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# Micelles and vesicles formation from supramolecular complexes based on proton-transfer hydrogen bonding

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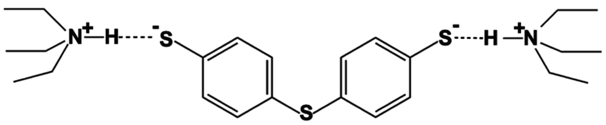
**A gemini type of supramolecular amphiphile with double ion-pair structure was fabricated through proton-transfer hydrogen bonding. In dioxane, the complexes could self-assemble into reverse micelles and vesicles.**

Extensive attention has been paid to colloidal particles, such as vesicles and micelles, due to their potential applications in drug or gene carriers, template synthesis and nanostructured devices.[1] The routine building blocks of these particles are amphiphiles including lipids, surfactants and block copolymers which are covalently synthesized.[2] On the other hand, chemists have also developed a variety of supramolecular amphiphiles (SAs) that is based on non-covalent interactions.[3] For example, Kunitake and Kimizuka adopted hydrogen bonding to fabricate SAs that showed disk-like aggregates in water.[4] Despite substantial investigation on hydrogen bonded complexes, studies focused on SAs are quite few and no examples, as far as we know, of SAs based on hydrogen bonding are described to produce micelles and vesicles, though it is possible.

Herein, we report for the first time that a novel supramolecular amphiphile with double ion-pair structure induced by proton-transfer hydrogen bonding self-assembles into micelles and vesicles in dioxane (see Scheme 1).



**Scheme 1** The structure of complex MPS/TEA.

We performed the experiment by adding triethylamine (TEA) into a solution of bis(4-mercaptophenyl) sulfide (MPS) in dioxane at a molar ratio of 2:1. Before introducing TEA, the solution of MPS was a colorless transparent liquid. Once TEA was added, the solution became milky simultaneously and after an aging time of 24h at room temperature, it turned into light green transparent liquid. The observed results imply MPS has a strong interaction with TEA and some assemblies were formed which seem time-dependent. Since MPS and TEA are all soluble in dioxane respectively, but a mixture of them can generate aggregates. This unusual phenomenon motivates us to confirm the structure of the resulting product and investigate its self-assembly behavior.

Complex phenol/triethylamine has been regarded as a model for studies of proton transfer.[5-8] Compared with phenol, thiophenol has a stronger acidity because of a larger radius and a weaker constraint force of sulfur atom. Thus we conclude MPS can bind with TEA, a lewis base, to form a proton transfer hydrogen bonding complex resulting an ion-pair structure ($S^{-}\cdots HN^{+}$), a similar case has been demonstrated by Henryk Ratajczak et al. on the complexation of thiophenol/triethylamine.[9] More supportive evidence was obtained from Fourier-transform infrared (FT-IR) and $^{1}$H NMR measurements. FT-IR spectra reveal the vibration peaks of S-H (2560 and 920 $cm^{-1}$) decrease while a set of peaks at 2800-3000 $cm^{-1}$ arise (corresponding to TEA) after TEA was added to MPS (Fig. S1, ESI). The results imply MPS has a strong interaction with TEA. $^{1}$H NMR measurements further demonstrate this point. In the mixture of MPS and TEA, the peak of S-H shows a significant shift (from 3.45 to 3.73 ppm) and becomes weak and wide. The peak of $CH_2$ and $CH_3$ of TEA moves to a lower field ($CH_2$: from 0.966 to 1.013 ppm, $CH_3$:

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from 2.483 to 2.526 ppm; Fig. S2, ESI). These observations indicate complexes of MPS/TEA were formed.

Direct observation of the micelles of complex MPS/TEA was performed by TEM. Before testing, the solution was sealed in a glass bottle and stood for 48h after mixing the two ingredients. Figure 1a shows the representative results which were obtained on a carbon coated copper grid after the solvent was evaporated at room temperature. It can be found the aggregates show a uniform sphere shape and the average diameter is estimated to be approximately 50 nm, which is consistent with the dynamic light scattering (DLS) results giving an average size of 64 nm (Fig. 1b). The corona of the micelles is very thin and it is consisted of the aliphatic chains of TEA which shows a lower contrast. Another point is that the micelles seem compound micelles (see insert image).[10] A considerable amount of small micelles (ca.10 nm) were also observed (Fig. S3, ESI). We conclude coalescence occurs easily especially for small micelles , which causes a wide size distribution. The main reason may rise in the thin corona consisted by the short chains of TEA which have less energy contribution. Adding the concentration of the complex or standing for a longer time, the size of the aggregates tends to increase (Fig. S4 and S6, ESI). A parallel case was reported by Lifeng Zhang and Adi Eisenberg on the “crew-cut” micelle-like aggregates of polystyrene-b-poly(acrylic-acid) with very short PAA block.[11]

