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ORIGINAL ARTICLE

Synthesis, Surface Property and Antimicrobial Activity of Cationic Gemini Surfactants Containing Adamantane and Amide Groups

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Abstract A series of novel cationic gemini surfactants, namely 1,3-adamantanedicarboxylic acid bis(alkyldimethyl-3-ammoniopropyl amide) dibromide designated as [Ad-2(amC$_n$)] (n = 12, 14, 16), containing adamantane, two amide groups, and two hydrocarbon chains, were synthesized from 1,3-adamantanedicarboxylic acid. The surface-active properties of the surfactants were investigated through surface tension and electrical conductivity measurement. A series of thermodynamic parameters such as standard free energy $\left(\Delta G_{\mathrm{m}}^{\circ}\right)$, enthalpy $\left(\Delta H_{\mathrm{m}}^{\circ}\right)$, and entropy $\left(\Delta S_{\mathrm{m}}^{\circ}\right)$ of micellization were evaluated from electrical conductivity measurements in the temperature range from 288 to 308 K. The micellization for [Ad-2(amC$_n$)] is entropy-driven at low temperature and enthalpy-driven at high temperature. Further, the antimicrobial activity of the synthesized gemini surfactants against both Gram-positive and Gram-negative bacteria was also investigated, and this study showed that the compound [Ad-2(amC$_{12}$)] has excellent antibacterial activity against all studied bacteria.

Keywords Gemini surfactants · Adamantane · Critical micelle concentration · Thermodynamic parameters · Antimicrobial activity

Introduction

Gemini or dimeric surfactants consist of two conventional single-chain surfactants which are chemically bonded by a spacer in a molecule. gemini surfactants have been used as detergents, gene delivery vector, antimicrobial agents, and so on. Numerous gemini surfactants with different chemical structures have been synthesized and investigated because these surfactants have superior properties with respect to conventional surfactants [1–3]. Many works have shown that the nature of the spacer plays an important role in the surfactant properties of gemini surfactants, and the spacer may be of various types: long or short, hydrophilic or hydrophobic, flexible or rigid [4–6]. It is interesting to investigate the effect of rigidity spacers on the properties of gemini surfactants.

Adamantane (tricyclo[3.3.1.1^{3,7}]decane), $C_{10}H_{16}$, is a very symmetric tricyclic hydrocarbon with three fused chair-form cyclohexane rings, the same structure as a diamond lattice (high rigidity) [7]. The particular structure of adamantane displays many useful chemical and physical properties, is a highly symmetric cage compound that imparts many interesting chemical and physical properties, such as high thermal and oxidative stability, extreme lipophilicity, and innocuity, etc. [8]. Amino derivatives of adamantane, such as aminoadamantanes which are known to have interesting biological properties, are used medically to treat influenza. It is interesting to study the biological activity of adamantane derivatives. However, until recently few studies have focused on the surfactants containing adamantane [9, 10].

Some researchers have been realized the antimicrobial activity of adamantane derivatives, and they were tested against some microorganisms, such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa* and so on. As expected, the antimicrobial activities of adamantane derivatives were relatively high [11, 12]. As we known, the cationic surfactants have proved themselves to have antimicrobial activities.

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Cationic gemini surfactants which consist of two symmetric quaternary ammonium groups exhibit much better antimicrobial potency [1]. Herein, the adamantane combine with the cationic gemini surfactants may have excellent antimicrobial activities.

In this paper, we report a series of novel cationic gemini surfactants containing amide groups and adamantane spacer, namely 1,3-adamantanedicarboxylic acid bis(alkyldimethyl-3-ammoniopropyl amide) dibromide (**[Ad-2(amC$_n$)]**), where ***n*** is hydrocarbon chain length of 12, 14 and 16). The **[Ad-2(amC$_n$)]** are synthesized from 1,3-adamantanedicarboxylic acid by three-step reactions, their surface-active properties (including CMC, γ_{CMC}, pC_{20}, Γ_{max}, and Π_{CMC}), thermodynamic parameters of micellization (including β, (ΔG_m°), (ΔH_m°) and (ΔS_m°)) and antimicrobial activity are systematically investigated. The synthetic route is shown in Scheme 1.

