ChemistrySelect

Research Article
doi.org/10.1002/slct.202303942

Chemistry Europe
European Chemical Societies Publishing

www.chemistryselect.org

Symmetric and Dissymmetric Pseudo-gemini Amphiphiles Based on Propoxylated Ethyl Piperazine and Fatty Acids

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Novel symmetric and dissymmetric pseudo-gemini surfactants are synthesized using ethylpiperazine, propylene oxide and six different fatty acids (capric, lauric, myristic, palmitic, stearic, oleic) as starting materials. The synthesis follows a simple pathway excluding heating or catalyst. Important surface activity properties including critical micelle concentration (CMC), surface tension at CMC (γCMC), surface pressure at CMC (πCMC), negative logarithm of concentration to achieve 20 mN/m reduction in surface tension (pC20), minimum area at interface (Amin) and maximum surface excess concentration (Γmax) are obtained through surface tension and electrolytic conductivity measurements. Antimicrobial properties of the synthesized amphiphiles are evaluated using disk diffusion method and are compared to those of standard antibiotic agents. Particle size distribution patterns are obtained using dynamic light scattering (DLS). This work investigates the effect of dissymmetry on various surface activity and antimicrobial properties. Dissymmetric pseudo-gemini amphiphiles have a few times higher CMC compared to analogous symmetric surfactants. However, better antimicrobial properties are observed when there is some dissymmetry between hydrophobic groups.

Introduction

Dimeric or gemini surfactants feature two polar centers and two non-polar alkyl chains connected via a spacer in their molecular structure. Considerable research focus is currently centered on the synthesis and study of this type of surface-active compounds. Gemini surfactants have become a new hope in the eyes of modern chemists to overcome numerous challenges in the way of application of amphiphiles to varying fields of cutting-edge science and technology, such as gene transfection,[1] drug delivery,[2] synthesis and stabilization of nanomaterials[3,4] corrosion inhibition.[5] The reason of this optimistic view is superior surface activity performance of gemini surfactants compared to their monomeric counterparts.[6] Gemini amphiphiles have one noteworthy feature that is missed by conventional surfactants: their molecular structure can be diversified to a significant extent by incorporating various types of structural moieties into the molecule. This phenomenon can be exploited to fine-tune the properties of gemini surfactants and obtain multitude of amphiphilic structures with desired features. Gemini surfactants can be classified according to their spacer structures as having flexible spacer or rigid spacer, short spacer, or long spacer, and polar or non-polar spacer. In addition, a gemini surfactant can have two non-identical polar heads or two non-identical hydrophobic tails. All these variations in structure have their unique effect on the properties of gemini surfactants.[7] Hydrophobic chain length and structure are known to be vital factors in affecting CMC.[8] CMC, being related to micellization in solution is a crucial parameter determining industrial efficacy of a surfactant molecule. Micellization of gemini surfactant is an important process since several properties like adsorption, solubilization and detergency etc. depend upon it.[9] Bearing these in mind, investigation of the effect of hydrophobic chain length and structure variations on the application properties of gemini surfactants is an appealing subject of study. When a gemini surfactant has hydrophobic tails of varying length or structure, it is named as dissymmetric gemini surfactant. Oda and coworkers did one of the earliest studies on the aforementioned topic.[10] They synthesized *n-2-m* type dissymmetric gemini surfactants from N,N,N′,N′-tetramethylethylenediamine and two *n* and *m*-alkyl bromides ($m = 10$, 12, 14, 16, 18 and $n =$ 12, 14, 16, 18). The effect of degree of dissymmetry on micellization patterns of the gemini surfactants was investigated. High degree of dissymmetry of *n-2-m* type surfactants (when n-$m > 2$) was associated with formation of worm-like micelles, while symmetric gemini surfactants was proved to form tubular micelles. When one of the chains was shorter than half of the other, only spherical and short micelles were formed. However, the CMC did not depend on the symmetry but only on the overall number of carbon atoms of the two hydrophobic chains. Xu et al.[11] synthesized 12-*s*-*n* type ($n = 8$, 10, 14, 16) dissymmetric gemini surfactants through a three-step process. The first step was esterification of n-alkyl acids ($C_{n-1}H_{2n-1}COOH$, $n = 8$, 10, 12, 14, 16) with 2-dimethylaminoethanol. In the subsequent step the ester product with dodecanoate group

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202303942

was reacted with epichlorohydrin and hydrochloric acid. Eventually, the obtained compound was reacted with each one of the ester products to synthesize dicationic amphiphiles. CMC of the obtained 12-*s*-*n* type dissymmetric gemini surfactants increased as *n* became grater. Surface tension at CMC also increased as *n* increased. In addition, the low foam height of these series of dissymmetric gemini surfactants was noted. Kang and Xu[12] synthesized *m*-3-*n* type esterquat dissymmetric gemini surfactants in three steps. In the first step a tertiary amine product was obtained from the reaction of n-alkanoyl chlorides ($C_{n-1}H_{2n-1}COCl$, n = 12, 14, 16) and 2-(N,N-dimethyl)aminoethanol. In the next step tertiary amine product with lauroyl moiety was quaternized with 1,3-dibromopropane. The final step was the reaction of products of the previous steps to obtain dimeric amphiphiles. The resultant gemini surfactants were 12-3-12, 12-3-14, 12-3-16, and 14-3-14. For 12–3-*n* type dissymmetric gemini surfactants CMC and A_{min} were shown to drop with increasing degree of dissymmetry. 14-3-14 and 12-3-16, having the same number of total carbon atoms, exhibited similar CMC, γ_{CMC}, π_{CMC} and pC_{20} values.

