# Self-reproducing catalytic micelles as early nanoscopic protocells

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## Abstract

Protocells at life's origin are often conceived as bilayer-ensheathed life precursors, whose self-reproduction rests on the early advent of replicating catalytic biopolymers. We explore an alternative scenario, whereby reproducing nanoscopic lipid micelles with catalytic capabilities were forerunners of biopolymer-containing protocells. This postulate gains considerable support from experiments describing micellar catalysis and autocatalytic proliferation, and more recently from reports on cross catalysis in mixed micelles, leading to life-like steady-state dynamics. Such results, along with evidence for micellar prebiotic compatibility, synergize with predictions of our chemically-stringent computer-simulated model, illustrating how mutually catalytic lipid networks may enable micellar compositional reproduction that could underlie primal selection and evolution. Finally, we highlight studies on how endogenously catalyzed lipid modifications could underlie further protocellular complexification, including micelle to vesicle transition and monomer to biopolymer progression. These portrayals substantiate the parsimonious inference that protocellular evolution could have been seeded by pre-RNA lipid assemblies.

Protocells are prebiotic precursors of living cells, typically described as self-reproducing, membrane-enclosed assemblages of mutually interacting compounds[1]. Crucial to protocellular function is that its molecular constituents will be capable of self-copying. In one origin of life scenario, the protocell includes vesicle-enclosed ribozymes that control their own replication[2,3]. In another scheme, the reproducing chemical entity is a population of small molecules, e.g. oligopeptides, that form a self-copying collectively autocatalytic set (CAS)[4-7], contained within a lipid vesicle[8].

However, for an entire protocell to breed true, the lumenal content has to synchronize kinetically with amphiphiles that make up the container. This may happen via internally-catalyzed amphiphiles production[9,10], and in parallel, via lipid-assisted polymerization of nucleotides[11,12]. More generally, what is required for successful protocellular reproduction is kinetic coupling between the inner molecular network and the membrane components[8] through specific mutually catalytic interactions. It would thus be important to examine the evidence for the capacity of lipids and their assemblies to manifest catalytic properties, a notion that is rarely invoked in both the Origin of Life and biochemistry literature.

In this perspective, we will explore the extensive experimental evidence for lipid micelle catalysis, including emerging recent accounts on life-like dynamic attributes of mixed micellar assemblies. Afterwards, we will point out the agreement between these experimental observations and results from our well-documented chemical kinetics model regarding the capacity of lipid assemblies to compositionally reproduce and bequeath chemical information to progeny. Taken together, such published accounts support the premise that lipid assemblies may have well played a central role in protocellular emergence and function, both in the traditional role of compartmentalization and in catalytic self-copying. We will thus put forward the idea that lipid micelles are strong candidates for initiating an evolutionary processes that subsequently enabled the advent of biologically-relevant biopolymers.

## Protocellular lipids

In accounts of present day life, lipid-mediated catalysis is largely non-existent. This is explainable by the fact that once high-fidelity protein and RNA catalysts have emerged, lipids gradually specialized towards chemistries that underlie effective containment, including barrier formation, material transport and signal transduction. However, primordial lipids appear to have been much more structurally and functionally diverse[13,14]. This likely included headgroups with catalytic moieties, allowing a broad spectrum of chemical characteristics, including selective enhancement of reaction rates[15] as detailed below. Thus, protocellular lipids could harbor both catalysis and compartment-forming features, justifying the term “lipozymes” for early lipid assemblies in a “Lipid World” scenario[16].

Terrestrial infall as well as energized synthesis appear to have led to a tremendous oceanic chemical diversity, often related to as the prebiotic soup or primordial “messy chemistry”[17]. This likely included a considerable assortment of amphiphilic molecules as found in carbonaceous meteorites[18,19] and, as recently reported, in computationally derived networks of prebiotic chemical reactions[7]. It is therefore appropriate to consider lipid molecules as prebiotically prevalent and chemically diverse, essential for their proposed significance at the dawn of life.

## Micellar protocells

A widely accepted protocell model involves a microscopic vesicular structure with a lipid bilayer enclosing a watery core. We explore herein the unconventional hypothesis that very early protocells were in fact nanoscopic lipid micelles - assemblies without an aqueous lumen[20]. In terms of proliferation, micelles are on par with vesicles, being able to undergo assembly growth and fission[21-23] (Fig. 1). Not less important, micelles have numerous properties in which they are advantageous when compared to vesicles in the prebiotic context (Fig. 2). A key micellar advantage is their nanoscopic size (Fig. 2a). While a micellar protocell would typically be composed of several hundred amphiphiles, a 1μm vesicular protocell would contain several orders of magnitude larger molecular counts. This could compromise the collisional capacity needed to establish effective mutual interactions. Other micellar advantages include augmented surface to volume ratio (Fig. 2c) and very high reactant concentrations (Fig. 2d), as well as substantial

chemical promiscuity regarding lipid size, geometry and functionality (Fig. 2b). The latter renders micelles compatible with high chemical multiplicity of planetary prebiotic environments[24]. While the micellar scenario entails the loss of an aqueous lumen, with its payload of life-related polar compounds, we note that lipid micelles can adsorb and/or enclose diverse molecules with a wide range of polarities, due to the polarity-gradient of their layered phases[25] (Fig. 2f).

As stated above, protocellular reproduction necessitates the involvement of catalysis. This begs the question of whether micelles reveal catalytic characteristics. It turns out, that while there are relatively few accounts of amphiphile catalysis in vesicular bilayers[26,27], there is a remarkable literature on micellar lipid catalysis, accumulated over several decades, as summarized in many monographs and reviews[25,28,29]. Numerous studies provide detailed information on the catalytic roles of diverse amphiphilic lipid molecules in a variety of micellar entities, as sampled in Fig. 3.