Experimental Section

Materials and Instrumentation

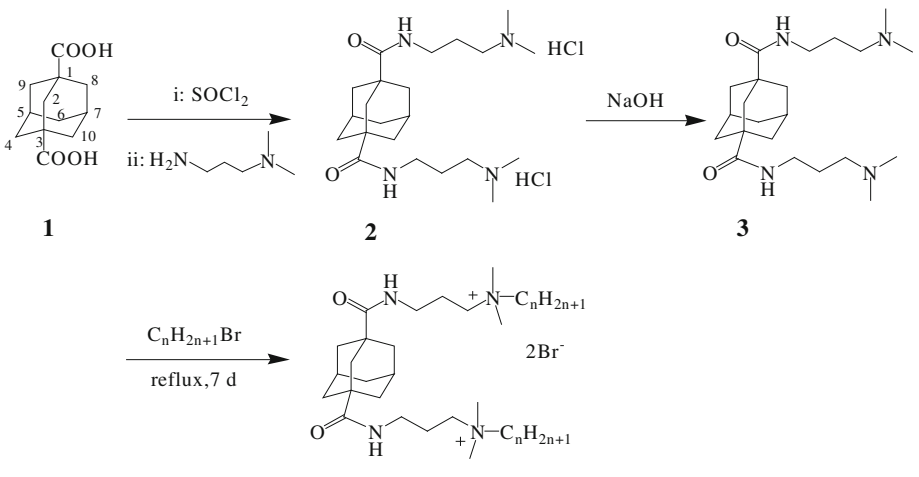
The 1,3-adamantanedicarboxylic acid was synthesized and purified as reported [13]. *N*,*N*-dimethyl-1,3-propanediamine, 1-bromododecane, 1-bromotetradecane, and 1-bromohexadecane were purchased from Aldrich and used without further purification. Thionyl chloride, sodium hydroxide, magnesium sulfate, dichloromethane, benzene, absolute ether, isopropanol, and acetone were all purchased from Guangzhou Chemical Reagent Factory (Guangzhou, China). Double-distilled water was used in all the experimental procedures.

The products were characterized by melting point (WRS-1B), ^{1}H NMR (Varian Mercury-Plus 300 Spectrometer). The surface tension of aqueous solutions was measured by a KSV Sigma 700 tensiometer at 298 K, and each sample was measured three times. This tensiometer works based on the Wilhelmy plate method. Prior to measurement, the surface tension of the doubled distilled water was confirmed in the range of 72.0 ± 0.3 mN/m. Electrical conductivity of surfactant solutions was performed on a conductivity meter (Model DDS-11A, Shanghai Precision & Scientific Instrument Co. Ltd., accuracy of ±2 %) at five different temperatures (288–308 K) for each surfactant.

Synthesis of 1,3-Adamantanedicarboxylic Acid Bis-(*N*,*N*-Dimethyl-3-Aminopropyl amide) (**3**)

The mixture of 1,3-adamantanedicarboxylic acid (5.0 g, 22.3 mmol) and thionyl chloride (50 mL) was refluxed under vigorous stirring for 3 h, and became transparent. The excess thionyl chloride was removed by vacuum distillation. This obtained solid was dissolved in distilled benzene (70 mL), and added dropwise to a being agitated solution of the *N*,*N*-dimethyl-1,3-propanediamine (4.69 g, 46 mmol) in distilled benzene (50 mL) over 30 min under a nitrogen atmosphere at 0 °C. The resultant mixture was stirred continuously overnight then allowed to warm to room temperature, during which a white solid was formed. The resultant white precipitate was isolated by filtration and dried in a vacuum, and then recrystallized from acetone to give compound **2**.

Compound **2**: yield = 76 %, white crystal, ^{1}H NMR (300 MHz, D_2O, δppm): 1.561 (br.s, 2H, $\boldsymbol{H}_{ad}$-6, this "ad" means adamantane), 1.634–1.675 (m, 8H, $\boldsymbol{H}_{ad}$-4, 8, 9, 10), 1.730 (br.s, 2H, $\boldsymbol{H}_{ad}$-2), 1.767–1.841 (m, 4H, 2 × CH_2-C$\boldsymbol{H}_2$CH_2), 2.075 (br.s, 2H, $\boldsymbol{H}_{ad}$-5, 7), 2.738 (s, 12H, 4 × NC$\boldsymbol{H}_3$), 2.935–2.988 (t, 4H, 2 × NC$\boldsymbol{H}_2$CH_2), 3.133–3.177 (t, 4H, 2 × CONHC$\boldsymbol{H}_2$CH_2).



