -\Gamma_1 \frac{\partial \beta F}{\partial S_1} \tag{12}$$

and

$$\frac{\partial S_2}{\partial t} = -\Gamma_2 \frac{\partial \beta F}{\partial S_2} \tag{13}$$

where Γ_1 and Γ_2 are phenomenological relaxation rates having no precise physical meaning (van der Schoot and Zandi, 2007). Reasonably, Γ_1 must be related to the speed at which material converts from the inactive to active state and Γ_2 to that at which the activated materials grows into polymers. So, one might call Γ_1 the activation rate and Γ_2 the elongation rate. Even at this level of coarse graining, where we have lost all detailed information about the reaction pathways, the set of coupled nonlinear equations is not easily solved analytically except in two extreme limits.

If the order parameter S_1 relaxes instantaneously, implying fast conversion of the inactive species into the active one and slow elongation, we find for the time dependence of the fraction active material

$$f(t) = f(\infty) - (f(\infty) - f(0))\exp[-\frac{1}{2}\Gamma_2 t] \tag{14}$$

.

In this case, the relaxation is single exponential and there is no sigmoidal kinetics.

If, on the other hand, S_2 relaxes instantaneously, so the conversion to the active species is now the rate-determining step, then the kinetics can be sigmoidal depending on whether the "quench" (a sudden change of solution conditions) induces a net polymerization or a net depolymerization of material, with

$$f(t) = \frac{f(0)f(\infty)}{(f(\infty) - f(0))exp[-t/t_*] + f(0)} \tag{15}$$

and t_* an inverse rate (a time)

$$t_* = \frac{X}{4(X-1)\Gamma_1} \tag{16}$$

that diverges if $X \to 1$. This makes the polymerization kinetics slow if the system is quenched near the polymerization point. For $X \gg 1$, so for high concentrations, $t_* \sim 1/4\Gamma_1$ levels off in accord with a more elaborate reaction rate theory (Powers and powers, 2006).

In Figure 7, we have plotted the response of the fraction active material to quench promoting assembly and (partial) disassembly. The model seems

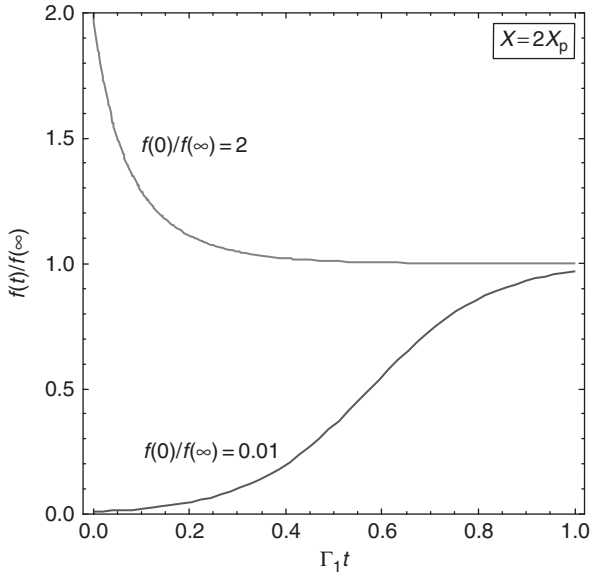

Figure 7 The fraction polymerized material f as a function of the dimensionless time $\Gamma_1 t$ according the kinetic Landau model discussed in the main text, with Γ_1 the nucleation rate. Shown are results valid in the limit where the nucleation reaction is rate limiting, for a quench to $X/X_p = 2$ where in equilibrium $f = 0.5$. Depolymerization is much faster than polymerization.

to capture the fundamentally different assembly and disassembly behavior of nucleation-limited polymerization as seen experimentally (Goldstein and Stryer, 1986; Hiragi et al., 1990; Hofrichter et al., 1974; Lomakin et al., 1996; Wang et al., 1989; Wentzel, 2006). The former is characterized by sigmoidal growth kinetics and the latter by in essence nearly instantaneous fragmentation, that is, slow assembly and fast disassembly. The difference between these diminishes with decreasing asymmetry in the nucleation and elongation rates.