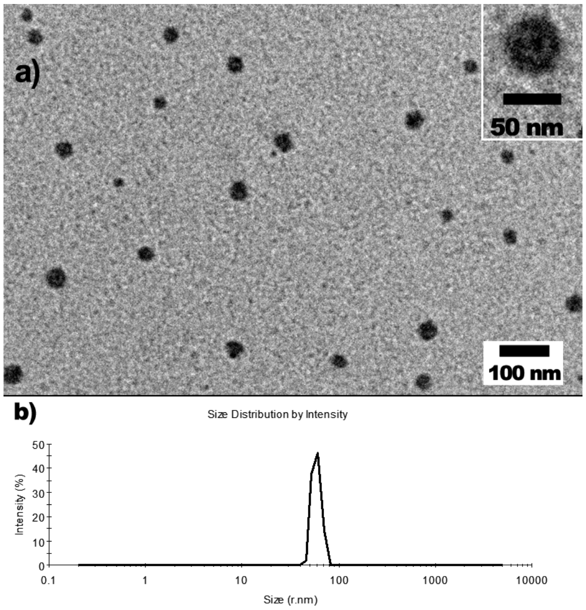

**Fig. 1** a) TEM images of MPS/TEA (4 mM) in dioxane on a carbon coated copper grid after the solvent was evaporated. b) The size distribution (measured by dynamic light scattering) of MPS/TEA (4 mM) in dioxane. The solutions were sealed in a glass bottle and stood for 48h before the above tests.

At a high concentration, complexes MPS/TEA could self-assemble into vesicles although accompanied with a small amount of micelles. Figure 2a reveals some vesicles were formed which were stained by phosphotungstic acid. The dark dense particles are micelles. It can be found some of the vesicles are overlapped and the vesicles display a wide distribution (Fig. 2b) rooting in lacking of efficient mechanism for size selection, as can be found in most systems of conventional vesicles formed by surfactants and polymersomes. Further observation shows the wall thickness of the vesicles is ca. 3.5 nm (Fig. 2c, 2d). Space-filling modeling reveals that the skeleton of complex MPS/TEA has a diameter of ca. 2 nm. These results imply the shells of the vesicles are bilayers. Another notable point is that the vesicles can be consisted by up to three walls, which would make the vesicles more robust (Fig. S5, ESI).

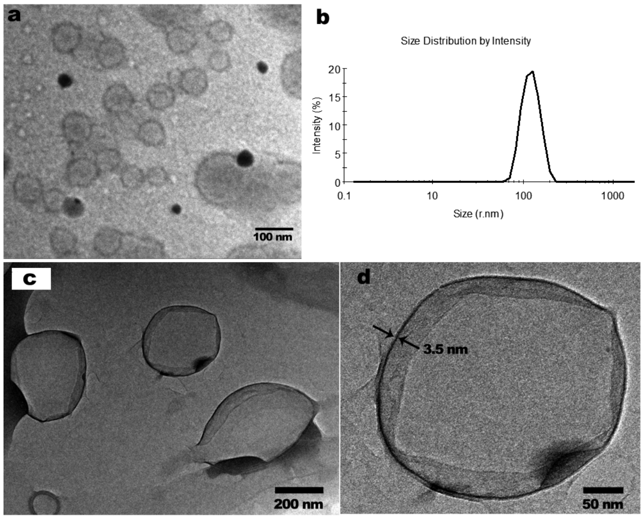

**Fig. 2** a) TEM images of the vesicles of MPS/TEA (40 mM) in dioxane on a carbon coated copper grid. The sample was stained by phosphotungstic acid in dioxane. b) The size distribution (measured by dynamic light scattering) of MPS/TEA (40 mM) in dioxane. c) and d) TEM images of the vesicles of MPS/TEA (40 mM) in dioxane on a ultra thin carbon coated copper grid. The solutions were sealed in a glass bottle and stood for 48h before the above tests.

