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Focus Article

A review of molecular phase separation in binary self-assembled monolayers of thiols on gold surfaces

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Abstract – Binary self-assembled monolayers (SAMs) on gold surfaces have been known to undergo molecular phase separation to various degrees and have been subject to both experimental and theoretical studies. On gold nanoparticles in particular, binary SAMs ligand shells display intriguing morphologies. Consequently, unexpected behaviors of the nanoparticles with respect to their biological, chemical, and interfacial properties have been observed. It is critical that the phase separation of binary SAMs be understood at both molecular and macroscopic level to create, and then manipulate, the useful properties of the functionalized surfaces. We look into the current understanding of molecular phase separation of binary SAMs on gold surfaces, represented by Au(111) flat surfaces and Au nanoparticles, from both theoretical and experimental aspects. We point out shortcomings and describe several research strategies that will address them in the future.

Introduction. – Thiol molecules are known to bind and order spontaneously on gold (Au) surfaces, a well-known example of self-assembly (SA) [1]. The SA occurs via a chemisorption process driven by the formation of the strong covalent S-Au bond at 45 kcal/mol. At sufficiently high surface coverage, the thiols assume a tightly packed arrangement extending from the surface maximizing the intermolecular van der Waals forces and the sulfur density on the surface. As “bottom-up” approach, SA of thiols is an attractive way to create organic coatings, and manipulate their properties through the functionalities of constituent thiol molecules. Several reviews have been dedicated to the chemistry and utilization of thiolated SAMs [1–4].

Mixtures of thiolated molecules are often utilized to functionalize flat Au surfaces or Au nanoparticles (AuNPs), due to the need for diverse functionalities on the substrates. The preparation of such a mixed monolayer is commonly divided into two methodologies:

1) co-adsorption of the thiols;
2) the so-called ligand exchange reaction when one ligand is displaced by the addition of a second. Here, not only the surface composition but also the distribution of thiols influences properties of the resulted binary SAM. For the latter, many interesting observations have been documented regarding the molecular phase separation (PS) of binary SAMs on both Au(111) surfaces and particularly AuNPs.

The focus of this article is to consider our current understanding of PS in mixed SAMs of thiols, by examining their morphology on both Au(111) flat surfaces and AuNPs. It is concerned mainly with two-component, i.e., binary, SAMs that are made of small thiol molecules. We draw prominent examples from the literature on self-assembly of binary SAMs on these two kinds of surfaces in order to present an overview of this field, the current challenges, and the future needs.

Molecular phase separation of binary SAMs on Au(111) surfaces. –

Observations. Binary-SAM functionalized surfaces exhibit various degrees of PS [5–28]. Mixtures of CH$_3$-terminated alkylthiols with chain length differences of
several CH$_2$ units have been shown to display mainly a patchy morphology. Chen et al. studied the effect of chain length difference and preparation methods on the PS of binary CH$_3$-terminated alkylthiols. C8 was combined with C12, C14, C16, and C18, in a study where Au substrates were immersed in 1 mM solution of thiols at room temperature and at 50°C. It was found that the PS was readily observed for C8/C16 and C8/C18 pairs, whereas for C8/C14 PS did not occur when the sample was prepared at 50°C, but patchy domains formed at room temperature. When the chain length difference was 4 carbons (C8/C12), a homogeneously mixed surface was present at both temperatures [6]. A similar binary SAM of C8/C12 prepared by co-adsorption at room temperature was studied at various ratios by Kim et al. [7]. Small patchy domains in the order of several nm$^2$ were observed. Binary SAMs of thiol pairs with large difference in chain length were studied by Tamada et al. [8]. For C4/C18, with solution composition ratios from 20/1 to 40/1, deposited from mixtures in ethanol, strong PS occurred. If instead, the solution composition was outside of this range, homogeneously mixed surfaces were obtained.