If the assembly is nucleation limited, the obtained relaxation rate $t_*^{-1} > 0$ is positive for $X > 1$, implying net polymer growth if $f(0) < f(\infty)$ and net disassembly if $f(0) > f(\infty)$ (see Figure 8). We find a negative rate $t_*^{-1} < 0$ for $X < 1$, signifying complete polymer disassembly because by construction $f(0) \geq f(\infty) = 0$. The slowing down of the polymerization kinetics near the polymerization point is reminiscent of the phenomenon of *critical slowing down* that occurs in phase transitions near a critical point and in fact near any bound of thermodynamic stability (Chaikin and Lubensky, 1995; Hohenberg and Halperin, 1977). The equivalent of the critical slowing down in the growth of seeds of actin has indeed been observed experimentally (Attri et al., 1991), but todate has not been

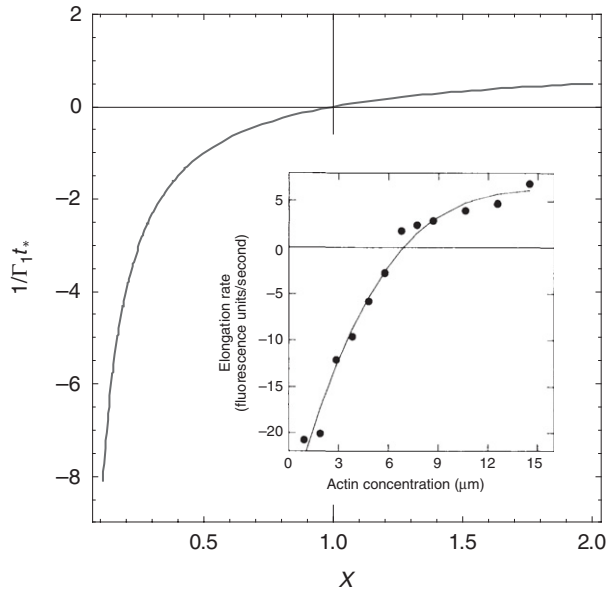

Figure 8 Dimensionless relaxation rate $1/\Gamma_1 t_*$ as a function of the dimensionless mass action variable X according the kinetic Landau model discussed in the main text, with Γ_1 the nucleation rate. Shown is the prediction in the limit where the nucleation reaction is rate limiting. Inset: experimental results from measurements on actin (Attri et al., 1991). Notice the zero growth at $X = 1$, the critical polymerization point.)

studied in supramolecular chemistry where more attention is paid to static properties and less to assembly kinetics.

In our model, this slowing down depends only on the distance from the polymerization point, not on the level of co-operativity. The reason is that the model presumes infinite co-operativity (or activation) for the fraction assembled material, which then behaves as if the polymerization transition were an actual phase transition. More elaborate calculations for reversible scission/recombination kinetics show that if $K_a > 0$: (i) the relaxation time t_* does not actually diverge at $X = 1$ albeit that it can become very large because $K_a \ll 1$ and (ii) that t_* is also sensitive to the precise value of K_a (Nyrkova and Semenov, 2007).

Although not commonly applied in the context of supramolecular assembly, an advantage of the Landau theoretical description is that it can easily be adapted to include a coupling of nucleated polymerizations to *macroscopic* phase transitions (Panizzay et al., 1998), including the isotropic-to-nematic transition. Although explored in the context of isodesmic assembly (van der Schoot, 1996; Taylor and Herzfeld, 1993), no theory has been put forward for nucleated assembly even though that the nematic transition is observed in, for example, actin solutions (Janmey et al., 1999) and in solutions of tape-forming oligopeptides (Aggeli et al., 2001). Perhaps even more interesting, the Landau description allows for straightforward application to the description of nonequilibrium phenomena such as shear banding under flow (Olmsted, 2008).

4. CO-OPERATIVITY AND NUCLEATION

Nucleated assembly emerges if intermediates stages between single monomers and long supramolecular polymers involve high-energy species. A high-energy intermediate can be a single assembly-active conformer but also a conglomerate of molecules that undergoes a conformational and bonding transition. In the cylindrical tobacco mosaic virus, for instance, conformational switching between a disk assembly consisting of 34 proteins and a protohelical lockwasher structure seems crucial in the co-operative encapsulation of the viral RNA (Butler, 1999). The switching involves not only a conformational change of the individual monomer units but also the way that they bond in the assembly. Calculations suggest that the free energy difference between a disk and a lock washer at neutral pH amounts to $1\,k_BT$ per protein subunit, corresponding to a activation energy g_a of $34\,k_BT$ for the complete protohelix (Kegel and van der Schoot, 2006). For actin, a similar scenario seems to be followed albeit that the intermediates involved in the nucleation event involve low-aggregation number species, that is, dimers and trimers (Janmey et al., 1999; Oosawa and Kasai, 1962; Oosawa and Asakura, 1975).

