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General Synthesis and Aggregation Behaviour of a Series of Single-Chain 1,ω-Bis(phosphocholines)

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Abstract: The synthesis and physicochemical characterisation of a series of polymethylene-1,ω-bis(phosphocholines) with even-numbered chain lengths between 22 and 32 carbon atoms is described. Two new synthetic strategies for the preparation of long-chain 1,ω-diols as hydrocarbon building blocks are presented. The temperature-dependent self-assembly of the single-chain bolaamphiphiles was investigated by cryo transmission electron microscopy (cryo-TEM), differential scanning calorimetry (DSC), and Fourier transform infrared spectroscopy (FTIR).

Keywords: aggregation · alcohols · amphiphiles · lipids · synthetic methods

Introduction

Bolaamphiphiles occur naturally in the lipids of archaebacteria,[1] which represent the third kingdom of organisms besides the prokaryotes and eukaryotes. The archaebacteria thrive under extreme conditions, such as high salt concentrations, anaerobic milieu and high temperatures with associated low pH values. Due to these living conditions their membrane lipids are quite different from those of other organisms; they exhibit branches in the hydrophobic chains, ether bonds instead of the common ester bonds in the glycerol backbone, and *sn*-2,3 stereochemistry. Whereas the membranes of halophilic archaebacteria consist of monopolar lipids, most of the membrane components of methanogenic and thermoacidophilic archaebacteria are bipolar and have two membrane-spanning chains. Especially these lipids are of great interest in biotechnology and materials science. Besides the more complex natural lipids and model systems[2,3] single-chain bola compounds also exhibit interesting properties.[4] A bolalipid with only one hydrocarbon chain of twenty two carbon atoms and phosphocholine head groups at both ends of the hydrocarbon chain was found in plants showing fungicidal activity.[5]

We recently reported the temperature-dependent aggregation behaviour of the symmetrical long-chain bolaamphiphile dotriacontane-1,32-bis(phosphocholine). Self-assembly of this lipid is exclusively driven by hydrophobic interactions. Formation of a dense network of nanofibres is observed, which is responsible for very efficient gelation of water.[6,7] Within these fibres, the molecules are arranged side by side but twisted relative to each other due to the bulky head groups. Above a transition temperature of about 50 °C, the fibres transform into smaller aggregates and the gel character is lost.

Here we present a new general synthetic approach to this class of interesting bolaamphiphiles with chain lengths of 22 to 32 carbon atoms. Polymethylene-1,ω-bis(phosphocholines) with even-numbered chains were prepared by double phosphorylation of the corresponding 1,ω-diols followed by quaternisation. The temperature-dependent aggregation properties of these new bis(phosphocholines) were investigated by means of cryo-transmission electron microscopy (cryo-TEM), differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR).

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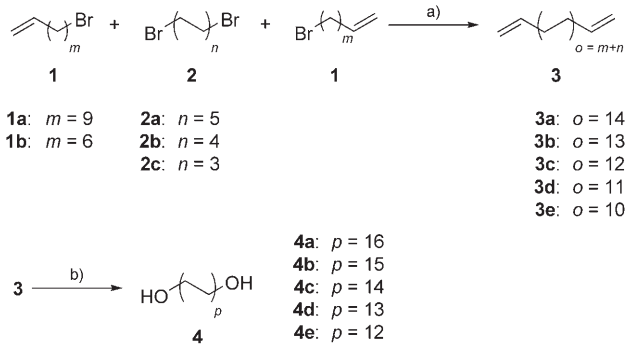
Results and Discussion

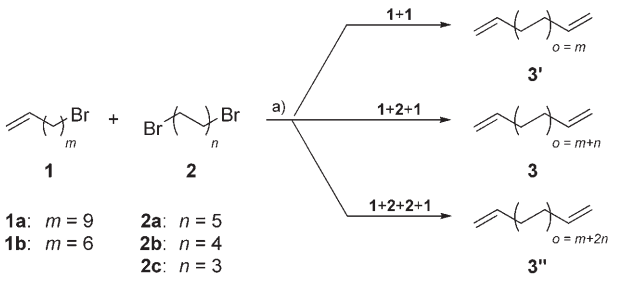
Synthetic methods: The synthesis of the bolalipids depends on an effective and high-yield preparation of the corresponding diols, which represent the hydrophobic part of the bolalipids. Diols with 22 or more C atoms were already synthesised by classical multistep procedures. These methods include the preparation of cyclic enamines followed by bisacylation with dicarboxylic acid dichlorides, hydrolysis of enamino ketones and ring opening and Wolff–Kishner reduction of bis(oxo acid)s and then reduction with $LiAlH_4$.[8,9] Double Wittig reaction with bis-phosphorylides and ω-functionalised aldehydes or suitably functionalised phosphorylides and bis-aldehydes is also described in the literature.[10] Both methods are expensive and preparation of the final reagents requires many steps.

Our investigations using reactive components with latent functionality led to the target diols in only two steps and high yield. Commercially available 11-bromoundec-1-ene (**1a**) was transformed into the corresponding Grignard reagent. Reaction of this compound with 1,ω-dibromoalkanes **2** in a ratio of 2:1 under catalysis with dilithium tetrachlorocuprate(II) according to the generally described procedure yielded terminal dienes **3**. The olefin structure is then simply and nearly quantitatively converted to diols **4** by the known hydroboration/oxidation procedure (Scheme 1). First attempts with 9-borabicyclo[3.3.1]nonane caused problems in purification due to the similar polarity of the long-chain diol and the cyclooctanediol resulting from the oxidation step. Therefore, disiamylborane was the reagent of choice.



Scheme 1. Synthesis of long-chain 1,ω-diols by copper-catalysed bis-coupling. a) Et_2O, Mg, reflux, 2 h; then THF, Li_2CuCl_4, 0 °C, 3 h; b) THF, BH_3, 2-methylbut-2-ene, 0 °C; then EtOH, NaOH, H_2O_2, 50 °C, 2 h.

The synthesis of dotriaconta-1,31-diene **3a** was already described[6] and includes very simple purification by a precipitation step with acetone from diethyl ether/THF, whereby the C_{22} homo-coupling product (see **3′** in Scheme 2) could be separated. For the preparation of the dienes with 30 (**3b**) and 28 carbon atoms (**3c**) the same Grignard reagent was coupled with 1,8-dibromooctane (**2b**) and 1,6-dibromohexane (**2c**), respectively. The Grignard reagent for the synthesis of the corresponding dienes with chain length

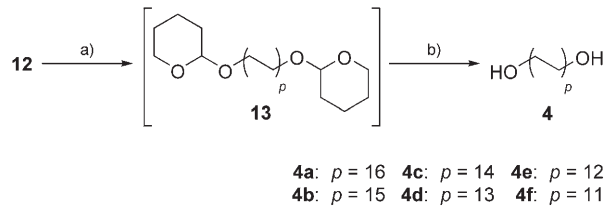


Scheme 2. Formation of "short-chain" (**3′**) and "long-chain" (**3″**) by-products during copper-catalysed bis-coupling. a) Mg, Et_2O, reflux, 2 h; then THF, Li_2CuCl_4, 0 °C, 3 h.