Micellar catalysis is sometimes attributed to physicochemical properties such as surface augmentation, reduced dimensionality, enhanced concentrations and effective lateral diffusion (Figs. 2c-e)[30]}. However, there is considerable evidence for the involvement of specific lipid chemical moieties, such as an amino acid[31] (Fig. 3a), a peptide[32], a metal chelator[33] and mixed-domain headgroups with molecular recognition traits[23,34] (Fig. 3g). Such specific catalytic groupings are conceptually analogous to the pivotal residues in protein enzymes. Indeed, many accounts of micellar catalysis highlight remarkable points of similarity between micelles and globular protein enzymes, including exceptional rate accelerations[35] and the involvement of dynamic catalytic dyads and triads[36,37] (Fig. 3b). In this vein, micelles can impart specific catalytic selectivity, stabilizing the relevant transition state by precise lipid interactions, and affording reaction stereospecificity[25,32,38] and substrate selectivity[39] (Fig. 3c). An extreme example of protein similarity are micelles that form conformationally-stable non-covalent structures[40], highly resembling folded proteins. Many of the above attributes are also compatible with prebiotic scenarios, where the lack of organic solvents is overcome by mixed-polarity lipid constituents, environmental heterogeneity challenges are addressed by catalytic diversity, and micellar intake of dilute reactants affords reaction-promoting augmented concentrations, all supporting mutually catalytic interactions.

## Reproducing Catalytic micelles

The proposed role of lipid micelles as early nanoscopic life-like protocells receives strong backing through studies of catalysis-mediated micellar growth and proliferation. These are cases in which micelles catalyze the metabolism-like modification or production from precursors of micelle-joining amphiphiles (Fig. 3c-g). In a pioneering study by Luisi and colleagues, fatty acid micelles were found to catalyze the hydrolysis of an ester precursor, leading to autocatalytic micellar reproduction[20]. These observations were followed by studies of Fletcher and colleagues, whereby a micelle-forming amphiphile is covalently synthesized from separate head and tail compounds. This process is catalyzed by reactants proximity within the micelles (physical autocatalysis)[41]. In parallel, there is evidence for the involvement of more specific

molecular recognition paths resembling template-based self-replication[23] (Fig. 3g). Such findings support a similarity between the chemical dynamics of micelles and that of living cells, including absorption of environmental compounds, metabolism-like processing, growth and proliferation (Fig. 1).

The foregoing experimental examples represent life-mimicking autocatalytic growth and generation of progeny. However, such single-amphiphile systems fall short of capturing the molecular diversity of living cells, and the consequential emergence of multi-component catalytic networks. Further, single-component micelles transfer trivial information from one generation to another, whereas mixed micelles harbor significant chemical information, which may be transmitted to progeny and mediate rudimentary selection[42]. Finally, with the immense chemical heterogeneity of the prebiotic milieu[17], multicomponent micelles would form with a much higher probability than single component ones. These arguments point to the relevance of recent studies focusing on heterogeneous catalytic micelles.

## Life-like catalytic mixed micelles

An important step towards catalytic mixed micelles is described by the Fletcher group[43], whereby in addition to the catalytic lipid and its building block reactants, several secondary catalysts are tested for their capacity to further enhance the rate of lipid formation. The more hydrophobic catalyst is found to be most effective, reflecting its propensity to join the micelle and exert its rate enhancement within the same compartment. These experiments, however, still involve only a single lipid product.

In a later paper[44], the same group has examined a more elaborate case of catalytic mixed micelles, using one headgroup and three different tail group precursors (Fig. 4a). In a flow reactor, under kinetic control, the three produced lipids assumed different dynamic steady state concentrations. Such asymmetry is attributed to autocatalytic and cross catalytic effects prevailing among the employed micellar components. These results, observed in a reproducing multi-molecular assembly, whereby a predominant lipid can emerge from the pool of equimolar competing precursors, are described as exhibiting life-like selection[44]. Significantly, when this system is allowed to progress towards equilibrium by stopping the reactor flow, a side product, which has a higher thermodynamic stability, assumes dominance in the reactor. This highlights the unique stationary non-equilibrium state prevailing while the flow is activated. A recent continuation paper[45] provides further evidence for life-like properties of self-assembling, self-reproducing protocell models. What is presented is competition among amphiphilic compounds, governing the structural features of the formed assemblies, as well as revealing dissipative self-assembly dynamics. Overall, the experiments described above show that even a simple mixed amphiphile system can display complex life-like behavior, including reproduction and selection.

Another revealing case of catalytic mixed micelles is embodied in a system in which the self-reproduction of micellar aggregates results in a spontaneous amplification of chiral excess[38]. The system includes two asymmetric headgroup enantiomers and a single symmetric apolar tail. When partially enantioenriched head precursors are used, strong enantioselection is observed in the lipid-catalyzed micellar lipid production (Fig. 4b). This is another noticeable case in which one possible micellar product is kinetically selected

over another. The authors point out that being capable self-assembly, catalysis and cross-generation compositional information transfer, this experimental system represents a plausible model for pre-polynucleotide Lipid World scenarios.

A highly pertinent case of lipid-catalyzed covalent synthesis, realized in lipid vesicles with direct relevance to micellar assemblies, has been described by Devaraj and co-workers[26]. In this multi-component system, a lipid-chelated $Cu^{+1}$ catalyst promotes the formation of another lipid, as well as itself, from head and tail reactants. This system is shown to formally constitute a lipid-embodied mutually catalytic network[24]. Significantly, this experimental setup also portrays selection, whereby longer tails are catalytically incorporated at higher propensity into the three-tailed lipid catalyst. Further, upon serial transfers, the inert carrier lipid is diluted, and the catalytically synthesized ones become dominant through a selection-like process. The results are described as relevant to modelled lipid-based prebiotic systems, which may propagate their chemical composition and exhibit homeostasis.

