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A-B-A-B-A Block Amphiphiles. Balance between Hydrophilic and Hydrophobic Segmentation

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Molecular segmentation is a widespread attribute of living systems, a fact well illustrated by bacteriorhodopsin. This protein is comprised of seven hydrophobic α-helices that embed themselves inside lipid bilayers. Interconnecting the helices are strands, rich in charged and polar amino acids, that lie in the water outside the bilayer. Thus, the activity of the protein can be ascribed in part to alternating hydrophobic and hydrophilic domains, that is, segmentation. Surprisingly, we know little about nonpolymeric segmented molecules, although they could serve, it would seem, as a basis for understanding biological systems (just as organic mechanisms serve as a basis for understanding enzyme action). This communication examines the self-assembly of penta-segmented organic molecules of the general structure A-B-A-B-A or B-A-B-A-B where A is a hydrophilic polyether and B is a hydrophobic carbon chain. We wondered, for example, how these molecules compare with the di-segmented A-A-A-B-B.[1]

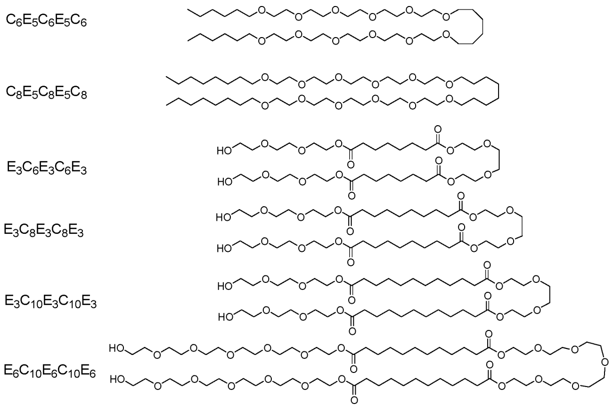
H.-J. Schneider in Saarbrücken is the most active proponent of additivity among multiple noncovalent interactions.[2] Thus, he and his co-workers found that Coulombic, van der Waals, and hydrogen-bonding stabilization of complexes can be quantified by simple additive increments (e.g., 5 kJ/mol per salt bridge in water for up to 12 such interactions). Corresponding data for segregated hydrophobic domains are scarce.

Six penta-segmented "block amphiphiles" are listed in Scheme 1. The top two are hydrophobe-terminated and have ether linkages connecting the segments; the bottom four are hydrophile-terminated with ester connections. These were prepared by multistep sequences given in the Supporting Information. Suffice to mention here that our concern for high purity (as judged by ^{1}H and ^{13}C NMR, HRMS, and EA) required column and preparative layer chromatography on the penultimate compounds. Amphiphiles were investigated via water solubilities, surface activities, cloud points, and self-diffusion coefficients (the latter obtained by Fourier transform pulsed gradient spin−echo NMR, abbreviated PGSE-NMR).[3]

Four of the six block amphiphiles ($C_6E_5C_6E_5C_6$, $C_8E_5C_8E_5C_8$, $E_3C_8E_3C_8E_3$, and $E_3C_{10}E_3C_{10}E_3$) turned out to be water insoluble at 25 °C. This seemingly prosaic development has, nonetheless, useful implications. The conventional surfactant, $C_{16}E_9$, is both water soluble and surface active (critical micelle concentration [or CMC] $= 4 \times 10^{-5}$ M, and aggregation number = 279).[4] Yet $E_3C_8E_3C_8E_3$, with an equivalent E/C content plus a second terminal hydroxyl, does not dissolve in water. Thus, three E_3 units lack the solubilizing capacity of a single E_9 unit, showing that Schneider's additivity principle is not applicable here.

$E_3C_6E_3C_6E_3$ and $E_6C_{10}E_6C_{10}E_6$, being water soluble up to at least 25 mM, were subjected to closer scrutiny. A surface tension versus concentration plot for $E_3C_6E_3C_6E_3$ (Figure 1A) shows only a modest surface activity up to its solubility limit (e.g., compare with the 36 mN/m attainable by $C_{16}E_9$).[5] Moreover, the plot reveals no sharp break indicative of large aggregates. In contrast, the surface tension plot of $E_6C_{10}E_6C_{10}E_6$ (Figure 1B) does in fact reveal a break at 0.19 mM, suggesting the onset of aggregation. By comparison, $C_{16}E_{21}$ has a CMC of only 3.9 μM and thus a much greater propensity to micellize even though it has three more E's and four fewer C's (both of which favor an elevated CMC).[6] Segmentation obviously impairs self-assembly. The packing peculiarities of $E_6C_{10}E_6C_{10}E_6$ are also revealed from a Gibbs plot[7] based on the linear preaggregation region of Figure 1B. This plot gives an interfacial area of 150 Å^2 per molecule, an area only about one-third of the cross-sectional molecular area. Consequently, a likely and intuitively reasonable conformation at the air/water interface has the E segments partially immersed in water, while the two C chains between them are looped in the air (Figure 2).

Scheme 1



$E_6C_{10}E_6C_{10}E_6$ has a cloud point of only 37 °C (40 mM), compared to 92 °C for $C_{16}E_{12}$,[8] emphasizing the ease with which the block surfactant can desolvate its ether groups and phase separate from solution.

