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## A Thermodynamics Model for the Emergence of a Stripe-like Binary SAM on a Nanoparticle Surface

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### Abstract

It has been under debate if a self-assembled monolayer (SAM) with two immiscible ligands of different chain lengths and/or bulkiness can form a stripe-like pattern on a nanoparticle (NP) surface. The entropic gain upon such pattern formation due to difference in chain lengths and/or bulkiness has been proposed as the driving force in literature. Using atomistic discrete molecular dynamics simulations we show that stripe-like pattern could indeed emerge, but only for a subset of binary SAM systems. In addition to entropic contributions, the formation of a striped pattern also strongly depends upon inter-ligand interactions governed by the physicochemical properties of the ligand constituents. Due to the interplay between entropy and enthalpy, we can categorize a binary SAM system into three different types depending on whether and under what condition a striped pattern can emerge. We hope our results help clarify the ongoing debate and our proposed principle can aid in the engineering of novel binary SAMs on a NP surface.

Formation of self-assembled monolayer (SAM)<sup>[1,2]</sup> is widely used in nanoparticle (NP) synthesis<sup>[3]</sup> and functionalization.<sup>[4]</sup> Different ligands can also assemble to form a mixed SAM in order to serve for multiple purposes and functions.<sup>[5,6]</sup> For instance, binary SAMs (bSAM) of two immiscible ligands of different chain lengths and/or bulkiness have been proposed to render a stripe-like pattern on gold NP (AuNP) surfaces.<sup>[7]</sup> Given challenges in characterizing the SAM structures on NP surfaces,<sup>[8]</sup> computational modeling<sup>[9–13]</sup> has been applied to bridge experimental observations and the actual molecular systems. Computational studies using both molecular dynamics (MD) and dissipative particle dynamics<sup>[9,10]</sup> suggested that such a striped pattern formation was driven by the gain of interface entropy upon partitioning into thin stripes on the curved NP surfaces. Coarsegrained simulations and theoretical analysis<sup>[11,12]</sup> found that differences in local curvature of non-spherical NPs could lead to a stripe-like microphase separation. Interestingly, although curvatures were found important in these computational and theoretical studies.<sup>[9–12]</sup> Monte Carlo simulations suggested that such a microphase separation may also take place on a planar surface.<sup>[13]</sup> Based on the entropy-driven principle.<sup>[9]</sup> AuNPs coated with two types of immiscible thiolated ligands of different chain lengths were synthesized for a range of novel

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applications, such as membrane penetration,<sup>[14,15]</sup> ion sensing,<sup>[16]</sup> and antifouling<sup>[17]</sup>. However, experimental evidences for the existence of striped patterns on NPs have been questioned lately,<sup>[18,19]</sup> partly because of the limitations of the adopted experimental methodologies. Therefore, we proposed to re-examine the entropy-driven principle for the generation of striped NPs due to the vast potential applications at stake.

Here, we applied atomistic discrete molecular dynamics (DMD) simulations to study the structure and distribution of bSAMs on NP surfaces. DMD is a special MD approach<sup>[20]</sup> featuring rapid dynamics sampling, which has been applied to delineate the structures and dynamics of biomolecules and engineered nanomaterial systems.<sup>[21,22]</sup> In these simulations, we did not model the exchange process between NP-bound and solution ligands,<sup>[4]</sup> which mainly occurs during the initial synthesis of the bSAM.<sup>[14–17]</sup> We only considered the cases where thiolated ligands could diffuse laterally on the NP surface to render equilibrium distributions.<sup>[23,24]</sup> Experimental studies suggested that non-diffusive ligands at room temperature may become mobile at elevated temperatures which would allow redistribution of the ligands.<sup>[25]</sup> In the latter case, the corresponding equilibrium states at high temperatures may be "frozen" when the system is guenched to room temperature as observed in the glass transition. We used all-atom representations to model each ligand, constrained the corresponding sulfur atom on the surface of an implicitly modeled NP, and assigned hard-sphere interaction between the NP and other ligand atoms to mimic the steric effect (Methods in Supplementary Information, SI). We assumed that the molecular systems were in equilibrium at physiological conditions and modeled inter-atomic interactions with van der Waals, solvation, hydrogen bond, and electrostatics. We did not model the recently observed Au-adatom-dithiolate structures.<sup>[26]</sup> The corresponding effect of covalent-like constraints between ligands<sup>[27]</sup> as well as the effect of ligand exchange require future studies with more complex molecular systems. We used an implicit solvent model, the effective energy function (EEF1) in CHARMM<sup>[28]</sup>, to compute the solvation energy; and the Debye-Hückel approximation to model the screened electrostatic interactions between charged atoms. The Debye length was approximately 1 nm by assuming water relative permittivity of 80, and a monovalent electrolyte concentration of 0.1 M. We did not include neutralizing counterions explicitly in our simulations.