The foregoing studies focus on micellar growth processes mediated by catalyzed covalent synthesis or hydrolysis. Analogous phenomenology has been described for non-covalent assembly growth that takes place via catalyzed accretion of environmental lipid monomers. In one relevant study small concentrations of long-chain fatty acids augment the rate of incorporation of short-chain ones into vesicles[46]. The same group also reported that an apolar membrane-joined peptide can enhance fatty acid uptake into vesicles[1]. Analogous sets of observations are the selective non-covalent anchoring of functionalized lipids in vesicles[47], and the capacity of specific lipid compositions to promote the stereospecific partitioning of organic compounds into mixed inverse micelles[48] and mixed liposomes[49]. Such studies further support the notion that catalysis-mediated growth of mixed lipid micelles, whether involving covalent or non-covalent reactions, may have played an essential role in life's emergence.

## Modelling micellar reproduction

The forgoing accounts involve experiments with rather limited molecular repertoires. The next step should tackle much more complex molecular networks and examine their capacity to reveal more elaborate life-like properties, such as dissipative non-equilibrium dynamics[45,50], more intricate selection properties and primitive evolution. This constitutes a major challenge to present-day experimental technologies, suggesting a need to pursue in parallel certain advanced computational analyses[7,51]. Such approach is embodied in the increasing success of Systems Chemistry in addressing prebiotic evolution[52] along with the advent of Systems Protobiology[24], so as to help guide future protocell experimentation[53-55].

In this vein, in the past two decades we have applied computer-based methodologies to fathom the dynamics of growth and fission of mixed lipid assemblies, addressing both catalyzed lipid accretion[56,57] and synthesis[58]. This was done in the context of a prebiotic Lipid World[16], based on the Graded Autocatalysis Replication Domain (GARD) chemical kinetics model. GARD is affiliated with the concept of membrane heredity, which points out that cell inheritance depends upon the direct genetic continuity of membranes[13,59,60].

Further, GARD is based on away-from-equilibrium, free energy-dependent formalism, general enough to be consistent with any set of amphiphilic chemical compounds. For GARD modeling, we employed chemically-realistic differential equations with experiment-based parameters that address lipid diversity[56]. Based on this model, we performed Monte Carlo computer simulations of catalytic micelles, with an exterior lipid repertoire of 30-300 types[24]. We note that such computational methodologies are known to faithfully mimic experimental results in realms such as surface diffusion, crystal growth and heterogeneous catalysis[61,62], all relevant to micellar dynamics.

Importantly, our GARD simulations of mutually catalytic networks provide strong support for the validity of the Collectively Autocatalytic Sets (CAS) concept[4,63]. We have shown explicitly that in a mixed micellar framework CAS indeed undergo self-copying[64] and portray catalytic closure, a centerpiece of the CAS literature[4]. Further, our simulations demonstrate that only rare catalytically-closed sets, those with specific chemical compositions (composomes), are capable of homeostatic growth. This monomer accretion behavior enables such unique molecular assemblies to transmit compositional information along growth-split cycles, a process synonymous with self-reproduction[24,65]. This key evidence was obtained by using widely acclaimed kinetic methodologies in the realm of dynamic Chemical Reaction Networks[66-68].

The foregoing simulations present dynamics that highly resembles that of present day living cells, in which metabolic networks allow homeostatic growth, manifested in the doubling of all molecular counts prior to cell division[69] or in lipid composition stability during organelle proliferation[70]. It is also akin to the abovementioned experiments with mixed micellar steady states along continuous growth and split dynamics[44], which demonstrate kinetically-controlled micellar compositions consistent with compositional homeostasis. The authors point out that these findings may have implications for evolution of amphiphile-based prebiotic chemical systems[44].

## Evolutionary prospects

The abovementioned portrayals establish a capacity of catalytic micellar protocells to store and transmit chemical information to progeny and undergo compositional reproduction and selection, a basis for primal evolutionary attributes. As such, micellar protocells constitute an appropriate departure point for a gradual progression towards more complex protocells. In this realm, it is obligatory to delineate how the supramolecular complexity of micelles composed of simple molecules begets increasing molecular complexity, as embodied in sequence-based biopolymers[71]. We envisage that the first steps relevant to such progression would be instances in which bio-monomers and bio-oligomers serve as functional lipid head groups[15] (Fig. 3a-b,d-f). Such modified lipids have recently shown to be generated by prebiotic chemical activation[72]. Additional reports show micelle-catalyzed oligopeptide synthesis and elongation[73-76] (Fig. 3d-e). These condensation reactions may be mediated by reduced hydrolysis in a partially non-aqueous lipid environment[77], equivalent to the effect of wet-dry cycles in aqueous medium[11,78].

In the realm of nucleic acids, several studies report micellar nucleolipid chemistries. This include a lipid-attached ribozyme that catalyzes oligonucleotide elongation[79]; lipids with nucleobase headgroups that catalyze an aromatic dephosphorylation reaction[80]; A role for complementary base pairing in modulating micellar nucleolipid synthesis[81] (Fig. 3f); and the observation of sustained Watson-Crick base-pairing between nucleolipids at a micellar surface[82]. Having lipid-attached amino acids and nucleobases on the same micellar surface could thus promote the co-evolutionary synthesis of peptides, oligonucleotides and other biomolecules, embodying even more life-like mutual interactions[72,83,84]. The prebiotic sources of free energy and catalysis for oligomer elongation reactions have been described in considerable detail[85-87].

In another realm of necessary evolutionary complexification, it is necessary to seek plausible chemical paths from micellar to vesicular lipid assemblies. Rewardingly, such transitions are well-documented[88], based on changes in the lipid admixtures, hence varying the packing geometry of the assembly constituents[89]. In one case micellar composition was altered by the in-situ catalytic synthesis of a two-chain lipid from simpler precursors[90]. In another case[91], reductive disulfide cleavage of a micelle-compatible gemini lipid induces a transformation to vesicles. In a more life-like case, a recent report[92] shows that micellar enzyme-free synthesis of natural two-chain phospholipids is accelerated by synergy between charge interactions and intra-micellar proximity. This allows gradual compositional alterations, resulting in a structural transition towards vesicles. Finally, we note that micelle to vesicle transitions may be induced by environmental changes, such as varying ion concentrations, which translate to chemical modifications of micellar components[14,93]. In the framework of lipid assemblies capable of compositional inheritance, the ensuing lipid aggregation states would be bequeathed along composition-preserving reproduction trajectories[45]. Once vesicles become dominant, their membrane catalytic components[94] and lumenal content has to be jointly reproduced (Fig. 5), as addressed under the title “metabolic GARD”[24].

