Designing Enhanced Entropy Binding in Single-Chain Nanoparticles

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Single-chain nanoparticles (SCNPs) are a new class of bio- and soft-matter polymeric objects in which a fraction of the monomers are able to form equivalently intra- or interpolymer bonds. Here we numerically show that a fully entropic gas-liquid phase separation can take place in SCNP systems. Control over the discontinuous (first-order) change—from a phase of independent diluted (fully-bonded) polymers to a phase in which polymers entropically bind to each other to form a (fully-bonded) polymer network—can be achieved by a judicious design of the patterns of reactive monomers along the polymer chain. Such a sensitivity arises from a delicate balance between the distinct entropic contributions controlling the binding.

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Introduction.—As elegantly epitomized in the van der Waals theory [1], in atomic systems the gas-liquid phase separation phenomenon originates from interparticle attraction. More recently, colloidal systems have provided evidence of purely entropy-driven "gas-liquid" phase transitions, as observed in the presence of depletion interactions [2,3], combinatorial attractions [4], and hard-core interactions between particles with specific shapes [5].

While depletion interactions have been studied in detail in the last 30 years [3,6], combinatorial attractions have received much less attention. In their seminal study, Safran and co-workers [4] investigated a system composed by microemulsion droplets linked by telechelic polymers [7]. The polymer body is exposed to the aqueous solvent while the hydrophobic ends are constrained to reside inside the same or in two distinct oil droplets. The different ways the polymer ends can be distributed over the accessible droplets leads to droplet condensation, i.e., to the liquid state. DNA-coated colloids provide further examples in which combinatorial entropy can be exploited to drive phase separation. Here particles are grafted with equal quantities of sticky ends and of their complementary sequence [8,9], or grafted with palindromic sequences [10,11]. In both cases, complete DNA hybridization can take place inside the same particle or between distinct particles and the balance between these two possibilities is controlled by a combinatorial entropic contribution.

In both telechelic polymers and DNA coated particles the dominant interparticle contributions are strong interactions of the lock and key type such that the system is constantly in its energetic ground (fully bonded) state. Particles can satisfy all possible bonds both in the gas phase (colloid poor) via intraparticle bonds as well as in the liquid phase (colloid rich), where bonds are shared between different particles. Being the number of bonds (and hence the energy) the same in both phases, entropy becomes the only driving force for condensation [12].

Functionalized polymers, in which a fraction of the monomers are able to form reversible bonds, have recently entered the radar of the soft-matter [13–21] and biophysics [22–26] communities, and have been experimentally synthesised even inside cells to promote gelation [27]. If the chain flexibility is large enough and the associative monomers can form only single bonds, then at low density bonding takes place essentially within the same polymer, forming soft nano-objects named single-chain nanoparticles (SCNPs) [17]. At larger densities the combinatorial entropy should favor phase separation. However, in this case the free energy has additional terms that stem from the polymeric nature of the nanoparticles. Indeed, in contrast to colloids, where in addition to bonding the only other contribution is provided by the steric repulsion, in SCNP systems one has to also take into account the conformational entropy contribution associated with the change from an intrapolymer to an interpolymer bond. The dependence of all these entropic terms on the number and type of attractive sites is complex [28] and has not been completely mapped out yet. In general, the interplay between the entropic contributions in play is subtle, and the resulting phase behavior difficult to predict. In the specific case of SCNPs, at high density no hints of a first-order transition have been observed in experiments [18,19] and simulations [29], consistent with predictions of mean-field theory [30]. By contrast, a continuous cross-over from isolated chains to percolating states has been observed [18,19,29], akin to the gelation without phase separation phenomenon observed in polymer and biopolymer systems [31,32].

Here we show that, opposite to what was previously found and thought, a fully entropic gas-liquid phase separation can take place in SCNP systems. By studying a series of differently functionalized polymers we demonstrate that phase separation in this system takes place due to both the attractive combinatorial entropy and the conformational entropy contribution associated with the change from an intrapolymer to an interpolymer bond. We show that this last term can be modulated by designing the sequence of reactive monomers, offering the possibility to discontinuously change, preserving all bonds, from a dilute gas of independent polymers to a phase in which different polymers bind to each other to form an extended network.

