A Combinatorially-Derived Structural Phase Diagram for 42 Zwitterionic Geminis

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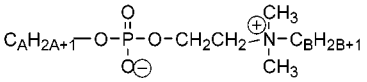
The phase diagram and the attendant Gibbs phase rule are components of most introductory physical chemistry courses. Thus everyone has had at least a passing acquaintance with those triangular diagrams in which phases are recorded as a function of concentrations. Temperature and pressure are often included as additional variables. We have now examined phase properties for large numbers (dozens!) of related compounds. As recognized by many others previously,[1] only by knowing how phases respond to structure can one obtain a molecular understanding of colloidal behavior. Accordingly, we have synthesized, purified, and examined (by electron and light microscopy, dynamic light scattering, and calorimetry) a group of 42 zwitterionic gemini surfactants. The resulting information was then used to construct a "structural phase diagram". As will be seen, phase behavior that might otherwise have escaped attention emerges from this combinatorial approach to colloid chemistry.[2]

Our work focused on gemini surfactants shown below. Varying



the chain lengths **A** and **B** allowed the acquisition of compounds where **A** and **B** are short−short, short−long, long−short, or long−long, respectively.[3] Geminis are attractive candidates for a structural phase diagram, relative to conventional surfactants, owing to their structural versatility. [4]

Figure 1 provides a structural phase diagram for the 42 geminis in which four main zones (identified as gels, micelles, coacervates, and vesicles) are visible. All phases were made by hydrating the solid gemini (5−50 mg/mL) without sonication for 1 h at 25 °C. The gels, micelles, and coacervates were found to be stable for several months. Gels are formed from highly asymmetric geminis in the upper left and lower right of the diagram (e.g. **A**22,**B**6) at 1−4 wt % concentrations. Cryo-high-resolution scanning electron microscope images (cryo-HRSEM) as in Figure 2 prove that the gel consists of a network of interconnected vesicle-sized particles. Although gels from densely packed vesicles have been previously reported,[5] this appears to be the first instance of water being rigidified by "strings" of monodisperse vesicle-like aggregates of 20−30 nm in diameter. Uncovering such a new type of soft material demonstrates the value of the combinatorial approach.

Inspection of the structural phase diagram shows that morphology depends on two parameters: (a) the "hydrophobicity" or total number of carbons in the two chains and (b) the asymmetry of

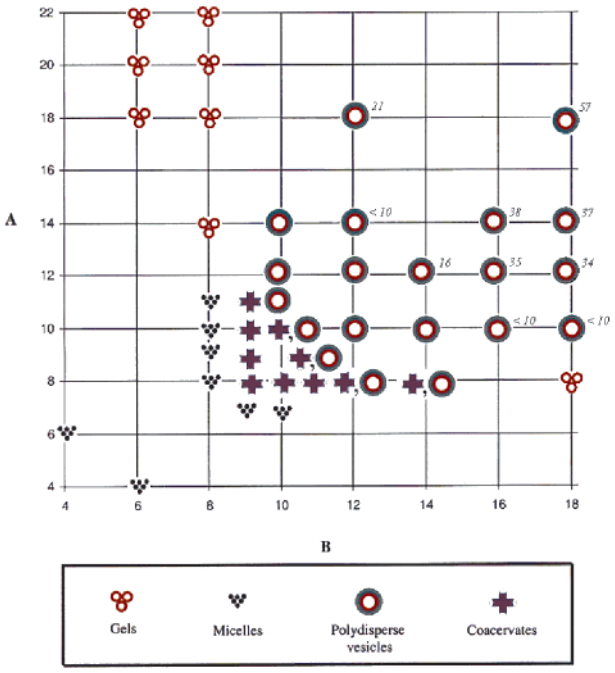


Figure 1. Structural Phase Diagram of 42 zwitterionic geminis. Numbers in the right-top corner of the circles represent gel-transition temperatures of the vesicles (T_m,°C).