A major challenge for further progress is attaining self-reproduction at a much higher chemical heterogeneity than employed experimentally so far, as befits life processes. Some suggestive tips for future experimentation in this realm may be derived from predictions of the GARD model. These relate to the tendency of GARD assemblies to undergo “selection for replication”[95], explainable by prevailing attractor dynamics[24,96]. This behavior is similarly observed in other computational analyses of chemical networks[97], as well as by experiments with mixed micelles, which attain the same compositional target state irrespective of initial conditions[44]. If realized, such attractor behavior would narrow the experimental search space for heterogeneous micellar protocells.

## Conclusions

Life consensually arose from chemical entities that could harbor both catalysis and reproduction. An acknowledged embodiment for such duality are polyribonucleotides, widely considered crucial for life’s origin. This paper provides evidence that lipid micelles may be endowed with a similar chemical duality. On the one hand we present extensive literature supporting catalytic properties of lipid micellar aggregates, thus bearing

similarity to globular proteins in structure, size and underlying chemical functionalities. On the other hand, we reveal strong evidence that mixed lipid micelles can generate their own copies by growth and fission, mediated by collectively catalytic interactions. Such observations lend credence to the proposition that nanoscopic micellar protocells could serve as evolutionary precursors for more complex protocells.

Further, micelles offer a considerably more parsimonious origin path than the competing models. First, these reproducing non-covalent nanoscopic assemblages form spontaneously in environments of high molecular heterogeneity and extreme physical conditions. This is in contrast to the unlikely covalent stringing of selected monomers in an orderly sequences necessary for biopolymer replication. Second, for micelles, the same molecular assemblages that mediate collective catalysis and reproduction also delineate spatial containment. This contrasts with a process in which, en route to protocellularity, biopolymers have to join forces with a separately formed chemically orthogonal lipid container. In other words, micellar aggregates made of appropriately functionalized lipids appear to be the only chemical entities that possess the three pillar attributes of life-like function in one go – catalysis, reproduction and containment.

The recently published pioneering results on non-equilibrium reproduction in heterogeneous lipid micelles via endogenous mutually catalytic interactions have strengthened previous studies on the reproduction of autocatalytic single-component micelles. Importantly, when the new experiments were performed in a flow chamber setting, the participating compounds showed a kinetically controlled steady state, i.e. the preservation of their relative amounts over time. Such homeostatic behavior echoes the chemical kinetic simulations, in which homeostatic growth followed by random fission is shown to be equivalent to compositional information transfer across generations, a life-like process that can support natural selection.

As expected from a proposed simple origin scenario, we describe specific paths that would enable micellar entities to complexify towards more chemically-elaborate protocells. Such paths are amply supported by documented experimentation, and additional progress along these lines could be amply supported by computer modeling and simulations. Among others, such simulations point out that having genotype- and phenotype-like attributes joined in one micellar entity opens the door to pre-evolutionary selection for reproduction, making the emergence of protocellular self-copying more plausible than previously thought.

In sum, this Perspective offers, perhaps for the first time, a detailed, well-based biopolymer-independent origin scenario, based on the amalgamation of experiments and modeling. Such a scenario affords spontaneous appearance of nanoscopic, highly parsimonious reproducers from messy chemistry, avoiding an unlikely leap from prebiotic mixtures to complex polyribonucleotides and polypeptides. This should eventually help outline a path in which templating biopolymers and encoded proteins would be the result of evolution rather than a prerequisite for it.

## Figure Legends

Fig. 1 – **Dynamics of Micellar Proliferation.** Micelles growth and fission: The progression includes (from left to right) spontaneous monomers accretion, pre-micelle nucleation, reaching a stable spherical micelles, the emergence of unstable states exemplified by elongation, and eventual fission[21-23]. In high aggregate concentrations, fusion between micellar assemblies is also expected to occur.

Fig. 2 – **Advantages of micellar systems for priming early life**. **a)** Nanoscopic scale: Micelles that typically contain 100 amphiphiles, are superior to vesicles with millions of monomers as they are much more sensitive to compositional changes and allow more effective all-against-all mutual interactions. **b)** Chemical promiscuity: Micelle formation is compatible with a broad spectrum of chemical moieties of different sizes, geometries and functional groups[36], affording resistance to prebiotic environmental conditions. **c)** Enhanced surface to volume ratio: this allows much higher activity for surface catalysis[44]. **d)** Greatly enhanced molecular concentrations: In pure amphiphilic bulk, molecular concentrations could reach one molar, several orders of magnitude larger than in a vesicular lumen or the external milieu. **e)** Augmented diffusional interactions: This is a case of "reduced dimensionality", leading to great enhancement of binding and rate parameters facilitated by fast lateral diffusion[77]. **f)** Polarity-gradient phases: Micelles can accommodate diverse compounds with contrasting polarities, distributed at the Stern layer, the palisade of apolar tails and the hydrophobic core, generating a polarity gradient conducive to enhanced catalytic interactions[25,98]. **g)** Mineral surface similarity: Micellar catalysis bears strong resemblance to heterogeneous catalysis on mineral surfaces, a phenomenon widely invoked in prebiotic catalysis reports[99]. **h)** Protein Similarity: Micelles and globular proteins share similar dimensions (5-20nm diameter); structure, with a hydrophobic core and a polar surface; and diverse catalytic capacities[36].