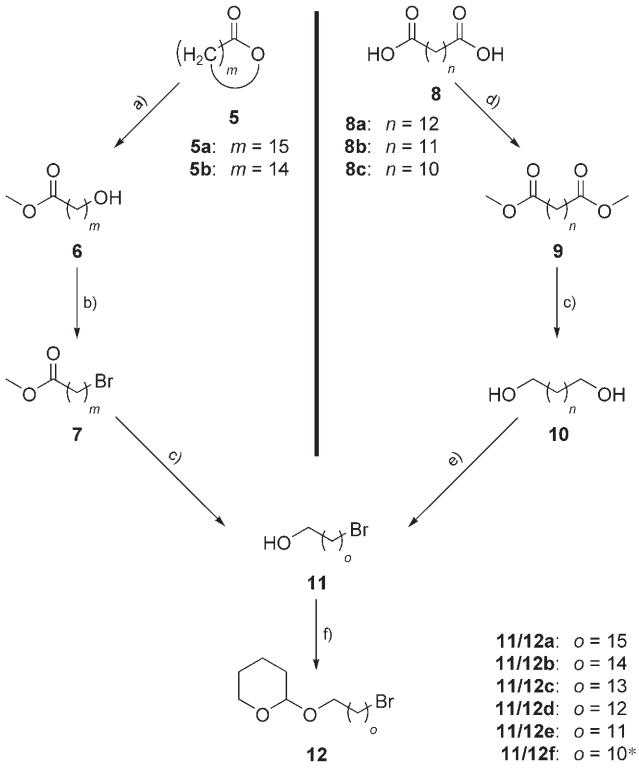
of 26 (**3d**) and 24 carbon atoms (**3e**) was prepared from commercially available 8-bromooct-1-ene (**1b**). For the purification of the longer dienes (**3b** and **3c**) the same procedure as described above was used, whereas for shorter chains (**3d** and **3e**) methanol was used for precipitation instead of acetone. We also found that filtration of the crude product over silica gel with heptane before precipitation was helpful. However, the product contained a few percent of higher coupling products with longer chains (see **3″** in Scheme 2) resulting from dimerisation of the 1:1 product of the Grignard reagent and the dibromide by transmetallation, already described in the pioneering work of Kochi et al.[11] Some attempts were made to avoid this side reaction, for example, by incubation of the Grignard reagent with the catalyst, reaction at lower temperature and changing the sequence of addition of the reactants, but without any effect on product composition.

Another method for the preparation of long-chain boladiols, first published by Schill et al.[12] and some years ago by another group,[13] uses 2:1 copper-catalysed Grignard bis-coupling starting from the Grignard reagents of the tetrahydropyranyl ethers of ω-bromo alcohols and corresponding 1,ω-dibromides. The authors did not describe the occurrence of side products in their reactions. However, in our hands we also found small amounts of the higher coupling products **3″** when following the protocol of Mohr et al.[13]

In the synthesis of docosa-1,21-diene by homocoupling of 11-bromoundec-1-ene[14] with its Grignard reagent, formation of higher molecular weight compounds is not possible. Thus our second strategy for the synthesis of the boladiols is based on this 1:1 reaction. However long-chain ω-bromo alkenes are not commercially available and the preparation of these compounds is very expensive. The alternative route is shown in Scheme 3 by homocoupling of compound **12** with the Grignard reagent of this bromo compound under copper catalysis. The ω-bromo alcohols **11** and the corresponding tetrahydropyranyl ethers **12** are also not commercially available, but they can be synthesised in a few effective steps from commercially available and inexpensive lactones **5** or dicarboxylic acids **8**, as shown in Scheme 4. In contrast to the synthesis via dienes and subsequent hydroboration the crude bis(tetrahydropyranyl ether)s **13** resulting from the coupling reaction were not purified but transformed into the corresponding diols **4** by cleavage of the tetrahydropyranyl



Scheme 3. Synthesis of long-chain 1,ω-diols by copper-catalysed homocoupling. a) THF, Mg, reflux, 3 h; then THF, Li_2CuCl_4, 0 °C, 3 h; b) MeOH, pyridinium *p*-toluenesulfonate, reflux.

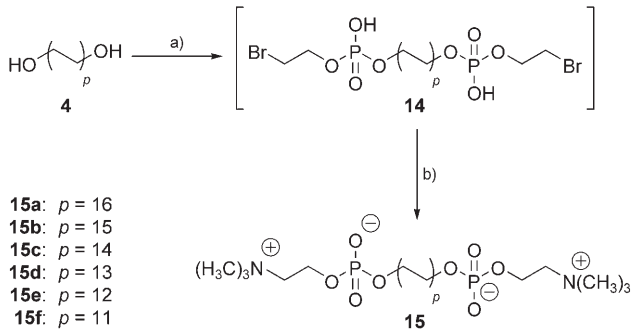


Scheme 4. Synthetic pathways for the preparation of ω-bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]alkanes. a) MeOH, *p*-toluenesulfonic acid, reflux, 24 h; b) $CHCl_3$, methanesulfonyl chloride, reflux; then acetone, LiBr, reflux; c) Et_2O, $LiAlH_4$, 0 °C; d) MeOH, H_2SO_4, reflux; e) Benzene, HBr, water trap, reflux; f) CH_2Cl_2, dihydropyran, pyridinium *p*-toluenesulfonate, 24 h. * **12f** was prepared from commercially available 11-bromoundecan-1-ol **11f**.

protecting groups. These compounds were isolated and recrystallised from heptane in 55–65% yield, similarly to the method described by Mohr et al.,[13] and they did not contain any higher condensation product. Thus, this strategy is preferred for the synthesis of long-chain diols.

In addition, we found that the high molecular weight by-products **3″** could be completely separated during the purification of the final bis(phosphocholines) **15** by MPLC with a gradient technique and chloroform/methanol/water as eluent. Thus, we have developed two new effective approaches to the long-chain 1,ω-diols **4** necessary for the preparation of bolaphosphocholines **15a–f**.

For the synthesis of bis-phosphocholines **15a–f**, common phosphorylating reagents such as β-bromoethylphosphoric acid dichloride and 2-chloro-1,3,2-dioxophospholanes or phosphites were used under mild conditions. However, the reaction did not proceed in a satisfactory way and the yield was rather low even after long reaction times. The limiting factor for these transformations was the insolubility of the diols in the normally used solvents such as chloroform and tetrahydrofuran. This problem could be solved by the following procedure in which the diol component, an excess of β-bromoethylphosphoric acid dichloride and the base (triethylamine, TEA) were first suspended in dry chloroform at room temperature. Then the mixture was brought to a temperature at which it became homogeneous (in the case of long-chain diols up to 60 °C). The mixture was then cooled to room temperature and no new precipitation occurred. After 24 h at this temperature phosphorylation was complete. According to other studies on bolaphospholipid synthesis,[15,16] the classic reagent β-bromoethylphosphoric acid dichloride was more efficient than the phospholane method. The last step in the reaction was quarternisation (Scheme 5) with a solution of trimethylamine in chloroform/acetonitrile/ethanol.



