Highlight Review

Sparkling Morphological Changes and Spontaneous Movements of Self-assemblies in Water Induced by Chemical Reactions

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Abstract

This review covers the drastic morphological changes, including division or birthing dynamics, and even spontaneous movements performed by molecular self-assemblies constructed by reactive amphiphiles with the imine group that connects hydrophilic and hydrophobic moieties. It turns out that the formation (dehydrocondensation) of such amphiphiles or their cleavage (hydrolysis) into individual moieties occurs depending on the reaction fields, such as in membranes, or at interfaces between water and self-assemblies constructed by the amphiphiles. Moreover these chemical conversions induce outstanding dynamics aforementioned. Hence these findings give a hint to understand hierarchical dynamics occurring in a living system.

◆ 1. Introduction

Organic chemists usually perform chemical reactions in organic solvents, although crystalline phase reactions[1] or solvent-free reactions[1,2] have drawn much attention from the aspect of Green Chemistry.[3] Recently extensive studies on sophisticated chemical transformations in water have been developed;[4] i.e., oxidation,[5] dehydrogenation/hydrogenation,[6] and alkylations.[7] On the other hand, biological reactions mainly occur in aqueous solution, reflecting that the plausible birth place for life is the sea.[8–10] Molecular conversions performed in reaction fields, such as in membranes or at interfaces between water and molecular assemblies created by amphiphiles,[10] which dissolve both in water and in oil, are one of the important events for a living system. Hence the elucidation and control of chemical reactions occurring in such reaction fields are the key issues of the current chemistry in reference to the biological functions. It is to be noticed that such reactions utilize hydrophilic and hydrophobic local environments within a membrane or its interface to perform seemingly impossible sequences of chemical transformations, such as oxidation and reduction, or condensation and hydrolysis.

In this review article, the authors have focused their attention on the chemical transformations of amphiphiles, which are composed of a hydrophilic part and a hydrophobic one, in membranes, in water or at interfaces of their self-assemblies. For this purpose, amphiphiles containing an imine group (C=N bond) of a benzylideneaniline-type[11] are appropriate because they are fairly stable in a hydrophobic environment, but will be hydrolyzed when placed in a hydrophilic environment (Figure 1; left). Therefore, the chemical reactions of amphiphiles can induce morphological changes or even spontaneous movements of self-assemblies of themselves due to the local stress or the gradient of the local concentrations caused by the products (Figure 1; right).

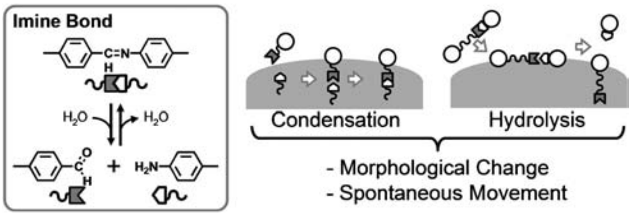

Figure 1. Schematic diagram of spontaneous dynamics induced by dehydrocondensation or hydrolysis of the imine bond.

Among the self-assembled structures arising from amphiphiles in water, a vesicle is often used as a cellular model because its shape is characterized as a hollow and closed structure composed of bilayer membranes (Figure 2b).[12] Vesicles can be spherical or tubular in shape, and their lamellarities are diverse ranging from single, multiple, or nested ones. Vesicles the diameters of which are larger than 1 µm (giant vesicles; GVs) can be observed by optical microscopy. The morphology of a vesicle is fairly stable in water but it can be deformed by the addition of mild surfactants which destabilize the membrane structure. Many examples of the morphological changes of vesicles induced by additives,[13] such as glucoses,[14] DNA,[15] oligopeptides,[16] have been reported. Amphiphiles (surfactants) also dissolve in oil droplets made of lipophiles in water and cover their surface, forming an oil–water (o/w) emulsion (Figure 2c).