Fig. 3 – **Representative cases of micellar catalysis**. In the forgoing examples the catalytic chemistry is enacted by lipid-attached functional moieties on a (mostly heterogeneous) micellar surface. In some cases the substrate and/or product are also lipid attached (cis), and in others they reside in the external milieu (trans). **a)** Ketone-azide cycloaddition that forms a triazole, directly catalyzed by a proline-derivatized lipid (trans)[31]. **b)** Esterolysis of p-nitrophenyl acetate by histidine-derivatized lipid, that turns over by a second lipid (trans, with cis intermediates). The reaction mechanism mimics that of the chymotrypsin catalytic triad, with rates comparable to those of the enzyme[37,100]. **c)** Multistep selective formation of peptide-like amide bonds via dehydrocondensation of amphiphile headgroups (cis), kinetically facilitated by a lipid-attached dimethoxytriazine (DMT)[39]. **d)** Catalyzed synthesis of lipid-attached 2-7 long oligo-glycine from S-alkyl ester lipids (cis)[75]. **e)** Concatenation of thiol-linked lipopeptides to form a longer biologically-relevant peptide by Native Chemical Ligation (cis)[76]. Dap, non-encoded amino acid 2,3-Diaminopropionic Acid; Ph, photocleavable linker. **f)** Synthesis of an AMP nucleolipid with an active epoxydodecane apolar precursor, catalyzed by cetyltrimethylammonium bromide (CTAB) lipid (cis). This reaction type

shows regioselectivity for AMP/UMP admixture, potentially stemming from nucleotide base-pairing[81]. **g)** Autocatalytic stereospecific synthesis of amphiphilic imines (cis) from head and tail precursors directed by molecular recognition. The resultant lipid flips to join the micelle, leading to micellar proliferation[23].

Fig. 4 – **Selection in heterogeneous catalytic micelles. a)** An experimental system based on micellar synthesis of lipids from one head and three tail precursors of different length, which shows non-equilibrium compositional selection among the three different catalytically synthesized lipids (different colors)[44]. A flow reactor is fed with heads and tails, which initially get synthesized slowly at a macroscopic phase interface, then reveals exponentially-increasing formation rates as more micelles form and proliferate. Different kinetically-controlled steady states are attained (right) based on unequal values of micellar autocatalytic and cross-catalytic effects acting on different precursor substrates (left). One explanatory scenario for the system steady state is that different tail concentrations prevail within growing individual micelles (center). When flow is stopped (red arrow), a competing lipid decomposition process leads to a non-lipid product that is more stable at equilibrium. **b)** A mixed micellar system portraying attributes of self-reproduction and selection[38]. Amphiphiles are synthesized from a hydrophobic tail and one of the two enantiomers of a chiral water-soluble headgroup. Micelles form by a process as invoked in (a), leading to catalytic formation of more amphiphiles and micelles. As in (a), unequal mutual catalytic values is at work (left), hence differential rates of production for the two lipidic enantiomers. In this particular case autocatalysis is strong: upon seeding a racemic reaction mixture with micelles enriched with the S enantiomeric lipid, an S enantiomeric excess is preserved along micellar growth (center and right).

Fig. 5 – **Micellar reproduction and evolution. a)** According to the GARD model, mutually catalytic interactions between micellar lipids and free lipidic monomers in solution influence the rates of entry (and exit) of monomers into (and from) the micellar assembly[24,56]. Upon catalyzed growth, micelles are shown to eventually assume specific lipid compositions (“composomes”) with narrower lipid repertoire. GARD simulations show that such kinetically-instructed compositions exhibit homeostatic growth. **b)** The grown micelle fissions while transmitting its compositional information to progeny, i.e. reproducing[24,56,57]. **c,d)** Upon growth and split, homeostatic compositional reproduction (curved arrows) with mutations (straight arrows) may involve both non-covalent accretion as seen in (a) and covalent lipid modifications as occurring in certain catalytically reproducing heterogeneous micelles[44]. These reactions could, among others, involve catalyzed oligomerization of micelle-attached amino acids and nucleotides (green and blue, respectively). **e)** Some lipid modifications, such as a conversion of single chain to double chain lipids, could result in a micelle to vesicle transition, including lumenal content and transmembrane molecules. The sequence of events depicted here portrays a gradual progression from micelles that undergo purely compositional inheritance, to more elaborate vesicular protocells that embody sequence-based replication and lumenal metabolism[24].

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## Competing Interests

The authors declare no competing interests.

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*Figure 1*

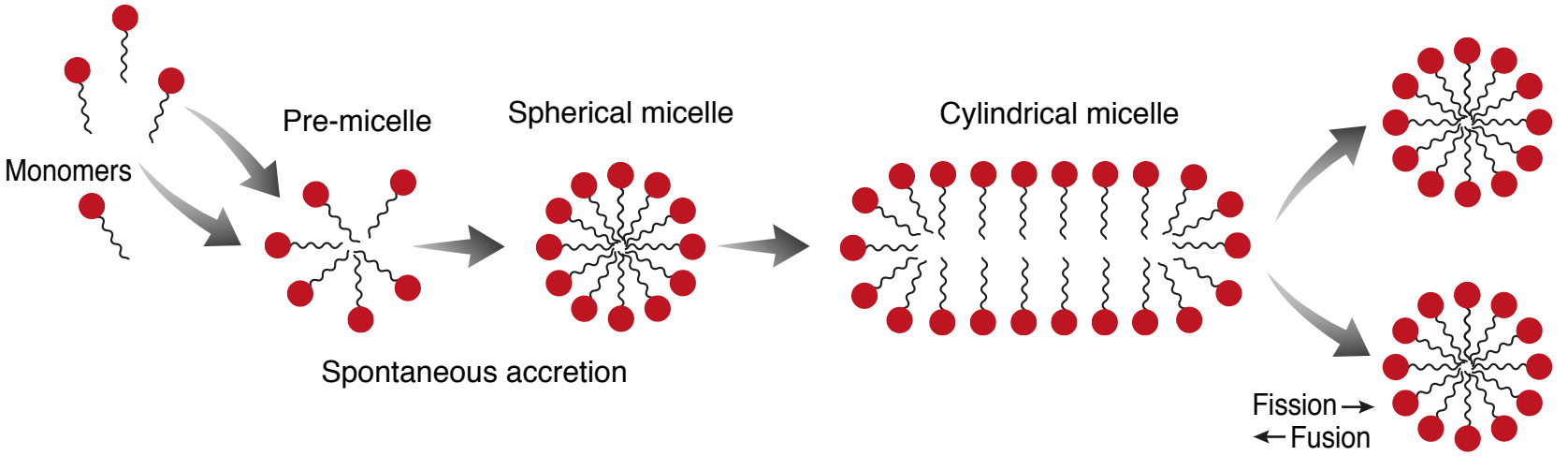

Monomers
Pre-micelle
Spherical micelle
Cylindrical micelle
Spontaneous accretion
Fission
Fusion

