Synthesis, aqueous solution behaviour and amphotropic liquid crystalline properties of glycerol based bolaamphiphiles

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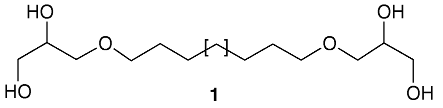
Two new homologous series of new single-chain diether bolaamphiphiles with glycerol headgroups have been synthesized: 1,1′-*O*-(alkane-α,ω-diyl)bis(*rac*-glycerol), **1**, and 2,2′-*O*-(alkane-α,ω-diyl)bis(glycerol), **2**, bearing 10 to 22 methylene groups (*n*). They were studied by surface tension measurements, microscopies and X-ray diffraction patterns. From the set of molecules **1**, we have shown the formation of amphotropic liquid crystals. A lamellar L_α phase has been identified at high temperature while a more complex second phase was detected at low temperature. In this case, the texture is also characteristic of a lamellar phase ($L_{\beta'}$) and its organization was found to be monoclinic by X-ray analysis. Furthermore, these compounds led to multilamellar vesicles in aqueous solution (liposomes) with the flexibility depending on temperature.

Synthèses, comportement en phase aqueuse, et propriétés cristal liquide de bolaamphiphiles à tête glycérol. Deux séries homologues de molécules bolaformes monocaténaires à tête glycérol ont été synthétisées: les 1,1′-*O*-(alkane-α,ω-diyl)bis(*rac*-glycerol), **1**, et les 2,2′-*O*-(alkane-α,ω-diyl)bis(glycerol), **2**, comportant de 10 à 22 groupes méthylène. Ils ont ensuite été étudiés par tensiométrie, microscopies et diffraction aux rayons X. Dans le cas des molécules **1**, nous avons observé la formation de phases cristal liquide. Une phase lamellaire L_α a été identifiée à haute température tandis qu'à basse température, une phase $L_{\beta'}$ est détectée. De plus, les composés conduisent à des vésicules multilamellaires en solution aqueuse dont la flexibilité dépend de la température.

In the past twenty years, many compounds with a bolaamphiphilic structure have been isolated from *Archaebacteria* cellular membranes.[1] These molecules are structurally defined by two polar headgroups, covalently linked at the ends of one or two hydrophobic chains. This original structure leads to the formation of monolayer lipid membranes (MLM) and is responsible for the exceptional capacity of *Archaebacteria* to live in extreme conditions of pH,[2] salinity[3] and/or temperature.[4] Liposomes have been formed from extracted *Archaea* lipids and high temperature and pH stabilities were observed.[5] Then, new synthetic bolaforms were reported in the hope of forming very stable vesicles in aqueous media.[6] As examples, various structures with a single chain and ionic,[7] nonionic[8] or mixed polar[9] heads have been described. In particular, Tschierske and co-workers[8b,c] investigated simple bipolar surfactants with nonionic heads of the 1,2-diol type. These simple bolaforms revealed *liquid crystal* phases formed by the 1,2-alkanediol units.



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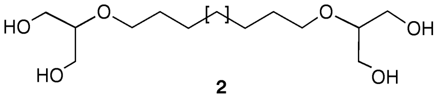

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As part of a more general research program,[10] we have started a study concerning the potentialities of polyglycerol based bolaforms. We describe here the synthesis and some physicochemical properties of the two series of glycerol based bolaforms **1** and **2** with 10 to 22 methylene groups.

Experimental

All reagents were of the best grade commercially available. Solvents were purified according to well-known procedures.[11] All melting and boiling points are uncorrected. ^1H (400.13 MHz) and ^{13}C (100.61 MHz) NMR spectra were obtained with an ARX 400 Bruker spectrometer. They were recorded in $CDCl_3$ with Me_4Si as internal standard unless otherwise indicated. The mass spectra were recorded on a Finnigan Mat-Incos 500 EX spectrometer using the chemical ionization technique and NH_3. Elemental analyses were performed on a Carlo Erba apparatus of Mod 110 type.

Synthesis of glycerol based bolaamphiphiles

***n*-Decane-1,10-diyl dimethanesulfonate, 4a.** At 0 °C, triethylamine (1.72 g, 17.21 mmol) in dichloromethane (4 ml) was added to a solution of *n*-decane-1,10-diol (1 g, 5.74 mmol) in 6 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). After dropwise addition of methanesulfonyl chloride (1.44 g, 12.63 mmol), the mixture was maintained at 0 °C for 2 h. After extractions and washing (cooled aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine), the organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (light petroleum–diethyl ether) to give **4a**, which was recrystallized from diethyl ether–dichloromethane. White solid; yield = 54%; R_f [light petroleum(PE)–diethyl ether(E) 2:8] = 0.27; mp = 75 °C. ^1H NMR ($CDCl_3$, δ, *J* Hz): 1.30–1.40 (m, 12H, CH_2); 1.71–1.78 (dt, 4H, CH_2, $J = 6.6 \times 7.4$); 3.01 (s, 6H, CH_3); 4.22 (t, 4H, OCH_2, $J = 6.6$). ^{13}C NMR ($CDCl_3$, δ): 25.37, 28.93, 29.09, 29.23 (CH_2); 37.36 (CH_3); 70.18 (OCH_2).

1,1-*O*-(Decane-1,10-diyl)bis(*rac*-isopropylidene glycerol, 5a. Solketal (1.98 g, 15 mmol), 12 ml of a 33% KOH solution and tetrabutylammonium bromide (0.24 g, 0.75 mmol) were vigorously stirred at 25–30 °C and **4a** (2.47 g, 7.5 mmol) was added

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dropwise. After addition, the solution was heated at reflux until **4a** was entirely consumed as monitored by TLC. The organic layer was then separated, dried ($MgSO_4$) and concentred. **5a** was finally isolated by column chromatography using PE–E. Colorless oil; yield = 60%; R_f (PE–E 2:8) = 0.86. ^1H NMR ($CDCl_3$, δ): 1.25–1.34 (m, 12H, CH_2); 1.36 (s, 6H, CH_3); 1.42 (s, 6H, CH_3); 1.52–1.61 (m, 4H, OCH_2CH_2); 3.33–3.51 (m, 8H, OCH_2); 3.73 (dd, 2H, OCH_2); 4.06 (dd, 2H, OCH_2); 4.27 (q, 2H, OCH). ^{13}C NMR ($CDCl_3$, δ): 25.42 (CH_3); 26.09 (CH_2); 26.77 (CH_3); 29.41, 29.53, 29.62, 29.68 (CH_2); 66.92, 71.87, 71.95 (OCH_2); 74.81 (OCH); 109.28 (OCO).