Biomimetic molecules such as those shown in Figure 6 behave very much like tobacco mosaic virus coat proteins in that the building blocks can convert between free monomers in solution, highly ordered helical aggregates and disordered linear assemblies, as evidenced, for example, by UV-vis, CD, NMR, and fluorescence decay spectroscopy (Brunsveld, 2001; Jonkheijm, 2005). For oligo(phenylene vinylene) in alkane solvents, the polymerization transition is sharp and seems to involve a helical transformation of disordered linear assemblies consisting of about 30 monomers (Jonkheijm and van der Schoot, 2006). For the discotic compound 1 shown in Figure 6, the polymerization, which can also switch between helical and nonhelical polymerized states, on the other hand, seems isodesmic yet the transition from disordered to helical state is very co-operative. Clearly, a less coarse-grained model than the nucleated assembly model is required to explain this.

A model that can describe conformational ordering transitions observed in supramolecular polymers is the so-called *self-assembled Ising chain*. It marries a simple mass action theory to the one-dimensional Ising model of ferromagnetism (Chaikin and Lubensky, 1995), which itself can be mapped onto the well-known Zimm–Bragg theory for the helix-coil transition in biopolymers (Ciferri, 2005; van Gestel, 2004a; van Gestel et al., 2003a; van der Schoot et al., 2000; Weiss and Terech, 2006). Basic ingredients are three free energies of bonding associated with two bonded states, so one more than the simple nucleated assembly model. To describe the bonded state of two neighboring monomers in an assembly, we assign an order parameter $S_i = \pm 1$ to each bond $i = 1, \ldots, N-1$ of an assembly consisting of N monomers. For instance, if $S_\mathrm{i} = +1$ then the bond is a helical one and if $S_\mathrm{i} = -1$ then it is nonhelical.

For the nonhelical bonded state, we assign a free energy g and for the helical one a free energy $h+g$. If $h<0$, then the helical bond is more favorable than the nonhelical bond, and if $h>0$ the opposite is true. It is reasonable to presume that in order to accommodate a particular kind of bond with a neighbor, the conformational state of the monomer must be affected. This implies that if a monomer is involved in two types of bond (helical and nonhelical) with its two neighbors, this should lead to *conformational frustration*. To account for this, a free energy penalty $j>0$ is introduced every time a molecule has to accommodate two unequal types of bonding. Within the model, the internal energy of a single aggregate then obeys

$$E(N) = -\frac{1}{2} j \sum_{i=1}^{N-2} [S_i S_{i+1} - 1] + \frac{1}{2} h \sum_{i=1}^{N-1} [S_i + 1] + g(N-1) \qquad (17)$$

which depends on the bound state of the monomers $\{S_i\}$. Note that j takes over the role of the coupling constant in the Ising model, and h that of the magnetic field (Chaikin and Lubensky, 1995).

From statistical mechanics, we deduce that the (dimensionless) number density $\rho(N)$ of aggregates of degree of polymerization N must obey

$\rho(N) = Z(N)\lambda^N$ with $Z(N) = \Sigma_{\{S_i = \pm 1\}} \exp[-\beta E(N)]$ the partition function of a single aggregate and λ the fugacity of the monomers (Ciferri, 2005). The latter is the Boltzmann weight of the chemical potential of the monomers and fixed by the conservation of mass, that is, by the condition that the overall concentration of material is fixed, $\phi = \Sigma_{N=1}^{\infty} N\rho(N)$. The partition function can be calculated exactly and allows one to calculate the mean aggregate size, $\overline{N}$, as well as the conformational state of the assemblies, say, the fraction helical bonds $f \equiv (\langle S \rangle + 1)/2$. Here, the ensemble averaging $\langle \ldots \rangle$ is implied over all bonds of all assemblies in the solution.

In the model, co-operativity enters in two ways: (i) through the conformational frustration that dictates the value of the free-energy penalty j and (ii) through the boundary conditions that we impose on the preferred state of the first and last bond, $S_i = \pm 1$ for $i = 1, N-1$. The coupling constant j produces correlations between bonded states, implying on average larger consecutive sequences of helical or nonhelical conformers the larger the value of j, and a sharper (more co-operative) transition from the nonhelical to the helical state of the assemblies. The boundary conditions dictate the extent to which the polymerization transition becomes nucleated. Because the first and last monomers are less strongly bound to the assemblies than monomers in the middle part of the chains, it seems plausible that either one or both should be nonhelical. Fitting of the theory to experiments confirms this scenario for a number of compounds, including compounds 1 and 2 of Figure 6 (Ciferri, 2005; van Gestel et al., 2003a; Weiss and Terech, 2006).