*Figure 2*

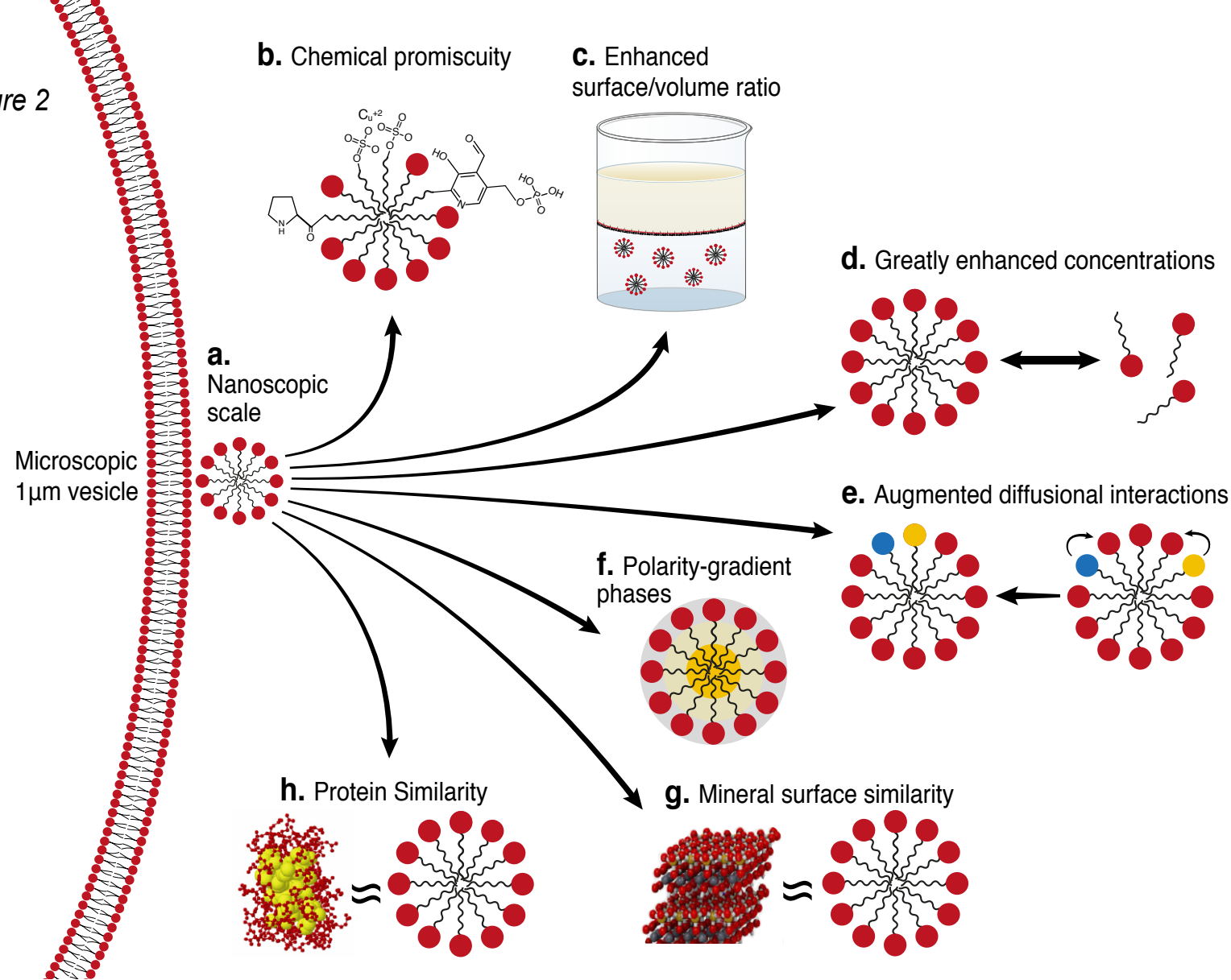

b. Chemical promiscuity
c. Enhanced surface/volume ratio
d. Greatly enhanced concentrations
a. Nanoscopic scale
Microscopic 1µm vesicle
e. Augmented diffusional interactions
f. Polarity-gradient phases
h. Protein Similarity
g. Mineral surface similarity

