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COMMUNICATION

Cross-linkable, phosphobetaine-based, zwitterionic amphiphiles that form lyotropic bicontinuous cubic phases†

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The design, synthesis, and lyotropic liquid crystal phase behaviour of six cross-linkable, phosphobetaine-based, zwitterionic amphiphiles are described. Two form a Q_{II} phase with aq. NH_4Cl solution, giving 3D-nanoporous membrane materials that can be used for water desalination and are not susceptible to ion exchange like traditional ionic analogues.

Introduction

Lyotropic liquid crystal (LLC) monomers are polymerizable amphiphiles (i.e., surfactants) that self-organize into ordered, phase-separated assemblies with added water or other polar liquids.¹ The resulting LLC phases can have different geometries (i.e., 1D hexagonal (H), 2D lamellar (L), and 3D-interconnected bicontinuous cubic (Q) phases) and are categorized as type I (i.e., normal) or type II (i.e., reverse) depending on whether the hydrophilic–hydrophobic interface curves away or toward the hydrophilic regions, respectively.^{1,2} Upon monomer cross-linking, these phases can be covalently locked-in to yield robust polymer networks with monodisperse, sub-nanometre-size pores lined by the hydrophilic headgroups.² LLC networks have been used for templated nanocomposite synthesis, heterogeneous catalysis, molecular size filtration, and enhanced ion transport.¹

Q networks are one of the most desirable LLC materials for membrane and transport applications because they have 3D-interconnected nanopores with cubic symmetry and high pore density.³ They do not require processing into aligned, monodomain films for good pore access and throughput, unlike lower-dimensionality H and L networks.³ Q networks prepared

from LLC monomers with ionic headgroups can be fabricated onto support membranes and used for water nanofiltration (NF) and desalination due to the intrinsic molecular-size- and charge-exclusion properties of the charged nanopores.^{3–5}

However, one problem with Q-phase polymer membranes made with traditional ionic LLC monomers (i.e., with separated cation-anion pairs) is exchange of the mobile counterions in the nanopores during saltwater filtration.^{4,5} This often results in unwanted changes in water flux or solute rejection performance when the composition of the aqueous feed solution is varied.^{4,5} This behaviour was observed for thin-film composite (TFC) type I bicontinuous cubic (Q_I) polymer membranes made from a cationic gemini (i.e., joined two-head/two-tail) imidazolium monomer containing mobile Br^- counterions.^{4,5} When this material was used to filter aq. salt solutions containing the same cation (i.e., Na^+) but different anions (i.e., Cl^- , Br^- , NO_3^- , and I^-), high salt rejection was maintained ($\geq 96\%$); however, the water flux changed significantly depending on the anion in the feed solution due to partial exchange with the original Br^- ions in the membrane pores.⁴ It was also observed that the molecular-size-exclusion properties of the material changed when different-size organosulfonate anions were exchanged for the original Br^- ions in the nanopores.⁵ Consequently, mobile counterion substitution in LLC membranes made from ionic monomers is a liability when it comes to saltwater filtration applications.

More-consistent water desalination and NF performance in LLC membranes, regardless of saltwater feed composition, could be achieved with a zwitterionic (i.e., amphoteric) nanopore environment. Zwitterions are doubly-ionic, net-neutral species in which the positively and negatively charged groups are covalently connected by a spacer of methylene segments, thereby eliminating the possibility of ion exchange.^{6–8} Zwitterions have been incorporated into a range of small-molecule and polymeric amphiphile motifs for myriad applications because of their unique properties.^{6–8} However, there are very few examples of zwitterionic LLC mesogens

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capable of forming Q phases and even fewer that are intrinsically cross-linkable systems.