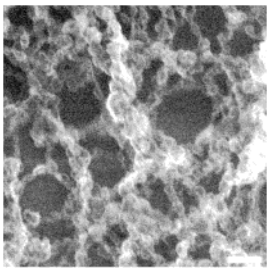


Figure 2. Cryo-HRSEM image of 1mM solution of **A**14,**B**8 showing network of interconnected strands of vesicular particles. Bar=100 nm. Similar images were obtained for **A**18,**B**8.

the two chains. The importance of hydrophobicity is seen from the following comparisons based on SEM, light microscopy, and dynamic light scattering (DLS): When both chains are short (e.g. **A**8,**B**8), micelles predominate (DLS diameter <10 nm). When both chains are sufficiently long (e.g. **A**12,**B**16), the geminis organize into vesicular systems of 30 nm to 100 μm in diameter (circles in Figure 1). Several gel-transition temperatures are given in Figure 1. As with phospholipids,[1b] more symmetrical geminis (e.g. **A**14,**B**16, T_m = 38 °C) have higher T_m values than asymmetrical geminis (e.g. **A**18,**B**12, T_m = 21 °C). More interestingly, when the chains are intermediate in length (e.g. **A**8,**B**10), SEM-visible[6] coacervates are formed (blue crosses). These are comprised of weak bilayers that tend to interconnect with one another, resulting in a rather esoteric type of colloid that has been likened to a "sponge" (Figure 3).[7] Physically, the coacervates in the region between micelles and vesicles appear as liquids that are immiscible with water (despite themselves being 82−86 wt % water) owing to the sponge framework that occupies the entire phase volume.

(1) (a) Oda, R.; Huc, I.; Candau, S. J. *Chem. Commun.* **1997**, 2105−2106. (b) Huang, C. *Klin. Wochenschrift*, **1990**, *68*, 149−165 and references therein. See any current masthead page for ordering information and Web access instructions.

(2) For an approach to combinatorial catalysis, see: Menger, F. M.; Eliseev, A. V.; Migulin, V. A. *J. Org. Chem.* **1995**, *60*, 6666−6667.

(3) The 2-steps synthesis was reported. See: Peresypkin, A. V.; Menger, F. M. *Org. Lett.* **1999**, *1*, 1347−1350. Variations were made possible by reacting the products of alcohols and 2-chloro-1,3,2-dioxaphospholane-2-oxide with different tertiary amines.

(4) Menger, F. M.; Keiper, J. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1906−1920 review the subject of gemini surfactants.

(5) Gradzielski, M.; Bergmeier, M.; Müller, M.; Hoffmann, H. *J. Phys. Chem. B* **1997**, *101*, 1719−1722 and references therein.

(6) Menger, F. M.; Peresypkin, A. V.; Caran, K. L.; Apkarian, R. P. *Langmuir* **2000**, *16*, 9113−9116.

(7) Strey, R.; Jahn, W.; Porte, G.; Bassereau, P. *Langmuir* **1990**, *6*, 1635−1639.

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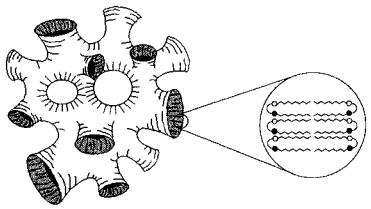

Figure 3. Sponge morphology of coacervates. (Adapted from ref 7).

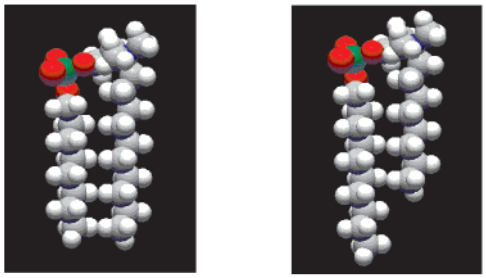

Figure 4. Proposed models of **A**8,**B**10 (left) and **A**10,**B**8 (right), in which central ($O-CH_2-CH_2-N$) bond is gauche and the chains are anti.

But hydrophobicity cannot be the sole factor controlling phases because two geminis of identical hydrophobicity, **A**8,**B**10 and **A**10,**B**8, for example, form a coacervate and micelles, respectively. This difference, which persists throughout the 0−80 °C temperature range, is attributable to chain asymmetry. Figure 4 shows space-filling models of the two geminis assuming a gauche conformation at the central CH_2-CH_2 bond (a conformation that brings the two chains, as well as the oppositely charged ionic groups, into proximity).[8] It is seen that the lengths of the two chains in **A**8,**B**10 are identical, whereas **A**10,**B**8 has a phosphorus chain about 4 carbons longer than its ammonium chain. **A**10,**B**8 asymmetry would be expected to destabilize possible bilayer formation (already weakened from its shorter-than-optimal chain lengths) and to favor organization into micelles. **A**8,**B**10, on the other hand, can pack smoothly into bilayers.