◆ 2. Dehydrocondensation in a Bilayer Membrane Surrounded by Water

An addition reaction of two kinds of substrates in an organized medium is likely to occur if the reactive sites are located in proximity,[1,17] but in the case of a coupling reaction the crystal needs enough space to incorporate small molecules which are liberated from the substrates;[18] otherwise the crystal collapses into

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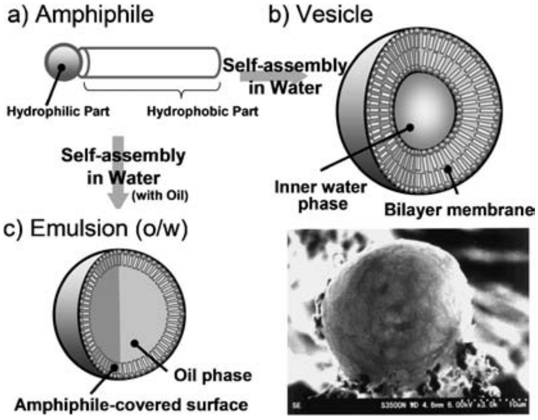

Figure 2. Amphiphiles self-assemble to form a vesicle, or they coat the surface of oil to form o/w emulsion in water.

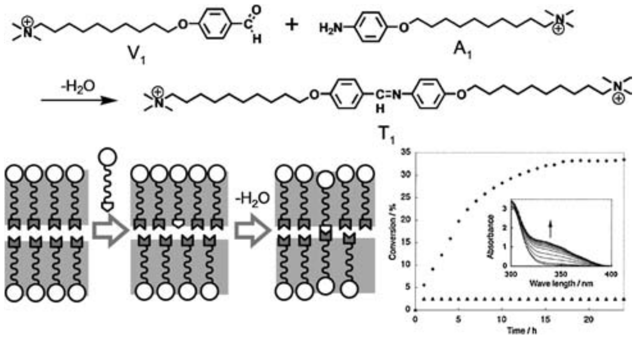

Figure 3. Dehydrocondensation between benzaldehyde and amine moieties of amphiphiles in bilayer membrane.

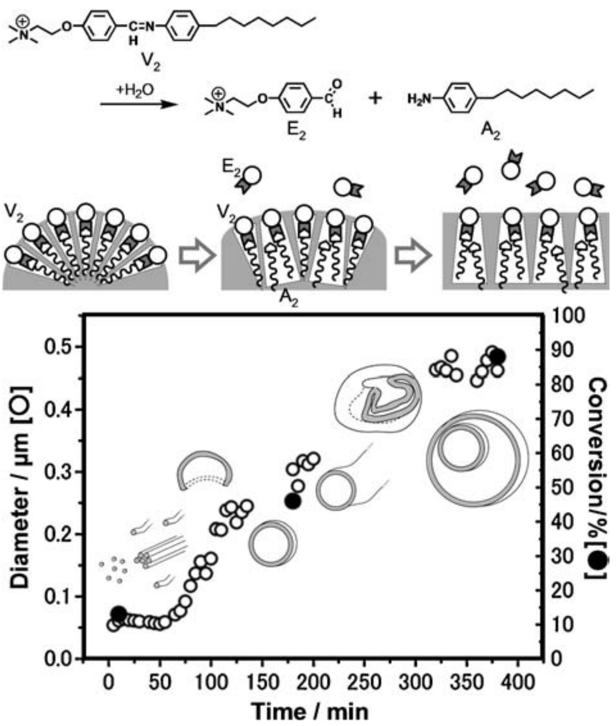

Figure 4. Spontaneous morphological evolution from spherical micelles to nested GVs, accompanied by the progress of hydrolysis of the imine bond of V_2.

pieces. However, in the case of flexible membranes, it was found that dehydrocondensation between two kinds of reactive amphiphiles occurred smoothly, the formed water molecules being removed from the hydrophobic membrane into water.

An aldehyde-type amphiphile V_1 with a hydrophilic head of a trimethylammonium group was synthesized.[11] An aniline-type amphiphile A_1 with a trimethylammonium head group was also prepared as a reaction partner for V_1. To a dispersion of GVs composed of V_1 and a two-leg-type amphiphile of the derivative of V_1 was added an aqueous solution of A_1, and the progress of the reaction was monitored by UV spectra at room temperature (Figure 3).[19] The absorption at 340 nm, which was assigned to diphenylazomethine T_1, increased as the condensation proceeded. Formation of the azomethines through the dehydrocondensation of V_1 and A_1 (2 and 10 mM) proceeded efficiently for the first 10 h, and then equilibrated at 34% after 20 h. The conversion of the amphiphilic aldehydes to the azomethines increased up to 81% when a more concentrated solution of A_1 (36 mM) was added to the giant vesicle dispersion (36 mM) of V_1. In contrast, when nonamphiphilic aldehyde (number of carbons: 2, 1 mM) and aniline (5 mM) were mixed, the conversion of the corresponding azomethine was only 2.5%.