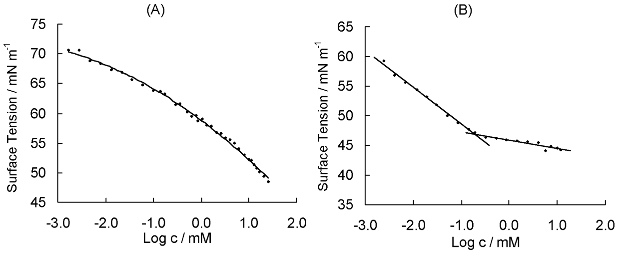


Figure 1. Surface tension versus concentration: (A) $E_3C_6E_3C_6E_3$ and (B) $E_6C_{10}E_6C_{10}E_6$. Lines are visual guides only.

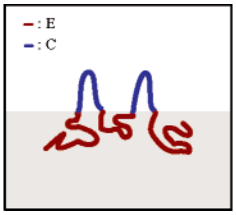


Figure 2. Proposed conformation of $E_6C_{10}E_6C_{10}E_6$ at the air/water interface.

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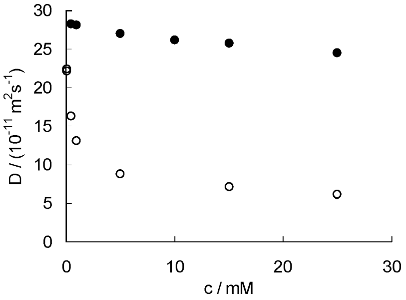

Figure 3. The observed self-diffusion coefficients of $E_3C_6E_3C_6E_3$ (●) and $E_6C_{10}E_6C_{10}E_6$ (○) at different concentrations (25 °C).

To acquire detailed information on the nature of the block amphiphile aggregates, we turned to PGSE-NMR, a technique that provides the self-diffusion coefficients (*D*) of species in solution. Translational mobility of a solute depends upon its effective size and, therefore, upon its self-assembly. All PGSE-NMR experiments were performed on a Varian INOVA 600 spectrometer equipped with a pulsed field gradient generator using a Hahn-echo sequence with intervening pulsed field gradients, that is, a complete pulse sequence of 90°−PG−180°−PG. In each experiment, the strength of the pulsed gradient was incremented in 16 steps, and the values of *D* were calculated from the attenuation of the relevant echo peaks via the Stejskal−Tanner equation. In all experiments, the observed echo decays were single-exponential and gave very good fits to the equation.

Plots of *D* versus concentration for the two block amphiphiles are given in Figure 3. If one assumes that excluded volume effects are negligible and that disperse molecules as well as the aggregates can be approximated as spheres, the *D* values provide effective sizes of the diffusing entities using the Stokes−Einstein equation.

At the lowest investigated concentration (0.5 mM), $E_3C_6E_3C_6E_3$ particles have a hydrodynamic radius of about 0.7 nm and a volume of 1.4 nm^3. This is roughly the volume of one solute molecule from which one can conclude that the amphiphile is predominantly monomeric. At 25 mM, *D* corresponds to a volume that is about 50% larger than the volume at 0.5 mM. Hence, the average aggregation number increases gradually with concentration, but only to a value of 1.5. Despite its 12 methylenes, $E_3C_6E_3C_6E_3$ exists only as monomers and dimers up to its solubility limit. Segmentation, plus possibly an "edge effect" of the proximate hydrophilic segments, severely impedes self-assembly.

The concentration dependence of *D* for $E_6C_{10}E_6C_{10}E_6$, which is much more pronounced than for $E_3C_6E_3C_6E_3$, resembles that of a conventional surfactant. The *D*'s of a typical micelle-forming amphiphile are, to a good approximation, represented by the population-weighted sum of the *D*'s for the monomers and micelles. If observed *D*'s are plotted versus the reciprocal of the concentration, one gets two straight lines intersecting sharply at the CMC. In Figure 4, such a plot is given for $E_6C_{10}E_6C_{10}E_6$ (circles) along with a hypothetical plot (dotted line) for a conventional surfactant with a CMC of 0.19 mM. The obvious deviation for $E_6C_{10}E_6C_{10}E_6$ at higher concentrations is most simply explained by a lower degree of cooperativity during self-assembly. In other words, the block amphiphile assemblies grow continuously as opposed to the molecules precipitously forming micelles of a discrete aggregation number.

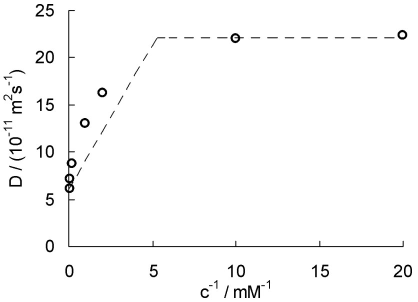

Figure 4. The self-diffusion coefficients of $E_6C_{10}E_6C_{10}E_6$ (○) plotted versus reciprocal concentration. The dashed line shows a prediction of the expected *D* for a conventional micelle-forming amphiphile with a CMC of 0.19 mM, a D_{monomer} of 2.2×10^{-10} m^2/s, and a D_{micelle} of 6.1×10^{-11} m^2/s (i.e., the observed *D* at 25 mM).

By again invoking the Stokes−Einstein equation, we estimated the hydrodynamic radii of the $E_6C_{10}E_6C_{10}E_6$ aggregates to be 2.2 and 3.2 nm at 5 and 25 mM, respectively. These correspond to maximum average aggregation numbers of approximately 20 and 60. The aggregation numbers are maximum values because each ethylene oxide group can be expected to bind several water molecules that contribute to the overall aggregate volume. The orientation of the surfactant molecules in the self-assemblies is not as well defined as it is at the air/water interface.

In summary, segmentation can have a dramatic effect upon solute properties, including solubility, propensity to self-assemble, aggregation number, and cooperativity.

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Supporting Information Available: Synthetic routes to the block amphiphiles and experimental details of the PGSE-NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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