We perform molecular dynamics simulations of Kremer-Grest polymers [33] complemented by attractive monomers that interact through a potential that enforces the single-bond per reactive monomer condition and enables a bond-swapping mechanism. The algorithm [34], recently applied to a variety of soft-matter systems [35–38], is capable of reshuffling the bonding pattern close to the fully bonded state, even when the thermal energy $k_BT \equiv 1/\beta$ is much smaller than the bond strength ϵ_b, overcoming kinetic bottlenecks (see Sec. S1 [39]).

We simulate polymers composed by $N_m = 254$ monomers, 24 of which are equispaced reactive and 230 inert. We study a model, named $(AAAA)_6$, in which all (A-type) reactive monomers are identical, a model in which A and B reactive monomers alternate, $(ABAB)_6$, and a model with four different (A, B, C, D) alternating reactive monomers, $(ABCD)_6$. A cartoon of the three studied polymer models is shown in Figs. 1(a)–1(c). Reactive monomers are able to form one and only one strong bond with another same-type monomer. We perform two types of calculations. In the first, we simulate two polymers to compute the effective potential as a function of the relative distance between their centers of mass, while in the second one we perform bulk simulations of 100–200 polymers with periodic boundary conditions to compute the equation of state and the coexistence between phases. Further information on the numerical methods are available in Ref. [39].

The problem.—Consider a SCNP, a polymer in which N_R of the constituent monomers are reactive. Each reactive monomer can form a strong bond with another reactive monomer of the same type on the same or on a nearby polymer. Different from functionalized colloidal (patchy) particles [44,45], in which the rigidity of the particle prevents reactive monomers belonging to the same object from bonding with each other, in the polymer case all reactive monomers can take part in intrapolymer bonds. Being $\epsilon_b \gg k_BT$, each polymer can assume a fully bonded (ground state) configuration in which it is disconnected from all other polymers [Figs. 1(d)–1(f)]. This raises the question whether this “independent-polymer” state is the highest entropy state for a system of such polymers or if swapping intrapolymer for interpolymer bonds can increase the system entropy even further. Even more important is the question about whether the increase in entropy, if present, is strong enough to induce condensation of a dense “liquid” phase starting from a dilute polymer solution.

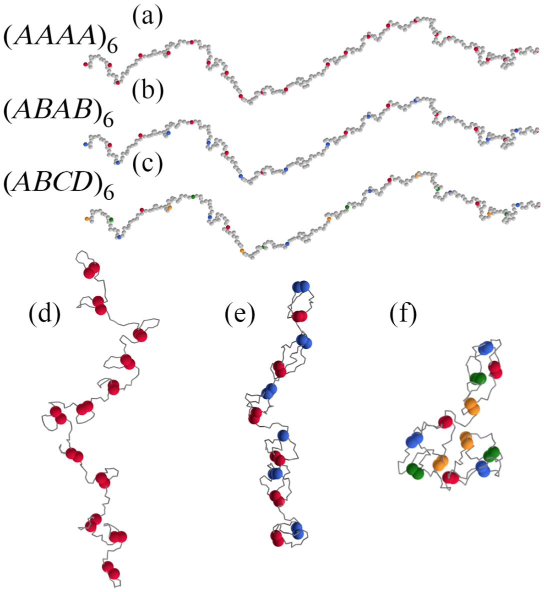

FIG. 1. Cartoons of the investigated polymers highlighting the different conformational changes associated with the formation of a fully bonded configuration in the three models considered. Here inert monomers are colored in grey, while reactive monomers are depicted as colored spheres. The three polymers are shown in an open, (a)–(c) and closed, (d)–(f), conformation. In (d)–(f) the inert monomers are not explicitly shown and the reactive monomers are shown with enhanced size for the sake of visibility.

Effective potential (expectations).—We begin investigating the effective potential $\beta V_{\mathrm{eff}}(R)$ between two polymers as a function of the relative center-to-center distance R, when $\epsilon_b \gg k_BT$. In this limit, the possible available configurations of two polymers are restricted to the ones in which all possible bonds are formed (either intra- or interpolymer bonds). Since the total number of bonds is always fixed, energy does not play any role in the interaction, leaving entropy as the only driving force. Three different entropic contributions determine $\beta V_{\mathrm{eff}}(R)$. The first contribution includes the cost of bringing two fully bonded polymers at relative distance R when only intrapolymer bonds are present. This is the standard polymer-polymer entropic repulsion [46–48]. The second contribution is a combinatorial term, which accounts for the entropy gain of swapping intra- with interpolymer bonds. The number of configurations in which both intra- and inter-bonds are allowed is larger compared to the case in which only intrapolymer bonds are present (Sec. S4 [39]), resulting in an attractive contribution [11,30].

