

Communication

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Characterizing the “Shell Phase” Formed from Amphiphilic Picolinates

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Jonathon Filley at the Colorado School of Mines was the first to synthesize and study 5-(1-dodecylaminocarbonyl) picolinic acid (**A** in Scheme 1) to combine the metal-ligating properties of picolinic acid with a micelle-inducing hydrophobic chain.¹ In the course of his work, he discovered an unusual phenomenon: When 3 mg of the compound was sonicated and vortexed (10 min each) with 10 mL of 0.25 M NaOH plus 10 mL of toluene, there were formed stable, marble-like macroscopic spheres as shown in Figure 1 at two different concentrations of **A**. Apparently, the spheres are encased by some sort of outer covering, and (with Filley's consent) we decided to further characterize this strange new “shell phase”.

Our initial efforts focused on defining the structural features necessary for shell formation. This led to our synthesizing nine analogues of **A** (Scheme 1) in which the tails, aromatic rings, and linkers were varied. A representative synthetic route for 8 of the 10 compounds (all identified by NMR, MS, and EA) is shown in Scheme 2.^{2–5}

Among the set of 10 compounds, only **A** and **C** form stable shells under the conditions described above. **B** also forms shells above 4 mg. When a vial of one of these systems was tipped, the spheres rolled around freely like glass beads. In contrast, **D**, **F**, and **G** formed only toluene-bearing foams (“aprons”) which were not further investigated. **E**, **H**, **I**, and **J** were intermediate in nature; their spheres were distorted, cloudy, attached, and poly-disperse as was also formed with **A** in heptane (Figure 2a). Thus, shell formation is favored by the following structural attributes: a picolinic acid scaffold, an amide linker bearing an NH, and a long hydrocarbon chain. No correlation was noted between shell formation and melting points (both **A** and **F**, for example, melt at >180 °C). Four conventional surfactants (Brij 30, Brij 97, CTAB, and SDS)⁶ and a phospholipid (DPPC)⁶ all failed to assemble into the shell phase under similar conditions.

Proof that the spheres are water-filled came from the following experiment. An orange aqueous solution of thymol blue (1 drop, 0.03 mg/mL) was injected with a syringe into an **A**-sphere with a needle syringe (Figure 2b). The interior remained homogeneous but turned bright blue as would be expected for the dye in basic aqueous medium. Since the sphere remained blue for months, there is no indication of leakage to the outside. ¹H NMR of liquid withdrawn from the interior (causing collapse of the shell) revealed water with no NMR-detectable presence of surfactant. Aside from identifying the sphere contents, the experiments showed that the shells can sustain a puncture wound and then quickly repair the resulting damage. However, spheres removed from the water/toluene interface (where they tend to reside) did not survive when they came into contact with the open air.

Under a light microscope, a population of spheres appears uniformly round (Figure 3a), and the surface of an individual is roughly textured (Figure 3b). The shell of a 200- μ m sphere is much more difficult to penetrate with a glass micropipet than is a giant vesicle of equivalent size but composed of phospholipid bilayers.

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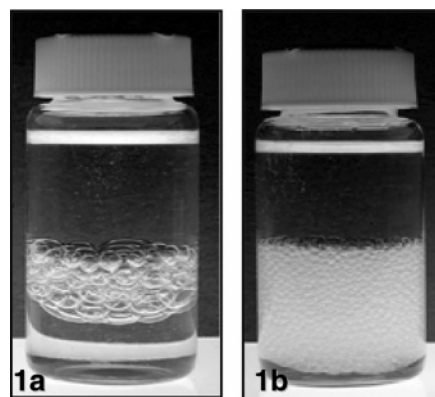
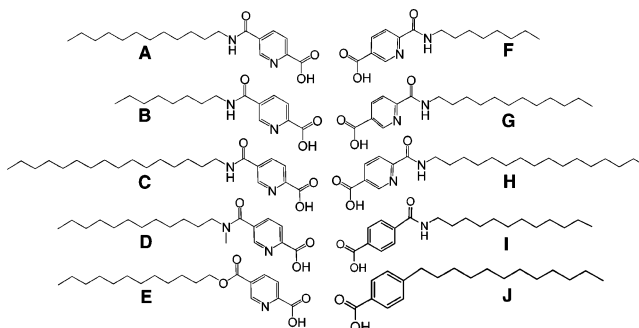
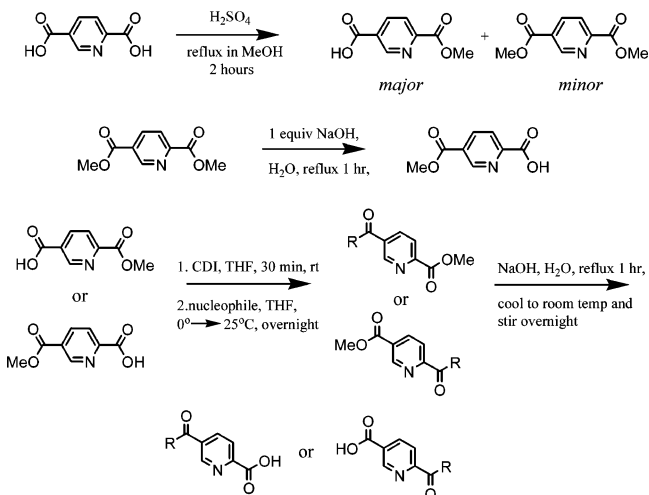


Figure 1. (a) Shell phase formed from 2.4 mg of **A**. (b) Shell phase formed from 5 mg of **A**. Toluene was used in both.