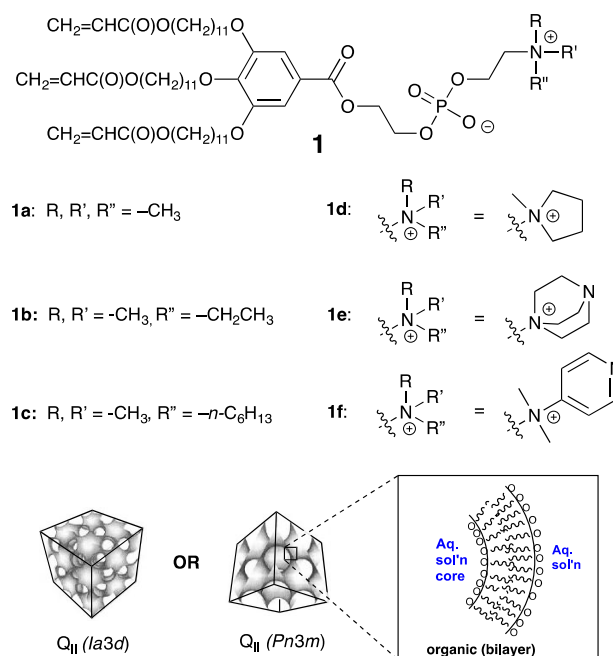
Many such systems have been designed based on sulfobetaine groups (i.e., an ammonium cation tethered to an anionic sulfonate group). For example, Ohno and co-workers as well as Ichikawa and co-workers reported amphiphilic sulfopyridinium mesogens (i.e., a non-polymerizable one-head/one-tail surfactant and a cross-linkable gemini amphiphile, respectively) that could each form Q phases for proton conduction.^{9,10} In addition, Kato and co-workers reported non-polymerizable dicyanoethenolate-imidazolium and sulfimidazolium wedge-shaped (i.e., one-head/three-tail) surfactants for the preparation of Q-phase lithium-ion-conducting materials.¹¹ Ichikawa and coworkers also showed that the aforementioned cross-linkable gemini amphiphile can be copolymerized with a non-cross-linkable, one-head/one-tail monomer analogue to afford more-pliable Q network films.¹²

Phosphobetaine zwitterions are of particular interest in LLC mesogen and monomer design because of their Q-phase-forming aptitude and their similarity to natural phospholipids in terms of headgroup chemistry (i.e., potential biomimetic properties).^{2,6-8} Generally, a phosphobetaine contains a positively charged quaternary nitrogen atom with a tethered anionic phosphate group (commonly referred to as phosphoethanolamine (PE) or phosphocholine (PC), depending on whether the nitrogen has all hydrogen or methyl substituents, respectively).^{2,6-8} Mixtures of PE- + PC-based lipid-like (i.e., one-head/two-tail) zwitterionic amphiphiles have been shown to form Q phases upon hydration.^{2,13} In particular, O'Brien and co-workers reported that a mixture of a polymerizable PE-based lipid and a cross-linkable PC-based lipid can form H_{II} or Q_{II} phases and be cross-linked with phase retention.¹³ In addition to these surfactants, amphiphilic polymers such as the random copolymer recently prepared by Asatekin and co-workers, have also benefitted from the use of PC-based phosphobetaines to form phase-separated, bicontinuous cubic membranes.¹⁴

An additional benefit of the phosphobetaine moiety is that it is highly customizable: The tethered ammonium unit is typically connected last and can vary in size, shape, and number of alkyl substituents. Two reports allude to the possibility of synthesizing a wide range of phosphobetaine variants if non-traditional, tertiary amines are used as reagents to form the quaternary ammonium group.^{15,16} However, previously reported Q-phase-forming phosphobetaine amphiphile designs have only employed PE- or PC-based headgroups,^{13,14} most likely due to limited routes for preparing and purifying other derivatives. To our knowledge, intrinsically cross-linkable, phosphobetaine zwitterionic LLC monomers that form a Q phase as a single-monomer system are unprecedented.

Herein, we present the design and synthesis of a series of novel, cross-linkable, wedge-shaped, zwitterionic LLC monomers (monomer platform **1**) containing different phosphobetaine headgroups (see Fig. 1). Of the six derivatives produced (**1a–f**), monomers **1b** and **1c** were found to form a type II bicontinuous cubic (Q_{II}) phase with 0.1 M aq. NH₄Cl solution and could be radically photo-cross-linked at 70 °C to

retain the phase nanostructure, as confirmed by polarized light microscopy (PLM), powder X-ray diffraction (PXRD), and small-angle X-ray scattering (SAXS). It was also observed that the bulkiness of the tethered quaternary ammonium unit on the phosphobetaine headgroup significantly impacts the LLC-phase-forming behaviour of these monomers. In addition, preliminary work showed that the Q_{II} phases of **1b** and **1c** can be solution-processed to form TFC membranes.