TABLE I. Entropy change $\Delta S_{\mathrm{o}\to\mathrm{fb}}/k_B$ from the open to the fully bonded state for the three polymer types. The error associated with $\Delta S_{\mathrm{o}\to\mathrm{fb}}/k_B$ is of the order of 10^{-1}. The last column reports the gyration radius R_g^2/σ^2, where σ is the unit of length, corresponding to the monomer diameter.

Polymer type	$\Delta S_{\mathrm{o}\to\mathrm{fb}}/k_B$	$\Delta S_{\mathrm{o}\to\mathrm{fb}}/k_B$ per reactive site	R_g^2/σ^2
$(AAAA)_6$	−93.0	−3.87	80
$(ABAB)_6$	−110.6	−4.60	55
$(ABCD)_6$	−119.3	−4.97	50

The third and last contribution (S_{conf}) is linked to the conformational change of the polymer on going from the all intrabond conformation to the mixed intra- and interbonds case. This entropic change accounts for the different number of configurations available to the inert monomers when the bonding pattern changes. S_{conf} is sensitive to the relative distances between identical reactive monomers along the polymers and hence it can be tuned to control the strength of βV_{eff} by changing the types of the reactive monomers along the chain. Interestingly, as discussed in the Supplemental Material (S2 A) [39], simply changing the number of inert monomers while leaving the type and number of reactive monomers invariant does not modify the effective potential if distances are rescaled by the gyration radius.

Figures 1(a)–1(c) show the three SCNPs discussed here in an open configuration, while Figs. 1(d)–1(f) show the same models in a fully bonded configuration, to highlight the importance of the conformational entropic contribution. The figure vividly shows that on increasing the number of distinct reactive types, the fully bonded polymer becomes more compact. Assuming that bonds between nearest reactive monomers are the ones preferentially formed [30] (a hypothesis supported by simulations), to a first approximation each polymer in the bonded state can be visualized as an independent "unit" of paired reactive monomers, where the number of independent units is controlled by the number of reactive monomers of the same type. The change in conformational entropy $\Delta S_{\mathrm{o}\to\mathrm{fb}}$ of single chains going from an open unbonded state (identical for all polymers) to a fully bonded state (different for each of the three polymers considered) can be calculated via Hamiltonian integration (Sec. S1 F [39]). The results, reported in Table I, confirm the progressive entropic cost of constraining the polymer into a configuration in which all bonds are formed on going from $(AAAA)_6$ to $(ABAB)_6$ and to $(ABCD)_6$. Differences of about 1 k_BT per reactive monomer characterize the $(ABAB)_6$ and the $(ABCD)_6$ polymers as compared to the $(AAAA)_6$ polymer, a significant configurational entropic cost required to satisfy all bond constraints, which can be partially regained when intrabonds are swapped with interpolymer bonds.

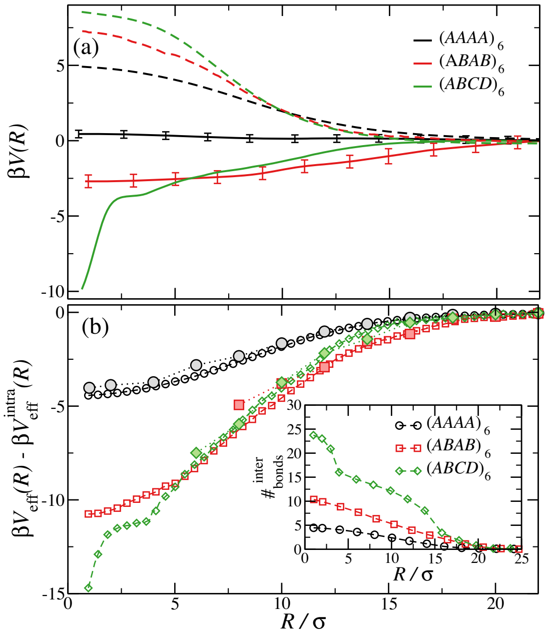

FIG. 2. (a) Effective potentials for the three polymers: $\beta V_{\mathrm{eff}}(R)$ and $\beta V_{\mathrm{eff}}^{\mathrm{intra}}(R)$ are shown with solid and dashed lines, respectively. The error bars are upper bounds estimated by splitting the data into two blocks and computing the absolute difference between the effective interactions in each block, divided by $\sqrt{2}$. (b) Attractive part of the potential estimated as $\beta V_{\mathrm{eff}}(R) - \beta V_{\mathrm{eff}}^{\mathrm{intra}}(R)$ (open symbols) and as $\ln p(0)$ [see Eq. (2), filled symbols]. The inset shows the average number of interpolymer bonds. Note that the abrupt decrease of $\beta V_{\mathrm{eff}}(R)$ for very short R in the $(ABCD)_6$ case originates from *zipping* of the bonds.