Herein we report the synthesis of six symmetric and five dissymmetric pseudo-gemini surfactants, all having the same spacer and head group. Unlike dissymmetric gemini surfactants described by other works, our work is discussing dissymmetric pseudo-gemini surfactants with non-covalent linking of hydrophilic and hydrophobic groups. Due to the mobile nature of non-covalent interactions the so-called “dissymmetric” pseudo-gemini amphiphiles can be simply viewed as the blend of different counterions. For the sake of conciseness, we have labeled these blended amphiphiles as “dissymmetric” in our work. The effect of blending dissimilar hydrophobic counterions on surface activity and antimicrobial properties of pseudo-gemini surfactants was evaluated by establishing a comparison between symmetric and dissymmetric pseudo-gemini amphiphiles.

Materials and Methods

Materials

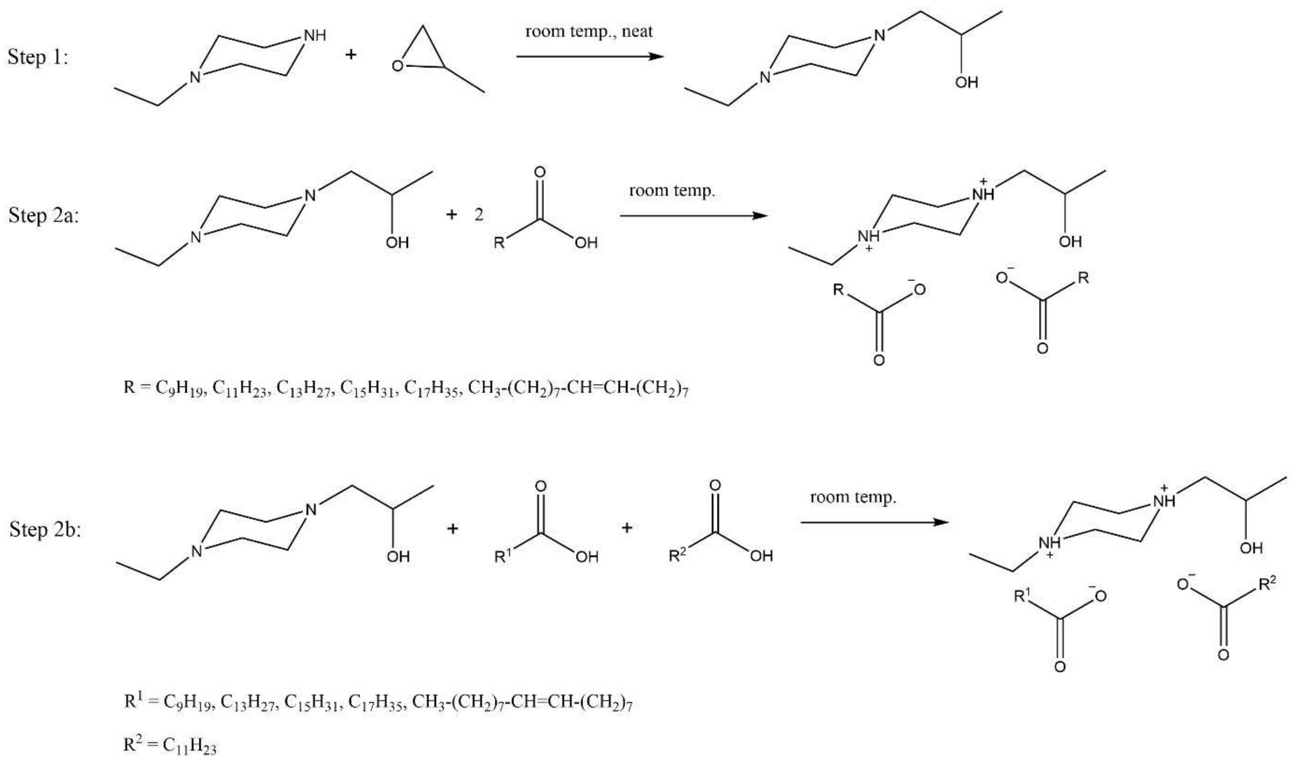
1-ethylpiperazine (98%) and oleic acid (99%) were purchased from Alfa Aesar. Capric acid (98%), lauric acid (98%), myristic acid (98%), palmitic acid (98%), and stearic acid (97%) were purchased from Sigma-Aldrich. Propylene oxide (99%) was the product of Azerikimya. All chemicals were used as received.