Q_{II} phases formed by **1b** and **1c** with 0.1 M aq. NH₄Cl solution

Fig. 1 Structures of cross-linkable, zwitterionic phosphobetaine monomers **1a–f** and schematic representations of the Q_{II} phase formed by **1b** and **1c** with 0.1 M aq. NH₄Cl solution. (Q_{II} unit cell images partially reproduced from Ref. 17 with permission. Copyright American Chemical Society, 1997.)

Results and discussion

Monomers **1a–f** were synthesized by first reacting 3,4,5-tris(11'-acryloyloxyundecyloxy)benzoic acid¹⁸ with ethylene glycol. The resulting hydroxy-ester derivative was then reacted with 2-chloro-1,3,2-dioxaphospholane-2-oxide to obtain the corresponding dioxaphospholane compound. Finally, the dioxaphospholane underwent a ring-opening reaction with the tertiary amine of choice to form the six different zwitterionic phosphobetaine functionalities. The structure and purity of the resulting phosphobetaine monomers **1a–f** were verified by ¹H and ¹³C NMR, correlated spectroscopy (COSY) 2D-NMR, Fourier-transform infrared (FTIR) spectroscopy, and elemental analysis (see ESI,† Section III for full synthesis and characterization details).

The three-tailed wedge-shaped motif based on tris(11'-acryloyloxyundecyloxy)benzoic acid was chosen because the carboxylic acid on this cross-linkable compound can be readily transformed into a variety of hydrophilic headgroups and the resulting compounds have been found to reliably form LLC phases with polar solvents,¹ including two examples of Q

phases.^{11,19} Tertiary amines were chosen to react with the dioxaphospholane in the final step to form phosphobetaines with tetraalkylammonium units that would be unaffected by pH changes.⁶ This is essential because the final membrane materials will be used under different saltwater filtration environments.

The LLC phase behaviour of **1a–f** was elucidated by first performing PLM-based solvent-penetration scan screening^{2c} to determine which combination(s) of phosphobetaine monomer and added polar solvent showed potential Q-phase formation, as described previously.²⁰ During this process, it was found that deionized (DI) water was not sufficiently miscible with the phosphobetaine monomers to penetrate the bulk materials and create a concentration gradient, but some dilute aqueous salt solutions and ionic liquids were suitable (see ESI,† Section IV for details). This is because the presence of added salt species decreases intermolecular interactions and improves zwitterionic surfactant solubility in aq. solution.⁶ Specifically, 0.1 M aq. NH_4Cl solution allowed for the facile formation of LLC phases, indicating the possibility of Q phase formation for each monomer (see ESI,† Fig. S14). This was attributed to the ions in 0.1 M aq. NH_4Cl solution pairing better with the zwitterionic headgroups than with DI water alone.⁶

Phase diagrams were then elucidated via variable-temperature PLM by blending each monomer with 0.1 M aq. NH_4Cl to create compositions ranging from 0 to 95 wt.% solvent, which were subsequently analysed from 25 to 100 °C. Changes in PLM optical texture with temperature and composition were used as phase transition points to plot the boundaries between different phases (see ESI,† Section V(a) for details). Quantitative identification of the observed LLC phases was done by room-temperature PXRD and SAXS analyses of radically cross-linked bulk films of compositions located within each phase region, in combination with PLM analysis: Q phases can be identified by the absence of light transmission in PLM, yielding a uniformly dark field of view, and diffraction peaks at particular ratios of scattering vectors (e.g., $\sqrt{6} : \sqrt{8} : \sqrt{14} : \sqrt{18} : \sqrt{20}$ for double gyroid ($Ia\bar{3}d$) or $\sqrt{2} : \sqrt{3} : \sqrt{4} : \sqrt{6} : \sqrt{8} : \sqrt{9}$ for $Pn\bar{3}m$).² H phases can be identified by a bright PLM optical texture and the occurrence of peaks at scattering ratios of $1 : \sqrt{3} : \sqrt{4} : \sqrt{7} \dots$ etc., whereas a L phase has a birefringent texture and peak location ratios of $1 : 2 : 3 : 4 \dots$ etc.² Finally, LLC phases that appear on the water-excessive side of an observed L phase are designated type I (i.e., normal phases).² whereas those on the water-deficient side are designated type II (i.e., reverse phases) (see ESI,† Section V(b) for more quantitative phase identification details).²