1,1-*O*-(Decane-1,10-diyl)bis(*rac*-glycerol), 1a. **5a** (280 mg, 0.7 mmol) was dissolved in 4 ml of acetonitrile in the presence of DOWEX 50X8 (26 mg, 0.14 mequiv.). The mixture was heated under vigorous stirring for 4 h. After evaporation of the solvent, the residue was dissolved in anhydrous methanol (5 ml), filtered and dried ($MgSO_4$). Recrystallization ($MeOH–CH_2Cl_2$) afforded **1a** as a white powder; yield = 83%; R_f (MeOH) = 0.70; mp = 75 °C. ^1H NMR (CD_3OD, δ, *J* Hz): 1.20–1.30 (m, 12H, CH_2); 1.46–1.53 (m, 4H, CH_2); 3.31–3.39 (m, 8H, OCH_2); 3.42 (dd, 2H, OCH_2, $J = 11.2 \times 6$); 3.49 (dd, 2H, CH_2OH, $J = 11.2 \times 5.1$); 3.66 (q, 2H, CHOH); 4.51 (br s, 4H, OH). ^{13}C NMR (CD_3OD, δ): 28.10 (CH_2); 31.48, 31.57, 31.61 (CH_2); 65.51 (CH_2OH); 73.15 (CHOH); 73.51 (OCH_2); 74.13 (OCH_2). MS (CI, NH_3): 340.44 (100) $[M + NH_4]^+$; 323.12 (57.3) $[M + H]^+$. Anal. calcd for $C_{16}H_{34}O_6$ (322.44): C = 59.60%; H = 10.63%; found: C = 59.37%; H = 10.77%.

Glycerol-1,3-dibenzyl ether, 6. Benzyl alcohol (31 ml, 300 mmol) in dry THF (100 ml) and NaH (7.2 g, 300 mmol) were kept below 25 °C for 1 h. Then, dry sodium iodide (1 g, 6.7 mmol) and epichlorohydrin (7.8 ml, 100 mmol) were added. The mild exothermic reaction was controlled with an ice bath. The mixture was then warmed to 50 °C overnight to complete the reaction. The product was obtained from partition between water and PE. Then, **6** was purified by distillation as a pale yellow liquid; yield = 59%; R_f (PE–E: 1:1) = 0.20; bp (2 mmHg) = 180 °C. ^1H NMR ($CDCl_3$, δ, *J* Hz): 2.59 (br s, 1H, OH); 3.51 (dd, 2H, OCH_2, $J = 9.7 \times 6.2$); 3.56 (dd, 2H, OCH_2, $J = 9.7 \times 4.6$); 4.01 (tt, 1H, CH, $J = 6.2 \times 4.6$); 4.54 (s, 4H, $PhCH_2$-*O*-); 7.26–7.36 (m, 10H, C_6H_5). ^{13}C NMR ($CDCl_3$, δ): 69.53 (CHO); 71.30 (OCH_2); 73.38 ($PhCH_2O$); 127.71, 127.88, 128.18, 128.39, 137.94 (C_6H_5).

2,2-*O*-(Decane-1,10-diyl)bis(1,3-dibenzyl glycerol) 8a. **6** (3.26 g, 12 mmol) was dissolved in 84 ml of toluene in the presence of KOH (5.9 g, 106 mmol). The mixture was heated at reflux for 2 h to remove water by azeotropic distillation. Then, **4a** (1.98 g, 6 mmol), dissolved in 6 ml of toluene, was added dropwise and the temperature maintained at reflux until **4a** was entirely consumed as monitored by TLC (≈4 h). After cooling, 40 ml of water was added to the solution. The organic layer was separated and the aqueous phase shaken twice with E. The combined organic layers were dried ($MgSO_4$), concentrated and purified by column chromatography. **8a** was isolated as a colorless oil; yield = 48%; R_f (PE–E 1:1) = 0.67. ^1H NMR ($CDCl_3$, δ, *J* Hz): 1.25–1.34 (m, 12H, CH_2); 1.55–1.63 (m, 4H, CH_2); 3.44–3.64 (m, 14H, OCH_2); 4.51 (s, 8H, $PhCH_2O$); 7.25–7.33 (m, 20H, C_6H_5). ^{13}C NMR ($CDCl_3$, δ): 26.09 (CH_2); 29.48, 29.76 (CH_2); 70.10, 70.58 (OCH_2); 73.33 ($PhCH_2$); 77.90 (OCH_2); 127.44, 127.5, 127.58, 128.3, 138.34 (C_6H_5).

2,2-*O*-(Decane-1,10-diyl)bis(glycerol), 2a. Under stirring, **8a** was treated with Pd/C catalyst [0.12 g, 7.3% (w/w)] in 15 ml of dry methanol under a hydrogen atmosphere for 12 h at room temperature. After filtration, distillation of MeOH and recrystallization ($HCCl_3$ or $MeOH–CH_2Cl_2$), **2a** was obtained as a white powder; yield = 81%; R_f (MeOH) = 0.69; mp = 94 °C. ^1H NMR (CD_3OD, δ): 1.20–1.30 (m, 12H, CH_2); 1.45–1.51 (m, 4H, CH_2); 3.44–3.54 (m, 14H, OCH_2); 4.52 (br s, 4H, CH_2OH). ^{13}C NMR (CD_3OD, δ): 28.03 (CH_2); 31.51, 31.57, 32.02 (CH_2); 63.32, 72.32 (OCH_2); 83.17 (OCH); MS (CI, NH_3): 340.16 (100) $[M + NH_4]^+$; 323.10 (73.8) $[M + H]^+$. Anal. calcd for $C_{16}H_{34}O_6$ (322.44): C = 59.60%; H = 10.63%; found: C = 59.54%; H = 10.79%.