If the first bond can for whatever reason only be of the nonhelical (disordered) kind, then a helical polymer has to be nucleated if this nonhelical bond represents an excited state, so $g > 0$. The size of the critical nucleus depends in that case on how favorable the helical bond is relative to the nonhelical bond, in other words, on how strongly negative h is, and on the frustration free energy $j > 0$ because there is at least one monomer involved in two types of bonding. Within the model, the assemblies of size $2 < N < 2 - (j+g)/(g+h)$ with $h < -g < 0$ are high-energy structures and are therefore statistically suppressed.

Three regimes emerge from the model, where monomers, nonhelical polymers, and helical polymers dominate. These regimes that have indeed been observed experimentally in a variety of systems, such as for those molecules depicted in Figure 6 and tobacco mosaic virus (Kegel and van der Schoot, 2006).

1. If $X = \phi \exp[-\beta g] \gg 1$, we have long self-assembled polymers that obey simple *isodesmic* polymerization. For $h > 0$, the assemblies are disordered whilst for $h < 0$ they are ordered. The conformational transition at $h = 0$ is sharper and more *co-operative* the larger the frustration free energy j. The fraction helical bonds f that can be obtained from circular dichroism

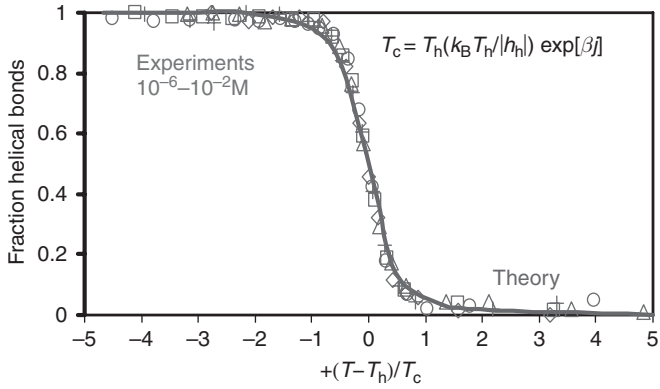

Figure 9 Fraction helical bonds as a function of the temperature T of the discotic compound 1 of Figure 6 in the solvent *n*-butanol. Symbols indicate experiments done in the range of concentrations of 10^{-6}–10^{-2} M (van der Schoot et al., 2000). The temperature has been scaled to the helical transition temperature T_h and a temperature $T_c = T_h(k_B T_h/|h_h|)\exp(j/k_B T_h)$ that depends on the frustration energy j and the excess enthalpy of the helical bond h_h. Remarkably, data taken over four orders in concentration collapse onto the theoretical curve, indicated by the drawn line.

spectroscopy (van der Schoot et al., 2000) follows a universal law as a function of the helical transition temperature T_h and a temperature scale T_c that depends on the coupling constant j and the excess enthalpy of the helical bond h_h. See Figure 9.

2. If $h > 0$, then helical assemblies do not form. There is an *isodesmic* polymerization from monomers to "disordered" supramolecular polymers that takes place around $X \approx 1$. The theory of Section 1 applies and the equivalent equilibrium constant obeys $K = \exp[-\beta g]$. Its value can be probed by means of radiation scattering, fluorescence decay, and UV absorption spectroscopy (Brunsveld et al., 2001; Jonkheijm et al., 2006).
3. If $X \ll 1$, disordered (nonhelical) assemblies do not form in any appreciable quantities. For $h < 0$, there is a polymerization transition from monomers to helical assemblies that is of the self-catalyzed nucleation type provided $\beta j \gg 1$. In the language of the coarse-grained self-catalyzed nucleated assembly model, the transition takes place near $X_p \approx \exp[\beta h]$ and we are able to assign an activation constant $K_a \approx \exp[-\beta j + \beta h]$. The theory of Section 2 approximately applies.

In practice, the relevant control parameters are not the concentration ϕ, and free energies g, h, and j but, for example, the concentration ϕ, the temperature T, and the type of solvent. In more complex systems additional variables can become important. By varying ϕ and T, we influence all these parameters via the various enthalpies that are therefore amenable to experimental

determination. This, however, is not a simple task because there are six free parameters associated with the three binding free energies: each free energy can be separated into contributions from the enthalpy and entropy. A very large number of very different kind of experiments have to be done as a function of ϕ and T to independently fix all the parameters (van Gestel et al., 2003a; van der Schoot et al., 2000).

To date, there are only a few molecules for which this has been done systematically, in particular the discotic and oligo(phenylene vinylene) compounds shown in Figure 6 (van Gestel et al., 2003; Jonkheijm et al., 2006), albeit that only for the former the diversity of the experiments allowed for independent cross-checking of the fitting parameters. The phase diagram of the discotic compound dissolved in *n*-butanol is depicted in Figure 10, showing good agreement between theory and experiment. The conformational switching exhibited by the assemblies at the helical transition temperature is highly co-operative and also resembles a phase transition. That this is indeed the case is illustrated in Figure 11, showing the tell-tale peak in the measured and calculated heat capacities (Brunsveld et al., 2000).

