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Zwitterionic Geminis. Coacervate Formation from a Single Organic Compound

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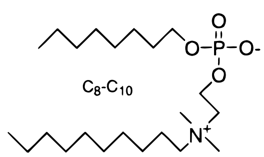
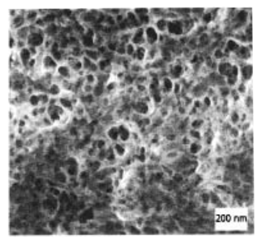
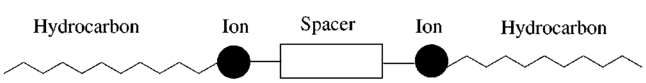
ABSTRACT





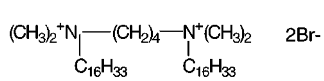
Easily "tunable" zwitterionic gemini surfactants were prepared with a wide variety of chain combinations. These geminis self-assemble into micelles, vesicles, and tubules at low concentrations in water. Two particularly remarkable geminis form a coacervate whose "sponge-like" structure is visible by cryo-high-resolution scanning electron microscopy.

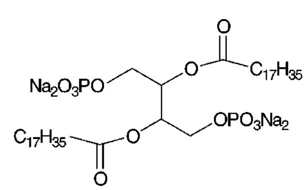
"Gemini surfactant" refers to surfactants with the general structure shown. The term, coined in 1991,[1] originally



denoted surfactants with rigid spacers (e.g., stilbene), but it is now applied to all spacers, rigid and flexible alike. Few people in 1991 had full appreciation for the attention that gemini surfactants would later attract. Nearly a hundred gemini publications, and scores of gemini patents, subsequently appeared on the scene. Reviews summarizing this work are now available.[2−4] Geminis have shown promise in skin care,[5] antibacterial regimens,[6] construction of high-porosity materials,[7] analytical separations,[8] and solubilization processes.[9] The value of geminis stems, in part, from the fact that they can be orders of magnitude more surface active than comparable conventional surfactants.[10]

In most previous reports of geminis, the two ionic moieties have been either both positive or both negative.[11] Two examples taken from the literature[12,13] are shown below.





We now report a synthesis of zwitterionic geminis in which one ionic group is negative (a phosphodiester) and the other

(1) (a) Menger, F. M.; Littau, C. A. *J. Am. Chem. Soc.* **1991**, *113*, 1451−1452. (b) Menger, F. M.; Littau, C. A, *J. Am. Chem. Soc.* **1993**, *115*, 10083−10090.
(2) Rosen, M. J. *Chemtech* **1993**, *23*, 30−33.
(3) Rosen, M. J.; Tracy, D. J. *J. Surfact. Deterg.* **1998**, *1*, 547−554.
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(5) Kwetkat, K. (Huls A.-G.) WO 9731890, 1997; *Chem. Abstr.* **1997**, *127*, 249754r.
(6) Pavlíková, M.; Lacko, I.; Devínský, F.; Mlynarčík, D. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1213−1228.
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(8) Chen, K.; Locke, D. C.; Maldacker, T.; Lin, J.-L.; Aawasiripong, S.; Schurrath, U. *J. Chromatogr. A* **1998**, *822*, 281−290.
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(10) Rosen, M. J.; Liu, L. *J. Am. Oil Chem. Soc.* **1996**, *73*, 885−890.
(11) For a nonionic gemini, see: Pestman, J. M.; Terpstra, K. R.; Stuart, M. C. A.; van Doren, H. A.; Brisson, A.; Kellogg, R. M.; Engberts, J. B. F. N *Langmuir* **1997**, *13*, 6857−6860.