1,1-*O*-(Docosa-10,12-diyne-1,22-diyl)bis(*rac*-isopropylidene glycerol), 10b. Copper(II) acetate monohydrate in pyridine (72 ml) was heated at 55 °C for 1 h. Under vigorous stirring, a solution of 3.44 g (12.19 mmol) of 1-*O*-(undec-10-ynyl)-*rac*-isopropylidene glycerol, **9b**, in 7 ml of pyridine was added to the green suspension. The solution was then kept at 55 °C for 2 h. After cooling and extraction (E), the organic layers were successively washed with water, cold aqueous HCl (10%) and water. The organic layer was dried over magnesium sulfate and concentrated. Isolation after column chromatography on silica gel (PE–E) gave 1.86 g (54%) of **10b** as a colorless oil. R_f (PE–E 1:1) = 0.62. ^1H NMR ($CDCl_3$, δ): 1.25–1.31 (m, 20H, CH_2); 1.36 (s, 6H, CH_3); 1.42 (s, 6H, CH_3); 1.51 (q, 4H, CH_2); 1.57 (q, 4H, CH_2); 2.24 (t, 4H, $CH_2C{\equiv}$); 3.40–3.53 (m, 8H, OCH_2); 3.73 (dd, 2H, OCH_2); 4.06 (dd, 2H, OCH_2); 4.27 (q, 2H, OCH). ^{13}C NMR ($CDCl_3$, δ): 19.20 ($CH_2C{\equiv}$); 25.43 (CH_3); 26.02 (CH_2); 26.78 (CH_3); 28.33, 28.82, 29.03, 29.39, 29.54 (CH_2); 65.24 (${\equiv}C{-}C{\equiv}$); 66.93 (OCH_2); 71.82, 71.86 (OCH_2); 74.75 (OCH); 77.53 ($CH_2C{\equiv}$); 109.36 (OCO).

1,1-*O*-(Docosane-1,22-diyl)bis(*rac*-glycerol), 1g. Following the procedure described for **2a**, catalytic hydrogenation of **10b** (1.6 mmol) gave 1.5 mmol of the saturated analog. The protecting group was removed under acidic conditions (DOWEX 50X8 in acetonitrile) and **1g** recrystallized from chloroform as a white powder; yield = 91%; R_f (MeOH) = 0.78; mp = 111 °C. ^1H NMR (CD_3OD, 50 °C, δ): 1.21–1.33 (m, 36H, CH_2); 1.45–1.52 (m, 4H, CH_2); 3.34–3.43 (m, 8H, OCH_2); 3.44 (dd, 2H, CH_2OH); 3.52 (dd, 2H, CH_2OH); 3.68 (q, 2H, CHOH); 4.49 (br s, 4H, OH). ^{13}C NMR (CD_3OD, 50 °C, δ): 28.12 (CH_2); 31.43, 31.55, 31.57, 31.58, 31.61 (CH_2); 65.68 (CH_2OH); 73.25 (CHOH); 73.61, 74.27 (OCH_2). MS (CI, NH_3): 508.25 (100) $[M + NH_4]^+$; 491.28 (28.0) $[M + H]^+$. Anal. calcd for $C_{28}H_{58}O_6$ (490.77): C = 68.53%; H = 11.91%. found: C = 68.45%; H = 11.98%.

Techniques

Surface tension measurements. The surface tension γ of aqueous solutions was measured by the duNouy ring method with a digital tensiometer K10T (Krüss). They were measured at 20 °C until constant values were obtained (the equilibrium was usually reached after 10 to 15 min). The accuracy of the measurement is 0.1 mN m^{-1}. All solutions were prepared using bidistilled water.

Polarizing optical microscopy. Investigations of the amphotropic phases have been performed by polarizing optical microscopy using a Leitz polarizing microscope equipped with a Mettler hot stage FP 82 (heating rate of 3–5 °C min^{-1} and cooling rate 0.5–1 °C min^{-1}). The scan penetration method was used to study lyotropic phases. The method consists in the successive introduction, into a flat capillary tube, of small quantities of crystalline sample and water. The concentration gradient at the surfactant/water boundary allows all the phases to develop as separate bands. In this way, the capillary tube gives a direct visualization of the water–surfactant binary diagram. This technique was also used to assess phase sequences in the phase diagram.

X-ray scattering. An X-ray camera of the Guinier type with a bent quartz crystal monochromator adjusted to give only $CuK\alpha_1$ radiation was used. The sample-to-film distance was fixed at 28 or 40 mm. An INEL radiation detector was used that permitted the simultaneous acquisition of a 2θ angular domain into 4096 channels. The X-ray scattering patterns were recorded at different temperatures using a Mettler hot stage FP 82. Powders were introduced into a quartz capillary tube of 1 mm diameter, then heated and stored well above the melting point. The temperature was then adjusted to the desired value.

Results and Discussion

Synthesis of glycerol based bolaamphiphiles

Two different procedures were used, depending on the hydrophobic chain length. The compounds with $n \leqslant 16$ (n: number of methylene groups) were prepared by two direct routes (Scheme 1). from commercial α,ω-alcanediols (Aldrich). For the other compounds ($n > 16$), the key step was an oxidative coupling between two acetylenic moieties (Scheme 2).

Routes A (Scheme 1). The starting α,ω-alkanediols were activated as mesylates[12] before reaction with the required protected glycerol synthons.

Compounds **1a–d** were obtained according to route A1 solketal was condensed on the bismesylates under phase transfer catalysis conditions.[13] Then, deprotection was performed *via* a heterogeneous acid hydrolysis with the acidic ion-exchange resin DOWEX 50X8 (Acros) in acetonitrile.

Compounds **2a–d** were obtained according to route A2: glycerol-1,3-dibenzyl ether, **6** was previously obtained by reaction of two equivalents of benzyl alcohol with epichlorhydrin in a suspension of NaH in THF.[14] The etherification step was best carried out in a homogeneous system (KOH–toluene under reflux).[14] The final compounds **2a–d** were obtained by classical deprotection of benzyl ethers under catalytic hydrogenation conditions (Pd/C in MeOH).