Scheme 5. Preparation of long-chain 1,ω-bis(phosphocholines) by high-temperature phosphorylation. a) $CHCl_3$, bromoethylphosphoric acid dichloride, 45–60 °C; then THF, H_2O, 2 h; b) $CHCl_3$, CH_3CN, EtOH, $N(CH_3)_3$, 45 °C.

Temperature-dependent aggregation: From recent investigations on the temperature-dependent aggregation of dotriacontane-1,32-bis(phosphocholine), PC-C32-PC, synthesised by copper-catalysed bis-coupling, we know that this bolaamphiphile forms long and flexible nanofibres with a diameter that corresponds roughly to its molecular length.[7] A temperature increase leads to disruption of the nanofibres until small nanoparticles are formed at high temperature. This temperature-induced change in aggregation was monitored by electron microscopy, differential scanning calorimetry (DSC) and FTIR spectroscopy. In the DSC curves at least two distinct endothermic transitions are observed, one at low temperature which is somehow connected to the breakdown of the nanofibres and the hydrogel, and a high-temperature transition which occurs inside the stability range of the nanoparticles and is presumably caused by further disordering of the chains inside the nanoparticle.

Since the self-assembly process of these bolaamphiphiles is exclusively driven by hydrophobic interactions of the long

alkyl chain, the question arises of the minimal chain length for which formation of fibres can be realised. With our new synthetic strategy for symmetrical single-chain bolaamphiphiles with different alkyl chain lengths, we were able to investigate the temperature dependent aggregation of bolaamphiphiles with 22 to 32 carbon atoms in the alkyl chain (**15a–f**).

The DSC thermograms of bolaamphiphiles **15a–f** (Figure 1A) show two endothermic transitions between 2 and 100 °C. The first peak always has the largest latent heat. Figure 1B shows the dependence of both transition temperatures on carbon chain length. With increasing carbon chain length both transition temperatures shift to higher values by an average of about 5 °C per additional CH_2 group. However, the temperature increase is not linear: the steepness decreases with increasing chain length (see Figure 1B). The width of the first transition narrows with increasing chain length. This also seems to be the case for the high-temperature transition. The transitions apparently become more cooperative at longer chain length.

The transition enthalpies for both transitions are summarised in Figure 1C. The chain-length dependence of both transitions is quite unusual. The transition enthalpy ΔH_1 for the low-temperature transition first increases with increasing alkyl chain length up to C_{26} and then decreases up to C_{32}. The C_{32} compound even has a lower transition enthalpy than its C_{24} analogue. The transition enthalpy ΔH_2 for the high temperature transition does not follow the same course. This high-temperature transition is very broad and the transition enthalpy is not easily determined. Therefore, the observed changes may not be significant. From these data it is not clear what the cause for this peculiar change in transition enthalpy is. It seems likely that the aggregation behaviour could change when the chain length is decreased below 24 carbon atoms. However, the transition temperatures show the expected behaviour and no unusual deviations.

Temperature-dependent aggregation of compounds **15a–f** was then monitored by cryo-TEM. Figure 2 shows electron micrographs of dilute aqueous dispersions of **15c–e** for different quenching temperatures, chosen according to the transition temperatures of the bolaamphiphiles, as determined by DSC (see Figure 1). At 20 °C, **15a–d** form a dense network of long and flexible fibres with diameters that correspond approximately to their molecular length (see Figure 2A and C; data for **15a,b** not shown). For **15d** additional stiff and shorter rods of larger diameter can be seen (Figure 2D). Investigation of aggregates of **15e,f** below the first transition temperature (see Figure 1) was not possible because quenching of the samples starting from temperatures below 10 °C could not be performed. At temperatures above the first transition the fibres of bolaamphiphiles **15a–c** transform into spherical micelles (see Figure 2B; data for **15a,b** not shown). Whereas disc-like aggregates with diameters up to 150 nm were observed for **15d** (see Figure 2E), stiff and short rods of larger diameter were obtained for **15e** (data not shown). Furthermore, we investigated **15e** above the second transition temperature, where spherical aggregates were found (see Figure 2F).

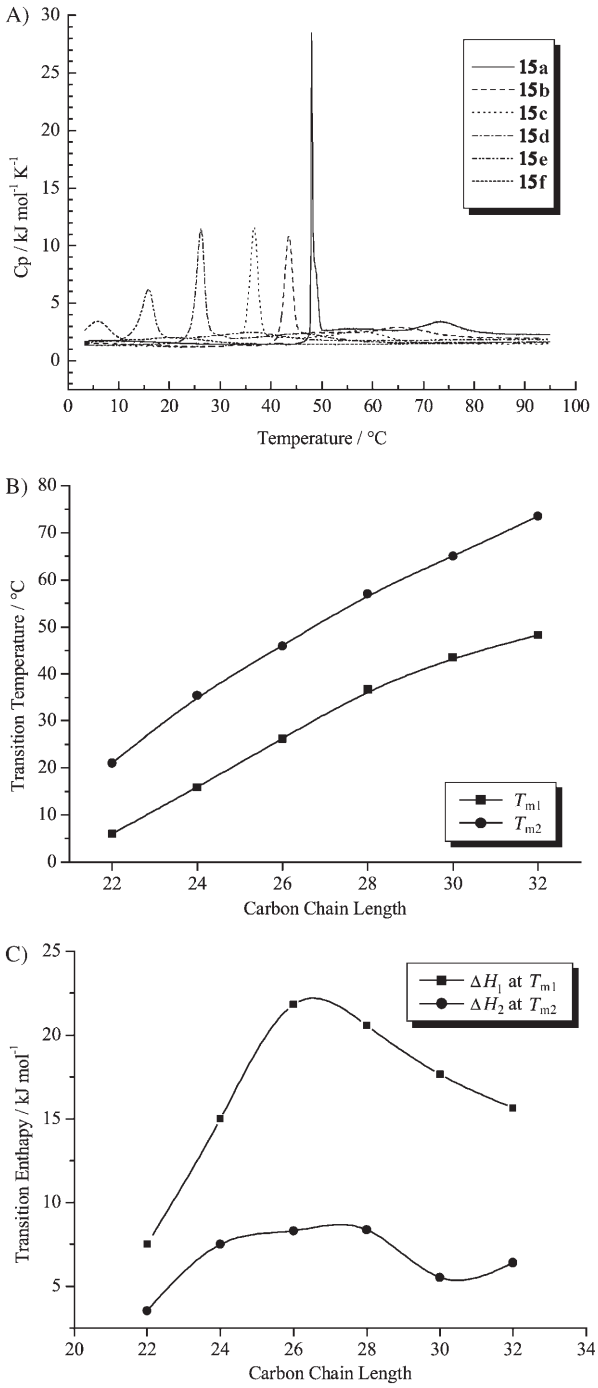


Figure 1. A) DSC curves of 1,ω-bis(phosphocholines) with chain lengths of 32 to 22 carbon atoms (**15a–f**). B) Dependence of transition temperatures (T_{m1} and T_{m2}) carbon chain length. C) Dependence of the corresponding transition enthalpies carbon chain length (the lines are guides to the eye).