Although less reported, homogeneously mixed surfaces are found in mixtures of thiols with large differences in chemical structure. For example, homogeneously mixed SAMs were found in a binary mixture of 3-mercaptopropionic acid (MPA) and 11-mercaptopoundecanoic acid (MUA) [9]. Likewise, a binary SAM of C11/MUA shows no distinct domain formation [10]. Anderson et al. reported that a binary SAM of C10/C12 prepared by co-adsorption yielded a randomly mixed surface. However, upon annealing and back filling with a second thiol, a patchy surface was created [11]. Interestingly, even a mixture of two thiol molecules of the same chain length but with different head groups can lead to patchy domains. Stranick et al. have shown that in a binary SAM of C16/CH$_3$O$_2$C(CH$_2$)$_{15}$SH, PS occurred resulting in irregularly shaped patchy domains of several nm$^2$ in size, (fig. 1) [5]. Similarly, Brewer et al. later showed that the presence of a hydroxyl terminal group could also drive PS. The thiols used were C12 and mercaptopoundecanol HS(CH$_2$)$_{11}$OH that have similar molecular length but the latter bearing a hydroxyl head group. The binary SAMs were characterized by friction force microscopy and chemical force microscopy that indicated the presence of small (approximately 15 nm$^2$) phase separated domains [12].

The combination of a CH$_3$-terminated alkylthiol with another thiol that has a very different chemical structure has been also studied. Binary SAMs of an aliphatic and an aromatic thiol were demonstrated by Fitzgerald et al. using C8/biphenyl-4-thiol mixtures [13]. The C8 was deposited via a vapor deposition technique. The second step involved the immersion of the C8 SAM in a solution of the biphenyl-4-thiol. The place exchange reaction of these thiols that have different molecular lengths led to a PS with clearly identified disordered patches [13]. Lüssem et al. showed that patchy domains and isolated ligands were obtained via solution immersion of a C12 SAM in a 4'-methyl-1,1'-biphenyl-4-butane (BP4) solution [14]. The patches of BP4 formed due to its insertion at defect sites of the C12 SAM. Isolated BP4 molecules were also observed inside C12 domains by high-resolution scanning tunneling microscopy (STM). Hobara et al. studied binary SAMs of C11/11-mercaptopoundecanoic acid and C16/ mercaptopropionic acid and found strong PS. Inspection by STM imaging revealed patchy domains with tens of nm in dimensions [15]. Hayes et al. demonstrated that the binary SAM of 4-aminothiophenol (4-ATP) and C18 yields a micellar form of PS in which islands of 4-ATP are surrounded by close-packed C18 molecules at low 4-ATP/C18 molar ratio. However, at a relatively high molar ratio, a mixture of both distinct phases and homogeneous mixing is found [16]. The combination of a long alkanethiol with a short carboxyl-terminated thiol seems always to result in patches. Munakata et al. systematically investigated binary mixtures of MPA with C8, C10, C12, and C16, respectively, and found that all mixtures yield distinct patchy domains [17]. The presence of a hydrogen bonding functionality in one component can enhance intramolecular interactions and hence induces stability in the PS. This was demonstrated by Lewis et al. for a mixture of C10 with an amide-containing alkanethiol (3-mercaptopropionamide, or similar derivatives bearing two or three amides), patchy domains form spontaneously at all compositions [18,19].

The progression of domain formation is scarcely reported. One exception is a case study by Tantakitti et al. where a binary SAMs of a synthetic tetrasaccharide-terminated oligo(ethylene glycol) thiol and a hydroxyl-terminated oligo(ethylene glycol) thiol (OEG) were examined with time [20]. The binary SAMs were made by co-deposition from aqueous solution. Patchy domains formed upon adsorption and over the course of 4 weeks.
the domains enlarged. The morphology of the surface was shown to be highly dependent on the molar ratio of the sugar terminated thiol to the OEG. At low molar ratio the morphology was micellar or island-like, whereas worm-like or continuous clustering was observed at high molar ratio (fig. 2).

This nonexhaustive list of examples for molecular-PS in binary SAMs points to a diverse range of surface morphologies, indicating that a slight change in molecular structure of one component can result in a drastic change in the form of the PS. Additionally, binary SAM morphology is substantially influenced by the preparation method.

Current understanding and challenges. When a SAM is composed of two or more components, the self-assembly is controlled by intra- and inter-molecular interactions. In general, the molecular organization is dictated by weak non-covalent chemical interactions that include van der Waals, π-π, and electrostatic interactions. Let us consider the example of alkanethiols; here the strength of tail-tail interactions shows the following preference: long-long > short-short > short-long. Steric considerations also have a significant impact on the formation and the final morphology of the SA. The PS thus reflects differences in chemical functionality, length, and bulkiness between molecular components and their resulting differing interactions in solution and at the solid-liquid interface.