Effective potential (numerical evaluation).—To evaluate the strength of the entropic contributions we compute (as described in S1 C [39]) $\beta V_{\mathrm{eff}}(R)$ for the three polymers. Note that we simulate under conditions that allow for bond breaking (such that the bond-swapping mechanism is active), but only configurations in which all possible bonds are formed are included in the statistical average. For each of the three models we also evaluate the potential, $\beta V_{\mathrm{eff}}^{\mathrm{intra}}(R)$ where only intrabonds are allowed. Results are shown in Fig. 2.

Consistent with mean-field theory [30] and recent simulations [49], in the $(AAAA)_6$ case, despite the smaller $\beta V_{\mathrm{eff}}^{\mathrm{intra}}(R)$, $\beta V_{\mathrm{eff}}(R)$ is always positive and close to zero for all R, indicating that there is no net attraction between the polymers: The entropic attraction almost completely compensates the entropic repulsion. Differently and strikingly, in the other two cases, $\beta V_{\mathrm{eff}}(R)$ is strongly attractive, suggesting the possibility of a phase separation. Thus an appropriate design of the reactive monomer types can be used to control the resulting interpolymer attraction. To confirm the enhanced interpolymer binding, the inset of Fig. 2(b) shows the number of interpolymer bonds for the three cases. In the $(AAAA)_6$ case only a limited number of interpolymer bonds are formed, even when the relative distance between the two polymers approaches zero. The conformational entropic gain of opening (two) intrapolymer bonds to form (two) interpolymer bonds does not sufficiently compensate the entropic repulsion. The difference $\beta V_{\mathrm{eff}}(R) - \beta V_{\mathrm{eff}}^{\mathrm{intra}}(R)$ provides a measure of the total entropic attraction between two polymers (sum of the combinatorial and of the conformational terms) and it is shown in Fig. 2(b). The contribution $\beta V_{\mathrm{eff}}(R) - \beta V_{\mathrm{eff}}^{\mathrm{intra}}(R)$ for the $(AAAA)_6$ and for the $(ABAB)_6$ [and the $(ABCD)_6$] sequences is quite different, confirming the different role played by entropy for the three polymer cases.

To support the numerical results for $\beta V_{\mathrm{eff}}(R) - \beta V_{\mathrm{eff}}^{\mathrm{intra}}(R)$ we estimate the entropic attraction in an independent way. The partition function Z of the system composed of two polymers at fixed relative distance, when both intra- and interbonds are possible, can be approximated as a sum over the number of interpolymer bonds N_b of a specific type, from 0 to the maximum number of bonds N_R:

$$Z = \sum_{\substack{0\leq N_b\leq N_R \\ N_b \text{ even number}}} \Omega_{N_b}. \tag{1}$$

The fully bonded condition imposes only even numbers for N_b. Here Ω_{N_b} counts the number of microstates available to the two chains when N_b interbonds are present. The analogous expression, with the constraint of only intrapolymer bonds, would include only the first term of the sum ($N_b = 0$) in Eq. (1). Hence the entropic loss $\Delta S/k_B$ on going from inter and intrabonds to only intrabonds is

$$\frac{\Delta S}{k_B} = \ln\frac{\Omega_0}{Z} \equiv \ln p(0). \tag{2}$$

The quantity $\ln p(0)$, which provides a neat (and independent) measure of the entropic attractive contribution, is also reported in Fig. 2(b) and favorably compares with $\beta V_{\mathrm{eff}}(R) - \beta V_{\mathrm{eff}}^{\mathrm{intra}}(R)$.

In Sec. S2 [39] we show that the observed trends are robust for changes in the polymer length (at fixed number of reactive monomers, by increasing the number of inert monomers) as well as for changes at fixed polymer length of the number of reactive monomers.