We first simulated two model systems that have been experimentally studied, including one with hydrophobic and charged ligands,<sup>[7]</sup> and another composed of hydrophobic and polar (neutral) ligands<sup>[16]</sup> (Fig. 1A and D). For comparison between the two molecular systems, we chose ~1:1 molar ratio although a 1:3 ratio was used for the latter case experimentally<sup>[16]</sup> (the effect of unequal mixture will be discussed later). The ligands with a number density of ~7.9/nm<sup>2</sup> were mixed on the surface of a NP of 4 nm in diameter. For the first system, thiolated hydrophobic octane (OT) and 3-mercaptopropionic acid (MPA) were mixed (Fig. 1A). To ensure equilibrium achieved in simulations, we started from three different initial configurations including mixed, striped, and phase-separated states, and performed constant temperature simulations (~100 ns) at temperatures from 250K to 300K. For the striped starting configuration, we assigned an ideal conformation with a stripe-separation of approximately ~2 nm as suggested experimentally.<sup>[7]</sup> Starting from different initial states, the molecular system rapidly reached similar potential energies (e.g. trajectories of potential energies at T=300K in Fig. 1B). Examination of structures along the trajectories indicates

that all simulations also reached similar configurations, which resembled the striped state. While the overall morphology of ligand distributions remained similar, the fine structures were highly dynamic (e.g. snapshots along the simulation trajectories in Fig. S1). We computed the time-averaged radial distribution function, g(r), for each type of ligand to characterize the corresponding equilibrium distribution. For comparison, we also computed g(r) for all the ligands assuming that the two types are indistinguishable, corresponding to the mixed state; as well as g(r) for the ideal striped state (Fig. S2). To better assess the formation of patterns, we used g(r) of random distribution as a reference and computed the normalized  $g^{*}(r)$  for each type of ligands (Fig. 1C). We found that the equilibrium state featured a similar periodicity as the ideal striped state. However, at longer distances the equilibrium state is less ordered, with the amplitude of  $g^*(r)$  approaching random distribution. The observed equilibrium patterned state with a weak long-range order at distances much larger than the interaction range of inter-atomic interactions (e.g. compared to the Debye length of  $\sim 1$  nm) is consistent with previous computational studies.<sup>[9,10]</sup> In the second system, thiolated linear hexane (S-C6) ligands with and without addition of polyethylene glycol (S-C6-[OCC]<sub>n</sub>-OH, with n=1,2,3) were mixed<sup>[16]</sup> (e.g. n=1 in Fig. 1D). Similarly to the OT/MTA system, we observed equilibration in simulations independent of the initial states (e.g. Fig. 1E). A major difference between this and previous system is the equilibrium states, where in this system the two ligand types became mixed within the simulated temperature range, as indicated by the normalized  $g^*(r)$  calculated for each ligand type (Fig. 1F). Taken together, our results revealed that mixing two immiscible ligands of different chain lengths does not always render striped patterns on NP surfaces.

Next, we evaluated factors that contribute to the pattern formation. We first considered entropic contributions to the free energy of a given state. The total entropy has two major components, including mixing and interface entropy. In terms of the mixing entropy, the mixed state assumes the highest value, the phase-separated state the lowest value, and the striped state with partial mixture has the intermediate value. The interface entropy originates from differences in either chain lengths or bulkiness. With ligands of different chain length, the interface entropy is related to the conformational spaces available for the ligands, especially for the longer ligands as noted before.<sup>[9,10]</sup> On average, a longer ligand in a mixed state usually has shorter ligands as its neighbors, while the same ligand in the phaseseparated state is more likely to be close to other longer ones. Due to steric hindrance by neighbors, the available conformational space is the largest for the mixed state, smallest for the phase-separated state, and intermediate for the striped state (Fig. 2A). Therefore, a gain of conformational entropy of longer ligands accompanies the gain of mixing entropy. Similarly, (partially) mixing of objects with different bulkiness results in a higher packing density compared to the phase-separated state (Fig. S3). In other words, with a fixed ligand density on NP surface, each ligand in the (partially) mixed state has a higher available volume on average and thus a higher translational entropy compared to the phase-separated state. We note that the described phenomenon is different from the depletion-attractiondriven phase-separation,<sup>[29]</sup> where a major assumption is the dominance of total entropy of one component of higher abundance than the other component of lower abundance. The effective attraction results from the entropic gain of the dominant component, which is larger than the entropic loss of the other component upon self-association. However, in the case of

large/small bSAM systems, both ligands are mixed with comparable amounts and none of two components plays a dominant role. Taking together, we conclude that  $S_{mixed} > S_{striped} > S_{separated}$  and note that such a relationship is not limited to spherical substrate systems<sup>[13]</sup>.

