CHEMISTRY IN CONFINING STRUCTURED SOLUTIONS

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Understanding the emergence of life – and designing synthetic life-like materials - appears to be largely rooted in uncovering how hierarchical molecular organization and corresponding spatial confinement facilitates far-from-equilibrium chemical transformations. For instance, reactions can be localized in “containers” such as organelles or transiently-formed droplets (e.g. biomolecular condensates [1]), taking place in crowded, complex environments ripe with interfaces. Even mixtures of small molecules, such as mixtures of water, oil, and cosolvents, can form nanoscale heterogenous domains in what otherwise appears by eye to be a single-phase solvent [2]. Chemicals partition in and out of these domains, thereby changing concentrations, creating gradients, may be protected from degradation, or experience a reaction environment with different physical properties that influence chemical reactivity [1]. Understanding and controlling how molecules distribute between phases in heterogeneous solvent environments, coupled with the tailoring of those environments, is critical to biasing outcomes of biological and chemical processes. How does solvent organization act as an “ingredient” to manipulate reaction kinetics, thermodynamics, chemical diversity, and chemical transformations? Like nature does, can scientists harness this relationship between solution structure and chemistry? The growing area of “systems chemistry” [3,4] often encompasses such questions. I will discuss two aspects related to these questions that we have been considering recently: 1) chemical partitioning in far-from-equilibrium phases [5], and 2) reaction kinetics in nanophase structured solvents [6,7].

Our contributions to understanding chemical partitioning in out-of-equilibrium phases. At thermodynamic equilibrium, equilibrium partition coefficients are employed to describe the distribution of molecules in a multiphase system. However, there are situations in which a system may be in a multiphase state only transiently, when far from equilibrium. One such example is that of oil-in-water droplets. Emulsion droplets, in general, are not at thermodynamic equilibrium and undergo processes like ripening, coalescence, dissolution, and solubilization. A droplet may exist for hours or days but disappear at equilibrium. Partitioning of molecules into a droplet can thus still occur while the droplet exists, but an equilibrium partition coefficient would not be definable (Fig. 1).

Recently, we characterized the partitioning of nonionic surfactant molecules in such a nonequilibrium multiphase system, wherein a microscopic oil droplet shrinks in volume over time and the equilibrium mixture of oil, water, and surfactant forms a single macroscopic phase [5]. We found that, within minutes, the surfactant concentration inside the droplet increased and reached a steady state (C_O^{ss}) (Fig. 1). In some cases, this steady state concentration was orders of magnitude higher than the aqueous phase surfactant concentration. As the oil droplet slowly lost volume over time due to solubilization, the accumulated surfactant (and oil) was, necessarily, released back into the continuous phase upon approach to equilibrium. This temporal release was a source of persistent, steep concentration gradients of oil and surfactant around the droplet which modified interfacial tensions and interfacial flows in non-intuitive ways. The timescales and length scales were important considerations, where the size of the droplet mattered, and the mismatch in rate of transport of oil out of the droplet compared to that of surfactant into the droplet was critical.

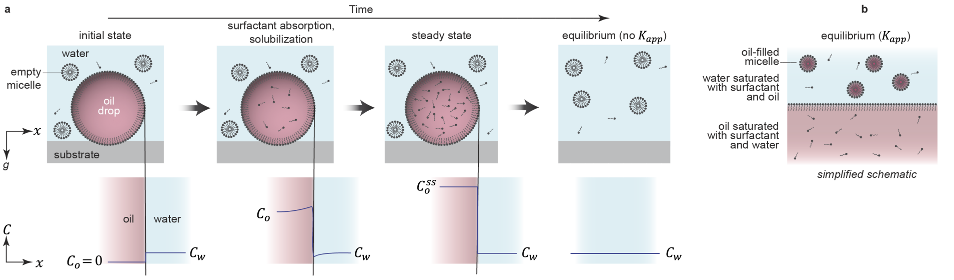

Fig. 1. Conceptual comparison of non-equilibrium partitioning into a solubilizing micro-droplet versus bulk equilibrium in an oil/water/surfactant system. **a**, Partitioning into the drop occurs quickly relative to solubilization, reaching a steady state surfactant concentration in the oil drop within tens of minutes. The droplet is completely gone at equilibrium (over hours) and the oil is “infinitely” diluted into the water. **b**, Surfactant partitioning between bulk oil and water at equilibrium. The water phase becomes oil-saturated, the oil phase becomes water saturated, and surfactant distributes between both coexisting phases. Reproduced from [5].

Our contribution to understanding chemical reactions in nanophase fluids. Nanoscopic phases, such as oil-enriched pockets dispersed in water, have been observed in ternary mixtures of oil, water, and cosolvent in the absence of surfactants. An example is the mixture of water, octanol, and propanol. Nanophases are found across a portion of compositions within the single-phase region of the ternary phase diagram, exist at equilibrium, and result from low-energy interactions on the order of k_BT. The nanophases are highly fluctuating but detectable by analytical scattering methods. However, the principles governing the formation of nanophases under certain conditions but not others, regarding both volumetric and chemical makeup, are unclear. Furthermore, chemical transformations are rarely studied in ternary solvent conditions or under conditions wherein nanophase structuring is known to exist.