In addition, the formation of vesicles was also confirmed by SEM. Figure 4 shows complexes MPS/TEA self-assemble into spherical vesicles. The image also reveals that the vesicles could combine to generate twins suggesting the larger vesicles were produced by the fusion of the smaller ones, which could be induced by gravity, Brownian motion, and intervesicular interactions.[12] Besides, some broken vesicles we observed further demonstrate the hollow feature of the vesicles. (Fig. S6, ESI)

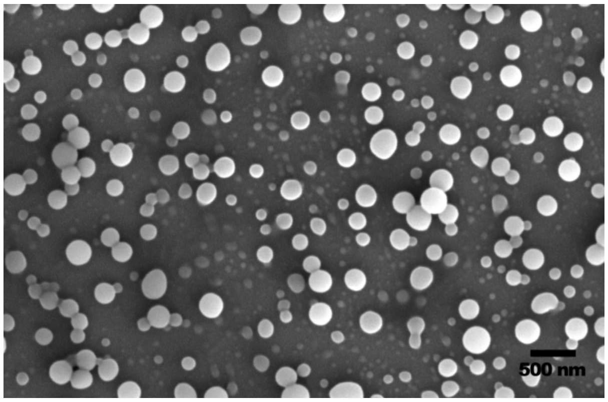

**Fig. 3** SEM images of MPS/TEA in dioxane (40 mM) on silica surface after the solvent was evaporated. The solution was sealed and stood for 48h before test.

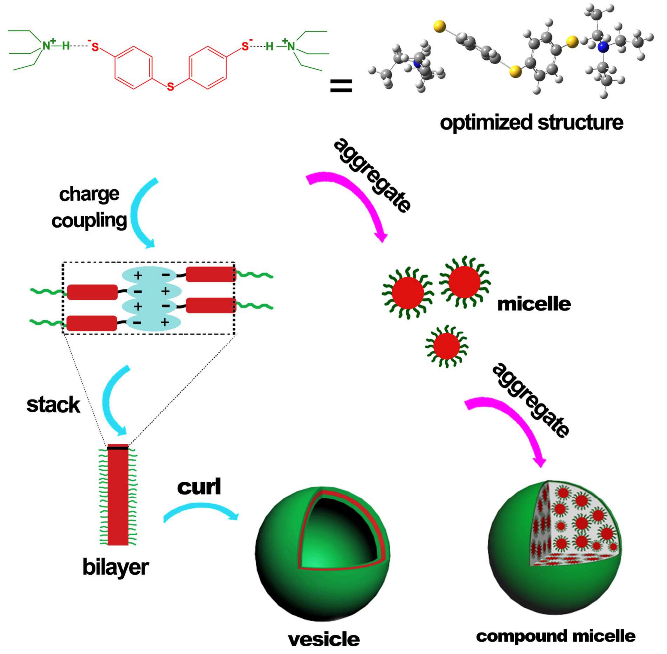

**Fig. 4** A model for the self-assembled nanostructures of complex MPS/TEA. Charge coupling of one end of complex MPS/TEA is suggested to provide a primary driving force for the formation of the vesicles which require a more powerful force to achieve a higher order compared to that of the micelles.

For a better understanding of the self-assembly process of complex MPS/TEA, an attempt to explicate the structure of the obtained micelles and vesicles was made. We note that once TEA was added to a solution of MPS in dioxane, a turbid solution was produced. However, SEM shows no well defined aggregates were formed until the solution became an almost transparent solution after a period of aging time (48h). Therefor, it is believed the proton transfer of MPS leading an ion-pair structure would further enhance polarity of MPS, thus reduced its solubility in dioxane (a solvent with low polarity). However, ordered aggregates could be formed thermodynamically after aging. We suggest the core of small single micelle is consisted by ionized MPS (Fig. 4) with the shell of TEA. However, it is unstable due to short chains of TEA. Therefore, small micelles tend to further aggregate into large compound micelles. To investigate the driving force stabilizing the vesicles, we confirmed the optimum configuration of complex MPS/TEA (b31yp/6-31g** optimized, conformation in vacuum). The perspective view indicates that the molecule of this complex is asymmetric. The twist of one aromatic ring in relation to the other is expressed. The nonplanar configuration of the complex would hinder the stack of the aromatic ring, thus weakening the $\pi$ - $\pi$ interactions. The aliphatic chains of TEA are short and it seems they can only provide limited stabilizing force, thus insufficient to producing robust vesicles. A notable point is that the vesicles were formed under a high concentration which is quite different from that of the conventional surfactants. In this condition, the interactions between solute molecules become more intense. Therefore, we believe the electrostatic interactions between the ion-pairs of complex MPS/TEA paly a key role in the formation of the vesicles. It is suggested a dimer composed of two complexes by charge coupling serves as the basic building block of the self-assembled architectures.[13] A bilayer is formed through extended electrostatic interactions which are expected to provide primary energetic contribution as well as order and directionality for the initial interaction. The other cooperative forces are attribute to the $\pi$ stacking of benzene rings and van der Waals interactions of the chains of TEA.