From a thermodynamic point of view, it has been suggested that molecular PS is caused by the competition between enthalpic energy gain due to the alkyl chain van der Waals interactions and the entropy of mixing favoring the random distribution of one component into the other. Molecular PS therefore occurs only if the enthalpy exceeds the entropy was not taken into account, a weakness of the

**Fig. 2:** (Colour online) AFM images (scale bar: 100 nm) of binary SAMs on a gold surface as a function of time. “Low” sugar and “High” sugar represent mixed SAMs of sugar/OEG prepared with 2:3 and 4:1 molar ratios, respectively. Reproduced from ref. [20].

**Fig. 3:** Partial phase diagram calculated for a binary system of benzenethiol/C12. Spinodal and binodal curves are represented by a dashed and a solid curve, respectively. The experimental data is illustrated by the horizontal dashed line for the composition x (mole fraction of benzenethiol) from 0.11 to 0.25. Reproduced from ref. [22].

strong intermolecular interactions, is slow, thus hindering the thermodynamic equilibration. Here, one needs to also make a distinct difference between the PS in the presence or absence of reservoir of thiols, because in the former there is continuous exchange of thiols between the film and solution. Progress towards thermodynamic equilibration can, however, be accelerated by heating the thiolated surfaces in a neat solvent, for instance.

A phase diagram for binary SAMs would be of great utility but is yet to be constructed experimentally. Instead, Yaliraki et al. used mean-field theory in an attempt to theoretically evaluate the phase diagram of binary SAMs of benzenethiol/C12 and corenoid/alkanethiol mixtures [22]. A typical phase diagram temperature-composition T-x is presented in fig. 3. There, one can find a range of composition and temperature conditions for which the binary SAM is unstable and PS is expected thermodynamically. The region between the binodal (solid curve) and spinodal (dashed curve) curve is where the film is metastable. However, in this region due to the translation of thiols on the surface, patchy domains can form. Homogenously mixed surfaces are expected thermodynamically outside this region. It remains an experimental challenge to record the molecular-PS states for a range of temperature and composition presented in such a simple phase diagram.

Shevade et al. studied the molecular PS of binary SAMs by configurational-bias Monte Carlo simulations and concluded that PS which results in patchy domains occurs if the two thiols have a difference larger than 3 carbon atoms in their hydrocarbon chain (fig. 4) [23]. Therefore, in the binary SAMs of C10 thiol with C11, C12, or C13 a mixed configuration is expected, whereas binary SAMs of C10 thiol with C14, C15, C16, C17 or C20 thiols should yield patchy domains. Recently, Nassoko et al. have explored theoretically a series of binary SAMs that are composed of two dissimilar thiol molecules [24]. Based only on the energy of adsorption, it was put forward that all combinations led to PS. However, the conformational entropy was not taken into account, a weakness of the
achieved by any current lithographic approaches. In our previous studies, we fabricated surface structures that go below the minimum size achievable by any current lithographic approaches. Here, there is an excellent opportunity to generate surface structures that go below the minimum size. This is especially true for those surfaces studied microscopically. For the patchy surfaces observed and reported, it should be mentioned that the stripe-domains are complex, showing variation in length [40]. Many techniques have been used to determine the actual phase composition. In our own preliminary study, both theory and experiment have pointed out the possibility of making nanoscale patterns from such PS.

Molecular phase separation of binary SAMs on Au nanoparticles. – Observations. It has often been observed that for binary-SAM–coated AuNPs, unusual properties of AuNPs appear that can no longer be explained satisfactorily only by the composition of the SAM, also known as the ligand shell. For example, nonlinear colloidal solubility with respect to the composition of the ligand shell was demonstrated in Centrone et al. [31]. Protein adsorption onto AuNPs with the ligand shell PS into stripe-like domains behaved differently from the AuNPs with randomly distributed mixed head groups or homogeneously charged head groups [32]. Many other unusual properties of Au nanoparticles conferred by the binary ligand shell have been reported. Those properties include catalysis, cell penetration, adhesion, and sensing that can be exploited for many applications. For example, stripe-like domains in the ligand shell of AuNPs help them spontaneously fuse with lipid bilayers [33]. This kind of nanoparticle has also been shown to be internalized by cells without bilayer disruption [34]. Recently, stripe-like domains in the ligand shell were demonstrated to be an excellent sensing platform for heavy metal cations [35]. In order to fully exploit AuNPs and to understand how new properties arise, it is critical to know not only the composition but also structure and morphology of the binary ligand shell.

