

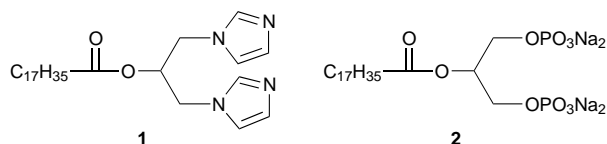
Dicephalic surfactants

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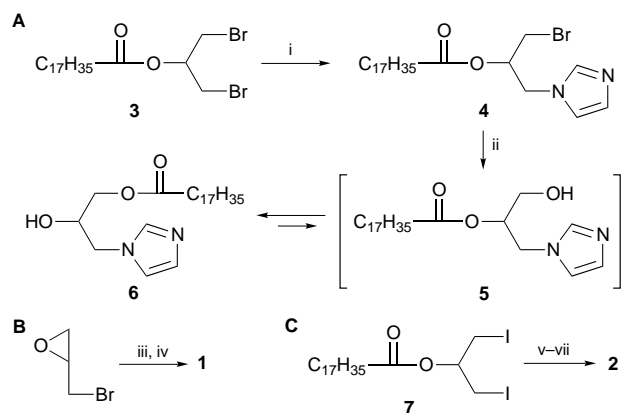
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Two examples of dicephalic surfactants, a new class of two-headed amphiphiles, were prepared and demonstrated to exhibit unexpected aggregation behaviour.

Recently several research groups have studied the aggregation behaviour of surfactants with unusual structural features in order to further understand the relationship between the structure of the amphiphile and the type of aggregates it forms. Examples include surfactants with hyperextended¹ and spiro² hydrocarbon chains, gemini surfactants³ and super surfactants, *e.g.* block copolymers of polystyrene and poly(propyleneimine) dendrimers.⁴ Gemini surfactants, a new class of amphiphilic molecules with two hydrocarbon chains and two polar head groups connected by a linker, display aggregation behaviour that is distinctly different from that of the constituting 'parent' surfactants.⁵ The interesting properties of gemini surfactants prompted us to design and synthesise another type of amphiphilic molecule for which we propose the name dicephalic (two-headed) surfactant. Molecules of this type consist of a single hydrocarbon chain and two polar head groups (**1** and **2**).[‡] Both compounds can complex metal ions: the former binds transition metals to its imidazole groups, the latter calcium ions to its phosphate functions.⁶ Here we report on the unusual self-assembling properties of the dicephalic surfactants.



The synthesis of compound **1** was initially tried by treating 1,3-dibromopropan-2-yl stearate **3**§ with imidazole in MeCN. Instead of the desired product **1** a mixture of compounds **4** and **6** was isolated. A mechanistic explanation is presented in Scheme 1A. Direct nucleophilic replacement of the second halogen atom in **3** by imidazole is difficult due to considerable



Scheme 1 (i) Imidazole-CH₃CN; (ii) aqueous work-up; (iii) NaH-imidazole-DMF; (iv) C₁₇H₃₅COCl; (v) AgOP(O)(OBn)₂-toluene, reflux; (vi) H₂/Pd/C; (vii) Dowex-Na⁺

steric hindrance as was evident from examination of CPK models.¶ During aqueous work-up a hydroxy group is probably introduced which gives **5** and after acyl migration⁷ the α -hydroxystearate **6**. Compound **1** could, however, be synthesised *via* a double nucleophilic attack of sodium imidazolide on epibromohydrin, followed by acylation of the alkoxide intermediate (Scheme 1B).

Reaction of **3** with tetraalkylammonium salts of mono- and di-benzyl phosphate, for similar steric reasons as mentioned above, did not lead to satisfactory yields of the respective desired bis-phosphates.∥ Compound **2** was prepared therefore by phosphorylation of the diiodide **7**§ with silver dibenzyl phosphate⁸ followed by catalytic hydrogenation over Pd/C and subsequent cation exchange (Scheme 1C). This indirect displacement of the halogen atoms by the dibenzyl phosphate ions is promoted by the formation of an AgI complex and the neighbouring group participation of the ester carbonyl function.