Routes B (Scheme 2). The starting acetylenic mesylates **8** reacted with solketal or glycerol-1,3-dibenzyl ether, **6**, to afford respectively the key intermediates **9** and **11**. The oxidative dimerization with copper diacetate in pyridine converted them into the conjugated diynes **10** and **12** with 18, 20 or 22 carbon atoms in the alkyl chain.[15] Bolaforms **1e–g** and **2e–g** were finally obtained after complete hydrogenation of the triple bonds and deprotection of the acetonides or benzyl ethers as described for **1a–d** and **2a–d**.

Surface tension of aqueous solutions of compounds 1 and 2

The new bolaforms revealed very low solubilities in water at 20 °C ($< 10^{-5}$M for $n > 12$). Thus, only compounds **1a–b** and **2a–b** could be studied. In order to compare the influence of the original geometry of the bolaforms on their aqueous behavior, we also determined, under the same conditions, the surface tension of solutions of the one-head analog of **1a–b** and **2a–b**, respectively **13a–b** and **14a–b** (Fig. 1).

1b and **2b** show low surface activity while **1a** and **2a** reduced the surface tension of water from 72 to 45 mN m^{-1}, but much less than the one-head equivalents (about 27 mN m^{-1}). But of course, this analysis is limited at 20 °C by their low solubility. Furthermore, in contrast to the monoglycerol ethers **13** and **14**, the four bolaamphiphiles present no indication of micellization. This result is in a good agreement with studies on micellization of single-chain bolaforms with ionic or non-ionic polar headgroups.[8e,16] It was observed that a minimum length of the alkyl chain is required to obtain micellar aggregation of amphiphilic compounds.[9b] Depending on the nature of the polar heads, this minimal length was assessed to be between 12 and 16 methylene groups.[8e]

The data obtained from the curves above are summarized in Table 1. The molecular area at the air/water interface at the CMC (A_{CMC}) was calculated using the slope of γ *vs.* log C curves below the CMC according to the Gibb's absorption isotherm. We show that the area per molecule at the interface is much higher for the bolaformes (about 110 *vs.* 30 Å^2). Again, the shortness of the lipophilic chain leads probably to a spread of the molecules at the interface (Fig. 2).[9b] It can be noticed that the measured value of the molecular area at the interface for the bolaamphiphiles is in quite good agreement with the one required. On the basis of an optimized network between the hydrophilic heads, we have evaluated this area using both X-ray data (see below), surface tension measurements of **13** and **14** and a length of 1.27 Å^2 *per* methylene for a fully extended hydrocarbon chain. Then, values between 110 and 140 Å^2 *per* molecule were calculated.

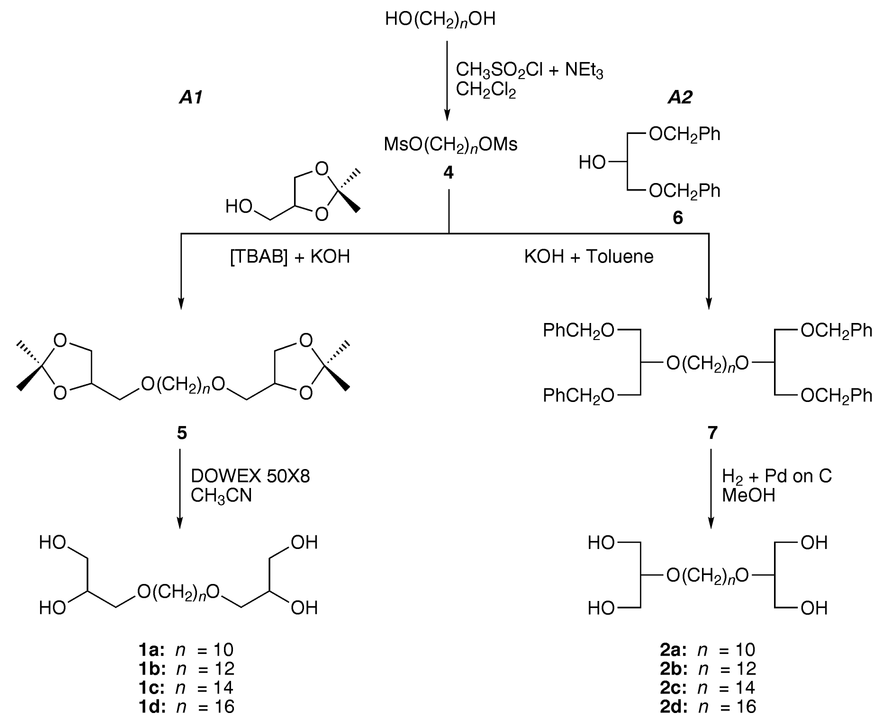
Characterization of liquid crystal properties

The behavior of bolaforms **1** in water-free and water-saturated states has been studied by microscopy and X-ray investigations. Phase identifications and determination of the phase transition temperature were carried out using a polarized light microscope equipped with a hot stage. The samples underwent a preliminary heating until they became isotropic. This treatment was realized in order to remove defects resulting from the thermal history of the product, which may have effects on mesophase formation. Consecutive cooling of samples was led at the rate of 1 °C min^{-1}.

Thermotropic properties. As reported previously in the case of bolaamphiphilic tetraols[8c] and, more generally, liquid crystal polyols,[14] we observed that the addition of a methylene group to the internal lipophilic chain leads to a 1.2 °C/CH_2 (**1**) and 1.4 °C/CH_2 (**2**) rise in the melting points (Table 2). As shown below, the thermotropic properties of **1** and **2** depend on the thermal history of the samples. Thus, the reported data are the highest observed melting points.