Two factors can account for the experimental results. One factor is that a high local concentration of the substrates in the membrane facilitates the collision between the two reactive groups. The other is that the hydrophobic environment shifts the equilibrium toward the product side by preventing the hydrolysis of the product, since the imine moiety of the product is located near the middle of the hydrophobic membrane. On the basis of these findings, it may be concluded that the dehydrocondensation occurs even in aqueous solution when the bilayer membrane provides an efficient hydrophobic reaction environment, as occurs in the case of V_1 with a long alkyl chain.

♦ 3. Morphological Evolution Induced by Hydrolysis of Amphiphile

If an imine group of the amphiphile is located in the vicinity of the hydrophilic part, it is able to be hydrolyzed even within a self-assembly to a lipophile and an electrolyte. If the products within an assembly are accumulated as the hydrolysis of the amphiphile progresses and their amounts finally exceed the critical component ratio, they become a trigger to induce drastic morphological change of the resulting multicomponent system. One of the representative examples is the hydrolysis of an amphiphile (*N*-benzylideneaniline derivative) in the self-assembly.

Figure 4 shows an overview of the spontaneous morphological evolution from a spherical micelle to a nested giant vesicle, being accompanied by the progress of the hydrolysis.[20] The continuous changes from a sphere micelle to a plain lamella observed in the submicrometer region were traced by transmission electron microscopy (TEM) by using the negative staining method. At first, spherical micelles with diameters of ca. 30–40 nm were observed, and 30 min later, needle-like structures composed of a bundle of threadlike micelles emerged. Thereafter, submicrometer-sized vesicles with the membrane thickness of less than 10 nm appeared, and fusion of vesicles can produce large vesicles with diameters larger than 1 μm.

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The morphological changes of vesicles were monitored by optical microscopy 30 min after the preparation of the sample. First, needle-like structures, the length of which is in the range of 0.8–10 μm, emerged. The needle-like structures transformed into a fluctuating plain lamella (jellyfish-like), and then these structures were converted to micrometer-sized spherical GVs (diameters in the range of 1–5 μm). Thereafter, they were transformed into a dumbbell shape, and converted into tubular GVs. Soon after, spherically nested GVs were generated by folding the tubular GVs. Then, oil droplets appeared gradually within the vesicular membrane, and eventually, only oil droplets were observed.

The above result suggests that one can prepare any morphology individually by just preparing the mixture of components of a suitable ratio. For example, if dispersions of $[V_2]/[E_2]/[A_2]$ at such ratios as 7/3/3, 5/5/5, and 3/7/7 (in mM) are prepared, needle-like structures, spherical GVs, and nested GVs, emerged from each dispersion.

From these experimental data, the following principles concerning the morphological evolution of self-assemblies composed of the reactive amphiphiles may be deduced as follows.[21]

1) Morphologies of assemblies are mainly controlled by the ratio of components. Hence they change with the progress of the reaction.

2) Accumulation of lipophiles in an assembly decreases the surface curvature to induce the morphological change.

3) Release of the polar head induces fusion of the assembly due to the decrease of the repulsive surface charge, and the assembly becomes larger.

4) The driving force of formation of nested GVs from tubular GVs might be derived from the minimization of the oily surface area in water.

4. Division of Giant Vesicles Induced by Chemical Reactions

4.1 Self-reproducing System of the Nutrient-containing Giant Vesicles

Luisi et al. reported that the number of vesicles composed of oleic acid increases in alkaline aqueous solution on adding oleic acid anhydride as a precursor of oleic acid.[22] In his model, oleic acid anhydride is transferred to the vesicular membrane by a surfactant (oleate) and it is hydrolyzed to oleic acid, leading to the increase of the number of vesicles self-catalytically. He claimed that this system was a self-reproducing system. However, hydrolysis may occur anywhere in an alkaline solution, hence the reaction field is not specified to the vesicular membrane.