From these data we can conclude that the exclusive formation of long and flexible fibres below and spherical micelles above the first transition is realised for chains longer than 26 carbon atoms. Shorter chain lengths lead to the formation of different aggregates above the first transition,

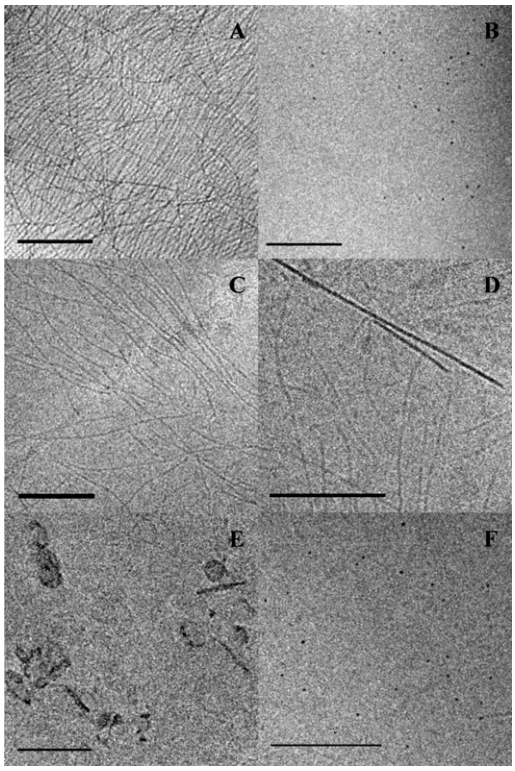


Figure 2. Cryo-TEM images of aqueous dispersions of 1 mg mL^{-1} 1,ω-bis-(phosphocholines) quenched from different temperatures (with two different magnifications). The scale bar corresponds to 200 nm. A) **15c**, 20 °C, flexible fibres; B) **15c**, 45 °C, spherical micelles; C) **15d**, 20 °C, flexible fibres; D) **15d**, 20 °C, stiff rods; E) **15d**, 35 °C, discs and sheets; F) **15e**, 55 °C, spherical micelles.

such as short and thick rods and disc-like structures. Obviously, a different packing of the bolaamphiphiles with their large head groups and small cross-sectional area of the alkyl chains is realised. Whereas fibres seem to be composed of stretched molecules, which are slightly twisted relative to each other and are stabilised by van der Waals interactions of the alkyl chains,[6] shorter chains contribute less to the stabilization of the fibre arrangement, and different packing motives are preferred. A striking property of highly dilute aqueous suspensions (1 mg mL^{-1}) of polymethylene-1,ω-bis-(phosphocholines) is their gel character, which was described for PC-C32-PC.[6] Below the first transition temperature the fibres entangle, and water is trapped within the fibre network, so that the suspension stops flowing.

The temperature-dependent course of the CH_2 stretching vibrational bands, investigated for aqueous suspensions (50 mg mL^{-1}) of **15a–f** by FTIR spectroscopy, is summarised in Figure 3. It shows two characteristic steps occurring at the same temperatures at which transitions are observed by DSC. The wavenumber of this band is an indicator for the conformational order of the alkyl chain. Below the first transition temperature, the peak position for **15a–e** is approximately 2849.5 cm^{-1}, which indicates relatively ordered extended alkyl chains in all-*trans* conformation. During the first transition the peak positions shift to significantly higher values that are characteristic for a decrease in the *trans*/*gauche* ratio in the chain. The smaller shift for longer alkyl chains indicates a slightly higher degree of order of the alkyl chains in the aggregates of the new phase. When the second transition temperature is passed, a further shift of the peak position is observed, which is characteristic for highly disordered molecules in small aggregates such as spherical micelles for **15e**.

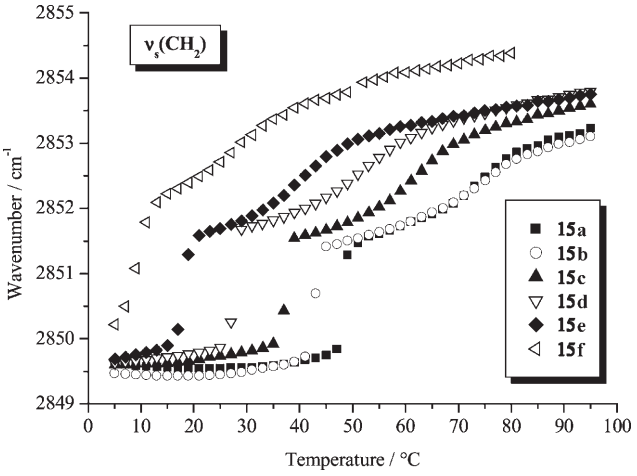


Figure 3. Wavenumber of the symmetrical methylene stretching vibrational band as a function of temperature for dispersions containing 50 mg mL^{-1} of 1,ω-bis(phosphocholines) with chain lengths of 32 to 22 carbon atoms (**15a–f**).

The analysis of the change in frequency at the first main transition shows the same tendency as the transition enthalpy measured by DSC. With increasing chain length above C_{26} the change in frequency decreases, as does the transition enthalpy. Also the frequency change at the second transition clearly decreases with increasing chain length, and the absolute value of the CH_2 vibrational frequency at high temperature is the lowest for the C_{32} compound. The FTIR data correspond to the DSC data and show that the major contribution to the transition enthalpy comes from fluidisation of the chains and not from contributions from head-group interactions.

Conclusion

Bolaphosphocholines were prepared from precursors synthesised in two different ways. Long-chain diols can be synthesised by the procedures of Schill et al.[12] and Mohr et al.[13] We prepared these compounds as hydrophobic precursors for the synthesis of bolaphosphocholines by two new strategies. The 2:1 bis-coupling of the Grignard reagent of commercially available 11-bromoundec-1-ene or 8-bromooct-1-ene with different 1,ω-dibromides results in a high yield of the diene containing a small amount of higher condensation products. These side products could be eliminated by MPLC purification of the bis(phosphocholines). The alternative route is 1:1 homocoupling of the corresponding ω-bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]alkanes of different chain lengths, which avoids higher condensation prod-

ucts and results in yields comparable to those of Mohr et al.[13] For the synthesis of the boladiols, this method is preferred. The phosphorylation of these diols to bolaphosphocholines is possible by using the conventional phosphorylation reagent used in phospholipid synthesis. The main problem was the insolubility of the diols in chloroform under the usual reaction conditions, which could be solved by an initial temperature increase at the beginning of the phosphorylation reaction.