Scheme 1 Synthesis of cationic gemini surfactant **[Ad-2(amC$_n$)]**

Then compound **2** was dissolved in water (100 mL), and then sodium hydroxide solution (80 mL, 1 mol·L^{-1}) was added, the mixture was stirred for 30 min at room temperature and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine and water, dried with anhydrous magnesium sulfate and then rotary evaporated to give the compound **3**.

1,3-Adamantanedicarboxylic acid bis-(N,N-dimethyl-3-aminopropyl amide) (**3**): yield = 68 %, light yellow colored oil, ^{1}H NMR (300 MHz, DMSO, δppm): 1.475–1.521 (m, 4H, 2 × $CH_2CH_2CH_2$), 1.573 (br.s, 2H, H_{ad}-6), 1.636–1.674 (m, 8H, H_{ad}-4, 8, 9, 10), 1.745 (br.s, 2H, H_{ad}-2), 2.042 (br.s, 2H, H_{ad}-5, 7), 2.099 (s, 12H, 4 × NCH_3), 2.145–2.195 (t, 4H, 2 × NCH_2CH_2), 3.021–3.041 (m, 4H, 2 × $CONHCH_2CH_2$), 7.501–7.537 (t, 2H, 2 × CONH).

Synthesis of 1,3-Adamantanedicarboxylic Acid Bis(alkyldimethyl-3-Ammoniopropyl Amide) Dibromide ([**Ad-2(amC$_n$)**])

The solution of alkyl bromide (40 mmol of 1-bromododecane, 1-bromotetradecane, or 1-bromohexadecane) in isopropanol (50 mL) was added to a stirred solution of compound **3** (10 mmol) in isopropanol (80 mL), the mixture was refluxed for 7 days. Then the resulting mixture was concentrated, washed with diethyl ether, and recrystallized from acetone to give the target gemini surfactants [**Ad-2(amC$_n$)**].

1,3-Adamantanedicarboxylic acid bis(dodecyldimethyl-3-ammoniopropyl amide) dibromide ([**Ad-2(amC$_{12}$)**]): yield = 69 %, white crystal, mp = 142.5–142.7 °C, ^{1}H NMR (300 MHz, $CDCl_3$, δppm): 0.857–0.901 (t, 6H, 2 × CH_2CH_3), 1.254–1.348 (m, 36H, 2 × $CH_2(CH_2)_9CH_2$), 1.692–1.784 (m, 10H, H_{ad}-6 and H_{ad}-4, 8, 9, 10), 1.922–1.962 (m, 4H, 2 × $N^+CH_2CH_2(CH_2)_9$), 2.084–2.140 (m, 6H, H_{ad}-2 and 2 × $N^+CH_2CH_2CH_2NHCO$), 2.340 (br.s, 2H, H_{ad}-5, 7), 3.323 (s, 12H, 4 × N^+CH_3), 3.370-3.424 (m, 8H, 4 × $N^+CH_2CH_2$), 3.712–3.729 (m, 4H, 2 × $CONHCH_2CH_2$), 7.639–7.674 (t, 2H, 2 × CONH).

1,3-Adamantanedicarboxylic acid bis(tetradecyldimethyl-3-ammoniopropyl amide) dibromide ([**Ad-2(amC$_{14}$)**]): yield = 62 %, white crystal, mp = 145.2–145.7 °C, ^{1}H NMR (300 MHz, $CDCl_3$, δppm): 0.863–0.907 (t, 6H, 2 × CH_2CH_3), 1.259–1.353 (m, 44H, 2 × $CH_2(CH_2)_{11}CH_2$), 1.699–1.809 (m, 10H, H_{ad}-6 and H_{ad}-4, 8, 9, 10), 1.929–1.966 (m, 4H, 2 × $N^+CH_2CH_2(CH_2)_{11}$), 2.098–2.171 (m, 6H, H_{ad}-2 and 2 × $N^+CH_2CH_2CH_2NHCO$), 2.347 (br.s, 2H, H_{ad}-5, 7), 3.319 (s, 12H, 4 × N^+CH_3), 3.366–3.457 (m, 8H, 4 × $N^+CH_2CH_2$), 3.730–3.748 (m, 4H, 2 × $CONHCH_2CH_2$), 7.671–7.674 (t, 2H, 2 × CONH).