In conclusion, we have constructed a novel amphiphilic supramolecule through proton-transfer hydrogen bonding on the basis of acid-base interaction. The ion-paired complexes could self-assemble into reverse micelles. At a high concentration, vesicles could be generated. The formed colloidal particles are chemically reactive which can be further modified. Moreover, this work provides useful information for the proper design of self-assembly structures, which may shed a new light on fabrication of supramolecular amphiphiles.

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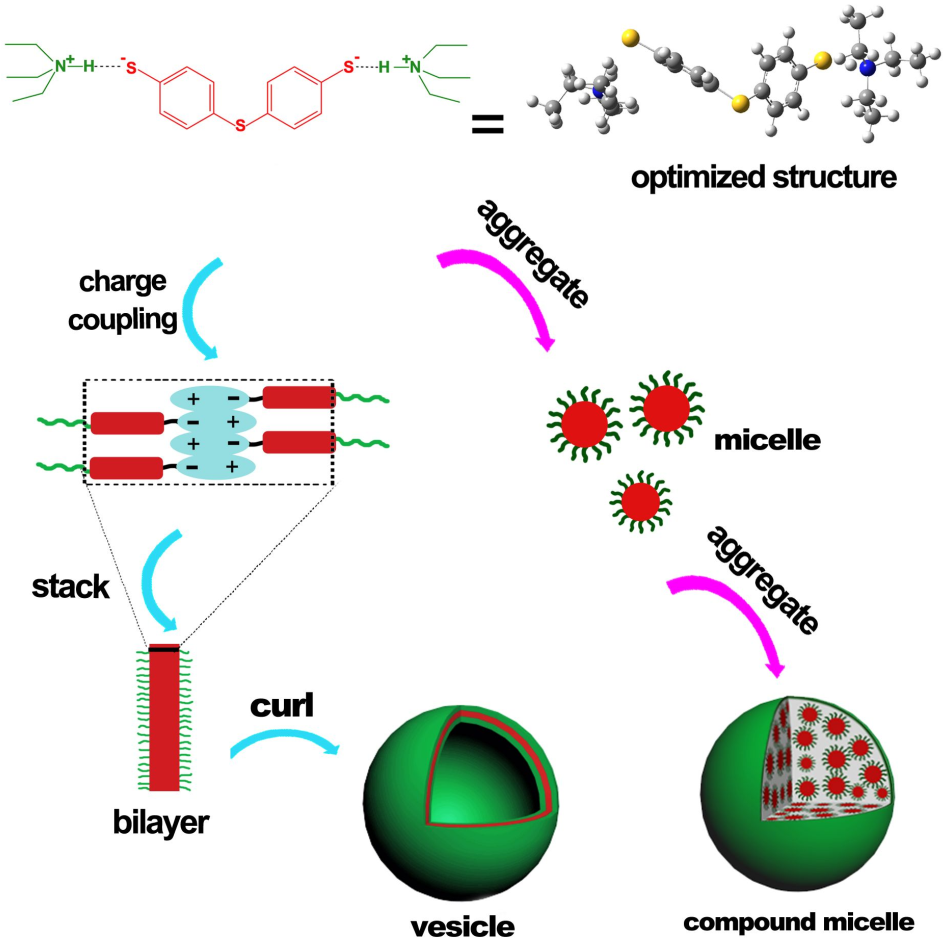

Gemini supramolecular complexes based on proton-transfer hydrogen bonding self-assemble into vesicles and micelles.