With this development of a new synthetic strategy for symmetrical single-chain bolaamphiphiles with different alkyl chain lengths, we were able to investigate the temperature-dependent aggregation of bolaamphiphiles with 22 to 32 carbon atoms in the alkyl chain. For chains longer than 26 carbon atoms, flexible fibres are observed below the first transition temperature. The fibres seem to be composed of stretched molecules which are slightly twisted relative to each other and are stabilised by van der Waals interactions of the alkyl chains. Above the first transition temperature these long-chain bolaamphiphiles form nanoparticles or spherical micelles. For bolaphospholipids with shorter chains, other types of aggregates are found above the first transition temperature, namely, short and thick rods and disc-like structures.

Experimental Section

General: The purity of all compounds was checked by TLC (Merck) and the following eluents were applied: A = heptane, B = heptane/$CHCl_3$ (4/6), C = $CHCl_3$/Et_2O (8/2), D = $CHCl_3$/MeOH/ammonia (50/50/15). The chromatograms were developed with Bromothymol Blue[17] for non-phosphorus-containing compounds and Molybdenum Blue[18] for phosphorus-containing compounds. Silica gel (Merck, 0.060–0.200 mm) was used for column chromatography. The purification of the final bolaamphiphiles was carried out by MPLC (Büchi) on silica gel (Merck, 0.032–0.060 mm). Melting points were determined with a Boetius apparatus and are uncorrected. ^1H and ^{13}C NMR analyses were performed on a Varian Inova 500 or Varian Gemini 2000 NMR spectrometer with $CDCl_3$ or CD_3OD as internal standard. Mass spectrometric data were obtained with a Finnigan mass spectrometer model MAT SSQ 710 C (ESI-MS) or were recorded on an AMD 402 (70 eV) spectrometer. Elemental analyses were recorded on a Leco CHNS-932. All solvents used were purified and dried. 11-Bromoundec-1-ene (**1a**), 8-bromooct-1-ene (**1b**), 1,10-dibromodecane (**2a**), 1,8-dibromooctane (**2b**), 1,6-dibromohexane (**2c**), hexadecanolide (**5a**), pentadecanolide (**5b**), tetradecanedioic acid (**8a**), tridecanedioic acid (**8b**), dodecanedioic acid (**8c**) and 11-bromoundecan-1-ol (**11f**) were supplied by Aldrich Co. β-Bromoethylphosphoric acid dichloride was prepared according to the literature.[19]

General procedure for the synthesis of terminal dienes 3 by Grignard bis-coupling: A solution of 11-bromoundec-1-ene (**1a**, 14 g, 60 mmol) or 8-bromooct-1-ene (**1b**, 11.5 g, 60 mmol) in dry diethyl ether (50 mL) was added dropwise under stirring to magnesium turnings (2.1 g, 85 mmol) under argon atmosphere. After the exothermic reaction had subsided, the mixture was heated at reflux for 2 h. The excess magnesium was removed and the Grignard solution was concentrated under reduced pressure at 10 °C. Dry THF (180 mL) was added to the oily residue at such a rate that the temperature remained below 0 °C. Then dilithium tetrachlorocuprate(II) (3.5 mL, 0.1 M solution in THF, freshly prepared) was added with stirring followed by a solution of the 1,ω-dibromo alkane **2** (20 mmol) in dry THF (20 mL). After 20 min the mixture was diluted with dry THF (20 mL) and stirring was continued for a further 3 h at 0 °C. For work-up diethyl ether (100 mL) was added and the resulting mixture was poured into a cold saturated solution of ammonium chloride (150 mL). The organic layer was separated and the aqueous phase was extracted twice with diethyl ether (50 mL). The combined organic phases were washed with water, dried over sodium sulfate, and concentrated to dryness under reduced pressure. For purification the residue was filtered over silica gel (100 g, 0.060–0.200 mm) with dry heptane (500 mL). Dry THF/diethyl ether (1/1) was added to the residue until a clear solution appeared. Dry acetone was added with stirring until no further precipitation of the diene **3a–c** occurred. In the case of C_{26} diene **3d** and C_{24} diene **3e**, dry methanol was used instead of acetone. The obtained precipitate was collected by filtration and dried in vacuo over phosphorus pentoxide.

Dotriaconta-1,31-diene (3a): Yield: 7.8 g (87 %); ^1H NMR (400 MHz, $CDCl_3$, 27 °C): $\delta = 1.24–1.28$ (m, 48H, $=CHCH_2CH_2(CH_2)_{24}CH_2CH_2$-CH=), 1.32–1.39 (m, 4H, $=CHCH_2CH_2(CH_2)_{24}CH_2CH_2CH=$), 1.99–2.05 (q, 4H, $2\times H_2C=CHCH_2$), 4.88–5.00 (m, 4H, $2\times H_2C=$), 5.74–5.85 ppm (m, 2H, 2×=CH); ESI-MS: *m/z*: 446 [M^+]; elemental analysis calcd (%) for $C_{32}H_{62}$ (446.83): C 86.01, H 13.99; found: C 86.01, H 13.96.

Triaconta-1,29-diene (3b): Yield: 6.7 g (80 %); ^1H NMR (500 MHz, $CDCl_3$, 27 °C): $\delta = 1.24–1.28$ (m, 44H, $=CHCH_2CH_2(CH_2)_{22}CH_2CH_2$-CH=), 1.33–1.39 (m, 4H, $=CHCH_2CH_2(CH_2)_{22}CH_2CH_2CH=$), 1.99–2.04 (q, 4H, $2\times H_2C=CHCH_2$), 4.89–4.99 (m, 4H, $2\times H_2C=$), 5.76–5.84 ppm (m, 2H, 2×=CH); ESI-MS: *m/z*: 418 [M^+]; elemental analysis calcd (%) for $C_{30}H_{58}$ (418.78): C 86.04, H 13.96; found: C 86.06, H 13.76.

Octacosa-1,27-diene (3c): Yield: 5.9 g (75 %); ^1H NMR (400 MHz, $CDCl_3$, 27 °C): $\delta = 1.24–1.29$ (m, 40H, $=CHCH_2CH_2(CH_2)_{20}CH_2CH_2$-CH=), 1.33–1.40 (m, 4H, $=CHCH_2CH_2(CH_2)_{20}CH_2CH_2CH=$), 1.99–2.05 (q, 4H, $2\times H_2C=CHCH_2$), 4.89–5.00 (m, 4H, $2\times H_2C=$), 5.75–5.85 ppm (m, 2H, 2×=CH); ESI-MS: *m/z*: 390 [M^+]; elemental analysis calcd (%) for $C_{28}H_{54}$ (390.73): C 86.07, H 13.93; found: C 85.90, H 13.98.