1,3-Adamantanedicarboxylic acid bis(hexadecyldimethyl-3-ammoniopropyl amide) dibromide ([**Ad-2(amC$_{16}$)**]): yield = 50 %, white crystal, mp = 135.5–135.8 °C, ^{1}H NMR (300 MHz, $CDCl_3$, δppm): 0.859–0.903 (t, 6H, 2 × CH_2CH_3), 1.255–1.346 (m, 52H, 2 × $CH_2(CH_2)_{13}CH_2$), 1.693–1.795 (m, 10H, H_{ad}-6 and H_{ad}-4, 8, 9, 10), 1.922–1.963 (m, 4H, 2 × $N^+CH_2CH_2(CH_2)_{13}$), 2.079–2.142 (m, 6H, H_{ad}-2 and 2 × $N^+CH_2CH_2CH_2NHCO$), 2.337 (br.s, 2H, H_{ad}-5, 7), 3.318 (s, 12H, 4 × N^+CH_3), 3.356–3.432 (m, 8H, 4 × $N^+CH_2CH_2$), 3.698–3.751 (m, 4H, 2 × $CONHCH_2CH_2$), 7.633–7.670 (t, 2H, 2 × CONH).

Antimicrobial Activity Test

Antimicrobial activity of the cationic gemini surfactants [**Ad-2(amC$_n$)**] were evaluated using the method for the broth macro dilution test [14, 15]. The antimicrobial activity of tested compounds was determined on the basis of their MIC (Minimal Inhibitory Concentration) values. The MIC means the lowest concentration of an antimicrobial agent that prevents visible growth of a microorganism in the broth dilution susceptibility test. The target gemini surfactants were dissolved in distilled water and after sterilization, a half milliliter of each concentration of the compound was added to the nutrient broth medium. Then the nutrient broths were individually inoculated with 20 μL of bacterial suspensions each containing separately bacteria cells. The concentration of the bacteria suspensions were approximately 10^6cfu/mL.

Five strains of a representative group of microorganisms were used: two Gram-positive bacteria (G^+): *S. aureus*, *B. subtilis*, and three Gram-negative bacteria (G^-): *E. coli*, *Pseudomonas aeruginosa* and *Vibrio parahaemolyticus*. Growth of the microorganisms was determined visually after incubation for 24 h at 37 °C.

Results and Discussion

Surface Active Properties

The surface tension measurement is a classical method of studying the critical micelle concentration (CMC) of surfactants. The variations of the surface tension (γ) with the surfactant concentration (C) at 298 K are shown in Fig. 1. The plots of γ versus Log C show a break at a concentration corresponding to the CMC of the three gemini surfactants. From Fig. 1, the values of CMC and the surface tension at the CMC (γ_{CMC}) are listed in Table 1. It can be seen that the gemini surfactants with longer hydrophobic chains have a lower CMC value and a higher minimum surface tension. The CMC value of [**Ad-2(amC$_{14}$)**] is 1 × 10^{-4}

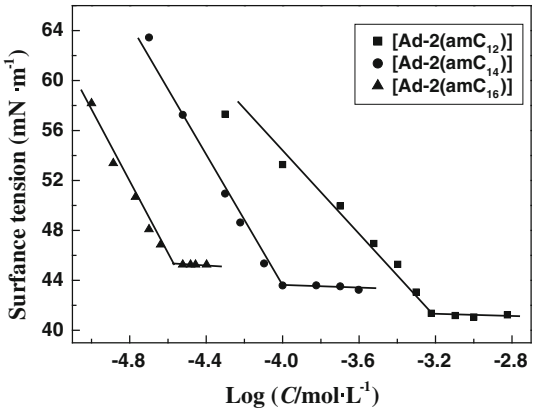


Fig. 1 Surface tension versus log C plot for the gemini surfactants **[Ad-2(amC$_n$)]** at 298 K