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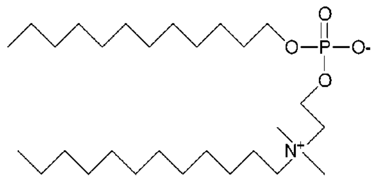
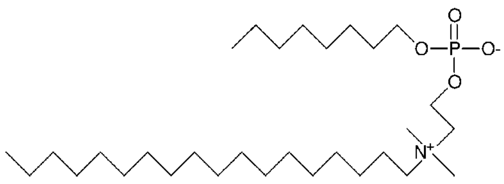
is cationic (a quaternary ammonium salt), the two being separated by a pair of methylenes.[14] Eighteen such compounds have been prepared, two of which are shown below along with their shorthand designation used throughout this text. Note that symbols such as C_8-C_{10} and $C_{10}-C_8$ refer to



C_{12}-C_{12}

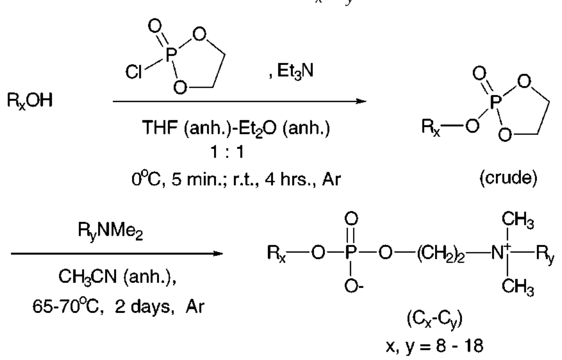


C_8-C_{18}

different compounds that can have, as will be shown, dramatically different properties.

The synthesis of the zwitterionic geminis is given in Scheme 1. Two points are particularly noteworthy. (a) The

Scheme 1. Synthesis of Zwitterionic Geminis of General Notation C_x-C_y



synthesis is short and relatively inexpensive. One can further decrease the cost by preparing the cyclic intermediate via R_xOH and $POCl_3$ and then follow this with ethylene glycol and triethylamine. (b) The synthesis allows easy access to geminis with two different chains. Geminis with unsymmetrical hydrocarbon substitution have been reported but are uncommon.[15,16] Tunability is important because it allowed us to scan a large series of structures and to discover, for example, that unsymmetrical geminis generally foam much less than their symmetrical analogues. Note finally that all geminis were structurally characterized by NMR (^1H, ^{13}C, and ^{31}P), IR, HRMS (FAB), and elemental analysis. Single ^{31}P signals are a particularly satisfying indication of purity.

Critical micelle concentration or CMC (i.e., the concentration at which surfactants abruptly transform from monomer to micelle) is the most common descriptor of surfactant systems. CMCs are often determined from surface tension vs concentration plots which bend sharply at the CMC. In the case of our zwitterionic geminis (Table 1), the situation

Table 1. CMCs and Surface Tensions at the CMCs (γ_{cmc}) for a Family of Zwitterionic Geminis[a]

$x + y$	C_x-C_y	CMC [M]	γ_{cmc} [mN m^{-1}]
16	C_8-C_8	1.0×10^{-3}	32
18	C_8-C_{10}	1.1×10^{-4}	25
	$C_{10}-C_8$	1.0×10^{-4}	30
20	C_8-C_{12}	1.4×10^{-5}	26
	$C_{12}-C_8$	1.8×10^{-5}	28
	$C_{10}-C_{10}$	1.3×10^{-5}	24
22	C_8-C_{14}	6.1×10^{-6}	27
	$C_{14}-C_8$	8.0×10^{-6}	30
	$C_{10}-C_{12}$	1.3×10^{-5}	24
24	$C_{10}-C_{14}$	5.3×10^{-6}	24
	$C_{14}-C_{10}$	5.5×10^{-6}	26
	$C_{12}-C_{12}$	9.0×10^{-6}	26
26	C_8-C_{18}	4.8×10^{-6}	31
	$C_{18}-C_8$	5.9×10^{-6}	29
	$C_{10}-C_{16}$	5.0×10^{-6}	26
	$C_{14}-C_{12}$	7.0×10^{-6}	28
	$C_{12}-C_{14}$	4.3×10^{-6}	24

[a] CMCs represent the point at which geminis aggregate into micelles or other assemblages.