Synthesis and Characterization

Synthesis of the gemini-like amphiphiles was achieved in two steps as described in Scheme 1: the initial step being the synthesis of 1-(propane-2-olyl)-4-ethylpiperazine and the second step being the neutralization with fatty acids.

Synthesis of 1-(propane-2-olyl)-4-ethylpiperazine

1-(propane-2-olyl)-4-ethylpiperazine was obtained from the reaction of 1-ethylpiperazine with equimolar amount of propylene oxide at room temperature under solvent-free, pH-neutral conditions (Step 1 in Scheme 1). The reaction path for the epoxide and amine reaction under neutral or basic conditions has been discussed by Sundaram and Sharma.[13]



R = C_9H_{19}, $C_{11}H_{23}$, $C_{13}H_{27}$, $C_{15}H_{31}$, $C_{17}H_{35}$, CH_3-$(CH_2)_7$-CH=CH-$(CH_2)_7$

R^1 = C_9H_{19}, $C_{13}H_{27}$, $C_{15}H_{31}$, $C_{17}H_{35}$, CH_3-$(CH_2)_7$-CH=CH-$(CH_2)_7$

R^2 = $C_{11}H_{23}$

Scheme 1. Synthesis pathway of gemini-like surfactants based on 1-(propane-2-olyl)-4-ethylpiperazine and fatty acids.

Synthesis of gemini-like amphiphiles

Gemini-like amphiphiles were prepared by simply mixing 1-(propane-2-olyl)-4-ethylpiperazine with six different fatty acids (capric, lauric, myristic, palmitic, stearic, oleic) in acetone. Upon mixing in organic solvent, cationic and anionic counterions are formed via proton transfer between carboxyl and amine groups. Amphiphiles having homogenous hydrophobic groups were prepared by mixing 1-(propane-2-olyl)-4-ethylpiperazine with a single fatty acid in 1:2 molar ratio (Step 2a in Scheme 1). Amphiphiles with heterogenous hydrophobic groups were prepared by mixing 1-(propane-2-olyl)-4-ethylpiperazine with lauric acid and one of the other five acids in 1:1:1 molar ratio (Step 2b in Scheme 1).

Characterization of products

All of the synthesized compounds were characterized with IR (Bruker LUMOS FT-IR, neat samples), ^{1}H NMR (Bruker TOP SPIN, 300.18 MHz and 400.13 MHz), and ^{13}C NMR (Bruker TOP SPIN, 75.46 MHz and 100.62 MHz). IR, ^{1}H NMR and ^{13}C NMR spectra of the products are available in Supporting Information.

Measurements

Surface tension

The surface tension of the aqueous solutions of gemini-like surfactants was measured using a Du Nouy ring KSV Sigma 702 tensiometer (Attension Biolin Scientific, Finland). Surface tension of the double distilled water used for preparing solutions was equal to 71.5 mN/m at 25 °C. Surface tension measurements were repeated three times and the average of three measurements was recorded. The measurements were accurate to 0.01 mN/m.

Electrolytic conductivity

Specific electrolytic conductivity of aqueous surfactant solutions was measured using a CO 3000 L benchtop conductivity meter (VWR® pHenomenal®, Germany). The measured values were referenced to 25 °C and were accurate to ±1%. Specific conductivity of double distilled water was ~1.4 μS/cm. The average of three separate measurements was recorded.

Krafft temperatures were determined with conductometry method using the approach described by Manojlović.[14]

Dynamic Light Scattering (DLS)

The size distribution of aggregates formed in aqueous solutions of surfactants was determined with DLS using a LB-550 Particle Size Analyzer (HORIBA Scientific, Japan). The samples were scanned at 25 °C with a 650 nm laser beam. CONTIN method was applied to generate the size distribution data. The average of three distinct measurements was recorded.

Viscosity and density

Dynamic viscosity and density of surfactant solutions at concentrations ranging from 0.1 to 1.0 wt% were measured with SVM 3000 Stabinger Viscometer (Anton Paar GmbH, Austria) at 25 °C in accordance with ASTM D7042. The accuracy of the measured values was within ±0.05%. Each measurement was repeated three times to obtain accurate results.

Antimicrobial properties

Antimicrobial properties of the products were tested via the modified disk diffusion method. Meat-peptone agar inoculated with gram-negative bacteria – *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and gram-positive bacteria – *Staphylococcus aureus* (MRSA), *Bacillus anthracis*, as well as Sabouraud agar inoculated with *Candida albicans* were used to perform the test. Broth suspensions used to inoculate the agar plates were diluted to 500 mln cells per mL. 6 mm diameter filter paper disks were impregnated with the surface-active compounds and placed onto the agar plates. The results were recorded after the agar plates were incubated at 37 °C for 24 hours. Each sample was tested three times, and the average value was recorded.