At a given temperature T, the state with the lowest free energy F corresponds to the equilibrium state. Assuming potential energy U and entropy S of a given state do not change with T, we have a linear dependence of F with respect to T(e.g. plots in Fig. 2B). We note that the vibrational component of the total U is usually linearly dependent on T, but the coefficients for different states should be the same due to the same ligand composition. Therefore, inclusion of the vibrational energy does not change the relative F of different states. Because two ligand types are immiscible, it is expected that the phase-separated state has a lower U than the mixed state,  $U_{mixed} > U_{separated}$ . Similarly, it is expected that  $U_{mixed} > U_{striped}$  since the striped state also features a partial phase separation. The question comes down to the relationship between Ustriped and Useparated. For two model systems simulated above, we computed the potential energies at a low temperature for different states (Methods). Interestingly, we found that at 1:1 molar ratio the OT/MPA system had  $U_{striped} <$ Useparated, while Ustriped of the S-C6/S-C6-[OCC]<sub>n</sub>-OH system was larger than Useparated (see computed potential energies of different states in Table S1). Based on the relative value of  $U_{striped}$  with respect to  $U_{mixed}$  and  $U_{separated}$ , we propose the feasibility of three types of bSAM systems depending on the available equilibrium states (Fig. 2B). Specifically, a type-I system has only two stable states - the phase-separated state at low temperature and the mixed state at high temperature. For the type-II system, the striped state can be populated at intermediate temperature. As for the type-III bSAM, the distribution of ligands stays as striped at low temperature and becomes mixed at high temperature. For instance, the OT/MPA system belongs to type-III, while the S-C6/S-C6-[OCC]<sub>n</sub>-OH system is likely type-I or type-II. The reason that we did not observe the phase-separated state for the second system was possibly because its separated/mixed phase transition temperature was below the simulated temperature range. To evaluate the effect of unequal mixing, we performed a similar potential energy calculation for S-C6/S-C6-[OCC]<sub>n</sub>-OH at a 1:3 molar ratio (Table S1). We found that changes in the mixing ratio did not affect the relative potential energies of different states while the absolute values of energy differences became smaller. It is interesting to note that the energy differences for n=1,2 were relatively small compared to other systems. Especially, in the case of n=1, the conformational entropy differences between states were also small, making the distinction of different states difficult, which might explain the experimentally observed different states for the same bSAM system using different synthesis approaches.<sup>[16]</sup> To further verify our proposed model, we next searched for a model bSAM system that behaved like the type-II.

The differential inter-ligand interactions between the above two systems arise from the difference in the charge state of the hydrophilic ligands, where MPA are negatively charged and experience electrostatic repulsion with each other. We hypothesized that the repulsion among one type of ligands might be important for the striped pattern formation. Therefore, we constructed a simple bSAM system composed of two types of linear chains (Methods; Fig. 3A). We assigned attractions between atoms of the same ligand type, and hard sphere interactions between atoms of different ligand types, so that the two ligands were usually

immiscible. We assigned a repulsive interaction potential between the tail atoms of the short ligand. For simplicity, we only varied the interaction strength of the tail-tail repulsion,  $\varepsilon_{rep}$ , and estimated the potential energies U of three different ideal states (Fig. 3B). We found that the relative U values of different states indeed changed with respect to  $\varepsilon_{rep}$ . With a weak repulsion,  $U_{striped}$  is closer to  $U_{mixed}$  and we expected the system to behave like the type-I bSAM (Fig. 2). With a very strong repulsion,  $U_{striped}$  became even lower than  $U_{separated}$ , resembling the type-III bSAM. We expected that a system with the  $\varepsilon_{rep}$ ~6.0 kcal/mol right before the crossover likely belonged to the type-II.

We performed simulations at a wide range of temperatures to study the dynamics of the model system with  $\varepsilon_{rep}$ =6.0kcal/mol (Methods). At low temperatures (e.g. T<0.8 kcal/mol/ $K_B$  in Fig. 4), the phase-separated state remained separated or in an intermediate state (e.g. snapshot structures at 0.6 and 0.7 kcal/mol/K<sub>B</sub>, Fig. 4B) with lower potential energies, compared to two other simulations starting from either mixed or stripe-like state. In the latter two cases, the system was either converted to or remained in the striped state with a higher potential energy. The displayed hysteresis suggests a first-order phase transition between separated and striped states with a high free energy barrier compared to thermofluctuations at low temperatures. This result also suggests that the free energy barrier between mixed and striped states was relatively small. At higher temperatures T 0.80 kcal/mol/ $K_B$ , independently from the starting conformation, the molecular system reached the same equilibrium states with similar potential energies and distributions of ligands (Fig. 4A,B). For instance, at T=1.0kcal/mol/ $K_B$ , the equilibrium state resembled the striped state with a weak long-range order according to the calculated  $g^*(r)$  plot (Fig. 4C). As T increased, the periodicity became weaker and then eventually disappeared, and the mixed state became most stable (e.g. T=3.0 kcal/mol/ $K_B$ ). Hence, with increasing temperature the thermodynamically stable distribution of ligands of the model system changed from separated to striped and then to mixed state, behaving like a type-II bSAM as predicted (Fig. 2B).