Phase behavior.—To confirm that the entropic attraction for the $(ABAB)_6$ and $(ABCD)_6$ polymers is sufficiently strong to condensate a "liquid" from the "gas," we evaluate their equation of state [Fig. 3(a)], calculated as discussed in S1 D [39]. Coherently with the two-body effective interaction results, the $(AAAA)_6$ system behaves essentially as an ideal gas. Interestingly, this θ condition originates from the ability of the entropic attraction to essentially compensate the usual polymer repulsion. By contrast, the pressure in both the $(ABAB)_6$ and $(ABCD)_6$ systems becomes quickly negative, suggesting the presence of a phase transition between two phases with significantly different polymer concentration. As a proof of the possible presence of a phase separation we perform direct-coexistence simulations (S1 E [39]) starting from configurations characterised by an inhomogeneous polymer concentration. Figure 3(b) shows the density profiles of the initial and final configurations for all three models. The density of the $(AAAA)_6$ system becomes homogeneous and the two interfaces that were present at time zero completely disappear. By contrast, the gas-liquid interfaces are stable in both the $(ABAB)_6$ and $(ABCD)_6$ systems over the course of the simulation. We find (not shown) that in the liquid phase at coexistence the system percolates and that each polymer binds with ≈10 other polymers for the $(ABAB)_6$ and $(ABCD)_6$ models.

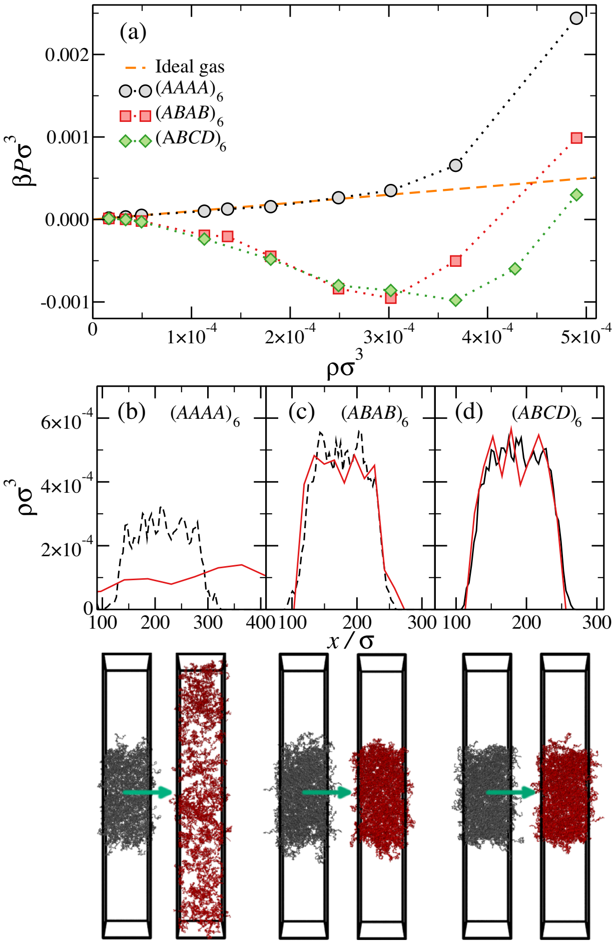

FIG. 3. (a) Equations of state of the three investigated systems (points) and theoretical expectation for an ideal gas of chains (orange dashed line). The statistical uncertainty is smaller than the symbol size. (b)–(d) Density profiles along x for the three investigated systems evaluated with direct coexistence simulations. We show the profiles of the density of the initial configuration (dashed black lines) and of the average density of the final state (solid red lines). Representative snapshots of the initial (grey) and final (red) states are shown below each plot.

Concluding remarks.—In summary, we have demonstrated that opposite to what was previously expected, a gas-liquid phase separation can appear in systems of SCNPs. By simply alternating two different types of reactive monomers, it is possible to tune the conformational entropy change on swapping intrabinding to interbinding. As a result, the strength of configurational and combinatorial entropy can be harnessed to induce a fully entropic first-order phase transition, even with a low overall concentration of reactive monomers. In view of the modern ability to force living cells to express SCNPs, it is foreseeable to imagine—guided by entropy—a fine-tuned control of the phase behavior of these particles in biologically relevant conditions [27] as well as a mechanism to optimize multivalent binding [50,51] in ligand-receptors equilibria. At the same time, the design principles reported here may help in achieving a better understanding of phase separation phenomena in cells, which are most often mediated by multivalent biomacromolecules [52–54]. Such phenomena are commonly termed “liquid-liquid” transitions, since in both phases proteins are dispersed in an aqueous solvent—the protein rich and poor phases being, respectively, the liquid and the gas in the present (implicit solvent) model.

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