is made more complicated by a time-dependence. Thus, surface tension vs time plots for $C_{10}-C_{14}$ (Figure 1) show that at very low surfactant concentrations (e.g., 5×10^{-6} M) it can take as long as 2 h for the gemini to reach equilibrium at the air/water interface. In contrast, equilibration at 1×10^{-4} M is instantaneous. The CMC values reported in Table 1, measured after allowing the gemini solutions to stand undisturbed for 24 h, are seen to be extremely low. For example, $C_{10}-C_{10}$ has a CMC $= 1 \times 10^{-5}$ M compared to a CMC $= 7 \times 10^{-2}$ M for $C_{10}H_{21}NMe_3{}^+Br^-$.[17] Although the former has two C_{10} chains, the number of chains *per ionic headgroup* is identical for the two cases. Our compounds have remarkably low CMCs even for geminis. For example, $C_{12}-C_{12}$ has a CMC $= 9 \times 10^{-6}$ M compared to a CMC $= 9 \times 10^{-4}$ M for $C_{12}H_{25}N^+$-$Me_2CH_2CH_2N^+Me_2C_{12}H_{25}$.[18]

(12) Zana, R.; Benrraou, M.; Rueff, R. *Langmuir* **1991**, *7*, 1072–1075.
(13) Sommerdijk, N. A. J. M.; Hoeks, T. H. L.; Synak, M.; Feiters, M. C.; Nolte, R. J. M; Zwanenburg, B. *J. Am. Chem. Soc.* **1997**, *119*, 4338–4344.
(14) For an example of a zwitterionic gemini (although not referred to as such), see: Jaeger, D. A.; Li, B.; Clark, T. *Langmuir* **1996**, *12*, 4314–4316.
(15) Renouf, P.; Mioskowski, C.; Lebeau, L. *Tetrahedron Lett.* **1998**, *39*, 1357–1360.
(16) (a) Oda, R.; Huc, I.; Candau, S. *J. Chem. Soc., Chem. Commun.* **1997**, 2105–2106. (b) Oda, R.; Huc, I.; Homo, J.-C.; Heinrich, B.; Schmutz, M.; Candau, S. *Langmuir* **1999**, *15*, 2384–2390.
(17) Haak, J. R.; Van Os, N. M.; Rupert, L. A. M. *Physico-Chemical Preperties of Surfactants II. Cationic Surfactants*; Shell Internationale Research Maatschappij: Amsterdam, 1989.
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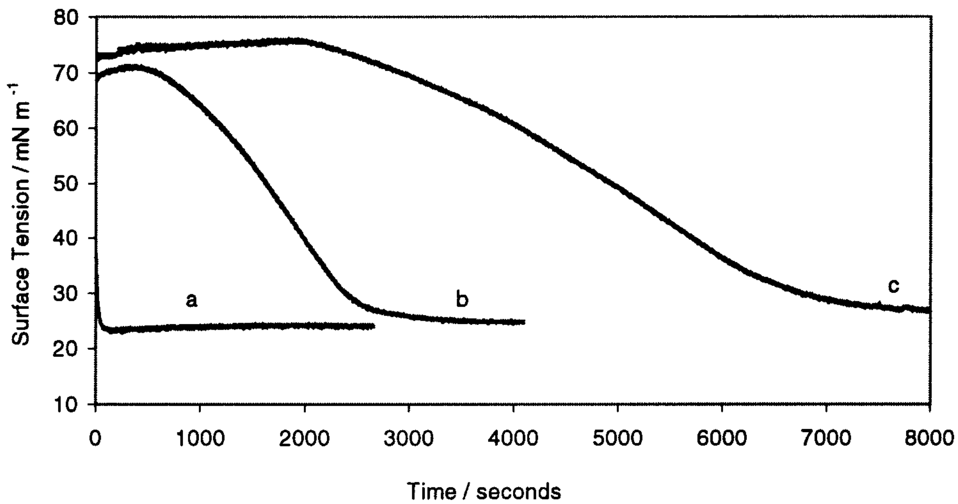

Figure 1. Time dependence of surface tension for $C_{10}-C_{14}$ at (a) 10^{-4} M, (b) 10^{-5} M, (c) 5×10^{-6} M.