Hexacosa-1,25-diene (3d): Yield: 5.9 g (82 %); ^1H NMR (500 MHz, $CDCl_3$, 27 °C): $\delta = 1.24–1.28$ (m, 36H, $=CHCH_2CH_2(CH_2)_{18}CH_2CH_2$-CH=), 1.33–1.38 (m, 4H, $=CHCH_2CH_2(CH_2)_{18}CH_2CH_2CH=$), 2.00–2.04 (q, 4H, $2\times H_2C=CHCH_2$), 4.89–4.99 (m, 4H, $2\times H_2C=$), 5.76–5.84 ppm (m, 2H, 2×=CH); ESI-MS: *m/z*: 362 [M^+]; elemental analysis calcd (%) for $C_{26}H_{50}$ (362.67): C 86.10, H 13.90; found: C 85.95, H 13.88.

Tetracosa-1,23-diene (3e): Yield: 5.2 g (78 %); ^1H NMR (400 MHz, $CDCl_3$, 27 °C): $\delta = 1.23–1.27$ (m, 32H, $=CHCH_2CH_2(CH_2)_{16}CH_2CH_2$-CH=), 1.32–1.39 (m, 4H, $=CHCH_2CH_2(CH_2)_{16}CH_2CH_2CH=$), 1.97–2.04 (q, 4H, $2\times H_2C=CHCH_2$), 4.87–4.99 (m, 4H, $2\times H_2C=$), 5.74–5.84 ppm (m, 2H, 2×=CH); ESI-MS: *m/z*: 334 [M^+]; elemental analysis calcd (%) for $C_{24}H_{46}$ (334.62): C 86.14, H 13.86; found: C 86.08, H 13.91.

16-Hydroxyhexadecanoic acid methyl ester (**6a**) and 15-hydroxypentadecanoic acid methyl ester (**6b**) were prepared from the corresponding lactones **5** according to the literature[20] and used without further characterisation and purification.

16-Bromohexadecanoic acid methyl ester (**7a**) and 15-bromopentadecanoic acid methyl ester (**7b**) were prepared from the methyl esters **6** according to the literature[21] and passed through a silica gel column with heptane/chloroform as eluent. Methyl esters **7** were used without further characterisation.

16-Bromohexadecane-1-ol (**11a**) and 15-bromopentadecane-1-ol (**11b**) were prepared from methyl esters **7** according to the literature[22] by reaction with lithium aluminium hydride in dry diethyl ether at 0 °C to avoid reduction of the bromo substituent.

Tetradecane-1,14-diol (**10a**), tridecane-1,13-diol (**10b**) and dodecane-1,12-diol (**10c**) were prepared from the corresponding dicarboxylic acids **8** by esterification with methanol/sulfuric acid to obtain the dimethyl esters **9**, which were reduced with lithium aluminium hydride by standard procedures. Diols **10** were used without further characterisation and purification.

14-bromotetradecan-1-ol (**11c**), 13-bromotridecan-1-ol (**11d**) and 12-bromododecan-1-ol (**11e**) were prepared from diols **10** according to the literature.[23]

Synthesis of ω-bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]alkanes 12: ω-Bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]alkanes **12** were prepared from the corresponding ω-bromo alcohols **11** according to the literature.[24] A

solution of ω-bromo alcohol **11** (50 mmol) and dihydropyran (7.6 g, 90 mmol) in dry methylene chloride (150 mL) was stirred at room temperature. After 24 h water (150 mL) was added to the mixture and the organic layer was separated. The aqueous residue was extracted with methylene chloride (25 mL). The combined organic phases were washed with water, dried over sodium sulfate and concentrated to dryness under reduced pressure. The crude residue was passed through a silica gel column by using the gradient technique and heptane/diethyl ether as eluent to obtain pure ω-bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]alkanes **12** as oils or white waxy substances in yields between 88 and 96% with respect to ω-bromo alcohols **11**, or in yields between 41–52% relative to the corresponding lactones **5** or dicarboxylic acids **8**.

General procedure for the synthesis of diols 4 by hydroboration/oxidation of dienes 3 (method A): A 250-mL round-bottomed flask was filled with 1 M borane/THF complex (40 mL) under argon atmosphere and cooled to −10 °C. A solution of 2-methylbut-2-ene (2 M in THF, 40 mL) was added dropwise at the same temperature. After stirring for 2 h at 0 °C, a solution of the diene **3** (10 mmol) in dry THF (40 mL) was introduced dropwise and the mixture was stirred at room temperature for approximately 18–24 h till TLC (solvent system A) showed complete conversion of the diene. For the oxidation ethanol (30 mL), 6 N NaOH (10 mL) and H_2O_2 (30%, 20 mL) were added slowly and the reaction mixture was held for 3 h at 50 °C. After cooling to room temperature potassium carbonate was added and the organic layer was separated. The aqueous residue was washed twice with diethyl ether (50 mL). The combined organic phases were dried over sodium sulfate and concentrated to dryness under reduced pressure. The crude residue was recrystallised from heptane and methanol to give the pure diols **4** as white crystals.

General procedure for the synthesis of diols 4 by Grignard homocoupling of ω-bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]alkanes 12 (method B): A solution of ω-bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]alkane **12** (22 mmol) in dry THF (50 mL) was added dropwise with stirring to magnesium turnings (0.8 g, 33 mmol) under argon atmosphere. After the exothermic reaction had subsided, the mixture was stirred at 55 °C for 3 h. The excess magnesium was removed and the Grignard solution was cooled to −5 °C. A freshly prepared solution of dilithium tetrachlorocuprate(II) (0.1 M in THF, 3.5 mL) was added with stirring. After a solution of the same ω-bromo-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]alkane **12** (19 mmol) in dry THF (50 mL) was added in one portion, stirring was continued for further 3 h at 0 °C. For work-up diethyl ether (150 mL) was added and the resulting mixture was poured into a cold saturated solution of ammonium chloride (150 mL). The organic layer was separated and the aqueous phase was extracted twice with diethyl ether (50 mL). The combined organic phases were washed with water, dried over sodium sulfate and concentrated to dryness under reduced pressure. For cleavage of the THP protecting groups the crude bis(tetrahydropyranyl ether)s **13** were dissolved in dry methanol (100 mL) and heated under reflux for 3 h with catalytic amounts of pyridinium *p*-toluene sulfonate. The hot suspension was filtered and the white residue was recrystallised from heptane to give the pure diols **4** as white crystals.

Dotriacontane-1,32-diol (4a): Yield: method A: 4.6 g (95%), method B: 5.8 g (63%); m.p. 115–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.24–1.34 (m, 56H, $HOCH_2CH_2(CH_2)_{28}CH_2CH_2OH$), 1.51–1.56 (m, 4H, $HOCH_2CH_2(CH_2)_{28}CH_2CH_2OH$), 3.61–3.63 ppm (t, 4H, 2×$HOCH_2$); MS (70 eV): *m/z* (%): 482 (5) [M^+], 446 (19) [M^+-2H_2O]; elemental analysis calcd (%) for $C_{32}H_{66}O_2$ (482.86): C 79.59, H 13.78; found: C 79.40, H 13.71.

