Vesicle Formation from Dimeric Surfactants through Ion-pairing. Adjustment of Polar Headgroup Separation leads to Control over Vesicular Thermotropic Properties

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Eight new vesicle-forming dimeric surfactants are synthesized: the polar headgroup separation in such dimeric amphiphiles strongly influences their vesicular thermotropic phase-transition behaviour.

A novel class of surfactant has recently been introduced.[1,2] These compounds *e.g.* **1** have been referred to as dimeric[1] or gemini[2] surfactants as they are made of two identical hydrophobic chains and two hydrophilic headgroups connected through a spacer at the level of ionic headgroup. Geminis are also possible candidates for the next generation of surfactants[3] and possess unusual properties. In particular, they form micelles at very low critical micellar concentrations and are highly efficient in lowering oil–water interfacial tension in comparison to their more conventional single-chain counterparts. Consequently, these novel micelle-forming systems are currently attracting a lot of attention.[4]

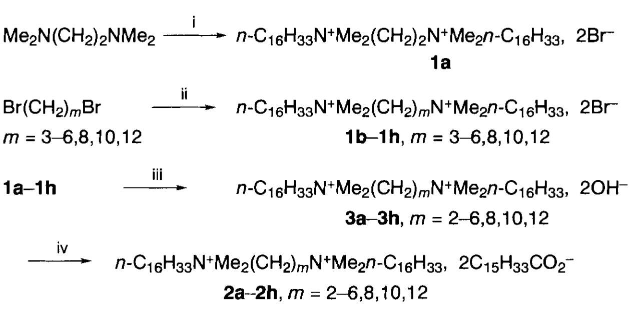
However, no analogous system is presently known that can assemble to form aggregates such as bilayers or vesicles. Vesicles from new synthetic systems are useful because of their potential in wide-ranging applications.[5] Synthetic surfactants that are capable of forming vesicles are being extensively investigated for diverse purposes such as drug entrapment and release,[6] or for developing reaction specific catalysts[7] or even in the use in photochemical solar-energy conversion.[8] We thought that access to gemini, vesicle-forming family of surfactants would be particularly interesting because of the presence of a hydrophobic polymethylene spacer chain as an element of control of the lateral distribution of the polar headgroup within a dimeric surfactant unit itself. At the same time, this novel system allows one to examine the properties of a hybrid of a bolaform[9] and conventional amphiphile. In this communication, we describe the syntheses of such a new family of gemini surfactants **2** and the formation and characterization of vesicles prepared from aqueous dispersion of such systems.

Altogether, eight 'dimeric' ion-paired[10] amphiphiles **2a–2h** were synthesized (Scheme 1) by passage of methanolic solutions of dicationic amphiphiles, n-$C_{16}H_{33}N^+Me_2$–$(CH_2)_m$–N^+Me_2-n-$C_{16}H_{33}$ $2Br^-$, **1** (n = 2–6,8,10,12, respectively) through an ion-exchange column (Amberlite IRA-900, OH^- form), followed by (*i*) treatment with 2 equiv. of freshly recrystallized palmitic acid in MeOH, (*ii*) removal of solvent under reduced pressure rotary evaporation and (*iii*) repeated recrystallizations from MeOH–EtOAc. All compounds reported herein were obtained as colourless solids and the spectroscopic data (^1H NMR, IR) and elemental analyses were consistent with the given structures.

Examination of vesicle forming abilities (reverse-phase evaporation)[11] of dispersions of **2a–2h** by TEM (JEOL TEM-200 CX instrument; 0.5% uranyl acetate) revealed the presence of spherical and ellipsoidal vesicles.[12]† The dispersion produced by this method gave multilameller vesicles and generally, the diameter of the vesicles increased with increase in n values. Two representative micrographs for **2b** (n = 3) and **2d** (n = 5) are shown in Fig. 1.

Bath sonication of dispersions of **2a–2h** in pure water (1 mg ml^{-1}) also afforded translucent suspensions that were optically stable for several weeks as judged by measurements of their time-dependent change in turbidity at 400 nm. Gel filtration of aqueous dispersions from **2a–2h** through a Sephadex G-50 (Pharmacia) column led to > 70% recovery and the profile was sharp.

The thermotropic transition behaviour of vesicles from **2a–2h** were examined independently by both the fluorescence method and differential scanning calorimetry and the results are given in Table 1. The fluorescence method measured the monomer vibrational intensity ratio (I_3/I_1) of bilayer doped pyrene as a function of temperature.[13] The temperatures related to the break on (I_3/I_1) *vs.* T plot (figure not show) for each



Scheme 1 *Reagents and conditions*: i, $C_{16}H_{33}Br$ (3.0 equiv.), dry EtOH, reflux, 48 h, 90% yield; ii, $C_{16}H_{33}NMe_2$ (3.0 equiv.), dry EtOH, reflux, 48 h, 70–90% yield; iii, Ion-exchange Amberlite IRA-900, OH^- form; iv, $C_{15}H_{31}CO_2H$ (2.0 equiv.), room temp. stirring for 12 h, 90–95% yield