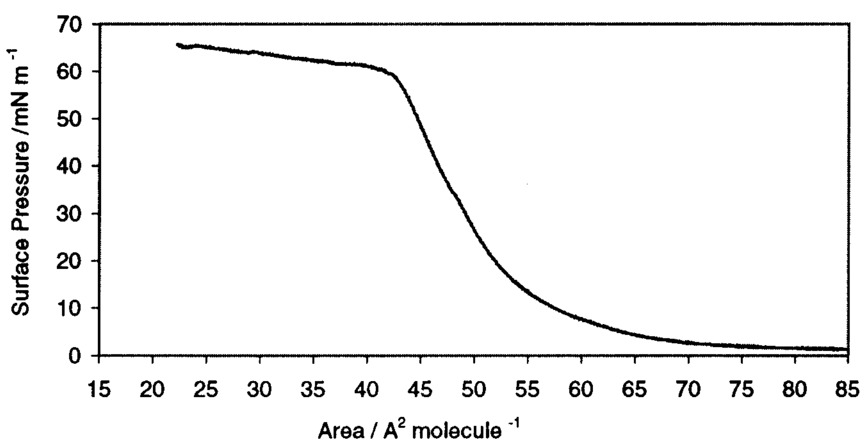

Figure 2. Pressure−area isotherm for $C_{18}-C_{18}$.

The low CMC values are accompanied by a high surface activity. The C_{20} values (i.e., the gemini concentration needed to lower the surface tension by 20 mN m^{-1}) are in the *micromolar* range for geminis ranging from C_8-C_{10} to $C_{10}-C_{16}$. This compares favorably with a C_{20} = 8 mM for $C_{12}H_{25}N^+Me_3$ and a C_{20} = 0.25 mM for $C_{12}H_{25}N^+Me_2CH_2CH_2OCH_2CH_2N^+Me_2C_{12}H_{25}$.[15,16] Several zwitterionic geminis ($C_{10}-C_{10}$, $C_{10}-C_{12}$, $C_{10}-C_{14}$, and $C_{12}-C_{14}$) reduce the surface tension at their CMCs to as low as 24 mN m^{-1}.

Gemini $C_{18}-C_{18}$ is water-insoluble and can be studied as a monomolecular film resting upon water using a Langmuir surface balance. The resulting pressure−area curve (Figure 2) shows a compact film with a liftoff area of only 75 Å molecule^{-1} and a high collapse pressure of 60 mN m^{-1}. Efficient packing in the film, due perhaps to electrostatic forces among the zwitterions, helps to explain the high surface activity of the surfactants seen in the surface tension experiments. It may be no coincidence that Nature also uses zwitterionic phospholipids to form her membranes.

Since $C_{14}-C_8$, C_8-C_{18}, and $C_{18}-C_8$ were found to be particularly viscous at 10 mM, a network of entangled threads might be forming here. A propensity to assemble into linear structures was seen by phase-contrast optical microscopy (Figure 3A) upon hydration of solid $C_{10}-C_{14}$. Actually, dynamic light scattering (DLS) suggests that among the geminis only C_8-C_8 creates micelles exclusively. All others self-assemble, possibly along with micelles, into tubules and vesicle-sized structures (so, in this sense, the term "CMC" may be a misnomer). For example, 20−30 nm vesicles (of unknown lamilarity) were detected by transmission electron microscopy on sonicated 0.5mM dispersions of $C_{12}-C_{12}$ (Figure 3B). Likewise, small vesicles up to 100 nm in diameter have been detected by DLS with C_8-C_{12}, $C_{12}-C_8$, $C_{10}-C_{14}$, and $C_{10}-C_{16}$. Figure 3C reveals clumped vesicular structures of unsonicated aqueous dispersions of $C_{14}-C_8$ as observed by cryo-high-resolution scanning electron microscopy (cryo-HRSEM). When solid $C_{12}-C_{12}$ is hydrated in

