Tuning the Supramolecular Expression of Chirality: Phospholipid Analogues containing Amide Linkages

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The supramolecular expression of chirality in aggregates of amide-containing phospholipid analogues changes with the position and charge of the phosphate head group.

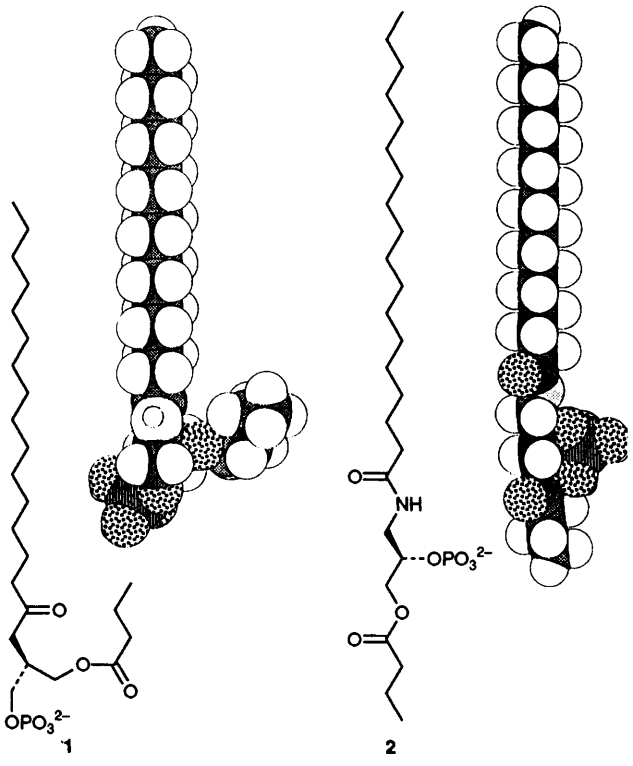
In recent years much attention has been devoted to the expression of chirality in aggregates formed by optically active surfactant molecules.[1] As part of our programme aimed at the development of enantioselective catalysts in aqueous media, we have studied the influence of chirality on the aggregation behaviour of synthetic phospholipid analogues,[2] which may serve as matrices for the anchoring of catalytic centres.

Here, we describe two novel amide containing phospholipid analogues **1** and **2** that differ in the positional arrangement of the phosphate head group and the amide linked hydrocarbon chain on the glycerol skeleton. It will be demonstrated that this simple isomeric difference has a dramatic effect on the expression of molecular chirality on the supramolecular level. Furthermore, it will be shown that this expression can be tuned by changing the pH.

Aqueous dispersions (2% m/m) of the surfactants **1** and **2**[3] were allowed to dry and subsequently shaded with platinum. Transmission electron micrographs of **1** revealed the presence of plate-like structures [Fig. 1(*a*)]. Electron micrographs taken of **2**, however, showed left-handed helical strands with a diameter of 22 nm, which coagulated to form rope-like structures [Fig. 1(*b*)].

In monolayer isotherms, a remarkable difference in the onset of the curve was observed between **1** and **2** (293 K, sub-phase pH = 6.5–7.0) *viz.* approximately 350 and 80 Å^2 per molecule, respectively (Fig. 2). No liquid-condensed phase was visible upon compression of **1**,† probably because the butyrate group is too short to allow a close packing of the hydrocarbon chains as normally observed in phospholipids. Remarkably, compression of the regio isomer **2** to a pressure of 15 mN m^{-1} did result in a transition to a liquid-condensed phase, suggesting a much higher degree of hydrocarbon chain organisation in this lipid than in **1**. This may be explained by assuming that the butyrate group of **2** is immersed in the sub-phase, resulting in an extended molecular conformation, as depicted in the CPK model.

Monolayers of **1** and **2** were studied using Brewster angle microscopy.[4] For compound **1** no distinct morphology was observed. However, in the case of lipid **2** this technique revealed the presence of chiral domains [Fig. 3(*a*) and (*b*)], which exhibited an overall counter-clockwise pattern. Similar domains were observed during fluorescence microscopy experiments,[5] but the size of these domains was drastically reduced [Fig. 3(*c*)]. The latter is probably resulting from the fact that the fluorescent probe‡ acts as an impurity,[6] which causes an increase in the number of nucleation sites. Furthermore, because the probe molecules are squeezed out from the



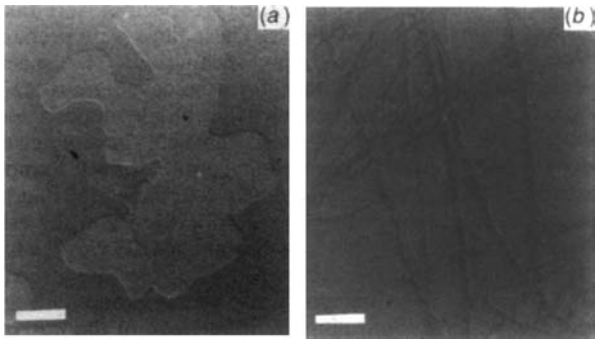


Fig. 1 Transmission electron micrographs of dried dispersions (2% m/m) of **1** (*a*) and **2** (*b*); bars represent 250 nm