Hydrophobicity and symmetry effects work in concert with **A**11,**B**8; **A**11,**B**9; and **A**11,**B**10 to produce a highly structurally sensitive phase sequence of micelles, coacervates, and vesicles, respectively.

NMR spectra of the colloids in D_2O (Figure 5) are consistent with the proposed model. Thus, micellar **A**10,**B**8, but not the coacervate **A**8,**B**10, has discernible terminal methyl signals (arrows). The same is true for micellar **A**11,**B**8 and coacervate **A**8,**B**11.

Having discovered, via a combinatorial-style synthesis, that two closely related geminis, **A**8,**B**10 and **A**10,**B**8, create totally different phases, we asked a quite natural question: What happens when the two geminis are mixed? To address this question, it is necessary to describe the procedure for preparing the coacervate: A sample of 100 mg of **A**8,**B**10 was added to 20 mL of water. Instantly, coacervate droplets fell out of solution and coalesced into a bottom layer of 0.6 mL. When 200 mg of gemini was added to the 20 mL, a coacervate layer of 1.2 mL was formed, but analyses showed that the two coacervate layers had the same gemini concentration and >99% of the added gemini. The coacervate volume, incidentally, is independent of the original amount of water.[6]

(8) The gauche conformation is the preferred conformation of the choline group of natural phospholipids, see: Hauser, H.; Guyer, W.; Spiess, M.; Pascher, I.; Sundell, S. *J. Mol. Biol.* **1980**, *137*, 265−282 and references therein.

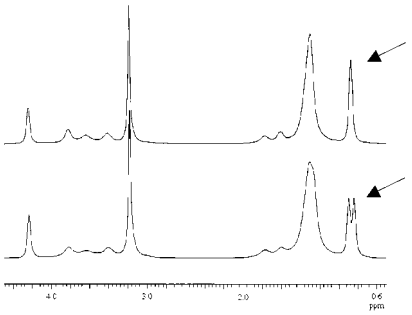

Figure 5. ^1H NMR spectra of **A**8,**B**10 (top) and **A**10,**B**8 (bottom) in D_2O. (400 MHz).

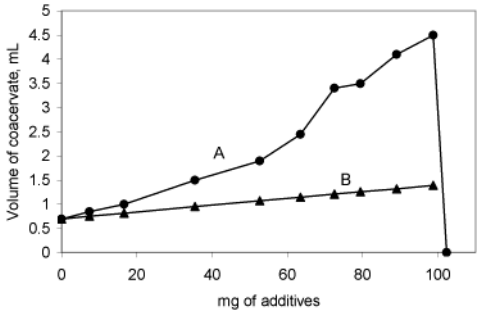

Figure 6. (A) Synergistic effect on coacervate volume upon addition of **A**10,**B**8 to a coacervate from 100 mg of **A**8,**B**10. (B) Addition of **A**8,**B**10 to itself as a control.

A plot of coacervate volume upon addition of 0−100 mg of **A**10,**B**8 to 100 mg of **A**8,**B**10 in 20 mL of water is given in Figure 6. One sees that micelle-forming **A**10,**B**8 enhances the coacervate volume from 0.6 mL to 4.5 mL (a remarkable synergistic effect considering that 200 mg of pure **A**8,**B**10 produces a volume of 1.2 mL).[9] Only when the two geminis are equimolar does the system suddenly revert to micelles (as proven by DLS). The most reasonable explanation is that **A**10,**B**8 incorporates itself into the sponge structure of **A**8,**B**10 where it increases the bilayer curvature and thus the pore size, so that the coacervate swells. With sufficient **A**10,**B**8, the sponge can no longer sustain the distortions, and the structure breaks down into high-curvature micelles characteristic of pure **A**10,**B**8.

Each point (i.e. each compound) on the structural phase diagram warrants a detailed physicochemical examination. This is clearly impractical for a collection of 42 surfactants. The value of a structural phase diagram, however, comes from its providing a sweeping view of phase behavior as a function of structure. Generalizations at the molecular level are thereby possible.

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Supporting Information Available: Experimental details, characterization of compounds, and additional data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For a recent theoretical analysis of synergistic effects, see: Bergström, M.; Eriksson, J. C. *Langmuir* **2000**, *16*, 7173−7181.