Triacontane-1,30-diol (4b): Yield: method A: 4.1 g (91%), method B: 4.8 g (55%); m.p. 112–114 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.23–1.34 (m, 52H, $HOCH_2CH_2(CH_2)_{26}CH_2CH_2OH$), 1.52–1.58 (m, 4H, $HOCH_2CH_2(CH_2)_{26}CH_2CH_2OH$), 3.60–3.64 ppm (t, 4H, 2×$HOCH_2$); MS (70 eV): *m/z* (%): 454 (7) [M^+], 418 (16) [M^+-2H_2O]; elemental analysis calcd (%) for $C_{30}H_{62}O_2$ (454.81): C 79.22, H 13.74; found: C 79.16, H 13.69.

Octacosane-1,28-diol (4c): Yield: method A: 3.7 g (87%); m.p. 109–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.24–1.35 (m, 48H, $HOCH_2CH_2(CH_2)_{24}CH_2CH_2OH$), 1.53–1.57 (m, 4H, $HOCH_2CH_2(CH_2)_{24}CH_2CH_2OH$), 3.60–3.63 ppm (t, 4H, 2×$HOCH_2$); MS (70 eV): *m/z* (%): 426 (15) [M^+], 390 (33) [M^+-2H_2O]; elemental analysis calcd (%) for $C_{28}H_{58}O_2$ (426.76): C 78.80, H 13.70; found: C 78.78, H 13.68.

Hexacosane-1,26-diol (4d): Yield: method A: 3.6 g (90%), method B: 4.5 g (60%); m.p. 106–108 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.24–1.35 (m, 44H, $HOCH_2CH_2(CH_2)_{22}CH_2CH_2OH$), 1.53–1.58 (m, 4H, $HOCH_2CH_2(CH_2)_{22}CH_2CH_2OH$), 3.60–3.63 ppm (t, 4H, 2×$HOCH_2$); MS (70 eV): *m/z* (%): 398 (1) [M^+], 362 (17) [M^+-2H_2O]; elemental analysis calcd (%) for $C_{26}H_{54}O_2$ (398.70): C 78.32, H 13.65; found: C 78.19, H 13.59.

Tetracosane-1,24-diol (4e): Yield: method A: 3.2 g (85%); m.p. 102–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.23–1.34 (m, 40H, $HOCH_2CH_2(CH_2)_{20}CH_2CH_2OH$), 1.52–1.57 (m, 4H, $HOCH_2CH_2(CH_2)_{20}CH_2CH_2OH$), 3.60–3.63 ppm (t, 4H, 2×$HOCH_2$); MS (70 eV): *m/z* (%): 370 (1) [M^+], 334 (12) [M^+-2H_2O]; elemental analysis calcd (%) for $C_{24}H_{50}O_2$ (370.65): C 77.77, H 13.60; found: C 77.68, H 13.56.

Docosane-1,22-diol (4f): Yield: method B: 4.2 g (65%); m.p. 96–98 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C): δ = 1.22–1.33 (m, 36H, $HOCH_2CH_2(CH_2)_{18}CH_2CH_2OH$), 1.52–1.56 (m, 4H, $HOCH_2CH_2(CH_2)_{18}CH_2CH_2OH$), 3.61–3.64 ppm (t, 4H, 2×$HOCH_2$); MS (70 eV): *m/z* (%): 342 (2) [M^+], 306 (20) [M^+-2H_2O]; elemental analysis calcd (%) for $C_{22}H_{46}O_2$ (342.60): C 77.13, H 13.54; found: C 76.97, H 13.50.

General procedure for the synthesis of the polymethylene-1,1′-diyl-bis(phosphocholines) 15: β-Bromoethylphosphoric acid dichloride (1.93 g, 8 mmol) was poured into dry chloroform (20 mL) under cooling with ice/water. A mixture of dry TEA (1.42 g, 14 mmol) and dry chloroform (20 mL) was added slowly with stirring, which was continued for 30 min at 0 °C. Diol **4** (1 mmol) was added as solid substance in one portion. The suspension was heated until the solid was dissolved (max. 60 °C), than rapidly cooled to room temperature. Stirring was continued for a further 24–48 h at room temperature. After TLC (solvent system C) showed complete conversion of diol **4**, crushed ice (40 mL) was added to the solution and the mixture was stirred for a further 2 h. The organic layer was separated and the aqueous phase was diluted with a cold saturated solution of sodium chloride (50 mL) and then extracted twice with chloroform (50 mL). The combined organic phases were concentrated under reduced pressure and the oily residue was dissolved in THF/H_2O (9/1, 30 mL). After 1.5 h the solvent was evaporated and the oily residue was transferred into a mixture of chloroform (30 mL), acetonitrile (30 mL) and an alcoholic solution of trimethylamine (10 mL, 4.2 M). The mixture was kept in a closed tube at 40–45 °C for 48–72 h. After TLC (solvent system D) showed formation of the product, the mixture was concentrated by evaporation of the solvent and the residue purified by MPLC on silica gel by using the gradient technique and chloroform/methanol/water as eluent. The bis(phosphocholines) **15** were dried in vacuo over phosphorus pentoxide at room temperature for two days. For physicochemical studies the products were dissolved in a small amount of dry chloroform/methanol (1/1). Dry acetone was then added to precipitate the white product. The precipitate was separated by centrifugation and dried in vacuo over phosphorus pentoxide.

Dotriacontane-1,1′-diylbis[2-(trimethylammonio)ethylphosphate] (15a): Yield: 0.49 g (60%); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 27 °C): δ = 1.15–1.22 (m, 56H; $OCH_2CH_2(CH_2)_{28}CH_2CH_2O$), 1.47–1.54 (m, 4H; $OCH_2CH_2(CH_2)_{28}CH_2CH_2O$), 3.11 (s, 18H; 6×$CH_3$), 3.47–3.51 (m, 4H; 2×$NCH_2CH_2O$), 3.72–3.77 (q, 4H; $OCH_2CH_2(CH_2)_{28}CH_2CH_2O$), 4.10–4.12 ppm (m, 4H; 2×NCH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 27 °C): δ = 25.65, 29.26, 29.45–29.52, 30.62, 30.70, 54.12, 54.15, 54.19, 58.63, 58.68, 65.72, 65.78, 66.44 ppm; ESI-MS: *m/z*: 813.8 [M^++H], 835.7 [M^++Na]; elemental analysis calcd (%) for $C_{42}H_{90}N_2O_8P_2\cdot H_2O$: C 60.69, H 11.16, N 3.37; found: C 60.72, H 11.23, N 3.53.