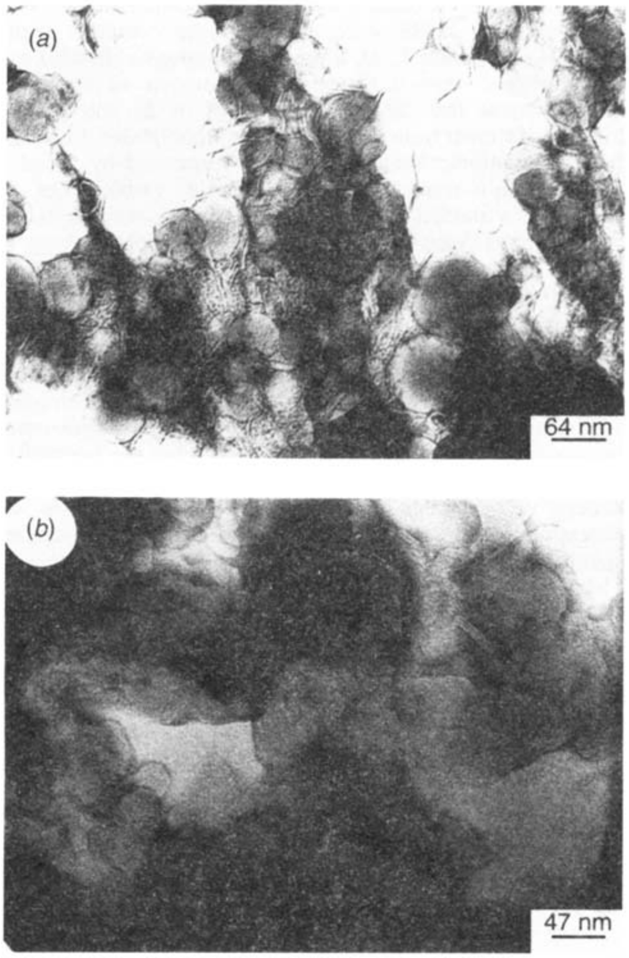


Fig. 1 Negative-stain transmission electron micrographs of vesicles of **2b** and **2d**, prepared *via* reverse-phase evaporation: (*a*) **2b** (n = 3) and (*b*) **2d** (n = 5)

Table 1 Gel-to-liquid crystalline main phase-transition properties for Ion-paired amphiphiles **2a–2h**

Amphiphile	T_m/°C (DSC)		T/°C	$\Delta H_{calc.}$[a]/	ΔS[b]/	ΔH_{vH}[c]/	CU[d]/
	Heat	Cool	Fluor.	Kcal mol^{-1}	cal K^{-1} mol^{-1}	kcal mol^{-1}	molecules
2a	74.1	71.7	76.2	9.32	55.67	1047.51	54
2b	66.2	64.6	62.5	15.64	46.10	766.00	49
2c	47.4	45.7	43.1	15.83	49.41	553.63	35
2d	45.6	42.9	45.0	19.66	61.72	586.32	30
2e	45.6	42.6	44.6	20.07	62.98	541.25	27
2f	42.8	40.4	42.2	20.36	64.45	494.30	24
2g	41.1	38.4	40.0	18.86	60.06	655.89	35
2h	38.9	37.7	37.7	20.51	65.75	523.18	26

[a] The ΔH values quoted are the average of the total enthalpy for successive runs. We estimate that transition enthalpies are accurate to ±0.5 kcal mol^{-1} (1 cal = 4.184 J). [b] ΔS values were calculated from $\Delta H/T_m$ assuming the phase transition as a first-order process. [c] ΔH_{vH}, van't Hoff enthalpy values were calculated from the relation, $\Delta H_{vH} = 6.9\ T_m^2/\Delta T_{\frac{1}{2}}$, where $T_{\frac{1}{2}}$ is the spread of temperature at half-height. [d] The CU cooperativity units values are the average for successive runs.

vesicular dispersions were taken as the apparent T_m. Dispersal of **2a–2h** in pure water by vortexing afforded lamellar gels (Perkin Elmer DSC-4). Well-defined, virtually reversible, phase transitions (gel → liquid crystalline) were readily observed for each dispersion. Importantly, the transition temperatures obtained from two unrelated measurements coincide well (Table 1). Interestingly, the phase-transition temperatures (T_m) were found to be strongly dependent on the n-value of the spacer chain [$-(CH_2)_n-$]. Thus, when $n = 12$, the apparent T_m is as low as 38.9 °C and the corresponding value recorded for $n = 2$ is as high as 74.1 °C. In addition, the transition process is less cooperative as the n-value increases beyond 3.

We rationalize the origin of such remarkable control of n-value over T_m on the basis of molecular mechanics studies. Ion-paired systems **2a–2h** were drawn in the computer using INSIGHTII (Version 2.3.0, Biosym Technology software) and their energies were minimized. Examination of structural features reveal that the packing modes in **2a** and **2b** are strikingly different from that of the other amphiphiles. In **2a** and **2b**, where cationic Me_2N^+ centres are separated by 2 and 3 methylene units respectively, the counterion carboxylates are available for mutual electrostatic interaction with both the Me_2N^+ centres. Such organization leads to efficient packing. In contrast, as the headgroup separation increases with higher n-values, the CO_2^- anions are confined to individual quaternary ammonium cations. Additionally, the other conformational states of the spacer polymethylene chain arise from rotations about the C–C bond as the n-value surpasses **3**. As the number of *gauche* conformers increases, the polymethylene chain starts to loop into the membrane interior in order to minimize water contacts and thus, impairing the packing within the assembly.[4] Thus, the phase-transition temperature as well as the number of 'dimeric' amphiphiles that cooperatively participate in the process of phase transition decreases with increased headgroup separation.

Manifestation of unusual thermal stability observed with **2a** and **2b** might have possible practical ramifications.[14] Consequently, studies that are now in progress are aimed at examining the influence of (*i*) 'stiff' spacers, (*ii*) differences in chain length, (*iii*) alteration in headgroup structure and (*iv*) chain tethering on different vesicular properties.

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Footnote

† Calculation of packing parameters on this basis[12] gives a P value of 0.63–0.65 for **2a** and **2b**. This predicts bilayer vesicle formation from **2**. This is indeed verified by the electron microscopic results.

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