According to preliminary DSC experiments, compounds **1** exhibit complex thermotropic properties, depending on their thermal history. In the **2** series, only the first member (**2a**) showed this kind of behavior. For the other compounds, **2b–g**, it seems that the position of the hydroxyl groups of the polar head is not convenient for a structuration of the hydrogen-bond network. No mesophase was observed (DSC, optical microscopy). The other compounds, **1** and **2a**, showed mainly monotropic liquid crystal properties on cooling. The behavior of **1d** is representative of their general thermotropic properties. Formation of lamellar α phase (L_α) between 89.5 and 90.4 °C has been observed [Fig. 3(*a*)]. This identification was based on the appearance, on cooling from the liquid phase, of bright objects in the form of rod-like micelles, which are characteristic of the growth of a Smectic A phase in focal conic textures.[17] However, the narrowness of the thermal domain of the L_α phase indicates its low stability. As the sample is cooled further, a new phase appears at 89.5 °C and is then conserved down to room temperature [Fig. 3(*b*)]. For the other compounds (**1** and **2a**), formation of this lamellar phase is always observed within a very narrow temperature range on cooling (about 1 °C), from the isotropic domain.

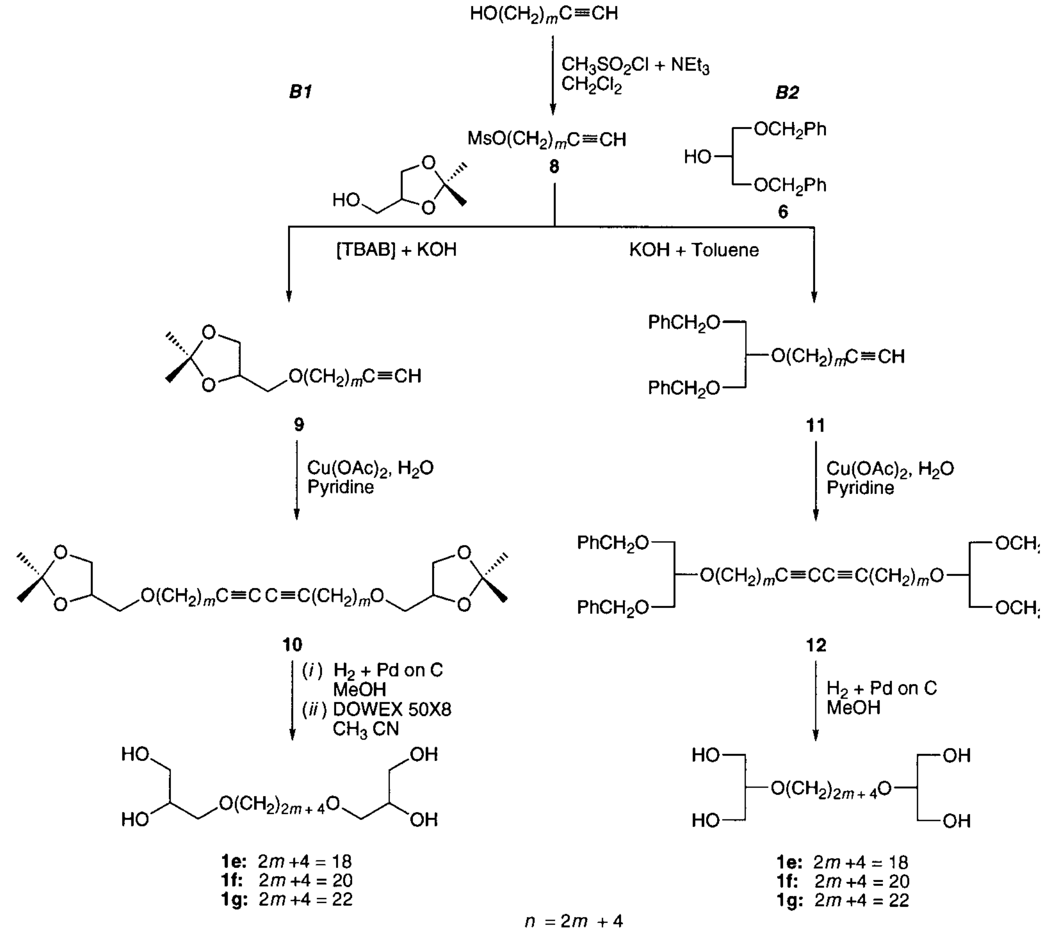
On this point, our results can be compared to those of Tschierske and co-workers[8d] on the α,β,ψ,ω-*n*-alkyltetraols, which are closely related to the bolaforms **1**. These biamphiphilic products exhibit a low temperature mesophase $L_{\beta'}$ which is highly ordered while a lamellar α phase (Smectic A) is detected at higher temperatures. Investigation of bolaforms **1** using X-rays were realized for compounds **1a–g**. All the samples observed show a similar organization, which is based on the piling of molecular monolayers. The positions of the first-order peaks appear as a function of the length of the alkyl chain (Fig. 4). It must be noted that these X-ray analysis were



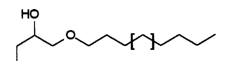
Scheme 1 Synthesis of 1,1′-*O*-(alkane-α,ω-diyl)bis(*rac*-glycerol), **1a–d**, and 2,2′-*O*-(alkane-α,ω-diyl)bis(glycerol), **2a–d** ($n \leqslant 16$)

carried out at 70–90 °C (depending on the sample). Upon cooling, no change was observed until room temperature.

In agreement with Tschierske and co-workers[8d] assessment concerning such a linear dependance, we can assume that the low temperature mesophase L exhibits rigid chains. The slope of the plot gives an increment of the interreticular distance of 1.11 Å *per* methylene group. For a paraffin chain, we know that the addition of a methylene group increases the length of the alkyl chain of 1.25 Å. From this, it may be deduced that the lamellar phase L studied implies a tilt of 25° with the layer planes. On the basis of this interpretation and according to the Luzzati nomenclature,[18] we identify the low-temperature



Scheme 2 Synthesis of 1,1′-*O*-(alkane-α,ω-diyl)bis(*rac*-glycerol), **1e–g**, and 2,2′-*O*-(alkane-α,ω-diyl)bis(glycerol), **2e–g** ($n > 16$)



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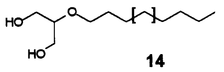

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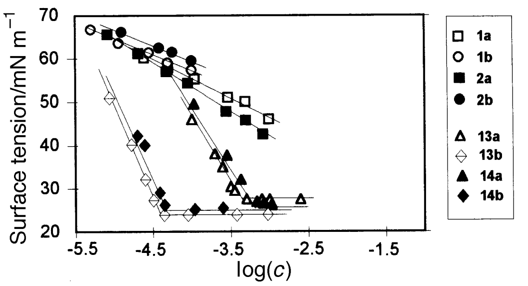