mol·L^{-1}, Compared with the monomeric surfactant with amide group and the same hydrophobic alkyl chain length, $C_{13}H_{27}CONHCH_2CH_2CH_2N^+(CH_3)_2C_2H_5{\cdot}Br^-$(**14monomer**), the CMC of **14monomer** is 1×10^{-3} mol·L^{-1}, it is apparent that the critical micelle concentrations of the gemini surfactants have much lower values compared with the conventional monomeric surfactant equivalents. Moreover, compared with other gemini surfactants, $C_{13}H_{27}CONHCH_2CH_2CH_2N^+(CH_3)_2(CH_2)N^+H_2CH_2CH_2CHNOCC_{13}H_{27}{\cdot}2Br^-$(**14-6-14**) (CMC $= 2.9 \times 10^{-4}$ mol·L^{-1}) [16], it is interesting that the **[Ad-2(amC$_{14}$)]** with a rigid adamantane spacer has a lower CMC value. It may result from the lipophilic adamantane in the middle of the spacer of **[Ad-2(amC$_{14}$)]**, which can also be regarded as the hydrophobic chain resulting in a lower CMC value.

To show the ability to decrease surface tension of solutions, the effectiveness of the surface tension reduction, Π_{CMC} is determined as follows:

$$\Pi_{CMC} = \gamma_0 - \gamma_{CMC} \quad (1)$$

where γ_0 is the surface tension of water and γ_{CMC} is the surface tension of the solutions when the concentration is above the CMC. The Π_{CMC} values are all listed in Table 1. The values of effectiveness are in the range of 27–31 mN·m^{-1}.

For the adsorption of **[Ad-2(amC$_n$)]** at the air–water interface, the maximum surface excess concentration (Γ_{max}) and the minimum surface area per molecule (A_{min}) at the air–water interface can be calculated using the Gibbs adsorption equation [17].

$$\Gamma_{max} = -\frac{1}{2.303\,nRT} \times \left(\frac{d\gamma}{d\ \log\ C}\right)_T \quad (2)$$

$$A_{max} = 10^{16} \times (N_A\Gamma_{max})^{-1} \quad (3)$$

where $R = 8.314$ J·mol^{-1}·K^{-1}, $T = 298$ K with γ expressed in mN·m^{-1}, $N_A = 6.02 \times 10^{23}$ mol^{-1}. The value of n is taken as 3 for a gemini surfactant. $(d\gamma/d\log C)_T$ is the slope in the surface tension isotherm when the concentration is near the CMC. The values of Γ_{max}, A_{min} are listed in Table 1. The estimated A_{min} values are 1.64, 1.07, 0.92 for **[Ad-2(amC$_{12}$)]**, **[Ad-2(amC$_{14}$)]**, and **[Ad-2(amC$_{16}$)]**, respectively. The data of minimum surface area of the short-chain surfactant molecules showed higher A_{min} of these molecules than those of longer hydrophobic chains.

The adsorption efficiency can be characterized by the value of the logarithm of the surfactant concentration C_{20} at which the surface tension of water is reduced by 20 mN·m^{-1} (pC_{20}), the larger the pC_{20} value, the greater the tendency of the surfactant to adsorb at the air–water interface *vs* forming a micelle in solution [18]. The value of pC_{20} is also listed in Table 1. It can be seen that the **[Ad-2(amC$_n$)]** with a longer hydrophobic chain has a higher adsorption efficiency.

Thermodynamic parameters of [Ad-2(amC$_n$)]

The electrical conductivity (κ) of **[Ad-2(amC$_n$)]** in aqueous solutions at five temperatures is shown in Fig. 2. In each of the plots, two straight lines with different slopes were obtained, which intersect at the point CMC. The degree of counterion dissociation (α) can be obtained from the ratio of the slopes above and below the break indicative of the CMC. Normally, the degree of counterion binding (β) and the degree of counterion dissociation have the following relationship: $\beta = 1-\alpha$. The β is an important parameter since it is the expression of how many counterions are contained in the Stern layer to counterbalance the electrostatic force that opposes micelle formation [19]. All the values of CMC and β at different temperatures are listed in Table 2.