A new self-reproducing giant vesicular system was proposed by Takakura et al. as shown in Figure 5.[23] The original vesicle consists of membrane molecule V_3, which is formed by a coupling reaction between amphiphile A_3 and lipophile B_3. Incidentally, reactive amphiphile A_3 is supplied as an inactive form A_3' so as not to react with any B_3 existing in the outer aqueous phase. Then A_3' is hydrolyzed to the active form (A_3) by catalyst (C) dissolving only in the vesicular membrane. Then, A_3 reacts with any B_3 on the surface of an oil droplet entrapped in the inner water pool and they produce membrane molecules V_3 (Figure 5; middle and bottom). Membrane molecules V_3 self-assemble to form daughter vesicles inside the original vesicle and new vesicles come out through the outer membrane to increase the number of vesicles. Accordingly, this whole process can be regarded as a self-reproduction of GVs.

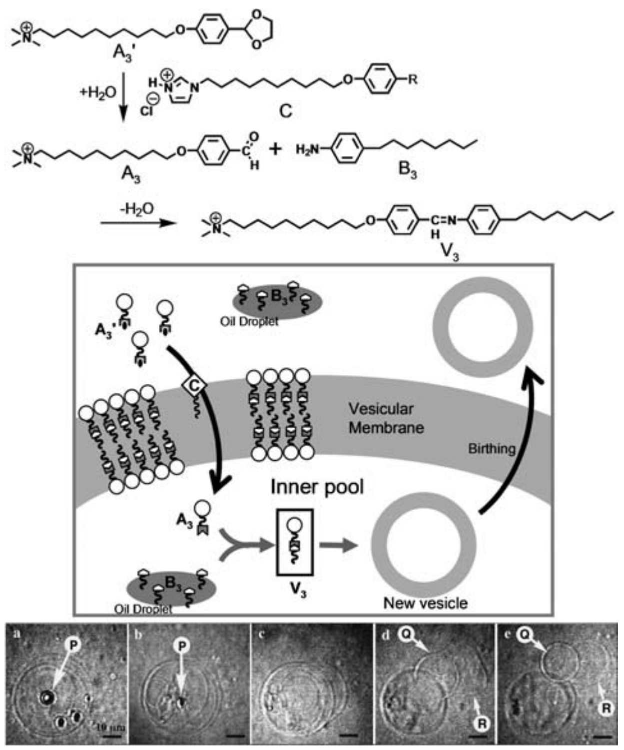

Figure 5. Self-reproducing dynamics of the nutrient-containing GVs.

4.2 Robustly Reproducing Giant Vesicular System

However, there is one problem in the above self-reproducing GV system. This system contains lipophilic precursors in the inner water pool, so that the reproduction stops when the oil droplets are consumed. One scenario of an improved self-reproducing GV system is depicted in Figure 6.[24] The membrane molecule (V_4) forms giant multilamella vesicles in water. The precursor of membrane molecule (V_4^*) is a bolaamphiphile (amphiphile carrying two polar heads at both ends of a hydrophobic chain), and it does not form vesicles, but small aggregates in water. When V_4^* is hydrolyzed on the surface of or inside the vesicular membrane containing catalyst C, it gives rise to membrane molecule V_4 and electrolyte E_4. The generated V_4 dissolves in the membrane to make the GVs corpulent.

It is worthwhile to mention the role of electrolyte E_4. Since the hydrolysis of V_4^* occurs not only on the surfaces of GV but also within water layers between the vesicular membranes, the local concentrations of E_4 in the water layers within GVs become higher because released E_4 in the outer aqueous phase diffuses away. Due to the osmotic pressure effect, the exchange of E_4 and outer water across the membrane takes place, associated with the reorientation of membrane molecules to create a channel for passing E_4 and water through. Such reorientation of membranes is transmitted to the inner membranes to induce the division of GVs.