Results and Discussion

Surface activity

The Gibbs adsorption isotherm of each surfactant was generated based on the surface tension measurements at 25 °C (see Figure 1). Both symmetric and dissymmetric surfactants display good surface activity. The achieved minimum surface tension is lower for amphiphiles having shorter alkyl chains in the case of symmetric surfactants. The surface tension reduction behavior of dissymmetric surfactants, on the other hand, is more or less similar to that of each other. Most probably, this is owing to the presence of the same C_{12} alkyl chain in the structure of each dissymmetric surfactant.

The critical micellar concentration (CMC) of each surfactant was obtained from conductivity measurements (see Figures S1–S11) and listed in Table 1. Conductometric CMC values have been shown on Gibbs isotherm of each surfactant with a circle (Figure 1). It can be inferred from the Gibbs isotherms that for most of our amphiphiles CMC values determined from conductometry are in good agreement with CMC values determined from surface tension measurement. This can be checked by determining if the point corresponding to conductometric CMC lies close to the region of Gibbs isotherm where sharp decline in surface tension ceases. This tendency is not observed for C_{10}–EPPO–C_{10} and C_{16}–EPPO–C_{16}, since their surface tension continues to drop even after CMC is reached, implying continuous adsorption at the interface beyond CMC. In fact, Menger et al.[15] stated that saturation of the interface and micellization can be observed at different concentrations.

CMC values of both symmetric and dissymmetric amphiphiles attain smaller values as alkyl chain length increases. This trend is disrupted reaching C_{16} alkyl chain and further. A similar phenomenon was observed in one of our previous works.[16] It is suggested that inferior solubility of long chain fatty acids can cause CMC to increase.

CMC of *n-s-m* type cationic dissymmetric gemini surfactants were proved to be between CMC values of its corresponding symmetric counterparts, *m-s-m* and *n-s-n*.[12,17,18] Our study shows that CMC values of dissymmetric pseudo-gemini surfactants tend to be several times greater than that of corresponding symmetric surfactants. This suggests that the structure of hydrophobic counterions may have more significance in the

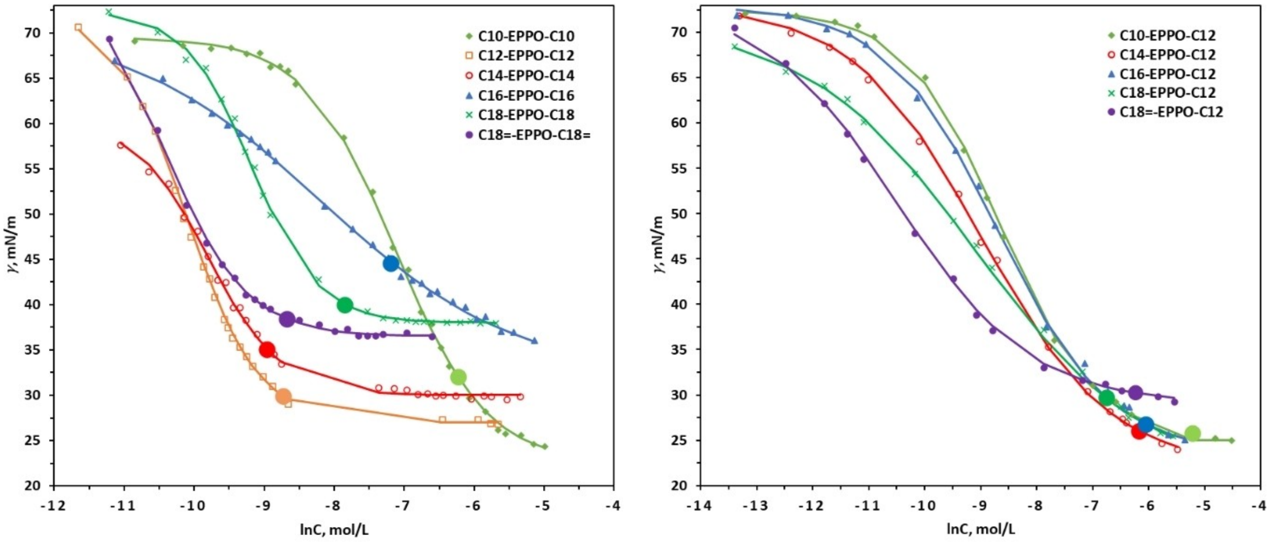


Figure 1. The Gibbs adsorption isotherms of gemini-like surfactants based on 1-(propane-2-olyl)-4-ethylpiperazine and fatty acids.