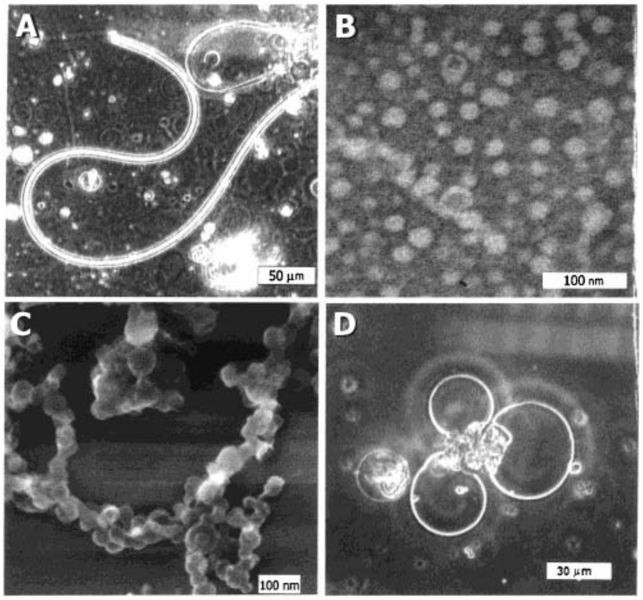

Figure 3. (A) Tubular structures formed upon hydration of solid $C_{10}-C_{14}$ as detected by phase-contrast optical microscopy; **(**B**)** 20−30 nm vesicles of $C_{12}-C_{12}$ as detected by transmission electron microscopy (TEM); **(**C**)** 20−50 nm vesicles of $C_{14}-C_8$ as detected by cryo-high-resolution scanning electron microscopy (cryo-HRSEM); **(**D**)** giant vesicles formed upon hydration of solid $C_{12}-C_{12}$ as detected by phase-contrast optical microscopy.

the absence of sonication or agitation, giant vesicles (visible by light microscopy) were formed (Figure 3D).[19]

Probably the most interesting behavior of the geminis relates to coacervate formation by C_8-C_{10} and C_8-C_{14}. Although geminis with 22 total chain carbons or less are normally water-soluble and form clear or opalescent solutions, the two mentioned geminis cause a phase separation into water-insoluble droplets when their concentration is brought up to 5−10 mM. A colloidal solution immiscible with its own solvent (usually water) is called a "coacervate".[20] Classically, coacervates are made from two components (e.g., polymers of opposite charge or a surfactant plus salt). A light microscope picture of C_8-C_{10} coacervate droplets is given in Figure 4A. A cryo-high-resolution

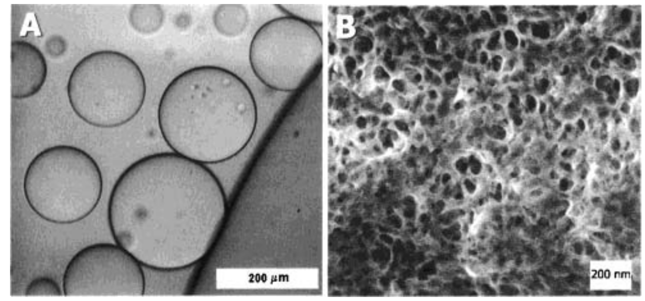

Figure 4. (A) Coacervate droplets of C_8-C_{10} as detected by light microscopy; **(**B**)** cryo-HRSEM image of a coacervate made of C_8-C_{10} (50 000 instrumental magnification; 1 nm Cr coating).

scanning electron microscope picture, showing a space-filling "sponge phase", is given in Figure 4B.[21] That such a single, simple organic compound can render an aqueous phase incompatible with water is truly remarkable. Also remarkable is the fact that whereas C_8-C_{10} forms a coacervate, its $C_{10}-C_8$ "reversomer" dissolves readily in water to give a clear, nonviscous solution that foams prodigiously.

In summary, a new class of surfactants has been synthesized that show a strong propensity to self-assemble at low concentrations, to lower surface tension, and to form (in two cases) coacervate phases. All these properties are attractive from the point of view of practical applications.

Acknowledgment. This research was supported by the Army Research Office. We appreciate technical assistance of Dr. Robert Apkarian and Mr. Kevin Caran with the electron microscopy.

Supporting Information Available: Synthetic methods, characterization data, and procedures for EM, DLS, and surface tension. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Nonzwitterionic geminis have also been reported to form vesicles. (a) Jaeger, D. A.; Brown, E. L. G. *Langmuir* **1996**, *12*, 1976−1980. (b) Sumida, Y.; Masuyama, A.; Maekawa, H.; Takasu, M.; Kida, T.; Nakatsuji, Y.; Ikeda, I.; Nojima, M. *J. Chem. Soc., Chem. Commun.* **1998**, 2385−2386. See also ref 12.

(20) Menger, F. M.; Sykes, B. M. *Langmuir* **1998**, *14*, 4131−4137. This paper, entitled "Anatomy of a Coacervate", gives many lead references on the subject.

(21) The cryo-HRSEM pictures (with a 1 nm Cr coating) were taken on coalesced droplets of 10 mM C_8-C_{10}.