The cross-linked bulk films were prepared by hand-mixing and centrifuging the appropriate amounts of each monomer and 0.1 M aq. NH_4Cl solution with 1 wt.% 2-hydroxy-2-methylpropiophenone (HMP, a radical photo-initiator) and then irradiating the samples under 365-nm light for 1 h with heating as needed (see ESI,† Section V(b)). This process allowed identification of LLC phases at room temperature, thereby avoiding LLC phase perturbation via solvent evaporation or ambient water uptake. It also revealed that the LLC phases of

these phosphobetaine monomers could be retained after photo-cross-linking.

The data from the above studies were compiled to produce the phase diagrams shown in Fig. 2 for **1b** and **1c**, and in Fig. S24 of the ESI† for the other four derivatives. Example SAXS spectra, photographs, and PLM images of cross-linked Q-phase bulk films of **1b** and **1c** are also shown in Fig. 3.

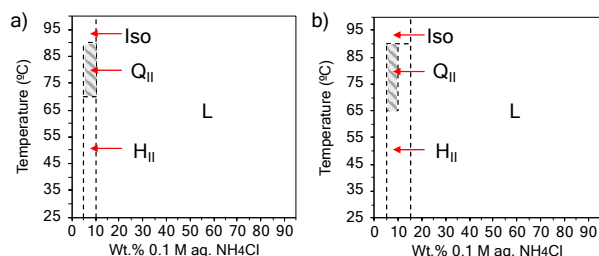


Fig. 2 Phase diagrams of monomers a) **1b** and b) **1c** revealing Q_{II} phase regions with 0.1 M aq. NH_4Cl solution, where Iso. = amorphous isotropic phase (i.e., no order by PXRD); Q_{II} = type II bicontinuous cubic phase; H_{II} = type II hexagonal phase; and L = lamellar phase. Heterogeneous regions omitted. Note: data compiled at Boulder, CO (altitude = 5328 ft, ambient pres. = ca. 623 torr); values may be different at other locations.

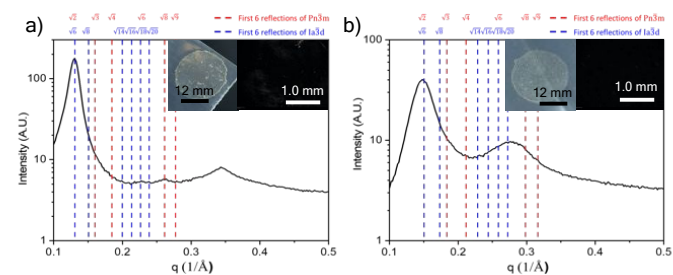


Fig. 3 SAXS profiles of bulk, cross-linked Q_{II} -phase films of a) **1b** and b) **1c** prepared from mixtures of monomer/0.1 M aq. NH_4Cl /HMP (95:5:1 (w/w/w)) photopolymerized at 70 °C. The positions of the first six reflections of the two most encountered Q phases (i.e., $Ia\bar{3}d$ and $Pn\bar{3}m$) are indicated in blue and red dashed lines, respectively. Insets: Photos (see scale bar for size) and PLM optical textures (50x) of bulk films.