Table 1. Surface activity parameters of gemini-like surfactants based on 1-(propane-2-olyl)-4-ethylpiperazine and fatty acids at 25 °C.[a]

Surfactant	Krafft point [°C]	γ_{CMC} [mN/m]	CMC×10^3 [mol/L]	π_{CMC} [mN/m]	pC_{20}	Γ_{max}×10^{10} [mol/cm^2]	A_{min} [Å^2]	β	ΔG^0_{mic} [kJ/mol]	ΔG^0_{ads} [kJ/mol]
C_{10}–EPPO–C_{10}	< 0 °C	32.08	1.961	39.42	3.227	1.268	130.95	0.184	−18.23	−21.34
C_{12}–EPPO–C_{12}	< 0 °C	29.94	0.161	41.56	4.426	1.255	132.30	0.332	−27.15	−30.46
C_{14}–EPPO–C_{14}	< 0 °C	35.12	0.129	36.38	4.455	0.815	203.86	0.213	−23.77	−28.24
C_{16}–EPPO–C_{16}	7 °C	44.56	0.778	26.94	3.561	1.057	157.07	0.252	−21.67	−24.22
C_{18}–EPPO–C_{18}	< 0 °C	40.03	0.390	31.47	3.895	0.938	177.09	0.480	−29.68	−33.04
$C_{18=}$–EPPO–$C_{18=}$	< 0 °C	38.45	0.170	33.05	4.387	1.082	153.48	0.268	−25.02	−28.07
C_{10}–EPPO–C_{12}	< 0 °C	25.82	5.427	45.68	3.870	1.105	150.27	0.196	−16.78	−20.91
C_{14}–EPPO–C_{12}	5 °C	26.04	2.072	45.46	4.058	1.035	160.48	0.162	−17.59	−21.99
C_{16}–EPPO–C_{12}	8 °C	26.77	2.353	44.73	4.069	1.168	142.21	0.234	−19.16	−22.99
C_{18}–EPPO–C_{12}	10 °C	29.68	1.161	41.82	4.141	1.277	130.04	0.371	−24.12	−27.40
$C_{18=}$–EPPO–C_{12}	< 0 °C	30.25	1.937	41.25	4.648	1.117	148.64	0.201	−18.69	−22.38

[a] The standard uncertainties (u) are u(T) = 0.1 °C and u(p) = 10 kPa. The combined expanded uncertainties U_c are $U_c(\gamma)$ = 0.1 mN/m, U_c(CMC) = 4×10^{-6} mol/kg, $U_c(\pi)$ = 0.1 mN/m, $U_c(pC_{20})$ = 3×10^{-5}, $U_c(\Gamma_{max})$ = 0.05 mol/cm^2, $U_c(A_{min})$ = 0.8 Å^2, $U_c(\beta)$ = 0.03, and $U_c(\Delta G)$ = 0.05 kJ/mol (0.68 level of confidence).

micellization process in comparison to the effect of covalently bonded hydrophobic moieties.

Surface pressure at CMC (π_{CMC}) and the negative logarithm of surfactant concentration required to achieve 20 mN/m reduction in surface tension (pC_{20}) were calculated for all surfactants. π_{CMC} expresses the effectiveness of surface tension lowering and is calculated using Eq. (1) below:[19]

$$\pi_{CMC} = \gamma_0 - \gamma_{CMC} \tag{1}$$

where γ_0 is the surface tension of pure water at 25 °C and γ_{CMC} surface tension at CMC. pC_{20} expresses the efficiency of adsorption. Higher values of π_{CMC} and lower values of pC_{20} are indicative of high surface activity performance. Synthesized dissymmetric pseudo-gemini surfactants tend to have higher π_{CMC} values compared to symmetric ones (see Table 1).

Based on the Gibbs adsorption isotherms, maximum surface excess concentration (Γ_{max}) was calculated with Eq. (2):[19]

$$\Gamma_{max} = -\frac{1}{nRT}\lim_{C \to CMC}\frac{d\gamma}{dlnC} \tag{2}$$

Where R is the universal gas constant (8.314 J mol^{-1} K^{-1}), C is surfactant concentration, T is the absolute temperature in K, γ is surface tension. n represents the effective number of molecular species at the interface. Different authors investigating gemini surfactants have assigned the value of n as 2 or 3[20,21,22,23,24] Li and coworkers[25] used neutron reflectivity studies for direct measurement of surface excess concentration of certain gemini surfactants. Direct measurement of surface excess concentration allowed to determine the correct value of pre-factor n in Eq. (2). Ideally, for a gemini surfactant with a divalent cation and two monovalent anions n = 3. However, n = 2 was found to be true for some of the gemini surfactants, which is explained by formation of cation-anion complex. On the other hand, for a gemini surfactant with rigid spacer and bulky divalent cation, complex formation was not favored, and n = 3 was generally true. Similarly, for our case n = 3 was chosen because of the rigid spacer structure and certain steric hindrance around the cationic centers.

The minimum surface area per molecule was calculated for each surfactant using Eq. (3):[19]

$$A_{min} = \frac{10^{16}}{N_A \Gamma_{max}} \tag{3}$$

where N_A is Avogadro's number, and A_{min} is in square angstroms (Å^2).