Inspection of CPK models of **1** and **2** revealed that both compounds have a very large head group section compared to their lipophilic part. According to the structure–shape concept,⁹ the formation of micelles may therefore be expected when these compounds are dispersed in water. Dispersion of **1** in water at pH 7.0 (0.1%, w/w) did not, however, lead to the formation of micelles, but to well defined multilayered platelets of micrometer size [Fig. 1(a)]. Powder diffraction experiments revealed a repetitive distance of 31 Å, indicating a structure in which the hydrocarbon chains are interdigitated. Electron diffraction showed several bands, indicative of the polycrystalline nature of the sample, and a strong phase transition at 58 °C ($\Delta H = 60 \text{ J g}^{-1}$) was observed by DSC. The pK_a values of **1** (3.6 and *ca.* 7), make it likely that the platelets consist of a mixture of protonated and deprotonated surfactant molecules. The possibility of intermolecular hydrogen bond formation over long distances, may account for the remarkable stability of these lamellar structures.

When 0.25 equiv. of CuSO₄ were added to a dispersion of **1** in water, vesicles with diameters of 50–250 nm were formed [Fig. 1(b)]. EPR and FTIR titration experiments showed that a complex of the type Cu(Imidazole)₄²⁺ had been formed,** but it was not possible to differentiate between a monomeric Cu^{II} **1**₂

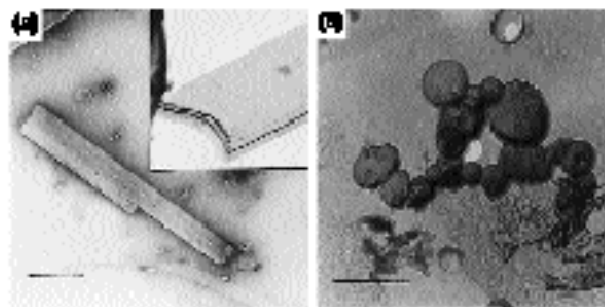


Fig. 1 Electron micrographs of (a) **1** (negative staining, inset Pt shadowing technique) and (b) a 2:1 complex of **1** and CuSO₄ (freeze fracture technique) in water. Bars represent 250 nm.

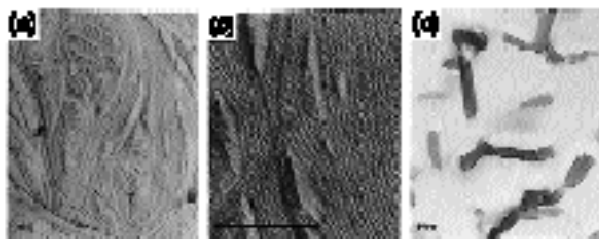


Fig. 2 Electron micrographs of **2** in (a, b) aqueous 2 mM PIPES buffer (pH 7.0, freeze fracture technique) and (c) aqueous 2 mM PIPES buffer containing 0.5 mM CaCl_2 (pH 7.0, Pt shadowing technique). Bars represent 100 nm.

complex and a polymeric coordination network. According to powder X-ray diffraction these vesicles had an interdigitated bilayer with a thickness of 32 Å. DSC revealed a phase transition at 15 °C ($\Delta H = 15 \text{ J g}^{-1}$), indicating that copper complex formation caused a dramatic change in the molecular packing.

For 0.1% (w/w) dispersions of **2** in an aqueous buffer of pH 7.0, electron microscopy [Fig. 2(a),(b)] revealed the formation of bundles of fibres each with a diameter of 65 Å, (approximately twice the molecular length) and lengths up to 15 µm (aspect ratio >2000). These fibres showed a faint phase transition at 23 °C ($\Delta H = 1.5 \text{ J g}^{-1}$) in DSC. The formation of very long structures suggests that intermolecular interactions must also play an important role in stabilising these aggregates. Since at pH 7.0 the phosphate groups will be in their monoprotonated form,¹⁰ a network of hydrogen bonds can be formed between protonated and unprotonated P–OH groups of neighbouring molecules (Fig. 3), which could account for the observed stability of these large structures.

Compound **2** is expected to form a 1:1 complex with calcium, either intramolecularly by chelation or intermolecularly by formation of a linear polymeric complex.¹¹ Addition of calcium chloride ($[\text{Ca}^{2+}] = 0.5 \text{ mM}$) to aqueous dispersions of **2** led to the formation of a precipitate consisting of small (200–500 nm) and irregularly shaped multilayered platelets [Fig. 2(c)]. These platelets were shown to be polycrystalline by electron diffraction and displayed a sharp phase transition at 148 °C ($\Delta H = 17 \text{ J g}^{-1}$) in DSC. Considering the relative volumes of the hydrophilic and hydrophobic parts of **2** it is