Fig. 1 Surface tension of bolaamphiphiles (**1** and **2**) and monoglycerol ethers (**13** and **14**) at 20 °C (**a**: C_{10} and **b**: C_{12})

mesophase as $L_{\beta'}$.[19] During the phase transition $L_{\beta'} \rightarrow L_{\alpha}$ previously discussed, aliphatic chains change from an ordered state where the methylene groups are in a *trans* conformation, into a disordered state in which some *gauche* conformations exist. This disorder is dynamic. For **1d**, the evaluation of the diffraction pattern on the base of a monoclinic cell of the mesophase $L_{\beta'}$ gave the following lattice parameters: $a = 8.43$ Å, $b = 4.65$ Å, $c = 30.51$ Å and $\beta = 90° + 25° = 115°$. These values are in good agreement with the value of the tilt angle of 25°.

Table 1 Micellization parameters for glycerol ethers at 20 °C

Compound	CMC/mM	γ_{CMC}/mN m^{-1}	A_{CMC}/Å^2
1a	—	—	107
1b	—	—	129
2a[a]	—	—	83
2b	—	—	139
13a	0.50	28	35
13b	0.04	24	25
14a	0.75	25	34
14b	0.05	25	28

[a] At 25 °C

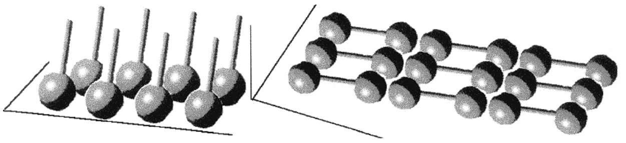

Fig. 2 Presumed organization of one- and two-head amphiphiles at the water–air interface

Table 2 Melting points of **1** and **2**

Compound	mp/°C
1a	75
1b	82
1c	88
1d	94
1e	99
1f	106
1g	111
2a	94
2b	97
2c	101
2d	105
2e	109
2f	112
2g	115

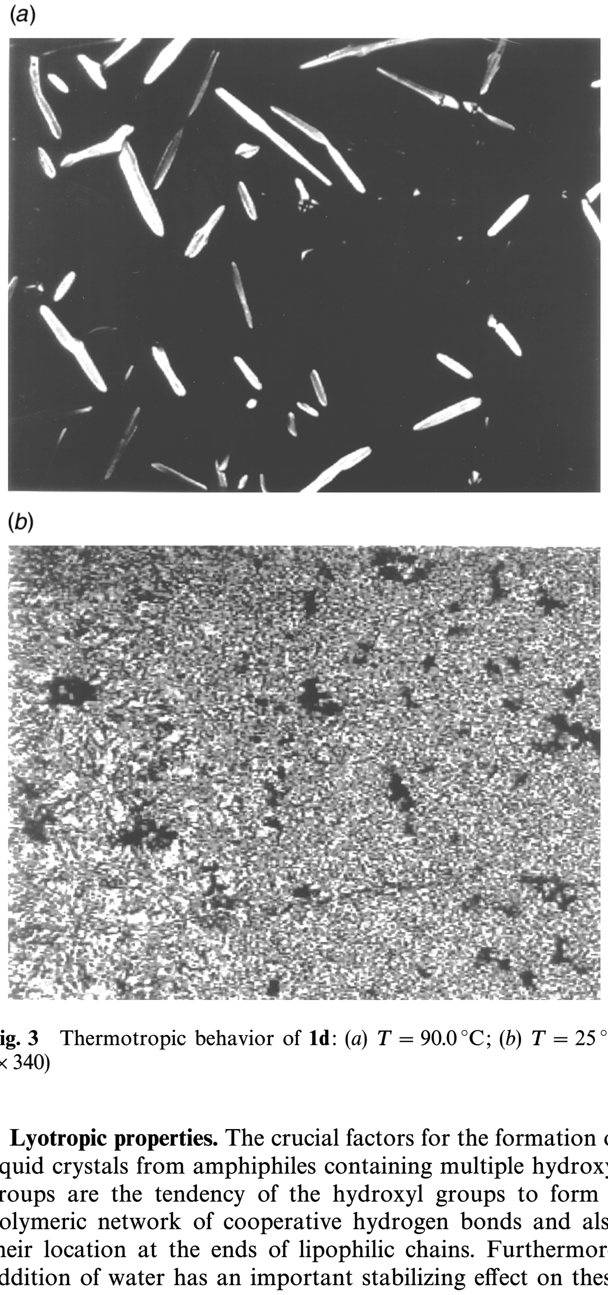

Fig. 3 Thermotropic behavior of **1d**: (*a*) $T = 90.0$ °C; (*b*) $T = 25$ °C (× 340)

Lyotropic properties. The crucial factors for the formation of liquid crystals from amphiphiles containing multiple hydroxyl groups are the tendency of the hydroxyl groups to form a polymeric network of cooperative hydrogen bonds and also their location at the ends of lipophilic chains. Furthermore, addition of water has an important stabilizing effect on these supramolecular structures. This probably implies a penetration of water molecules in the network of hydrogen bonds between the polyol head groups. In the case of bolaforms, the covalent link between the parallel hydrophilic sheets leads to a preorientation of the polar heads and then increases the stability of the self-assembling structure. Only the lyotropic properties of compounds **1** were studied.