From Table 2, one can be seen that the CMC of all the surfactants increased as the temperature increased. This may be because the water structures surrounding the hydrophobic chains are destroyed as the temperature

Table 1 The surface properties of the gemini surfactants **[Ad-2(amC$_n$)]** at 298 K

Surfactants	CMC (mmol·L^{-1})	γ_{CMC} (mN·m^{-1})	Π_{CMC} (mN·m^{-1})	$\Gamma_{max} \times 10^{10}$ (mol·cm^{-2})	A_{min} (nm^2)	pC_{20}
[Ad-2(amC$_{12}$)]	0.60 ± 0.04	41.3 ± 0.2	31.0	1.01 ± 0.08	1.64 ± 0.01	3.84
[Ad-2(amC$_{14}$)]	0.10 ± 0.04	43.5 ± 0.3	28.8	1.55 ± 0.04	1.07 ± 0.03	4.31
[Ad-2(amC$_{16}$)]	0.025 ± 0.005	45.3 ± 0.1	27.0	1.81 ± 0.05	0.92 ± 0.03	4.80

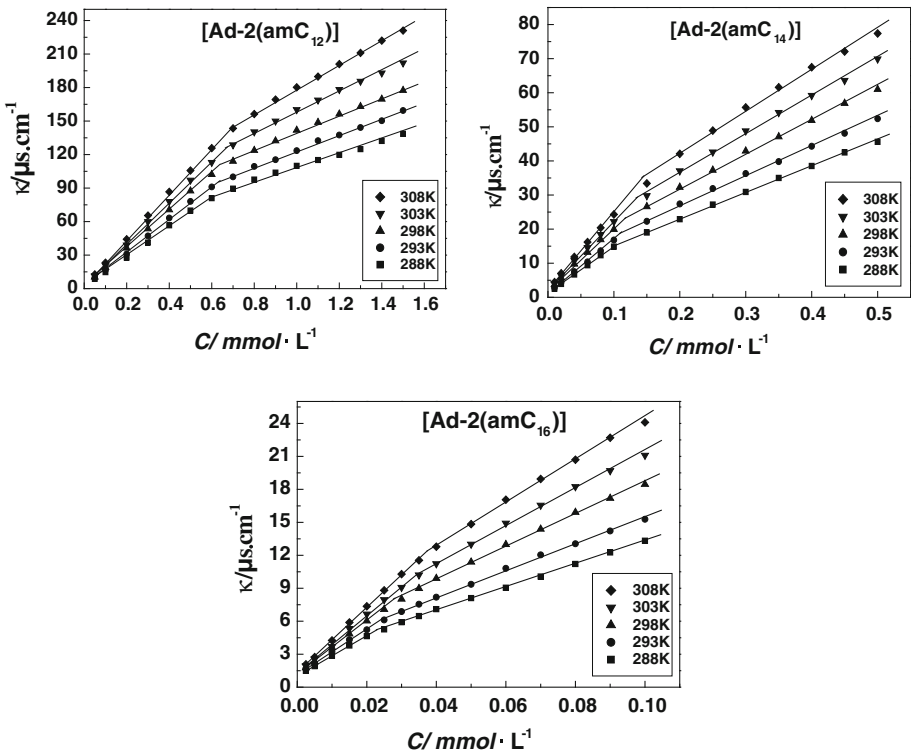


Fig. 2 Electrical conductivity (κ) *versus* the concentration (C) of **[Ad-2(amC$_{12}$)]**, **[Ad-2(amC$_{14}$)]** and **[Ad-2(amC$_{16}$)]** at five temperatures: 308 K (*filled diamonds*), 303 K (*filled inverted triangles*), 298 K (*filled triangles*), 293 K (*filled circles*), 288 K (*filled squares*)

Table 2 The thermodynamic parameters and CMC with error bars for **[Ad-2(amC$_n$)]** determined by the electrical conductivity at five different temperatures