A_{min} values listed in Table 1 for symmetric and dissymmetric pseudo-gemini surfactants indicate that dissymmetry does not significantly alter the packing density of the molecules at the surface. Only slight improvement in packing density is observed as the difference between hydrophobic chain lengths becomes greater. Reported data by Sikirić et al.[17] indicate that A_{min} becomes greater for dissymmetric gemini surfactants in comparison to symmetric counterparts having the identical spacer, while another work proves the opposite.[12]

Based on conductivity measurements counterion binding degree (β) of each surfactant was calculated with Eq. (4):[19]

$$\beta = 1 - \alpha = 1 - \frac{S_1}{S_2} \tag{4}$$

where S_2 and S_1 are the slope of conductivity (κ) vs. concentration plots below and above the CMC, respectively (see Figures S1–S11). The counterion binding degree shows the fraction, 1-α, of an ionic surfactant's counterions that are associated with the micelles. For example, if C_{Mic} is the concentration of surfactant molecules forming the micelles, then the concentration of counterions associated with the micelles would be $(1\text{-}\alpha)\cdot C_{Mic}$. the total concentration of the dissolved surfactant would be $C_T = C_{Mic} + C_{Mon}$, where C_{Mon} is the concentration of surfactants in monomeric form, i.e., not participating in micellization.[26]

According to the data presented in Table 1, β shows an inclination to increase with increasing alkyl chain length, even though the relationship is not clear-cut. For dissymmetric pseudo-gemini surfactants β becomes greater as the difference between hydrophobic chain lengths increases. The same phenomenon was observed for *m-s-n* type cationic dissymmetric gemini surfactants.[27] Pseudo-gemini surfactants with oleate counterions ($C_{18=}$–EPPO–$C_{18=}$ and $C_{18=}$–EPPO–C_{12}) shows an exception to the above trend. This can be attributed to decreased effective chain length of oleate anion due to rigid "V" shape imparted by cis-double bond.

Thermodynamics of micellization and adsorption

Standard free energy of micellization can be calculated theoretically to evaluate the degree of the spontaneity of micellization. Depending on the surfactant structure different formulas are available to calculate free energy of micellization. The Eq. (5) below suggested for dimeric surfactants with monovalent counterions by Zana[28] was used in our work:

$$\Delta G^0_{mic} = RT(0.5 + \beta)\ln X_{CMC} - \left(\frac{RT}{2}\right)\ln 2 \tag{5}$$

where R is the universal gas constant (8.314 J mol^{-1} K^{-1}), T absolute temperature in K, X_{CMC} the mole fraction of surfactant at CMC in aqueous solution.

Standard free energy of adsorption was calculated using the Eq. (6) deduced from Rosen and Aronson:[29]

$$\Delta G^0_{ad} = \Delta G^0_{mic} - 0.6023\pi_{CMC}A_{min} \tag{6}$$

where A_{min} is in units of Å^2/molecule and π_{CMC} in units of mN/m only. Calculated values of $\Delta G^0{}_{mic}$ and $\Delta G^0{}_{ads}$ are listed in Table 1. Both $\Delta G^0{}_{mic}$ and $\Delta G^0{}_{ads}$ values of symmetric pseudo-gemini surfactants are more negative in comparison to $\Delta G^0{}_{mic}$ and $\Delta G^0{}_{ads}$ values of corresponding dissymmetric surfactants. However, increasing the difference between lengths of hydrophobic groups of a dissymmetric surfactant seems to decrease both $\Delta G^0{}_{mic}$ and $\Delta G^0{}_{ads}$. Wang et al.[27] also reported a positive correlation between the degree of dissymmetry and $\Delta G^0{}_{mic}$.

Dynamic Light Scattering (DLS)

An insight into the aggregation behavior of the synthesized surfactants was obtained via applying the DLS method. Particle size distributions of the surfactant aggregates were generated at concentrations of 1×CMC and 2×CMC (see Figure 2). Size distribution curves show that particle sizes of symmetric pseudo-gemini surfactants tend to increase along with increasing hydrophobic chain length. At CMC C_{10}–EPPO–C_{10} and C_{12}–EPPO–C_{12} are forming only small aggregates (3–10 nm). C_{14}–EPPO–C_{14} and $C_{18=}$–EPPO–$C_{18=}$ have middle-sized aggregates widely distributed over 30–300 nm interval. C_{16}–EPPO–C_{16} and C_{18}–EPPO–C_{18} are forming larger aggregates with hydrodynamic diameter of 1000–5000 nm. Raising solution concentration to 2×CMC does not produce a considerable change in the particle size distribution of the aggregates formed by symmetric pseudo-gemini surfactants, with the exception of C_{14}–EPPO–C_{14} aggregates shifting to larger diameters and producing a bimodal distribution curve.