The model outlined in this section seems specific but in actual fact is very versatile. It applies not only to helical transitions in supramolecular polymers but can easily be adapted to model other types of structural reorganization (Bouteiller et al., 2005), chirality amplification (Palmans and Meijer, 2007) of both the sergeants-and-soldiers (van Gestel et al., 2003b), and the majority-rules type (van Gestel, 2004b) and the so-called *templated* assembly. We come back to the phenomenon of templated assembly below.

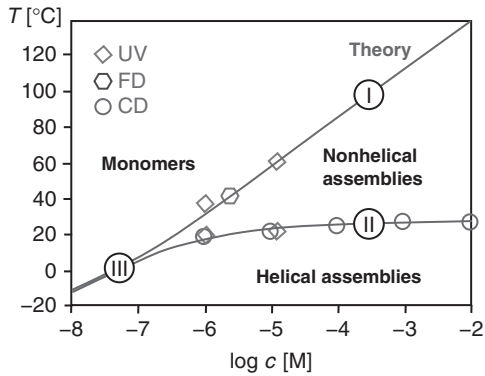

Figure 10 Assembly diagram of compound 1 of Figure 6 in the solvent *n*-butanol (adapted from van Gestel, 2004a; Weiss and Terech, 2005). Symbols represent results from UV-vis absorption, UV, fluorescence decay, FD, and circular dichroim spectroscopy, CD, and the drawn line the theoretical fits to the data. There are three types of transition: I, isodesmic polymerization; II, helical transition of long supramolecular polymers; and III, nucleated helical assembly of the monomer units.

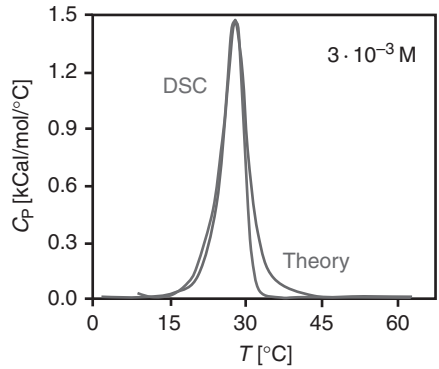

Figure 11 Comparison of prediction of the self-assembled Ising model with the experimentally determined heat capacity of compound 1 of Figure 5 around the co-operative helical transition point (Brunsveld, 2001; Brunsveld et al., 2000).

5. COARSE GRAINING REVERSED

The assembly models discussed in the preceding sections are presumably the simplest ones that one can set up for co-operative supramolecular polymerization. Their advantage is the relatively small number of adjustable parameters and conceptual simplicity. Disadvantage is the lack of a detailed description of the processes that actually led to the assembly becoming nucleated and that are system specific, that is, that depend on the details of the molecules involved and how precisely they interact.

The nucleated assembly model has the highest level of abstraction in which processes that potentially involve a hierarchy of high-energy intermediates are represented by as few as two free energies that give rise to four thermodynamic parameters: two binding enthalpies and two binding entropies. To interpret values of the model parameters as obtained by fitting the model to experimental data, one would need to go beyond the bounds of the coarse-grained model and explicitly consider the molecular details of the system and, in a way, "fine grain" the model post hoc.

Not surprisingly, post hoc fine graining is system specific and no *general* recipe can be provided how to do this. By way of illustration we discuss in more detail two relevant examples. The simplest situation arises if conformational switching upon binding occurs at the level of the individual monomeric building blocks. A molecular interpretation of the model in the light of experimental data is in that case straightforward. This turns out so for the assembly of short oligopeptide chains into β-sheet fibrils, a supramolecular polymerization that belongs to the class of nucleated assemblies we focus attention on (Nyrkova et al., 2000) (see Figure 1).

For this type of monomer unit, the polymerization requires the stretching of the chains in free solution for the hydrogen bonds to be able to form upon attachment of these chains to the growing β-sheet tape. The stretching of the coil-like chains reduces their conformational freedom and hence their entropy. Clearly, this loss of conformational entropy must be compensated for by the gain in free energy through the formation of the hydrogen bonds.