*Figure 3a*

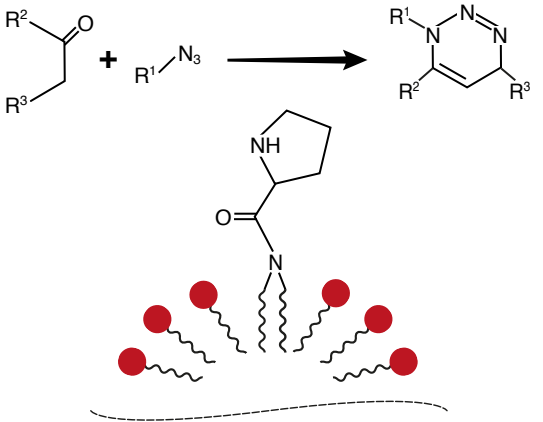


*Figure 3b*

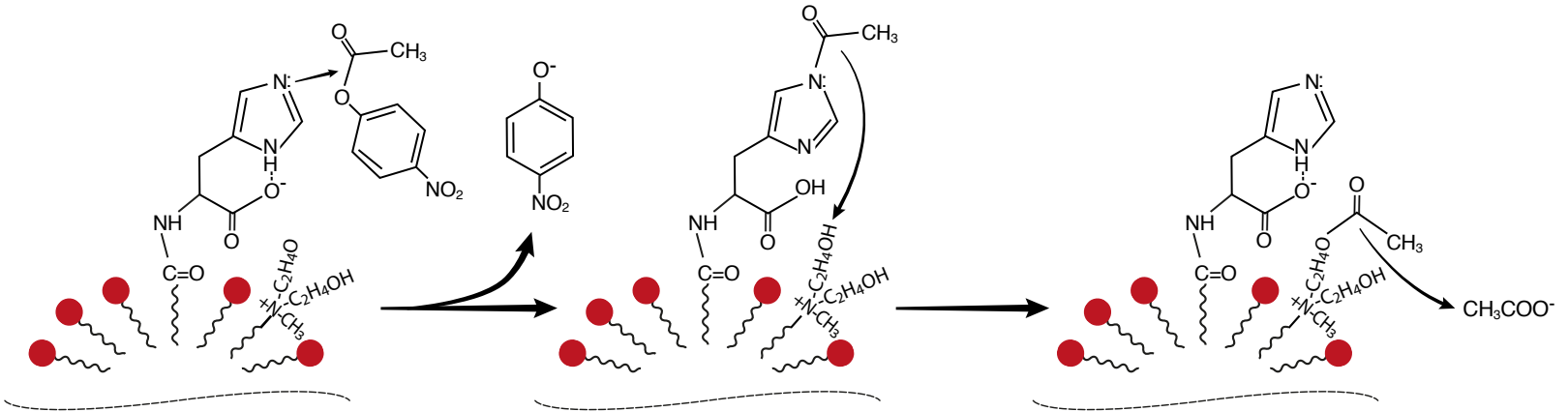

O
CH3
N:
O
N
H
O-
NO2
NH
C=O
O
+N-C2H4OH
-CH3
O-
NO2
O
CH3
N:
N
OH
NH
O
C=O
+N-C2H4OH
-CH3
N:
N
H
O-
O
NH
C=O
O
O
CH3
+N-C2H4OH
-CH3
CH3COO-

*Figure 3c*

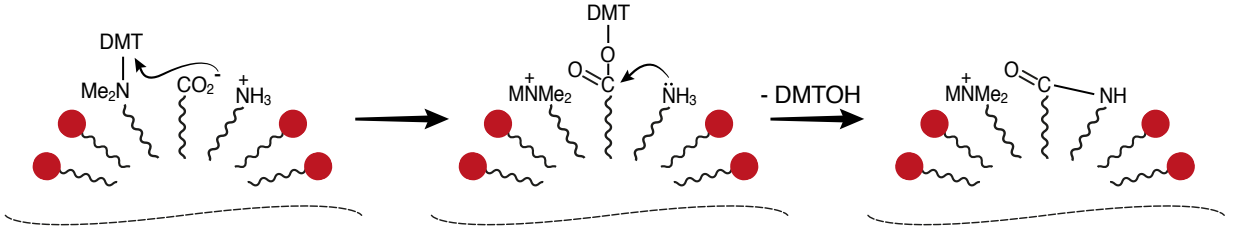


*Figure 3d*

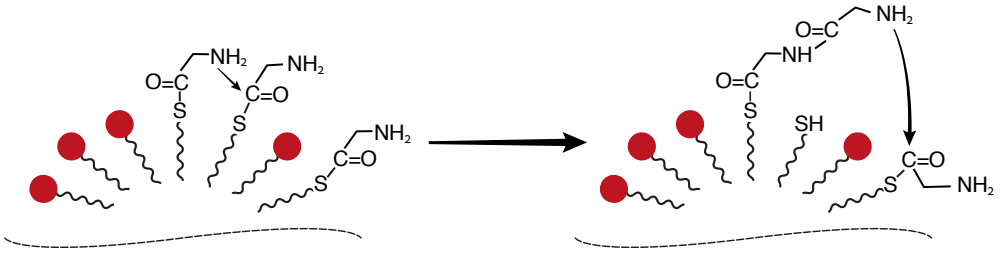
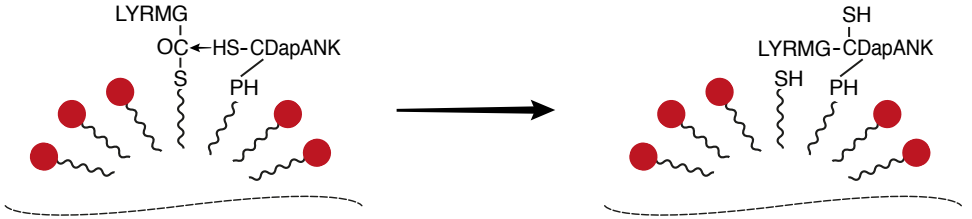


*Figure 3e*



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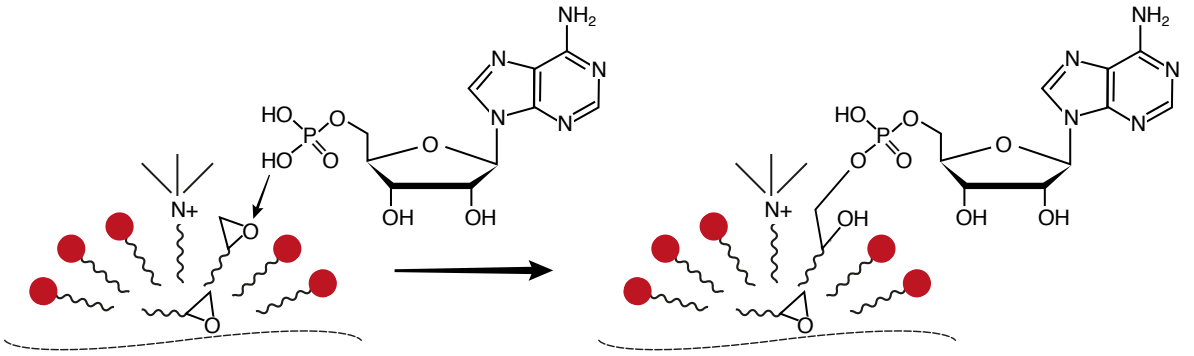