Many articles have shown PS as well as randomly mixed phases of the binary SAMs ligand shells. In a seminal work by Jackson et al., a binary mixture of C8/MPA was used to functionalize AuNPs (d ∼ 4.0 nm), and stripe-like domains were discovered in the ligand shell at all compositions tested [36]. In several mixtures of dissimilar molecules such as 4-mercaptop-1-undecanol (C11ol)/4-mercaptop-1-butanol (C4ol), C8/MPA, C12/C6, and C9/4-methylbenzenethiol (MBT), stripe-like domains were also observed [37–39]. This unusual type of domain has a spacing of 1 nm, or the thickness of a single molecule. Along the domains, the thiols are molecularly packed with the intermolecular distance of 0.5 nm, close to that of thiols on a Au(111) surface. Detailed observations have highlighted that the stripe-domains are complex, showing variation in thickness and defects along and between the domains [37]. Binary SAMs of C11 and C8, however, have been confirmed to show only random structures despite their difference in length [40]. Many techniques have been used to determine PS on NPs. The original approach used scanning tunneling microscopy (STM). The technical issues with this approach were discussed in the literature, and the issues raised have been fully addressed [41,42]. Additional experimental techniques and a large number of simulations have fully confirmed PS in NPs. A completed discussion on this topic can be found in two recent reviews [43,44].
Various degrees of PS, from small domain patchiness to a complete PS, i.e., the Janus structure, have been demonstrated in binary ligand shells. Harkness et al. explored a series of combinations of two thiols using mass spectrometry and quantitatively estimated the degree of patchiness in the ligand shell that deviates from theoretical binomial distributions [45]. Merz et al. and Farrell et al., using the same method, systematically studied the correlation of length mismatch in binary mixtures of alkanethiols with patchiness [46,47]. On silver NPs, it was found that C12/C4 combination formed Janus or striped structures, while C12 combined with C11 to C5 showed a progressively decreasing degree of patchiness [46,47]. Posocco et al. studied the PS of binary SAMs of PEG-derived alkylthiols where one of the components was perfluorinated. The role of the chemical functionality, composition, and particle size on the formation of patchiness was studied [48]. With respect to the particle size, it was concluded that for small particles (d < 2 nm) there was a strong tendency to form Janus morphology while at larger size, striped domains could be observed. Kim et al. studied larger ligands with significant difference in functionality such as polystyrene (dPS) and poly(methyl methacrylate) [49]. The authors demonstrated that if the two high-molecular-weight ligands were used, Janus morphology formed, while for a combination of lower-molecular-weight thiolated polymers, random ligand arrangement or small patches were obtained [49].

It has been noted that the arrangement of thiols was sensitive to AuNPs synthesis technique. Harkness et al. first observed that binary SAMs of AuNPs made by the ligand exchange reaction showed more PS than those made from direct synthesis techniques [45]. The effect of synthesis was clearly demonstrated by Iida et al. in a recent paper where mixed SAMs made of EG-derived alkylthiol of various lengths were examined (hexaethylene glycol ligands with different alkyl chains from C3, C7, to C11) [50]. In a one-step technique in which citrate-coated AuNPs were dispersed in a solution containing both E6C3 and E6C11, the authors found that the resulting binary ligand shell adopted random or patchy morphology. In a two-step approach, E6C3 was first used to replace citrate on gold nanoparticles. The E6C3-coated nanoparticles were dispersed in a solution containing the second thiol E6C11 to make binary-SAM–coated AuNPs of the same size as those in the one-step approach. In stark contrast to the one-step process, the partial ligand replacement reaction in the two-step method induced a Janus-type morphology (fig. 5).

By utilizing the ligand exchange reaction, one can easily make binary-SAM–coated AuNPs, and the resulting ligand shell displays a variety of morphologies. However, how ligand shell morphology evolves during the course of the reaction has not been not known until recently (fig. 6) [51]. Biphenyl-4-thiol (BPT) was added to a chloroform dispersion of mono-dispersed C12 functionalized AuNPs under vigorous stirring. As the ligand exchange proceeded, the reaction was quenched at several time points by excess methanol, and the nanoparticles were washed and then inspected by MALDI-TOF. It was found that at 5 minutes of reaction time, 9% of BPT was found on the surface of the particles, and the ligand shell assumed random distribution. PS started to appear when the composition of BPT reached about 18% (30 minutes of reaction time).
and strong PS occurs after 8 hours (32%) when coverage is almost saturated. Afterwards, the ligand exchange reaction drastically slowed down and the ligand shell kept evolving and finally yielded a patchy domains. In a reaction where the concentration of precursors was increased 10-fold, the same morphological evolution was also observed; that is the BPT ligand replaced C12 on the AuNPs surface in a random fashion in the beginning and then patches developed over time. In the same fashion, 4-butanethiol (BT) replaced C12 on AuNPs and formed small patchy domains in the ligand shell in the end. When the ligand exchange reaction was performed for deuterated C12 (dC12) on C12-coated AuNPs, it had been expected that the PS should be minimal due to the similarity of these two molecules. Indeed, the final morphology of the binary-SAM ligand shell was found to be randomly mixed. However, following the time course of the reaction, it was clearly revealed that this randomly mixed shell evolved from patchy domains forming at the initial stage. In the beginning, the ligand exchange reaction proceeded quickly, yielding about 16% dDDT after 5 minutes. Hence, it was suggested that the kinetics of the ligand exchange reaction dictated the initial morphology of the ligand shell. Similarly, for the C11 replacement reaction with C12-coated AuNPs, it was found that the ligand shell was patchy initially and gradually evolved into a random arrangement after 24 hrs.