4.3 Dynamics of Self-reproduction Exhibited by Giant Vesicles

Luisi et al. discusses the self-reproduction of a molecular self-assembly in the absence of a template molecule as follows. In the case of vesicular self-reproduction, similar-sized vesicles of the

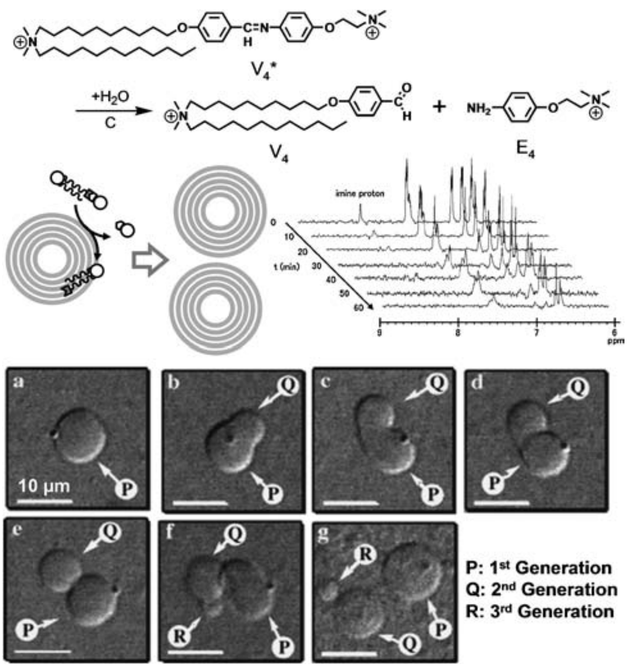

Figure 6. Repeatable self-reproduction of vesicular system. The progress of the hydrolysis was traced by ^{1}H NMR spectroscopy.

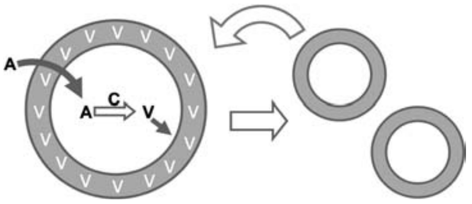

Figure 7. Definition of self-reproduction of a self-assembly.

same components as the original are produced from the original vesicle (Figure 7).[9] For example, a vesicle made of a membrane molecule (V) picks up a precursor molecule (A) and converts it into V within the vesicle. Then it becomes corpulent and self-divides. These dynamics are regarded as self-reproduction.

In contrast, if a vesicle picks up the membrane molecule directly (without first obtaining A) and self-divides without any metabolic reactions, this process is not an example of self-reproducing dynamics. Incidentally, the self-reproduction differs from the self-replication in which a replicate molecule is synthesized with the aid of a template.

Since the number of vesicles that can be observed under a microscope is limited, it is necessary to monitor the self-reproduction dynamics by a different technique. Then the flow cytrometry technique was applied to monitor this robust self-reproducing dynamics of GVs on a mass scale (10^5).[25] It was found that the self-reproduction of GVs continues for at least several cycles in average and the number of GVs increased by ca. 10^2. As described above, a robust self-reproducing GV system is achieved by the cooperative dynamics between membrane precursor V_4*, membrane molecule V_4, catalyst C, and, in particular, electrolyte E_4 which plays the key role in this dynamical division event. The self-reproduction of GV system can be regarded as an indispensable dynamics for an artificial cell.

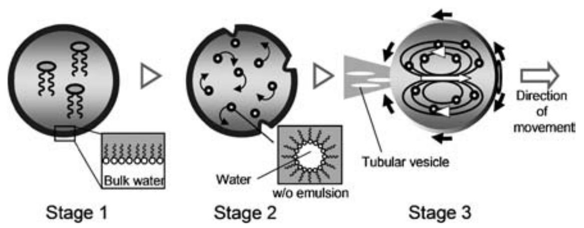

Figure 8. Mechanism of self-propelled oil droplet (see text).