Within this kind of "reconstruction" of a molecular picture from the abstract model, an estimate based on ideal-chain statistics would suggest that the free energy cost associated with the bonding of the monomeric units would amount to $+(n-1)\varepsilon_a$, where n is the number of bonds involved in the backbone of the chain and $\varepsilon_a > 0$ a model-dependent constant of order unity. The parameter $\varepsilon_a > 0$ may itself again be quantified using, for example, a rotational isomeric state model commonly applied in polymer physics (Mattice and Suter, 1994). As for the driving force for the tape polymerization, let $m \propto n$ be the number of hydrogen bonds that each oligopeptide chain can form. One would surmise that the free energy of bonding must then be equal to $-m\varepsilon$, where $\varepsilon > 0$ is the free energy gained when a hydrogen bond is formed.

In conclusion, if an assembly consists of N bound oligopeptide chains, the overall free energy of binding would be equal to $N(n-1)\varepsilon_a - (N-1)m\varepsilon$. This in turn implies that in order to describe the equilibrium between the free oligopeptides and the very polydisperse tapes, we have in terms of the parameters of the nucleated assembly model of Section 2 $g_a = (n-1)\varepsilon_a > 0$ and $g = (n-1)\varepsilon_a - m\varepsilon < 0$ as a function of the length of the chains, n, and the number of hydrogen bonds, m, formed per chain. Note that the tapes self-assemble into a hierarchy of higher order structures including ribbons, fibrils, and fibers that require separate theoretical description outside of the scope of this review (Aggeli et al., 2001; Nyrkova et al., 2000).

In this particular example, estimates for both free energy parameters g and g_a of the coarse-grained model are obtainable from more detailed molecular models albeit that strictly speaking they depend not only on the chemical composition and structure of the molecular building blocks but in principle also on the solvent properties. It is important to stress again for it is often ignored, the solvent molecules not only drive the assembly but have been shown to play an active role in structural reorganizations of supramolecular assemblies (Bouteiller et al., 2005; Jonkheijm et al., 2006). Ideally, their influence should not be absorbed in adjustable parameters as is almost always done.

Much more sophisticated models are needed to explicitly deal with the role of the solvent and presumably the only sensible way to make headway here is by means of detailed, that is, atomistic computer simulations. Unfortunately, detailed computer simulations of the self-assembly of large polymeric objects are often not very practical because they require excessive computer processing times, in particular if the solvent molecules are

explicitly included or if timescales are to be probed comparable to those of the actual assembly kinetics in experiments.

Nonetheless, atomistic or quasi-atomistic simulations remain highly valuable indeed because they (i) provide insight into the three-dimensional structure of the assemblies, (ii) produce estimates for the binding energies of the monomer units that can be used in coarse-grained models, (iii) aid guide model building at higher levels of coarse graining, and (iv) give insight in predominant assembly pathways (Auer et al., 2007; Chennubhotla et al., 2005; Cellmer, et al., 2007; Foster, 2002; Jahn and Radford, 2008; Lehn, 2004; Phelps et al., 2000; Sept and McCammon, 2001).

One might presume that the larger the molecular building blocks are, the more difficult a sensible theoretical description becomes. Whilst this is true at the atomistic level, the opposite is actually true for coarse-grained descriptions because these become *more* accurate the larger the molecules involved in the assembly. The reason is that with increasing size of the molecules that make up a supramolecular assembly, the number of chemical groups on them that are engaged in the intermolecular interactions also increases. This (in a sense) averages out the contributions of the individual chemical moieties to the overall binding free energy. It explains why interactions between protein molecules, which belong to the chemically most complex of molecules, can often quite successfully be described in terms of relatively simple, effective potentials in which chemical detail enters only statistically, for example, in some average of the surface properties of the molecules (Kegel and van der Schoot, 2004, 2006; Prinsen and Odijk, 2004; Sear, 2006).

For example, the main driving force for the self-assembly in aqueous solution of protein molecules to produce larger scale structures such as fibers or virus coats results from hydrophobic interactions between apolar patches or functional groups on the surfaces of these molecules (Lauffer, 1975). The hydrophobic interaction is of an entropic nature and becomes stronger with increasing temperature. It has its origin in the statistics of the short-range structure of fluid water. A plausible estimate for the bare binding free energy of two proteins would then be $-2\gamma a_h$ where $\gamma > 0$ is the macroscopic surface tension of the hydrophobic patch and a_h its area. This is a reasonable estimate: if two water-loathing surfaces of area a_h are removed from contact with water, this must liberate two times the surface energy of each patch (Kegel and van der Schoot, 2004, 2006).