Current understanding and challenges. It is generally understood that Janus ligand shell morphology forms when a mixture of highly incompatible molecules are used. In this case, to avoid the energetic penalty from enthalpy, single-component domains occupy on opposite sides of the nanoparticle. At the other extreme, where highly compatible molecules are used, homogeneous mixing should occur in the ligand shell. It was pointed out that microscopic consideration of the molecular conformation was critical to determine the final morphology. In the case of stripe-like domains, for example, the gain in the conformational entropy at the domain boundaries was the key for their formation [52]. The enthalpic penalty of complete PS is counterbalanced by gains in the conformational entropy by the longer molecules by allowing them to bend over the shorter molecules in this pattern. When the length mismatch is sufficiently long, stripe-like domains should occur. The role of the conformational entropy, realized by the increasing free volume occupied by the tail of the long ligands, is directly linked to curvature of the substrate. In other words, the molecular PS on AuNPs is strongly influenced by the particle size. This is highlighted by both simulation and experiment, stripe-like domains form on AuNPs only at a certain size range, below which Janus morphology is favorable [53].

One might question if the stripe phase is actually the thermodynamic equilibrium state. Indeed, no experimental data has fully addressed this issue. Theoretical studies conducted by Fetisov et al. using a configurational bias Monte Carlo technique showed that a binary SAM of C6/C14 led to Janus-like morphology in the end. Stripe-like domains were also found but only transiently before the final Janus morphology was reached [54]. Ge et al. addressed the issue by atomistic discrete molecular-dynamics simulation of experimentally reported systems that present stripe-like domains in their ligand shells: C8/MPA and C6/ethylene glycol-terminated alkanethiols (n = 1, 2 or 3 ethylene glycol (EG) units) [55]. It was confirmed that the striped domains could actually be the thermodynamic equilibrium state. This state was highly selective for certain combinations of thiolated molecules.

In practice, a suggestion for the existence of kinetically trapped states is the variation of morphology reported for the same or similar mixtures as a result of different functionalization techniques [45,50]. Furthermore, the ligand shell was suggested to undergo morphological change depending on the environment [56,57]. In order to address this issue, it is possible to design an experiment where AuNPs are heated and held at various temperatures. Techniques such as SANS [38] are available to follow the change of the ligand shell, and mass spectrometry [51] for a quenched solution. From there, phase diagrams of the ligand shell can be constructed for the thermodynamic equilibrium morphology. Additionally the same composition of thiol molecules can be studied for both AuNPs and flat Au(111) surfaces, where the role of conformational entropy predicted theoretically can be actually confirmed and quantified.

It is worth noting that the morphologies reported are highly dependent on the capacity of the characterization technique to differentiate different morphologies. The reader is referred to the latest reviews to get an overview of the techniques available to characterize ligand shells of mixed SAM on AuNPs [43,44]. One of the great challenges for understanding molecular PS of binary-SAM-coated AuNPs is to develop a characterization tool or set of characterization tools to observe and quantitatively measure the ligand shell morphology.

Conclusions. In this article, we look at the molecular PS on binary SAMs of small thiol molecules on gold substrates. Despite the vast literature concerning the binary SAMs on both flat Au(111) surfaces and AuNPs, the details of how the separation proceeds and what equilibrium phase might form are still not well understood. This prompts us to look into the process from both theoretical and experimental directions in our future studies. The field is open for the development of theory/simulation, characterization tools and new experiments to understand this phenomenon fully.

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