5. Spontaneous Movement of Self-assemblies

5.1 Self-propelled Oil Droplets

The spontaneous movement of a self-assembly is another important types of dynamics beside the self-reproducing dynamics.[26] If a surfactant is formed or decomposed at the interface between the molecular assembly and water and this reaction leads to a cascade of dynamics, spontaneous movement may occur spontaneously. However the methodology to induce self-propelling dynamics by chemical reactions has not been established yet. Yoshikawa et al. demonstrated that oil droplets in water move laterally by accumulating surfactants adsorbed to a glass substrate.[27] The driving force of their oil droplets is derived solely from a physical phenomenon occurring at the interface.

Recently it has been reported that a self-assembly of lipophiles exhibited the self-propelled motions that are derived from a chemical reaction.[28] When an oil droplet of oleic anhydride (or a mixture of oleic anhydride and nitrobenzene) is added to an alkaline (pH 12) aqueous solution of oleic acid, the oil droplet starts to move spontaneously after a brief induction due to hydrolysis of oleic anhydride to oleic acid and oleate at the surface of the droplet. The overall dynamics consists of three stages (Figure 8). In the first stage, the hydrolysis of oleic anhydride occurs at the surface of the oil droplet, and the surface of an oil droplet of a liphophile (oleic anhydride) is coated by surfactants (oleate). In the second stage, along with the hydrolysis, tiny water droplets are dissolved into the oil droplet by the effect of surfactants. These tiny water droplets move randomly in the droplet. In the third stage, the active reaction site of the hydrolysis is concentrated to a certain point at the oil surface due to the thermal fluctuation (breakage of symmetry); soon after, a pair of convections emerge inside the droplet. Releasing tubular vesicles made of oleic acid and oleate from the posterior side, the droplet moves in the opposite direction that is parallel to that of the convection. Since the inside the oil droplet is stirred by convection (Marangoni instability),[29] fresh oleic anhydride is conveyed towards the front edge (active reactive site) of the droplet to accelerate the convection flow, which induces a positive feedback loop.

In this section, we give two examples of self-propelled self-assemblies comprised of chemicals synthesized according to the reaction design inspired by this fortuitous finding.

5.2 Self-propelled Oil Droplets Forming Vesicular Amphiphile

If the dehydrocondensation between an aniline-type amphiphile and a reactive lipophile occurs on the surface of an oil droplet containing an acidic amphiphile as a catalyst, it will afford a vesicular amphiphile. When a liquid of 3-(*n*-octyloxy)-

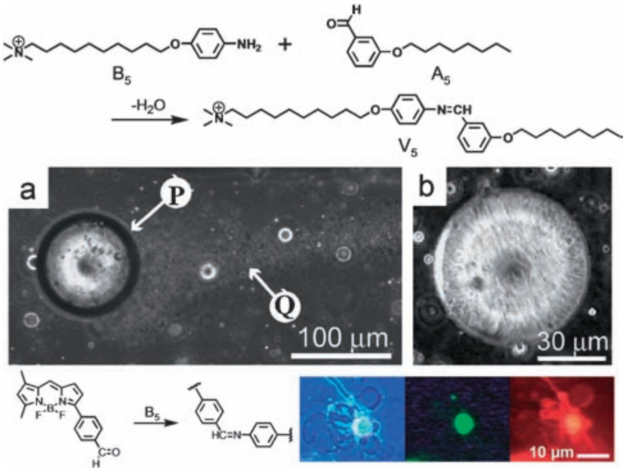

Figure 9. Self-propellants for self-movement of oil droplet driven by dehydrocondensation between aniline and benzaldehyde derivatives.

benzaldehyde A_5 with the cataryst C was added to an aqueous solution of 10-(4-aminophenoxy)decyltrimethylammonium bromide B_5, oil droplets, the sizes of which were in range of 50–120 µm, swam autonomously (maximum speed ca. $11\,\mu m\,s^{-1}$) with a trail composed of vesicles behind (Figure 9).[30]

The conversion of A_5 to vesicular amphiphile V_5 in the aqueous dispersion was traced by ^1H NMR spectroscopy; it turned out that the conversion yield of A_5 to product V_5 was only ca. 1% at 2 h and 50% after 5 d. In order to clarify that the trailing GVs were composed of vesicular amphiphile V_5, they synthesized a reactive fluorescent indicator containing a 4,4-difluoro-4-bora-3*a*,4*a*-diaza-*s*-indacene (BODIPY) moiety with a *p*-formylphenyl unit linked directly to the chromophore (Figure 9; bottom).