However, proteins are almost always charged (Dello'Orco et al., 2005), for otherwise they would drop out of the solution, that is, phase separate macroscopically. Indeed, this is what usually happens near the isoelectric point of the proteins, i.e. their point of zero net charge. If two proteins bind to become part of an assembly, charged patches on them get on average closer together and hence repel each other when of the same sign. In other words, Coulomb repulsion between the proteins

should actually oppose the formation of an assembly (Kegel and van der Schoot, 2004). The strength of the Coulomb repulsion depends on the net surface charge density, σ_c, that itself depends on the pKs of all water-exposed acidic and basic groups and on the solution pH (Kegel and van der Schoot, 2006).

An estimate of the free energy of the Coulomb repulsion between two bound proteins is $+k\sigma_c^2 a_c \lambda_B \lambda_D$, where k is a geometrical factor, σ_c the *effective* surface charge density, a_c the area of the water-exposed part of the proteins, λ_B the so-called Bjerrum length, and $\lambda_D = 1/\sqrt{8\pi\lambda_B I}$ the Debye screening length with I the ionic strength of the solution (Kegel and van der Schoot, 2004). The Bjerrum length is the distance at which two point charges interact with a Coulomb energy equal to the thermal energy $k_B T$, in water about 0.7 nm. For salts of monovalent cat- and anions, the Debye length obeys $\lambda_D \approx 0.3/\sqrt{c_s}$ nm with c_s the concentration of salt in moles per liter. It measures how far Coulomb interactions reach before they are "screened" (made ineffective) by the presence of small, mobile ions in the solution.

This gives the following estimate for the protein–protein binding energy in an assembly,

$$g \approx -2\gamma a_h + k\sigma_c^2 a_c \lambda_B \lambda_D \tag{18}$$

provided the salt concentration is not very low. Although derived for weak surface charge densities, it seems to be reasonably accurate too at surface charge densities high enough for nonlinear screening effects to take over (Šiber and Podgornik, 2007), and describes the pH, salt, and temperature dependence of the in vitro assembly of the coat proteins of a number of viruses (Kegel and van der Schoot, 2004, 2006). Here, the details of the chemical composition of the coat proteins come in via the parameters γ, a_h, σ_c, and a_c. The last three of these can be estimated from information present in protein databases, where the pH dependence of σ_c follows from the Henderson–Hasselbalch relation,

$$\sigma_c a_c = \sum_{i_b} (1 + 10^{\mathrm{pH} - pK_{a,i_b}})^{-1} - \sum_{i_a} (1 + 10^{pK_{a,i_a} - \mathrm{pH}})^{-1}, \tag{19}$$

where i_a and i_b refer to the acidic and basic groups on the surface of the protein with $pK_{a,j}$ the (negative logarithm of the) acid dissociation constants for $j = i_a, i_b$ (Kegel and van der Schoot, 2006). Additional dependence on the solvent conditions might come in via the activation step of the polymerization, that is, via g_a (Dell'Orco et al., 2005; Niranjan et al., 2003). Application of this kind of seemingly simplistic modeling to the in vitro

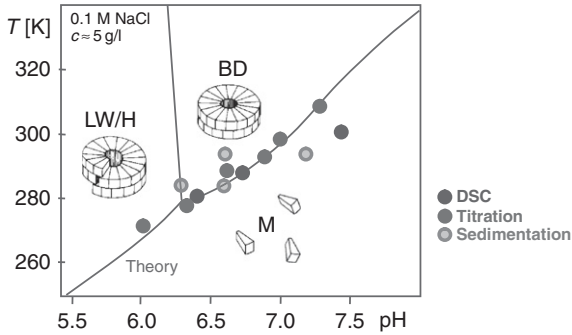

Figure 12 Diagram of assembled states of the coat protein of tobacco mosaic virus: M free monomers, BD cylindrical disks, LW/H protohelices and helices. Symbols: results from differential scanning microscopy DSC, titration, and sedimentation experiments, lines: theory. The theory is based on binding energy Equation (9) and presumes competing repulsive Coulomb and attractive hydrophobic interactions (Kegel and van der Schoot, 2006).

assembly of the coat protein of tobacco mosaic virus proves quite successful (see Figure 12).

The solution conditions enter the description through the pH, λ_B, and λ_D. Expression (19) provides an explanation for why self-assembled protein structures become more stable with increasing concentration of salt, which seems to be true for a wide variety of systems, including spherical and cylindrical viruses (Kegel and van der Schoot, 2004, 2006).

6. SUMMARY AND OUTLOOK

Reversible supramolecular polymerization takes place in solutions of melts or molecules that combine moieties of quite different polarity. This process can be driven by specific interactions, such as hydrogen bonds and/or generic types of (solvophobic) interaction. Very often, supramolecular polymerization is isodesmic. This points to the existence of a single predominant energy scale associated with the binding of a monomer unit to a growing polymer chain. Isodesmic self-assembly is a relatively weak function of the external conditions such as temperature or concentration and large aggregation numbers imply large binding energies.

