The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/14223

Please be advised that this information was generated on 2018-02-11 and may be subject to change.
Dicephalic surfactants

Nico A. J. M. Sommerdijk,‡ Theo L. Hoeks, Kees Jan Booy, Martinus C. Feiters, Roeland J. M. Nolte* and Binne Zwanenburg*

Department of Organic Chemistry, NSR-Institute for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

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 hyperextended\(^1\) and spiro\(^2\) hydrocarbon chains, gemini surfactants\(^3\) and super surfactants, \textit{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 (\(1,3\)-dibromopropan-2-yl stearate \(\text{1}\)), \textit{e.g.} block copolymers of polystyrene and poly(propyleneimine) dendrimers.\(^4\) Dicephalic surfactants exhibit unexpected aggregation behaviour.

The synthesis of compound \(\text{1}\) was initially tried by treating 1,3-dibromopropan-2-yl stearate \(\text{3}\) with imidazole in MeCN. Instead of the desired product \(\text{1}\) a mixture of compounds \(\text{4}\) and \(\text{6}\) was isolated. A mechanistic explanation is presented in Scheme 1A. Direct nucleophilic replacement of the second halogen atom in \(\text{3}\) by imidazole is difficult due to considerable steric hindrance as was evident from examination of CPK models.\(^6\) During aqueous work-up a hydroxy group is probably introduced which gives \(\text{5}\) and after acyl migration\(^7\) the \(\alpha\)-hydroxystearate \(\text{6}\). Compound \(\text{1}\) could, however, be synthesised \textit{via} a double nucleophilic attack of sodium imidazolide on epibromohydrin, followed by acylation of the alkoxy intermediate (Scheme 1B).

Reaction of \(\text{3}\) 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.\(^\text{2}\) Compound \(\text{2}\) was prepared therefore by phosphorylation of the diiodide \(\text{7}\) with silver dibenzyl phosphate\(^8\) followed by catalytic hydrogenation over Pd/C and subsequent cation exchange (Scheme 1C). This indirect displacement of the halogen atoms by the dibenzyl phosphate ion is promoted by the formation of an AgI complex and the neighbouring group participation of the ester carbonyl function.

Inspection of CPK models of \(\text{1}\) and \(\text{2}\) 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 \(\text{1}\) 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 (\(\Delta H = 60\ J\ \text{g}^{-1}\)) was observed by DSC. The \(P_K\) values of \(\text{1}\) (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 CuSO\(_4\) were added to a dispersion of \(\text{1}\) 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]\(_2\) was formed,\(^\text{2}\) but it was not possible to differentiate between a monomeric Cu\(\text{II}\) \(\text{1}\),

\[\begin{align*}
\text{C}_1\text{H}_5\text{Br} & \quad \text{O} & \quad \text{C}_1\text{H}_5\text{Br} & \quad \text{O} & \quad \text{OP(O)}(\text{O})\text{Na}_2 \\
\text{C}_1\text{H}_5\text{Br} & \quad \text{O} & \quad \text{C}_1\text{H}_5\text{Br} & \quad \text{O} & \quad \text{OP(O)}(\text{O})\text{Na}_2
\end{align*}\]

Scheme 1 (i) Imidazole–CH\(_3\)CN; (ii) aqueous work-up; (iii) NaH–imidazole–DMF; (iv) C\(_7\)H\(_5\)COCl; (v) AgOP(O)(OBn)\(_2\)–toluene, reflux; vi \(\text{H}_2/\text{Pd/C}\); (vii) Dowex-Na\(^+\)

Fig. 1 Electron micrographs of (\(a)\) \(\text{1}\) (negative staining, inset Pt shadowing technique) and (\(b)\) a 2:1 complex of \(\text{1}\) and CuSO\(_4\) (freeze fracture technique) in water. Bars represent 250 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 (ΔH = 15 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 (ΔH = 1.5 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, a network of hydrogen bonds can be formed between protonated and unprotonated P–OH groups of 148 °C (aspect ratio > 2000). These fibres showed a faint phase transition at 23 °C (ΔH = 1.5 J g⁻¹) in DSC. The formation of these large structures is expected to form a 1 : 1 complex with C₅H₅N⁺. 2 was led to the formation of a precipitate consisting of 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 (ΔH = 17 J g⁻¹) in DSC. Considering the relative volumes of the hydrophilic and hydrophobic parts of 2 it is reasonable to assume that the lamellar structures formed upon complexation of calcium ions consist of intercalated bilayers.

In summary, 2 are examples of a new class of amphiphiles whose aggregation behaviour in water does not follow the structure–shape concept. 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. Cu²⁺ ions to 1 and Ca²⁺ 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

d E-mail: tjzdnk@sci.kun.nl
d Physical data for 1: mp 88 °C (Calc. for C₇₃H₁₅₂NO₆: C, 70.70; H, 10.11; N, 12.21. Found: C, 70.67; H, 10.20; N, 11.99%; m/e (El) 458 (M⁺); δH(CDCl₃) 0.88 (t, J 6.7, 3 H, CH₃); 1.25 [28 H CH(C₆H₄CH₂)₃, CH₃]; 1.56 [m, 3 H, C(O)(O)(CH₂)₃]; 2.31 [t, J 7.5, 2 H, C(O)(O)(CH₂)₃]; 4.07 (ABX, 4 H, CH₂N), 5.33 (ABX, 1 H, CH-O), 6.92 (s, 1 H, 5-H), 7.11 (s, 1 H, 4-HM), 7.47 (s, 1 H, 2-HM); vKBr/cm⁻¹ 3100 (C–Hsp), 2910, 2860 (C–H), 1740 (C=O), 1530−1490 (fm H). For 2, R0.17 (silica, BuOH–AcOH–H₂O 4:1:1) (Calc. for C₅₇H₁₁₀O₇Na₂H₂O: C, 39.2; H, 6.84; Na, 14.3; Found: C, 39.0; H, 6.74; Na, 14.0%; m/e (FAB–free acid) 541 (M + Na)+; δH(ClO₄)O–2.27; vKBr/cm⁻¹ 2910, 2860 (C–H), 1740 (C=O), 1200 (PO₂).

* 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 Cu²⁺ ions. In addition a signal attributed to free CuSO₄ was observed in the EPR spectrum when the Cu II : 2 ratio exceeded 0.5.

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

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

\[ \text{3} \]

Notes and References

8 L. Zevya, Naturwissenschaften, 1939, 27, 317.
13 A. R. Jones and G. Fakhouri, Xenobiotica, 1979, 9, 595.

Received in Cambridge, UK, 14th January 1998; 8/00395E

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 CaCl₂ (pH 7.0, Pt shadowing technique). Bars represent 100 nm.

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.