Our thermodynamics model is centered on the relationship of U and S between different states. Even without the contribution of conformational entropy due to the differences in ligand lengths and sizes, the mixing entropy for different states should still obey the relationship of  $S_{mixed} > S_{striped} > S_{separated}$ . Therefore, ligands of the same length and size can also have striped patterns as observed in previous simulations.<sup>[10]</sup> Our model does not exclude the possible role of entropic gain in pattern formation due to the disparity in ligand lengths. With increases in the length difference between chains, we expect increases of entropy difference (e.g. Fig. 2) for the patterned and mixed states with respect to the phaseseparated one. Such changes in S might lead to a transition from the non-striped type-I system to the type-II (Fig. S4), allowing observations of striped patterns.

In sum, our study revealed that striped domain separation could indeed take place on NP surfaces, but only for a subset of molecular systems. The striped pattern formation strongly depended upon the physicochemical characteristics of composite ligands that dictate their interactions. Our results also suggest that the effective repulsion between one of ligand types of a bSAM, e.g. electrostatic repulsion, was important for the formation of stable stripe-like patterns. Due to its simplicity and predictive power, we hope that this model helps clarify the

ongoing debate regarding the feasibility and origin of striped pattern formation on spherical NPs and anticipate the proposed design principle can aid in the engineering of novel bSAMs with regulated ligand distribution on a NP surface for applications in chemical and materials synthesis, nanobiotechnology, environmental sensing and nanomedicine.

#### Supplementary Material

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#### Figure 1. DMD simulations of two experimental binary SAM systems

(A, B, C) thiolated OT and MTA, and (D, E, F) thiolated linear hexane (S-C6) with and without the addition of polyethylene glycol (-[OCC]<sub>n</sub>-OH, n=1,2,3; only results of n=1 were shown here). (A, D) The schematic diagram of ligands used in simulations. (B, E) The trajectories of potential energy as the function of simulation time, in DMD time unit (t.u., see Methods). The results were obtained from DMD simulations at 300K with three different initial configurations including mixed, striped and separated states. The initial and final structures with each ligand shown in spherical reorientation (long ligands in red and short ones in cyan) were shown as inset. (C, F) The normalized radial distribution function,  $g^*(r)$ , as the function of geodesic distance, *r*, for each type of ligands, 1 & 2. Only simulations with different starting structures reached equilibrium. For comparison, the  $g^*(r)$  functions for the ideal striped conformation were shown in gray.



#### Figure 2. Estimation of free energies for different states

(A) Three-dimensional structures (top) and corresponding schematic diagrams (bottom) illustrate difference in available conformational space for each of the three states, including Mixed, Striped, and Separated, due to steric hindrance. (B) Free energy as a function of temperature. Due to differences in relative potential energies, a binary SAM system can be categorized into three different types based on available equilibrium states (illustrated by the shaded regions) from low to high temperatures: Separated/Mixed for type I, Separated/ Striped/Mixed for type II, and Striped/Mixed for type III.



Figure 3. The model binary SAM system

(A) Schematic diagram of the model system (left) and the assigned interaction potential as the function of inter-atomic distance (right). The details are described in the Methods section. (B) The total potential energies for different states were estimated as a function of the repulsive energy,  $e_{rep}$ .



#### Figure 4. DMD simulations of the model binary SAM system with *e*<sub>rep</sub> = 3.0 kcal/mol

(A) Starting from different ligand distributions, average potential energies of the stable or metastable states in simulations were computed as a function of temperature with standard deviations denoted as error bars. The results were shown for simulations at a wide range of temperatures, varying from 0.5 kcal/mol/ $K_B$  to 3.0 kcal/mol/ $K_B$ . The left panel corresponds to the zoomed-in view at low temperatures, highlighting the hysteresis between the separated-to-striped transitions. (B) Final snapshot structures of the simulations starting from different states at various temperatures. The final structures of the simulations starting from the separated state at T=0.6 & 0.7 kcal/mol/ $K_B$  (inside the dashed box) resembled the intermediate between separated and striped states. (C) The normalized  $g^*(r)$  for simulations at T = 0.5, 1.0, and 3.0 kcal/mol/ $K_B$ . At T = 0.5 kcal/mol/ $K_B$ ,  $g^*(r)$  was computed from simulations with an initially separated state, showing the system maintained its state. At

higher temperatures, we computed the  $g^*(r)$  functions using simulations starting from the mixed state.