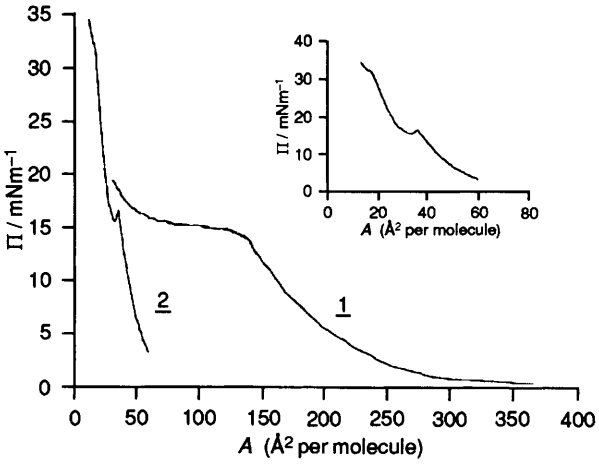


Fig. 2 Monolayer isotherms of **1** and **2** at 293 K. Inset: enlargement of isotherm of **2**.

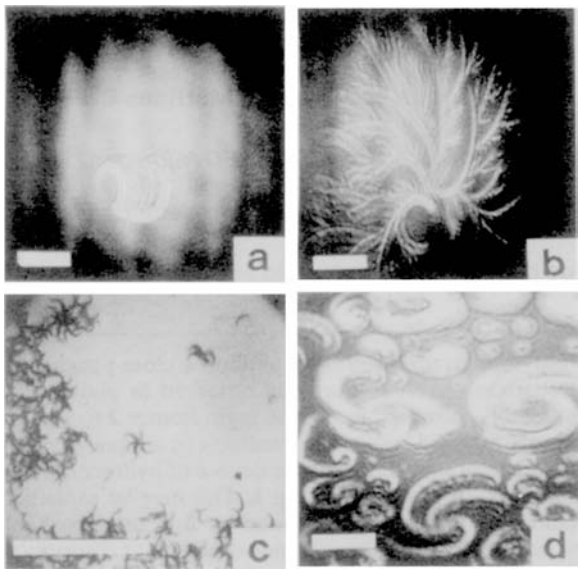


Fig. 3 Morphology of monolayers of **2**. (*a*) Brewster angle micrograph taken at $\Pi = 5$ mN m^{-1}. (*b*) Idem at $\Pi = 16$ mN m^{-1} (pH = 6.5). (*c*) Fluorescence micrograph taken at $\Pi = 15$ mN m^{-1} (pH = 6.5). (*d*) Brewster angle micrograph taken at $\Pi = 16$ mN m^{-1} pH = 1.5). Bars represent 100 μm.

liquid-condensed phase, the high probe concentration at the liquid-condensed–liquid-expanded interface will limit the growth of the domains.

In order to investigate the role of hydrogen bonding in the aggregation behaviour of **1** and **2**, FTIR-spectra§ were taken of oriented films of the two lipids. These films were prepared by the iso-potential spin drying technique.[7] The spectra revealed that both compounds form so-called *trans*-amide polymers,[8] *i.e.* structures in which the amides have a *trans* conformation and are aligned through intramolecular hydrogen bonding. The ester carbonyl group of **1** was found to participate in a hydrogen-bonded network, indicating that it is located in the hydrogen belt area.[9] In a dried film the ester carbonyl group of **2** displayed a vibration at 1738 cm^{-1}, which is typical for a free ester. After wetting of the film a second peak at 1706 cm^{-1} arose, typical for a ester group hydrogen bonded to water,[8] confirming the immersion of the butyrate group into the aqueous phase.

Since the size of the head group usually is an important factor in the packing of surfactant molecules, we investigated whether protonation of the phosphate groups can be used to tune the molecular organisation of **2**. Monolayer experiments were carried out at pH-values at which the phosphate group of **2** is fully protonated.¶ Using Brewster angle microscopy a change in the direction of the pattern of the domains could be visualised (Fig. 3(*d*)]. This phenomenon is unprecedented in the literature. Apparently, the reduction of head group repulsion by protonation leads to a change in molecular organisation, and hence to a different long range tilt order in the domains.[10]

From the experiments described above, we may conclude that the location and orientation of the butyrate group with respect to the longitudinal axis of **1** and **2** play an essential role in the ability of the molecules to form chiral supramolecular structures. The possibility to tune the chiral expression of these structures opens interesting possibilities for catalysis. For instance, it can be imagined that the stereoselectivity of synthetic (metal complexes) or biological (enzymes) catalysts embedded in aggregates of **2** depends on the supramolecular chirality of the system.

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Footnotes

† The observed plateau in the isotherm is actually a collapse of the monolayer, as could be visualised using Brewster angle microscopy, see below.

‡ 0.5 mol% of sn-1,2-dipalmitoyl-3-glycerolphosphatidylethanolamine-sulforodamine was used as the fluorescence probe.

§ Relevant IR-vibrations of oriented films are **1**: ν(AgCl, cm^{-1}) = 3300, 3285, 3094, 3069 (NH-stretch); 1729, 1718 (ester C=O); 1645 (amide I); 1548, 1560 (amide II); **2**: ν (AgCl, cm^{-1}) = 3311, 3070 (NH-stretch); 1738 (ester C=O); 1641 (amide I); 1576 (amide II).

§ The pK_a values of **2** were determined to be 4.3 (pK_{a1}) and 10.9 (pK_{a2}).

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