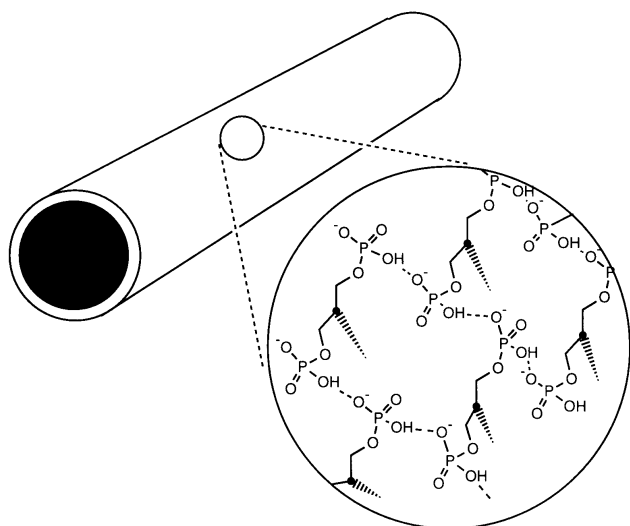


Fig. 3 Schematic representation of the possible hydrogen bonding arrangement of molecules of **2** in the fibers presented in Fig. 2(a,b). The dashed lines represent the lipophilic parts of the molecules, pointing towards the interior of the fiber.

reasonable to assume that the lamellar structures formed upon complexation of calcium ions consist of intercalated bilayers.

In summary, **1** and **2** are examples of a new class of amphiphiles whose aggregation behaviour in water does not follow the structure–shape concept.⁹ The extended intermolecular interactions which are possible because of the dicephalic character of the molecules lead to the formation of lamellar platelets in the case of **1** and fibres in the case of **2**. Complexation of metal ions, *i.e.* Cu^{II} ions to **1** and Ca^{2+} ions to **2**, gives rise to a change in molecular organisation resulting in the generation of lamellar structures in both cases. Further studies are underway and will be presented elsewhere.

Notes and References

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‡ *Physical data for 1*: mp 88 °C (Calc. for $\text{C}_{27}\text{H}_{46}\text{N}_4\text{O}_2$: C, 70.70; H, 10.11; N, 12.21. Found: C, 70.67; H, 10.20; N, 11.99%); m/z (EI) 458 (M^+); δ_{H} (CDCl_3) 0.88 (t, J 6.7, 3 H, CH_3), 1.25 [m, 28 H $\text{CH}_2(\text{CH}_2)_{14}\text{CH}_3$], 1.56 [m, 3 H, $\text{C}(\text{O})\text{CH}_2\text{CH}_2$], 2.31 [t, J 7.5, 2 H, $\text{C}(\text{O})\text{CH}_2$], 4.07 (ABX, 4 H, CH_2N), 5.33 (ABX, 1 H, $\text{CH}-\text{O}$), 6.92 (s, 1 H, 5-ImH), 7.11 (s, 1 H, 4-ImH), 7.47 (s, 1 H, 2-ImH); $\nu(\text{KBr})/\text{cm}^{-1}$ 3100 (C– H_{im}), 2910, 2840 (C–H), 1740 (C=O), 1530–1490 (Im).

Physical data for 2: R_f 0.17 (silica, $\text{BuOH}-\text{AcOH}-\text{H}_2\text{O}$ 4 : 1 : 1) (Calc. for $\text{C}_{21}\text{H}_{40}\text{P}_2\text{O}_{10}\text{Na}_4\cdot\text{H}_2\text{O}$: C, 39.2; H, 6.84; Na, 14.3. Found: C, 39.0; H, 6.74; Na, 14.0%); m/z (FB^+ , free acid) 541 ($\text{M} + \text{Na}^+$); $\delta_{31\text{P}}$ (D_2O) –2.27; $\nu(\text{KBr})/\text{cm}^{-1}$ 2910, 2860 (C–H), 1740 (C=O), 1200 (P=O).

§ **3** and **7** were prepared by acylation of the corresponding alcohols using stearoyl chloride and a catalytic amount of AlCl_3 (ref 12). The alcohols were prepared according to literature procedures (refs. 13, 14).

¶ The molecular structure of **3** is such that one of the bulky groups on the C(2) atom, *i.e.* the stearoyloxy group or the methylene imidazole group, blocks the incoming second imidazole group.

|| Tetra-*n*-butylammonium dibenzyl phosphate (ref. 15) and tetraethylammonium (ref. 16) monobenzyl phosphate were used, respectively, following modified literature procedures.

** The stoichiometry of the complex was determined by monitoring the intensity of a new imidazole vibration at 1521 cm^{-1} in the FTIR spectrum upon addition of Cu^{II} ions. In addition a signal attributed to free CuSO_4 was observed in the EPR spectrum when the $\text{Cu}^{\text{II}} : \mathbf{2}$ ratio exceeded 0.5.

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