Nucleated supramolecular polymerization, on the other hand, is a much more sensitive function of the external conditions. Indeed, a sharp polymerization point can be identified below which almost no material is in the polymerizated state and above which the self-assembled polymers exhibit a strong variation of their mean size with varying concentration, temperature, and so on. Nucleated equilibrium polymerization requires the existence of

at least two competing energy scales. A competing energy scale emerges naturally with conformational switching.

Three kinds of conformational switching may be identified:

1. Individual monomeric building blocks interconvert between assembly-inactive and assembly-active conformational states;
2. Assembled states interconvert between different conformers characterized by differently bound states of monomers that themselves remain inert;
3. Switching between different aggregated states resulting from a switching between different conformational states of the monomer units.

If the conformational switching is that between high-molecular weight polymeric species, then the structural transition between them can be highly co-operative but the assembly remains by and large isodesmic. So, co-operativity is a required but not a sufficient condition for creating nucleated supramolecular polymerizations.

Simple, coarse-grained models of nucleated assembly have a number of advantages over more detailed ones. First, coarse-grained models have only a limited number of free energy parameters. Second, analytical predictions can be obtained, if not in general then usually in practical limits. Third, they apply to a wide range of materials that may differ in detail but not in principle. This allows for a relatively straightforward fitting to experiments and comparison between materials, where the analysis can be made system specific by post hoc fine graining.

Both isodesmic and nucleated assembly produce polymeric species of a wide range of aggregation numbers and hence molecular weights. This makes self-assembled polymers very polydisperse and in fact is a result of the law of mass action. Self-assembled polymers cannot be made monodisperse, unless forced to form on a template of fixed and uniform length (Hannah and Armitage, 2004). The binding of the molecular building blocks to a "template" or "tape measure" molecule, itself a polymer, sets a maximum to the self-assembled polymer length. If all the binding sites on the monodisperse tape measure molecule are occupied, then the self-assembled polymer is by construction also monodisperse.

Complete coverage of the template molecule, for example, by hydrogen bonding is not so easily achieved, however, at least in theory. The reason is that even if the polymer is a three-dimensional object, templated assembly is in essence a one-dimensional adsorption process. One-dimensional ordering phenomena are dominated by spontaneous fluctuations that kill the fully ordered state (Chaikin and Lubensky, 1995), here the fully covered template. A simple model equivalent to the self-assembled Ising chain discussed in Section 4 shows that complete coverage should indeed be nearly impossible (McGhee and von Hippel, 1974), in particular if the binding free energy is not high and/or the monomeric building blocks do not vastly outnumber the binding sites on all of the template molecules.

Yet, nature has somehow worked itself around the entropy problem, because the coat proteins of linear viruses do spontaneously assemble around single-stranded viral RNA (Butler, 1999), and so do the so-called movement proteins involved in the shuttling of viral RNA from one cell to another (Citousky et al., 1990; Kiselyova et al., 2001). Interestingly, the length of the tails of tailed bacteriophages seems also to be set by co-assembly of the tail proteins with a tape measure molecule (Chiu et al., 1997; Kushner, 1969). The question arises how nature circumvents the entropy problem? In other words, what mechanisms are available that can make template-based assembly productive? The answer may plausibly again be found in high-energy intermediates (Butler, 1999). In biology, many molecular self-assembly processes are controlled by helper molecules such as scaffold molecules and molecular chaperones, usually but not exclusively proteins (Kentsis and Borden, 2004). Hence, the problem merits attention and a better understanding of it may boost the application of templates within supramolecular science.

Of course, with the eye on potential technological applications (Lehn, 2004) of supramolecular polymers in, for example, responsive gels (Kato et al., 2006), smart coatings (van der Gucht et al., 2004; Zweistra and Besseling, 2006) and opto-electronic devices (Flynn et al., 2003; Meegan et al., 2004; Würthner et al., 2004) and tissue engineering (Dankers and Meijer, 2007), more insight is also needed in how these materials respond to external pertubation, phase transitions, and so on (Auvray, 1981; Blankschtein et al., 1985; Feng and Fredrickson, 2006; Odijk, 1996; Oosawa, 1970). Whilst a large body of literature exists on how isodesmic supramolecular polymers behave, in particular in the form of linear surfactant micelles, considerably less is known about the macroscopic properties of nucleated self-assembled polymers. Systematic physicochemical investigation of the physical properties of the latter is much needed, and simple, coarse-grained models can prove valuable in analyzing experimental observations and further our understanding of this fascinating class of materials.

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