The observations made with **1d** and various amounts of water were particularly representative. The introduction of small amounts of water (10%) leads to a smooth modification of the liquid crystal behavior of **1d**. From the isotropic

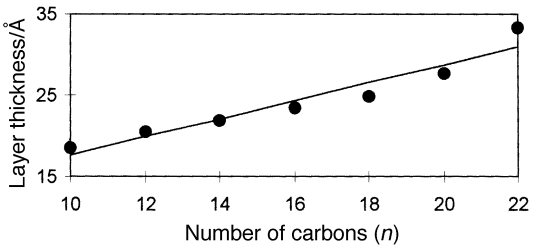

Fig. 4 Interreticular distance *d vs.* number of methylene groups in the lipophilic chain for **1** (80 °C, $L_{\beta'}$)

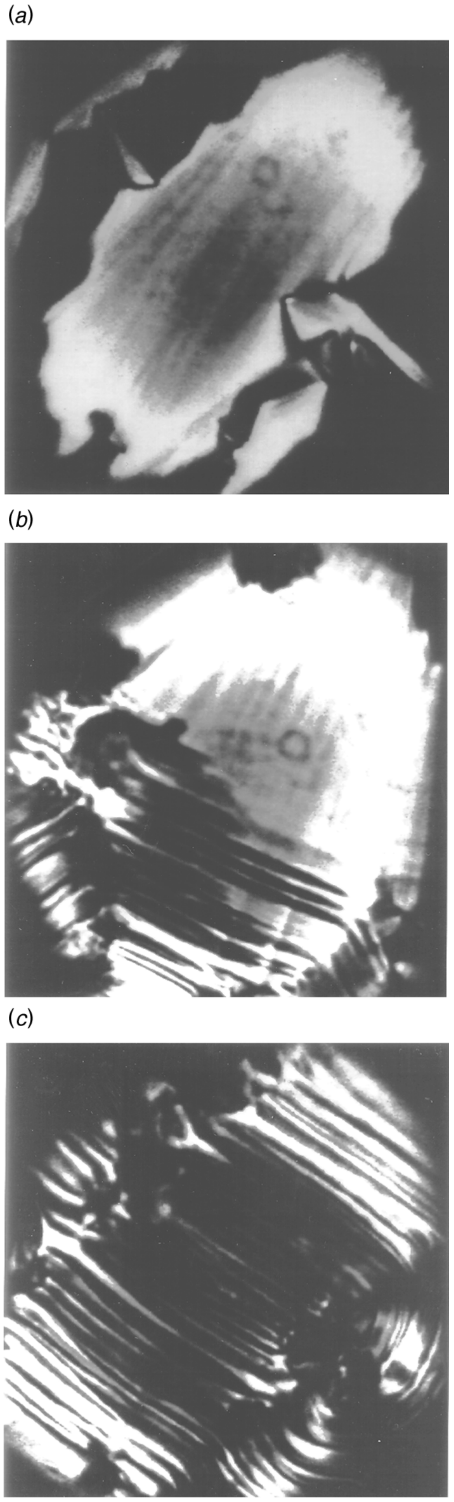

Fig. 5 Lyotropic behavior of **1d** with a low water concentration: (*a*) $T = 91\,°C$; (*b*) $T = 85.5\,°C$; (*c*) $T = 85.4\,°C$ (× 200)

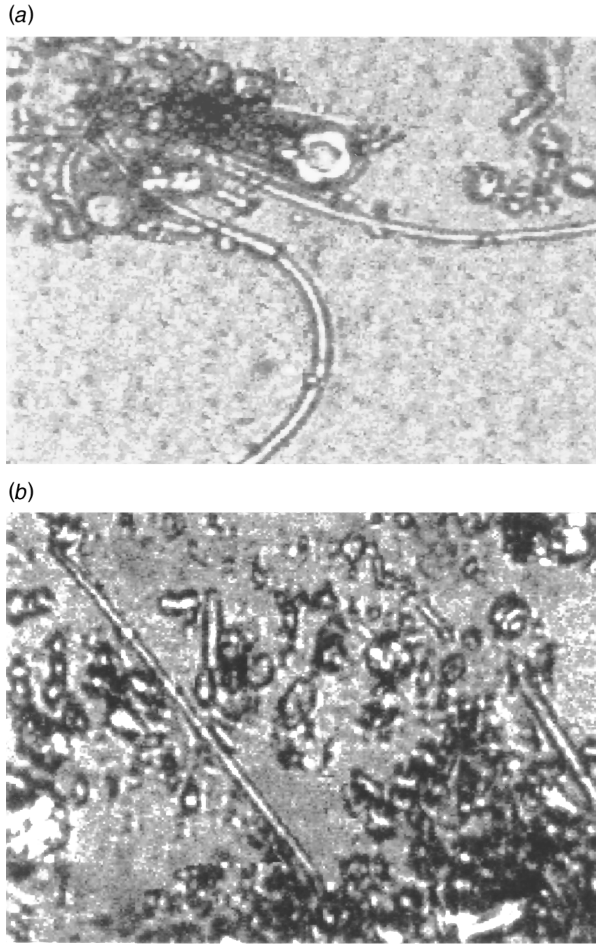

Fig. 6 Lyotropic behavior of **1d** in a diluted phase: (*a*) $T = 70\,°C$; (*b*) $T = 50\,°C$ (× 220)

domain, the first mesophase was formed on cooling at 92.4 °C. The appearance of rods revealed the formation of a lamellar α phase having a fan-like growth [Fig. 5(*a*)]. This mesophase was sharply changed at 85.5°C in favor of the $L_{\beta'}$ lamellar phase, which was then conserved down to room temperature [Fig. 5(*b*), (*c*)].

From these observations, we can conclude that the first lamellar phase that appeared upon cooling was present over a larger domain of temperature than the thermotropic phase [(85.5–92.4 °C) *vs.* (89.5–90.4 °C)]. Accordingly, the mesophase stability was improved by addition of water. The phenomenon was more pronounced with water-saturated samples. In this case, the two mesophases described above were observed again but they formed supramolecular arrangements of elongated vesicles. These aggregates, in the form of filaments, had a length between 100 and 300 μm and a diameter of 5 μm. The temperature of the transition $L_{\beta'} \rightarrow L_{\alpha}$ was determined to 60 °C. The stability domain of the L_{α} phase was highly dilated. Above 60 °C, the vesicles were flexible along the longitudinal axis [Fig. 6(*a*)]. Below 60 °C, the structure was highly rigidified, which implied a supplementary molecular order [Fig. 6(*b*)].