Triacontane-1,1′-diylbis[2-(trimethylammonio)ethylphosphate] (15b): Yield: 0.46 g (58%); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 27 °C): δ = 1.09–1.19 (m, 52H, $OCH_2CH_2(CH_2)_{26}CH_2CH_2O$), 1.42–1.46 (m, 4H, $OCH_2CH_2(CH_2)_{26}CH_2CH_2O$), 3.04 (s, 18H, 6×$CH_3$), 3.40–3.42 (m, 4H, 2×$NCH_2CH_2O$), 3.66–3.70 (q, 4H, $OCH_2CH_2(CH_2)_{26}CH_2CH_2O$), 4.04–4.05 ppm (m, 4H, 2×NCH_2CH_2O); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 27 °C): δ = 25.94, 29.78, 54.39, 58.88, 58.94, 66.04, 66.10, 66.74 ppm; ESI-MS: *m/z*: 785.8 [M^++H], 807.7 [M^++Na]; elemental analysis calcd (%)

for $C_{40}H_{86}N_2O_8P_2{\cdot}2H_2O$: C 58.51, H 11.05, N 3.41; found: C 58.52, H 10.98, N 3.41.

Octacosane-1,1′-diylbis[2-(trimethylammonio)ethylphosphate] (15c): Yield: 0.47 g (62%); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 27°C): $\delta =$ 1.01–1.15 (m, 48H, $OCH_2CH_2(CH_2)_{24}CH_2CH_2O$), 1.36–1.43 (m, 4H, $OCH_2CH_2(CH_2)_{24}CH_2CH_2O$), 2.98 (s, 18H, $6\times CH_3$), 3.34–3.36 (m, 4H, $2\times NCH_2CH_2O$), 3.61–3.66 (q, 4H, $OCH_2CH_2(CH_2)_{24}CH_2CH_2O$), 3.96–4.02 ppm (m, 4H, $2\times NCH_2CH_2O$); ESI-MS: *m/z*: 757.8 [M^++H], 779.4 [M^++Na]; elemental analysis calcd (%) for $C_{38}H_{82}N_2O_8P_2{\cdot}2H_2O$: C 57.55, H 10.93, N 3.53; found: C 57.59, H 11.04, N 3.41.

Hexacosane-1,1′-diylbis[2-(trimethylammonio)ethylphosphate] (15d): Yield: 0.47 g (65%); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 27°C): $\delta =$ 0.93–1.05 (m, 44H, $OCH_2CH_2(CH_2)_{22}CH_2CH_2O$), 1.26–1.33 (m, 4H, $OCH_2CH_2(CH_2)_{22}CH_2CH_2O$), 2.88 (s, 18H, $6\times CH_3$), 3.25–3.27 (m, 4H, $2\times NCH_2CH_2O$), 3.51–3.56 (q, 4H, $OCH_2CH_2(CH_2)_{22}CH_2CH_2O$), 3.89–3.90 ppm (m, 4H, $2\times NCH_2CH_2O$); ESI-MS: *m/z*: 730.0 [M^++H], 751.9 [M^++Na]; elemental analysis calcd (%) for $C_{36}H_{78}N_2O_8P_2{\cdot}2H_2O$: C 56.52, H 10.81, N 3.66; found: C 56.54, H 10.89, N 3.59.

Tetracosane-1,1′-diylbis[2-(trimethylammonio)ethylphosphate] (15e): Yield: 0.42 g (60%); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 27°C): $\delta =$ 0.89–0.99 (m, 40H, $OCH_2CH_2(CH_2)_{20}CH_2CH_2O$), 1.22–1.29 (m, 4H, $OCH_2CH_2(CH_2)_{20}CH_2CH_2O$, 2.84 (s, 18H, $6\times CH_3$), 3.21–3.23 (m, 4H, $2\times NCH_2CH_2O$), 3.46–3.51 (q, 4H, $OCH_2CH_2(CH_2)_{20}CH_2CH_2O$), 3.83–3.88 ppm (m, 4H, $2\times NCH_2CH_2O$); ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$, 27°C): $\delta =$ 25.46, 29.30, 30.41, 30.48, 53.58, 58.54, 58.59, 65.54, 65.60, 66.09, 66.12 ppm; ESI-MS: *m/z*: 701.8 [M^++H], 723.7 [M^++Na]; elemental analysis calcd (%) for $C_{34}H_{74}N_2O_8P_2{\cdot}2H_2O$: C 55.41, H 10.67, N 3.80; found: C 55.53, H 10.71, N 3.72.

Docosane-1,1′-diylbis[2-(trimethylammonio)ethylphosphate] (15f): Yield: 0.36 g (54%); ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$, 27°C): $\delta =$ 0.86–0.94 (m, 36H, $OCH_2CH_2(CH_2)_{18}CH_2CH_2O$), 1.17–1.26 (m, 4H, $OCH_2CH_2(CH_2)_{18}CH_2CH_2O$), 2.81 (s, 18H, $6\times CH_3$), 3.17–3.20 (m, 4H, $2\times NCH_2CH_2O$), 3.42–3.47 (q, 4H, $OCH_2CH_2(CH_2)_{20}CH_2CH_2O$), 3.80–3.84 ppm (m, 4H, $2\times NCH_2CH_2O$); ESI-MS: *m/z*: 673.6 [M^++H], 695.6 [M^++Na]; elemental analysis calcd (%) for $C_{32}H_{70}N_2O_8P_2{\cdot}2H_2O$: C 54.22, H 10.53, N 3.95; found: C 54.29, H 10.56, N 3.83.

Sample preparation: Homogenous dispersion of the bolaamphiphile in the aqueous phase was achieved by heating the aqueous mixture to 80°C and vortexing.

Cryo-TEM: Electron microscopy was performed with a Zeiss 902 A instrument operating at 80 kV. Specimens were prepared by a blotting procedure, performed in a chamber with controlled temperature and humidity. A drop of the sample solution (1 mg mL^{-1}) was placed on an EM grid coated with a perforated polymer film. Excess solution was then removed with a filter paper to leave a thin film of the solution spanning the holes of the polymer film on the EM grid. Vitrification of the thin film was achieved by rapid plunging of the grid into liquid ethane held just above its freezing point. The vitrified specimen was kept below 108 K during both transfer to the microscope and investigation.

DSC: DSC measurements were performed with a MicroCal VP-DSC differential scanning calorimeter (MicroCal Inc., Northampton, MA, USA). Before the measurements, the sample solution (1 mg mL^{-1}) and the water reference were degassed under vacuum while stirring. A heating rate of 20°C h^{-1} was used and the measurements were performed in the temperature interval from 2 to 100°C. To check the reproducibility, three consecutive scans of each sample were recorded. The reference thermogram (water/water baseline) was subtracted from the thermograms of the samples and the DSC scans were evaluated with the MicroCal ORIGIN 5.0 software.

FTIR spectroscopy: Infrared spectra were measured on a Bruker Vector 22 Fourier transform spectrometer with a DTGS-detector operating at 2 cm^{-1} resolution. The sample with a concentration of 50 mg mL^{-1} was placed between two BaF_2 windows, which were separated by a 56 μm spacer for measurements in D_2O. IR spectra were measured every 2°C in the temperature range from 5 to 95°C. After an equilibration time of 8 min, 32 scans were recorded and accumulated. The corresponding spectra of the solvent were subtracted from the obtained sample spectra by using the OPUS software supplied by Bruker.

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