We systematically explored the nanophase behavior of ternary mixtures of water with a suite of cosolvents and oils containing strategically chosen functional groups to probe the role of intermolecular interactions [6] (Fig. 2a). Dynamic light scattering was used to characterize the nanophase structure. Stronger intermolecular interactions such as H-bonding or n-Π* interactions between oil and cosolvent notably contributed to forming thermodynamically stable nanophases. Ternary mixtures in which the oil had only van der Waals interactions with the water and cosolvent did not stabilize nanophases detectable by dynamic light scattering, although it is possible that nanophases exist beyond the detection limit. Aromatic groups favored nanophase formation. The most prominent structuring (highest number and largest sizes of nanophases) was found in water-rich compositions near the miscibility gap.

To gain insight as to how the nanophases affect reaction kinetics, we employed a high-throughput spectroscopic screening methodology to explore the impact on the kinetics of a strain promoted azide alkyne click reaction [7] (Fig. 2b). By analyzing hundreds of different solvent compositions, we found that ternary mixtures favoring oil-in-water nanophase structuring led to significant increases in reaction rate between two hydrophobic reagents. Rates exceeded that of the pure solvents and binary solvent containing water. In contrast, when a hydrophilic-hydrophobic reagent pair was used, or the ternary solvent was formulated to reduce nanophase stability, the rate enhancement disappeared. However, the simple presence of oil-in-water nanophases, which were detectable across a broad swath of the phase diagram, was on its own not enough to guarantee faster kinetics; enhanced rates were found within a much smaller range of compositions. We speculate that differences in nanophase concentrations and composition could be playing a role, as similar considerations for balance of effects have been discussed in the context of condensates and micellar reactions. Our observations suggest that nanophase structuring itself, as opposed to changes in solvent properties like polarity, viscosity, or introduction of hydrogen bonding, can have significant impact on reagent co-localization that facilitates faster kinetics.

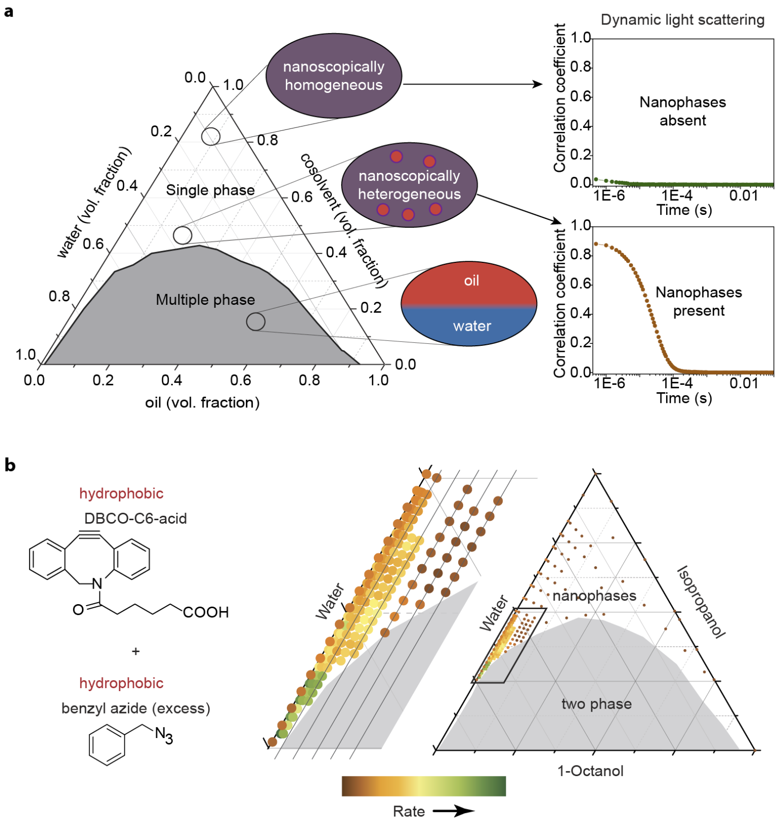

Fig. 2. Nanophase structures exist within ternary solvent mixtures and can affect chemical reactions. a, Schematic illustration of a general ternary phase diagram. Nanophase structuring is typically found at compositions in the single-phase region closer to the miscibility gap. Exemplary dynamic light scattering (DLS) autocorrelation functions are shown that would indicate, generally, the absence or presence of scattering by nanophases. b, Kinetics of the click reaction between the two given hydrophobic reagents was explored for many solvent conditions across the single-phase region of the ternary phase diagram of water, isopropanol, and octanol. (Other reactions and solvents were also explored [7] but not shown here). The fastest rates were found in ternary solvent mixtures near the water-rich corner of the single-phase region and nanophases were confirmed by DLS. Partially reproduced from [6,7]

Outlook. Solvent organization, compartmentalization, and confinement, whether formed at equilibrium or far from equilibrium, can have significant impact on chemical reactions and transformations. Studying chemical reactions in such systems can be challenging; some challenges include that the systems are “messy”, containing mixtures of many molecules, can be difficult to purify or analyze, the combinatorial compositional space is vast and high-throughput analytical methods may not easily applied; and pinpointing the precise mechanism by which the solvent organization or structure impacts a reaction can be difficult to ascertain and decouple from other solvent effects. However, uncovering ways in which we can harness solvent organization across the nano/microscale with chemical processes, including potentially chemotaxis/motility [8], may help us to understand the matter-to-life transition, design life-like and adaptive materials, and develop different chemical synthesis strategies.

Acknowledgments

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