This reaction-sensitive fluorescence indicator was applied to monitor the imine-coupling reaction to give a vesicular amphiphile. To an emulsion of oil droplets of A_5 containing 5 mol % of the fluorescence indicator was added an aqueous solution of B_5. As imine-coupling proceeded, membranes began to grow from green fluorescent oil droplets; the growing vesicles glittered red (Figure 9; right). This observation clearly indicates that the vesicular amphiphile V_5 was indeed produced in/on the oil droplets by way of imine formation between A_5 (and indicator) and B_5.

It is probable that the thin film of B_5 that is formed at the specific site of the oil surface is stripped off at an inlet position of the convection, releasing vesicles at the posterior side. This may be the reason why the oil droplet moves in one direction associated with the flow pattern of convection inside of the running oil droplet. Although the detailed mechanism remains elusive, the authors claimed that this is the first artificially designed system made of synthesized organic molecules to demonstrate self-propelled motions coupled with the formation of the membrane molecule.

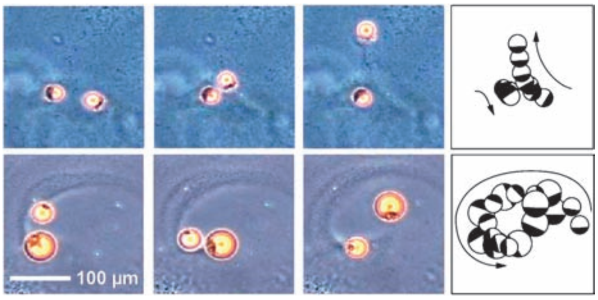

Figure 10. Interplay between self-propelled motions of oil droplets mediated by chemicals released as trails.

5.3 Self-propelled Oil Droplets Consuming Surfactant as Fuel

Another type of a self-propelled oil droplet made of lipophile containing an amphiphilic acid catalyst was reported. The constituting molecules are the same as those depicted in Figure 4.[31] Here, an oil droplet exhibits a self-propelled motion by consuming fuel that is supplied from a bulk aqueous dispersion. In this advanced model, an amphiphilic precursor V_2, that is, a hydrolysable surfactant V_2 used as a "fuel," is dissolved in the outer aqueous solution. Accompanied by the hydrolysis of V_2 to afford lipophile A_2 and electrolyte E_2 on the surface of an oil droplet made of lipophile (*p*-octylaniline A_2), a pair of convections emerges inside the oil droplet. The generated A_2 forms oily microparticles on the surface of the mother oil droplet and eventually microparticles are released one-by-one from the rear, forming a trail. The trail presumably consists of a dense emulsion of the lipophile A_2 and electrolyte E_2 as "wastes." Interestingly, the self-propelling droplet is eventually entrapped by the trail composed of wastes, since a trail does not contain the fuel surfactant.

An intriguing phenomenon was found. When two droplets approach from the front, they do not collapse but escape from each other presumably to the charge repulsion between the coated amphiphiles (Figure 10). On the other hand, when another droplet approaches from behind, the newcomer follows the precedent oil droplet and they move towards the direction where the concentration of the fuel is higher (chemotaxis towards the fuel), and at the same time the latter droplet is going to be entrapped by the trail of the precedent (negative chemotaxis towards the waste). In the precedent examples (Section 5.2), the authors pointed out the significance of the movement induced by the chemical reaction occurring in the assembly. The novelty of this system (Section 5.3) exists in a phenomenon that the movement of a self-assembly is influenced by the chemicals released from the other.

6. Summary

It is a surprise that fundamental chemical reactions, such as formation of the imine bond (dehydrocondensation) of reactive amphiphiles and its cleavage (hydrolysis) occurring inside the self-assembly and at the interface between the assembly and water can drive the drastic morphological changes or even self-propelled movements. Such dynamics are somewhat relevant to those exhibited by animate objects. Hence these newly developed molecular systems may give a hint to understand the essence of sophisticated reaction cycles or autonomous movements manifested by a living system.[32]

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