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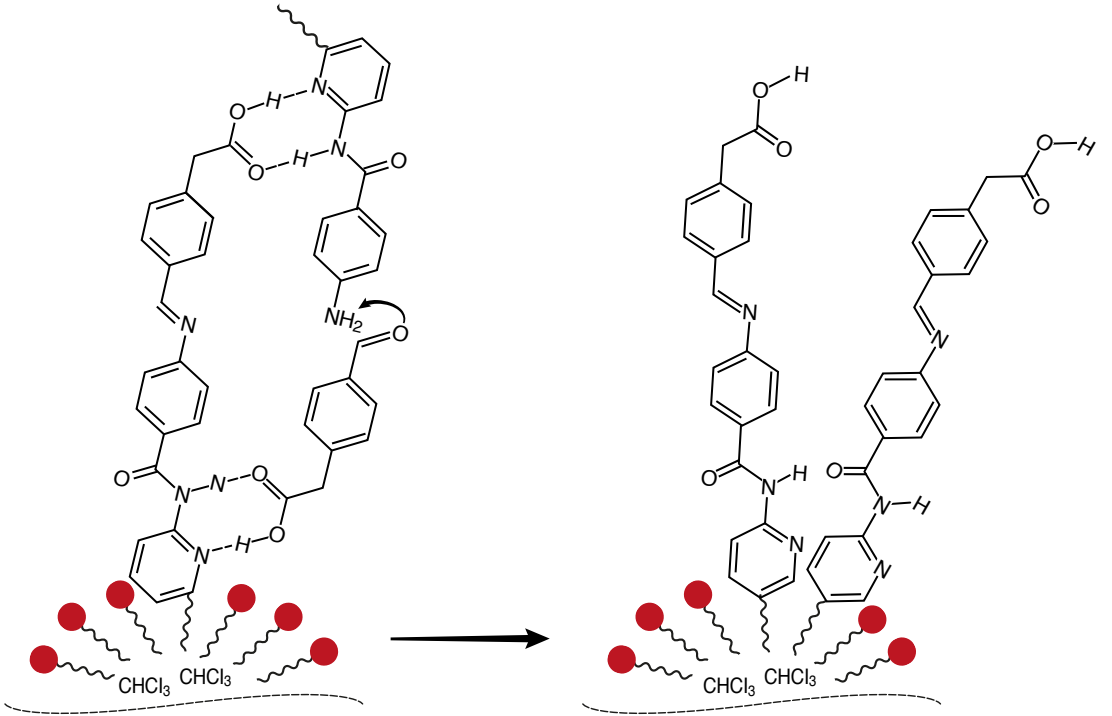

*Figure 4*

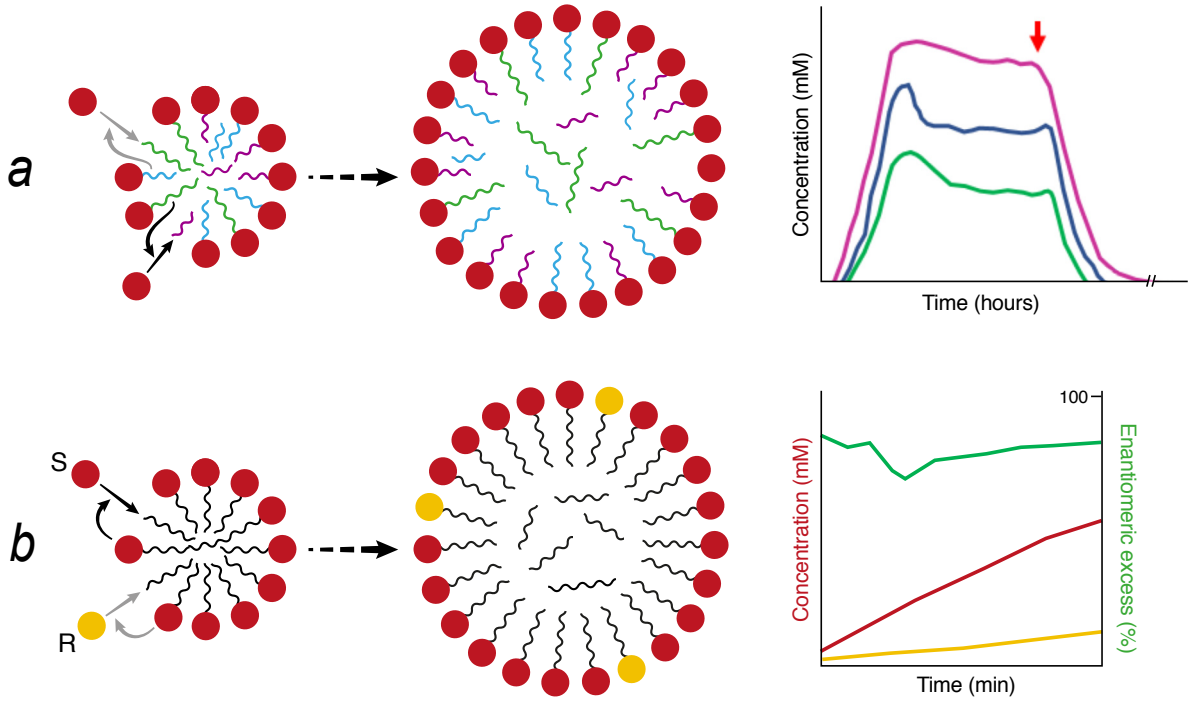
a
Concentration (mM)
Time (hours)
b
S
R
100
Concentration (mM)
Enantiomeric excess (%)
Time (min)

*Figure 5*