Seemingly, dissymmetric pseudo-gemini surfactants produced larger aggregates compared to corresponding symmetric surfactants. However, the size distribution curves of these series of surfactants are flatter. Flat size distribution curve indicates aggregates of varying sizes and shapes coexist in the solution. Another study group also reported differently sized aggregates of dissymmetric surfactant[17] at various concentrations. Shifting

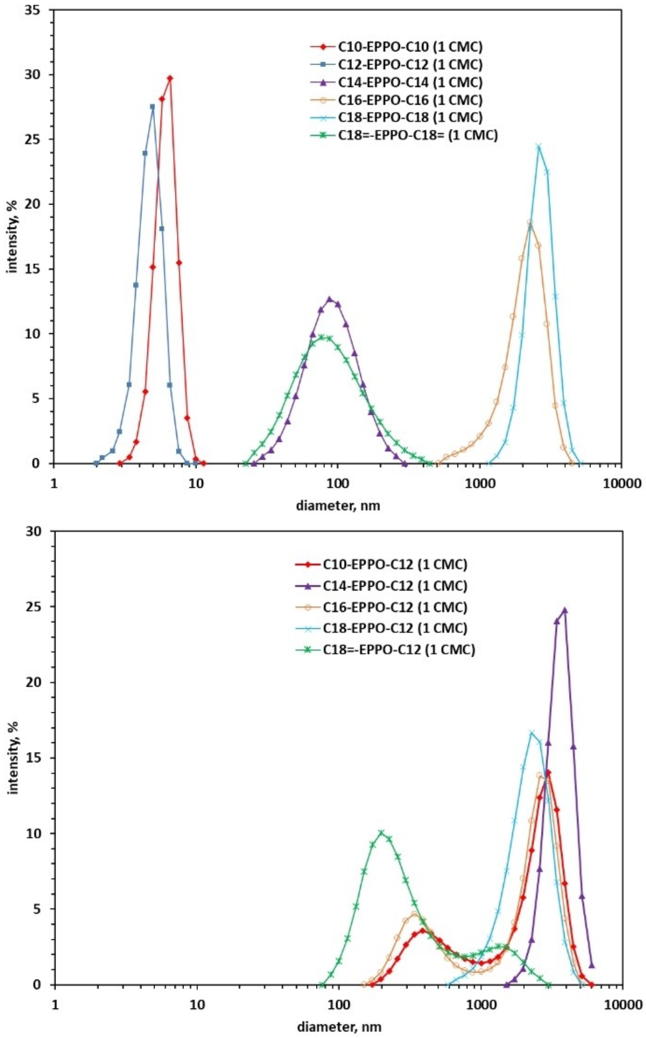


Figure 2. DLS-measured aggregate size distribution of gemini-like surfactants based on 1-(propane-2-olyl)-4-ethylpiperazine and fatty acids.

from 1×CMC to 2×CMC does not produce any major variation in particle size distribution patterns of dissymmetric pseudo-gemini surfactants. Predicting the net effect of dissymmetry on surfactant particle size is difficult since the actual concentration of solutions of dissymmetric surfactants was a few times higher than that of symmetric counterparts.

Viscosity and density

The viscosity of surfactant solutions is an indicator of the presence of ordered structures in the aqueous phase. Ordered packing of surfactant molecules through the aqueous medium produces a highly viscous solution. The viscosity of both symmetric and asymmetric pseudo-gemini surfactants in our work was not much different from that of pure water at 0.1–1.0 wt% concentration range (see Tables S1 and S2). These results indicate that synthesized pseudo-gemini surfactants do not have a tendency to form highly structured phases in the aqueous medium. In our previous works[16,30] we reported a dramatic uprise in solution viscosities of pseudo-gemini surfactants with palmitate and stearate tails from 0.1 wt% to 1.0 wt%. However, C_{16}–EPPO–C_{16} or C_{18}–EPPO–C_{18} did not produce viscous solutions in the given concentration range. This indicates the role of dicationic counterion on the formation of ordered phases in the aqueous medium. The effect of hydrophobic groups' dissymmetry on solution viscosity cannot be predicted since recorded viscosities of both series of surfactants were not different to any significant extent.

Antimicrobial properties

Surfactant molecules can interact with the cell membrane of bacteria with both their tail groups and polar head groups, causing eventual disruption of the cell membrane and death of the microorganism. Little is known about the effect of structural dissymmetry of gemini surfactants on their antimicrobial properties. The results of disk diffusion test performed on both symmetric and dissymmetric pseudo-gemini surfactants have been presented in Table 2. In general, the effect of antimicrobial agent is considered strong if the diameter of the inhibition zone exceeds 25 mm, moderate if in the range 15–25 mm, and weak if less than 15 mm. As the data in Table 2 indicates, symmetric pseudo-gemini surfactants had a very weak to no effect on inhibiting the growth of bacteria. Moderate fungicide activity that was detected against *Candida albicans* becomes less pronounced as hydrophobic tail length increases. However, dissymmetric pseudo-gemini surfactants exhibited better antimicrobial properties compared to their symmetric counterparts. C_{10}–EPPO–C_{12} was effective against all microorganisms except for *Escherichia coli*. The remaining dissymmetric amphiphiles showed weak activity against tested cultures and no activity against *Escherichia coli* and *Bacillus anthracis*. However, $C_{18=}$–EPPO–C_{12} displayed varying degrees of activity against all tested microorganisms. These results suggest that hydrophobic group structure can have a definitive effect on the antibacterial properties of gemini-like surfactants.