As can be seen from the collected data, when the phosphobetaine monomers were mixed with 0.1 M aq. NH_4Cl , only **1b** and **1c** demonstrated the ability to form a Q phase. The Q phases formed by **1b** and **1c** are Q_{II} phases because they appear on the hydrophilic-solvent-deficient side of a L phase.² Unfortunately, it was not possible to identify the exact unit cell of these Q_{II} phases due to the lack of additional diffraction peaks that would allow for more-thorough indexing. However, $Ia\bar{3}d$ and $Pn\bar{3}m$ space groups are frequently observed for Q LLC phases reported in literature, and we speculate that the systems here correspond to one of those.^{1,2} Monomers **1a**, **1d**, **1e**, and **1f** demonstrated the potential to form a Q phase during initial PLM-based solvent-penetration scan screening (see ESI,† Figure S14); however, no data indicating a Q phase were observed for these four monomers during detailed phase diagram elucidation.

The ability of **1b** and **1c** to form Q_{II} phases, while the other four variants are not able to, can be correlated to the relative size and conformational mobility of the different tetraalkylammonium cations on the phosphobetaine headgroups. It is known that the overall molecular shape of an

amphiphilic mesogen influences the packing preferences and interfacial curvature energy considerations that influence its overall LLC-phase-forming behaviour.^{2,21} Consequently, the type of alkyl substituents on the ammonium group and the bond motion dynamics of the tethered charged components will have a significant impact on the effective size, conformational mobility, interfacial energy, and hydrophilicity of the phosphobetaine headgroup on the amphiphile and its ability to form certain phases.^{2,6,21} Therefore, at a very simple level, it appears that the PC-based derivative, **1a**, has too small a headgroup while **1d**, **1e**, and **1f** contain bulky, cyclic substituents that are too large and rigid to favour Q_{II} phase formation. Only **1b** and **1c** have phosphobetaine headgroups with the right combination of tetraalkylammonium size and mobility to do so for this wedge-shaped zwitterionic amphiphile platform.

In order to show that Q-phase TFC polymer membranes can be prepared with **1b** and **1c**, mixtures of the monomer/0.1 M aq. NH₄Cl/HMP (95:5:1 (w/w/w)) were prepared as 20 wt.% solutions in MeOH, blade-cast onto commercial ultraporous poly(ether sulfone) (PES) support films, and photopolymerized under 365-nm light for 1 h at 70°C after MeOH evaporation. The successful formation of dense, thin (ca. 6.4- μ m-thick), Q_{II}-phase polymer films on top of the PES support was confirmed by scanning electron microscopy, FTIR, and SAXS (see ESI,† Section VII for full fabrication and characterization details). The 0.1 M aq. NH₄Cl solution is used only to induce LLC phase formation of the amphiphilic monomers and will be rinsed out of the polymer nanopores via DI water soaking prior to filtration testing, as described previously for LLC membrane characterization.³⁻⁵ Consequently, the NH₄Cl solution will have no effect on the zwitterionic headgroups in the final membrane or its filtration performance. Future work will concentrate on (1) confirming more-consistent desalination performance for these new zwitterionic Q_{II} TFC membranes via filtration studies with different saltwater solutions; and (2) determining their pore size via NF studies with different-size, uncharged molecular solutes as described previously.^{4,5}

Conclusions

The design, synthesis, and LLC phase behaviour of a series of novel, intrinsically cross-linkable, wedge-shaped, phosphobetaine zwitterionic LLC monomers (**1a–f**) has been described. Of note, monomers **1b** and **1c** were found to form a Q_{II} phase with 0.1 M aq. NH₄Cl solution and can be radically photo-cross-linked to retain the phase nanostructure as free-standing films. Monomers **1a**, **1d**, **1e**, and **1f** exhibited anisotropic and disordered LLC phases but did not show a Q phase. The relative size and conformational mobility of the tethered tetraalkylammonium unit on the phosphobetaine headgroup can be correlated to the ability of these wedge-shaped zwitterionic monomer derivatives to form a Q phase. Finally, preliminary work showed that **1b** and **1c** can be solution-processed to form Q_{II} TFC polymer membranes; these will be tested in water desalination and NF studies as part of on-going research.

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Conflicts of interest

There are no conflicts to declare.

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