Surfactants	T (K)	CMC (mmol·L^{-1})	β	(ΔG_m°) (kJ·mol^{-1})	(ΔH_m°) (kJ·mol^{-1})	$-T\Delta S_m^\circ$ (kJ·mol^{-1})
[Ad-2(amC$_{12}$)]	288	0.60 ± 0.01	0.55 ± 0.01	−28.74 ± 0.232	−5.57 ± 0.053	−23.18 ± 0.179
	293	0.63 ± 0.01	0.53 ± 0.01	−28.56 ± 0.237	−5.65 ± 0.055	−22.91 ± 0.182
	298	0.65 ± 0.01	0.54 ± 0.01	−29.25 ± 0.242	−5.90 ± 0.057	−23.35 ± 0.185
	303	0.68 ± 0.01	0.52 ± 0.01	−29.06 ± 0.247	−5.99 ± 0.059	−23.07 ± 0.188
	308	0.70 ± 0.01	0.47 ± 0.01	−28.02 ± 0.253	−5.88 ± 0.061	−22.13 ± 0.192
[Ad-2(amC$_{14}$)]	288	0.10 ± 0.01	0.44 ± 0.01	−29.77 ± 0.100	−13.64 ± 0.145	−16.13 ± 0.045
	293	0.11 ± 0.01	0.45 ± 0.01	−30.38 ± 0.116	−14.27 ± 0.150	−16.12 ± 0.034
	298	0.13 ± 0.01	0.45 ± 0.01	−30.51 ± 0.145	−14.76 ± 0.155	−15.75 ± 0.010
	303	0.14 ± 0.01	0.44 ± 0.01	−30.52 ± 0.160	−15.10 ± 0.161	−15.42 ± 0.001
	308	0.15 ± 0.01	0.43 ± 0.01	−30.53 ± 0.173	−15.43 ± 0.166	−15.10 ± 0.007
[Ad-2(amC$_{16}$)]	288	0.023 ± 0.001	0.42 ± 0.01	−32.37 ± 0.257	−11.70 ± 0.127	−20.67 ± 0.130
	293	0.025 ± 0.001	0.41 ± 0.01	−32.39 ± 0.268	−14.51 ± 0.159	−17.88 ± 0.109
	298	0.028 ± 0.001	0.39 ± 0.01	−31.97 ± 0.281	−17.24 ± 0.194	−14.73 ± 0.087
	303	0.034 ± 0.001	0.38 ± 0.01	−31.71 ± 0.295	−20.24 ± 0.230	−11.47 ± 0.065
	308	0.038 ± 0.001	0.36 ± 0.01	−31.25 ± 0.306	−23.09 ± 0.269	−8.17 ± 0.037

increases, which disfavors the formation of micelles and increases the CMC [20]. It also can be observed that β values decreases slightly with increasing hydrophobic chain length at the same temperature.

According to the pseudophase model of micellization, the standard Gibbs free energy change of micellization, (ΔG_m°), can be calculated from the equation below [21]:

$$\Delta G_m^\circ = RT(0.5 + \beta) \ln X_{CMC} \quad (4)$$

where $R = 8.314$ J·mol^{-1}·K^{-1}, X_{CMC} is the CMC in molar fraction, $X_{CMC} = CMC/55.4$, the 55.4 comes from 1 L of water corresponding to 55.4 mol of water at 298 K, and β is the degree of counterion binding which was calculated previously. The standard enthalpy change of micellization,

Table 3 The minimal inhibitory concentration (MIC) values of the target gemini surfactants **[Ad-2(amC$_n$)]**

Compound	MIC (μg·mL^{-1})				
	S. aureus (G^+)	*B. subtilis* (G^+)	*E. coli* (G^-)	*P. aeruginosa* (G^-)	*V. Parahemolyticus* (G^-)
[Ad-2(amC$_{12}$)]	0.7	0.3	2.1	4.2	2.1
[Ad-2(amC$_{14}$)]	2.8	1.1	71.0	71.0	71.0
[Ad-2(amC$_{16}$)]	5.9	4.7	>300.6	94.0	150.3
BAC[a]	2.0	3.7	3.7	29.9	–[b]
DABB[c]	–[b]	16	16	32	–[b]

[a] Data from reference [24]

[b] Not determined

[c] Data from reference [25]

$\left(\Delta H_m^\circ\right)$, can be determined using the Gibbs–Helmholtz equation for aqueous solutions,

$$\Delta H_m^\circ = \left[\frac{\partial(\Delta G_m^\circ/T)}{\partial(1/T)}\right] = -RT^2(0.5+\beta)\frac{\mathrm{d}\ln X_{CMC}}{\mathrm{d}T} \quad (5)$$

The standard entropy of micellization, $\left(\Delta S_m^\circ\right)$, can be calculated according to the following relation:

$$\Delta S_m^\circ = (\Delta H_m^\circ - \Delta G_m^\circ)/T \quad (6)$$

All the values of $\left(\Delta G_m^\circ\right)$, $\left(\Delta H_m^\circ\right)$, $-T\Delta S_m^\circ$ calculated at five different temperatures are listed in Table 2. It can be seen that all the standard Gibbs free energy changes $\left(\Delta G_m^\circ\right)$ are negative, indicating that the micellization is spontaneous. And the values of $\left(\Delta G_m^\circ\right)$ become more negative with increasing hydrophobic chain length. The more negative of $\left(\Delta G_m^\circ\right)$ means the stronger aggregation at the air/water interface. The increase in chain length is favorable to forming micelles due to the increase in the hydrophobic interactions between the hydrophobic chains. The values of standard enthalpy changes $\left(\Delta H_m^\circ\right)$ for micellization are negative as well, implying that the micelle formation process is exothermic [22]. For **[Ad-2(amC$_{12}$)]**, the value of the standard entropy of micellization $\left(-T\Delta S_m^\circ\right)$ is larger than enthalpy changes $\left(\Delta_m^\circ\right)$, indicating the micellization is entropy-driven. But for **[Ad-2(amC$_{14}$)]** and **[Ad-2(amC$_{16}$)]**, when the temperature is more than 308 and 298 K, respectively, the $\left(\Delta H_m^\circ\right)$ is larger than $T\Delta S_m^\circ$, which indicates that the micellization for **[Ad-2(amC$_n$)]** is entropy-driven at low temperature and enthalpy-driven at high temperature.

Antimicrobial Activity

The antimicrobial activity of the cationic gemini surfactants **[Ad-2(amC$_n$)]** on various gram-positive bacteria (G^+) and gram-negative bacteria (G^-) were evaluated by determining the minimal inhibitory concentration (μg·mL^{-1}), the values for which were given in Table 3. From Table 3, it can be seen that these target gemini surfactants **[Ad-2(amC$_n$)]** exhibit antimicrobial activities. And their antibacterial activities decrease with the increase in alkyl chain length of **[Ad-2(amC$_n$)]** (From $n = 12$ to 16). As expected, the compound **[Ad-2(amC$_{12}$)]** had the lowest MIC value against all studied bacteria and exhibited the strongest antimicrobial activity. These results are in agreement with results obtained previously, which showed that the optimal length of the alkyl chain has been noted to be twelve carbon atoms of cationic surfactants [23].

According to researchers dealing with the mode of action of cationic amphiphiles compounds on different microorganisms [24, 25], the most preferable explanation is the adsorption of amphiphile molecules on the outer cellular membrane of the microorganism due to their amphipathic characteristics. The positively charged headgroups of the cationic molecules interact with the negatively charged bacterial cell membrane, thus disrupting it with the aid of electrostatic and hydrophobic interactions leading to the release of K^+ and cytoplasmic constituents and finally cell death. The antibacterial activity depends on the hydrophilic-hydrophobic balance of the cationic amphiphiles. When the further increases in the alkyl chain length (traditionally $n > 12$) increase the hydrophobic character, which may be too high to facilitate transport through the bacterial cell membrane. Additionally, increasing the length of the alkyl chain decreases the solubility of water [26], the lower antibacterial activity of dimeric amphiphiles [**Ad-2(amC$_{14}$)**] and [**Ad-2(amC$_{16}$)**] also may be due to the poor solubility in water. That is probably why the [**Ad-2(amC$_{12}$)**] exhibits the best antimicrobial activity compared with [**Ad-2(amC$_{14}$)**] and [**Ad-2(amC$_{16}$)**].

For comparison, the MIC values of the gemini surfactant also contain the amide groups and twelve carbon alkyl chains, *N*,*N*-bis(*N*-dodecyl-*N*,*N*-dimethylglycine)-1,4-diaminobutane dihydrochloride (**DABB**) [23], are also listed in Table 3, it is interesting that the surfactant **[Ad-2(amC$_{12}$)]** with adamantane spacer have much lower MIC values for all studied bacteria, which indicates that the adamantane may plays an important role in the antimicrobial activity.

Finally, this study showed that the compound **[Ad-2(amC$_{12}$)]** have excellent antibacterial activity. The MIC values of all studied bacteria were lower than 5 μg·mL^{-1} (For *S. aureus*, *B. subtilis*, *P. aeruginosa*, *V. Parahemolyticus*, and *E. coli*, the MIC for **[Ad-2(amC$_{12}$)]** were 0.7, 0.3, 2.1, 4.2, and 2.1 μg·mL^{-1}, respectively.), and also lower than that of **BAC** (benzalkonium chloride) [27], which is currently utilized for disinfectants in hospital. This work, integrating adamantane and cationic gemini surfactants, leads to possible advances in the formulation of new types of bactericides.

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