Scheme 1. Structures of 10 Compounds Studied



Scheme 2. Synthetic Route to A–H



When tapped quickly with a micropipet, a sphere responds like a pool ball hit by a cue. No birefringence was observed under a light microscope with crossed-polarizers. A sphere quickly dried under high vacuum produced needlelike structures observable by SEM

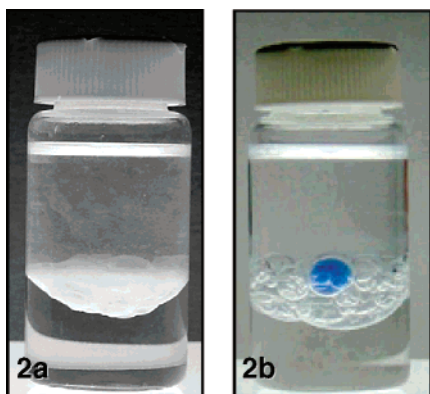


Figure 2. (a) “Imperfect” shell phase formed from **A** using heptane. (b) Image in which one sphere contains a water-soluble dye.

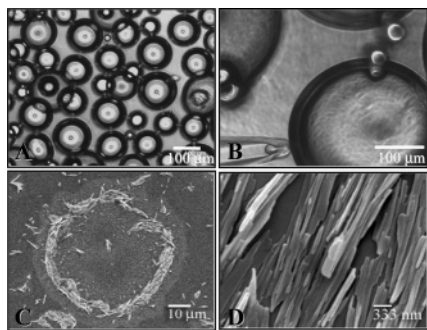


Figure 3. (a) Light microscopy image of spheres formed from 26.9 mg of **A** in water/toluene. (b) Light microscopy image of shell formed from 10.3 mg of **A** in water/toluene. (c) SEM image of dried shell. (d) SEM image of shell wall.

(Figure 3c,d), suggesting a propensity to self-assemble tangentially to the sphere surface. Unfortunately, lack of single-crystal production prevented X-ray analysis.

To make well-developed spheres, the organic phase must be aromatic (PhCH₃, PhCl, PhBr, and PhCN were tested) or cyclohexane. Ether, ethyl acetate, chloroform, *n*-heptane, and cooking oils are unsatisfactory solvents (Figure 2a). Addition of 4 parts toluene to 6 parts *n*-heptane allowed formation of “clean” spheres, suggesting that toluene may be a component of the shell structure. Consistent with this view, spheres made in toluene/water could be transferred to pure ether or ethyl acetate (two solvents unfavorable to shell formation) where the spheres persisted happily at the bottom of the vials. Transfer to protic solvents such as ethanol caused instant bursting. Although spheres do form in buffers (pH = 7–9), an aqueous phase of 0.25 M NaOH (or >1 equiv base) gives the highest quality and largest volume of spheres. Varying the ionic strength by adding NaCl (0, 0.25, 0.5, and 3 M) to 0.025 M NaOH had virtually no effect upon formation of the shell phase.

Solubility properties in water turned out to be critical for shell formation. Quantitative HPLC analysis (C18 reverse-phase column; 60/40 CHCl₃/CH₃OH; evaporative light-scattering detector) showed a 0.1–0.2 mM toluene solubility for the carboxylate salts of eight compounds in Scheme 1. Water solubilities for **A** and **C**, two compounds amenable to shell formation, are very low: <10 μM. Borderline cases **H**, **I**, and **J** also fall below our detectability. In

contrast, **D**, **F**, and **G** which do not form shells, have higher water solubilities of 0.2, 3.8, and 0.040 mM, respectively. It seems, therefore, that shell formation is predicated upon low solubility in both water and toluene. Compound **B**, with a water solubility of 1.2 mM, is particularly relevant in this regard. At 3 mg/10 mL base (our standard conditions), the water solubility of **B** has not been exceeded, and shells do not form. But at 4 mg/10 mL the amount of **B** exceeds its solubility, and shells now form. Thus, the presence of insoluble compound is necessary for shell formation in those compounds prone to form this phase. Water-insoluble amphiphilicity cannot, however, be the only factor dictating shell formation because poorly water-soluble gemini surfactants⁷ fail to form shells. It seems, therefore, that intermolecular hydrogen bonding involving the amide-NH and pyridine nitrogen, coupled with toluene-assisted molecular mobility, are the key to the creation of shells.

Average diameter measurements under the microscope showed that sphere size decreases with amount of compound (Figures 1 and 3a,b). It was a simple matter to estimate the average surface-area-per-molecule in the shell by knowing the concentration and total surface area. Thus, we calculated $1 \pm 0.3 \text{ \AA}^2$ per molecule **A** in agreement with Filley.¹ Assuming that a picolinate molecule fits in a $5 \text{ \AA} \times 5 \text{ \AA} \times 23 \text{ \AA}$ box, and that the boxes close-pack, the shell thickness is estimated to be roughly 600 Å.

In summary, the shell phase forms when certain picolines are subjected to energy input (via sonication or vortexing) while exposed to a water/toluene mixture. A shell, about 600 Å thick and containing the picolinate and (very likely) toluene, surround the water droplets that are always produced during the mixing process. Solubility in either phase appears to be deleterious to shell formation. The shells, stable for months, are not easily distorted but can be punctured, even skewered, with a syringe needle without destroying the sphere. Yet there is enough mobility among the molecules to repair the physical damage after the needle is removed. This, plus the absence of evidence for crystallinity, suggests a solid or semisolid film forms when picolines, with the aid of an aromatic solvent, are provided the energy to rearrange themselves on water droplet surfaces. Structure–activity comparisons among the 10 compounds studied indicate that chain–chain association and intermolecular hydrogen bonding are dominant forces in a side-by-side self-assembly of the molecules within the shells.

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