Conclusion

Two series of bolaforms were prepared *via* two different pathways, depending on the length of the lipophilic spacer. They showed low solubilities in water. In the case of the shortest spacers (C_{10} and C_{12}), no micellization process could be detected, owing to the inability of the alkyl chain to bend. Investigations on the liquid crystal behavior of compounds **1** showed their abilities to give stable lamellar phases over a large range of temperatures. In particular, a $L_{\beta'} \rightarrow L_{\alpha}$ transition was observed at a temperature depending both on the length of the linker and the added water amount. These properties and the observations of vesicules in diluted aqueous solutions proves that these compounds offer manifold and attractive potentialities as additives to stabilize lipid membranes, liposomes and other self-assembling systems. More complex bolaforms with larger polar heads are now under investigation for encapsulation purposes.

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References

1 (*a*) M. Kates, in *Membrane Lipids of* Archaea, *the Biochemistry of* Archaea (Archaebacteria), ed. M. Kates, D. J. Kushner and A. T. Matheson, Elsevier, Amsterdam, 1993, p. 261 and references therein; (*b*) M. Kates in *The* Archaebacteria: *Biochemistry and Biotechnology*, ed. M. J. Danson, D. W. Hough and G. G. Lunt, Portland Press, London–Chapel Hill, 1992, p. 51; (*c*) D. G. Sprott, *J. Bioenerg. Biomembr.*, 1992, **24**, 555.

2 M. de Rosa, *Thin Solid Films*, 1996, **284**, 13.

3 K. Yamauchi and M. Kinoshita, *Prog. Polym. Sci.*, 1993, **18**, 763 and references therein.

4 Y. Koga, M. Nishihara, M. Morii and M. Akagawa-Matsushita, *Microbiol. Rev.*, 1993, **57**, 164.

5 (*a*) C. G. Choquet, G. B. Patel, T. J. Beveridge and G. D. Sprott, *Appl. Microbiol. Biotechnol.*, 1994, **42**, 375; (*b*) S. Bauer, K. Heckmann, L. Six, C. Strobl, D. Blöcher, B. Henkel, T. Garbe and K. Ring, *Desalination*, 1983, **46**, 369; (*c*) J. H. Fuhrop and R. Bach, in *Advances in Supramolecular Chemistry*, ed. G. W. Gokel, Jai Press, Greenwich, CT, 1992, vol. 2, p. 25; (*d*) R. Rudolph, H. Wiesner, M. Engelhardt and H.-J. Freisleben, *Biol. Chem. Hoppe-Seyler*, 1993, **374**, 145.

6 J.-M. Kim and D. H. Thompson, *Langmuir*, 1992, **8**, 637; (*b*) K. Yamauchi, A. Moriya and M. Kinoshita, *Biochim. Biophys. Acta*, 1989, **1003**, 151; (*c*) K. Yamauchi, Y. Sakamoto, A. Moriya, K. Yamada, T. Hosokawa, T. Higuchi and M. Kinoshita, *J. Am. Chem. Soc.*, 1990, **112**, 3188; (*d*) F. M. Menger and X. Y. Chen, *Tetrahedron Lett.*, 1996, **37**, 323.

7 (*a*) D. H. Thompson, C. B. Svendsen, C. Di Meglio and V. C. Anderson, *J. Org. Chem.*, 1994, **59**, 2945; (*b*) Y. Okahata and T. Kunitake, *J. Am. Chem. Soc.*, 1979, **101**, 5231; (*c*) Y. Moroi, Y. Murata, Y. Fukuda, Y. Kido, W. Seto and M. Tanaka, *J. Phys. Chem.*, 1992, **96**, 8610.

8 (*a*) E. Baumgartner and J.-H. Fuhrhop, *Angew. Chem.*, 1980, **92**, 564; (*b*) C. Tschierske and H. Zaschke, *J. Chem. Soc., Chem. Commun.*, 1990, 1013; (*c*) F. Hentrich, C. Tschierske and H. Zaschke, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 440; (*d*) F. Hentrich, S. Diele and C. Tschierske, *Liq. Cryst.*, 1994, **17**, 827; (*e*) F. Brisset, R. Garelli-Calvet, J. Azema, C. Chebli, I. Rico-Lattes and A. Lattes, *New J. Chem.*, 1996, **20**, 595.

9 (*a*) G. Descotes, J. Ramza, J.-M. Basset and S. Pagano, *Tetrahedron Lett.*, 1994, **35**, 7379; (*b*) S. Munõz, J. Mallen, A. Nakano, Z. Chen, I. Gay, L. Echegoyen and G. W. Gokel, *J. Am. Chem. Soc.*, 1993, **115**, 1705.

10 N. Noiret, Y. Rivaux, H. Patin, J.-A. Laffitte and P. Brochette, Fr. Pat. 9613906, 1996.

11 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., Pergamon Press, New York, 1988.

12 R. K. Crossland and K. L. Servis, *J. Org. Chem.*, 1970, **35**, 3195.

13 P. Sonnet and E. Antonian, *J. Agric. Food Chem.*, 1988, **36**, 856.

14 H. A. van Doren, R. van der Geest, R. M. Kellogg and H. Wynberg, *Recl. Trav. Chim. Pays Bas*, 1990, **109**, 197.

15 (*a*) K. Stockel and F. Sondheimer, in *Organic Syntheses*, ed. W. E. Norland, John Wiley & Sons, 1988, vol. 6, p. 68; (*b*) F. Sondheimer, *Acc. Chem. Res.*, 1972, **5**, 81.

16 (*a*) S. Yiv, K. M. Kale, J. Lang and R. Zana, *J. Phys. Chem.*, 1976, **80**, 2651; (*b*) R. Zana and S. Yiv, *J. Colloid Interface Sci.*, 1988, **77**, 449; (*c*) R. Zana and S. Yiv, *ibid.*, 1988, **77**, 456; (*d*) J. R. Johnson and R. Fleming, *J. Phys. Chem.*, 1975, **79**, 2327.

17 (*a*) D. Demus and L. Richter, *Textures of Liquid Crystals*, Verlag Chemie, Weinheim–New York, 1978 and references therein; (*b*) G. W. Gray and J. W. Goodby, *Smectic Liquid Crystals–Textures and Structures*, L. Hill, Glasgow–London, 1984.

18 A. Tardieu, V. Luzzati and F. C. Reman, *J. Mol. Biol.*, 1973, **75**, 711.

19 G. H. Brown and P. P. Crooker, *Chem. Eng. News.*, 31 January, 1983, 24.

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