The inhibitory effect of certain standard antibacterial agents on the test microorganisms has been presented in Table 3 for comparison. The diameter of the inhibition zone on our test microorganisms is about 13–16 mm for standard antimicrobial agents such as Gentamicin, Tobramycin, Amikacin, Netilmicin, and Ampicillin.[31,33] This value is roughly the same as that of our dissymmetric pseudo-gemini surfactants. Only Piperacillin and Ceftriaxone displayed better antibacterial performance in comparison to dissymmetric pseudo-gemini surfactants. Most of the above antibacterial drugs has no effect on *Bacillus anthracis* cultures, while for C_{10}–EPPO–C_{12} and $C_{18=}$–EPPO–C_{12} diameter of inhibition zone on *Bacillus anthracis* was 15 mm and 12 mm, respectively. Most of our pseudo-gemini amphiphiles exhibited equivalent or superior antifungal activity against *Candida albicans* in comparison to Voriconazole.

Conclusions

One series of symmetric and another series of dissymmetric pseudo-gemini surfactants were synthesized from 1-(propane-2-olyl)-4-ethylpiperazine and fatty acids. Their surface activity performance, adsorption and micellization behavior and antimicrobial properties were evaluated and compared to gain an insight into the influence of dissymmetry on performance properties of this class of gemini surfactants. Both symmetric and dissymmetric pseudo-gemini amphiphiles exhibited similarly good performance in terms of effectiveness of surface tension lowering (π_{CMC}), efficiency of adsorption (pC_{20}) and effectiveness of adsorption (Γ_{max}). However, CMC values of symmetric pseudo-gemini surfactants were a few times lower than that of corresponding dissymmetric surfactants. The Gibbs free energy of adsorption and micellization of symmetric pseudo-gemini surfactants were slightly lower compared to dissymmetric surfactants. DLS-measured particle size distribution data indicates that dissymmetric surfactants produce larger aggregates at concentrations equal to or higher than CMC. According to viscosity measurements neither symmetric nor dissymmetric pseudo-gemini amphiphiles had a strong ten-

Table 2. Antimicrobial properties of gemini-like surfactants based on 1-(propane-2-olyl)-4-ethylpiperazine and fatty acids.

Micro-organisms	C_{10}–EPPO–C_{10}	C_{12}–EPPO–C_{12}	C_{14}–EPPO–C_{14}	C_{16}–EPPO–C_{16}	C_{18}–EPPO–C_{18}	$C_{18=}$–EPPO–$C_{18=}$	C_{10}–EPPO–C_{12}	C_{14}–EPPO–C_{12}	C_{16}–EPPO–C_{12}	C_{18}–EPPO–C_{12}	$C_{18=}$–EPPO–C_{12}
	Diameter of inhibition zone (mm)										
Escherichia coli	0	0	0	0	0	0	0	0	0	0	11
Pseudomonas aeruginosa	11	0	9	0	8	0	11	11	0	10	16
Klebsiella pneumoniae	0	0	0	0	0	0	15	17	12	11	12
Staphylococcus aureus	0	0	0	0	0	0	11	0	10	13	14
Bacillus anthracis	0	0	0	0	0	0	15	0	0	0	12
Candida albicans	24	22	17	12	12	8	19	15	19	15	20

Table 3. Antimicrobial properties of standard antibiotics.

Microorganisms	Gentamicin	Tobramycin	Amikacin	Netilmicin	Piperacillin	Ampicillin	Ceftriaxone	Voriconazole
	Diameter of inhibition zone (mm, susceptibility I)							
Escherichia coli	13–14 [31]	13–14 [31]	15–16 [31]	13–14 [31]	18–20 [31]	14–16 [31]	31 [32]	–
Pseudomonas aeruginosa	13–14 [31]	13–14 [31]	15–16 [31]	13–14 [31]	15–20 [31]	–	–	–
Klebsiella pneumoniae	13–14 [33]	–	16 [33]	–	–	14–16 [33]	22–28 [34]	–
Staphylococcus aureus	13–14 [31]	13–14 [31]	15–16 [31]	13–14 [31]	18–20 [31]	14–16 [31]	30 [32]	–
Bacillus anthracis	0 [35]	0 [35]	0 [35]	0 [35]	0 [35]	0 [35]	11 [35]	–
Candida albicans	–	–	–	–	–	–	–	15–16 [36]

dency to form structured phases in aqueous media. However, this is likely to be caused by irregular molecular geometry of the dicationic counterion. Superior antimicrobial properties of dissymmetric pseudo-gemini surfactants compared to symmetric ones might indicate how critical hydrophobic group structure can be in determining biological activity of a surface-active compound.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: adsorption · antibacterial · micelles · pseudo-gemini surfactant · surface tension

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Manuscript received: September 30, 2023