Supporting Information

Comparative Studies on the aggregate formation of synthesized zwitterionic gemini and monomeric surfactants in the presence of amphiphilic antipsychotic drug chlorpromazine hydrochloride in aqueous solution: an experimental and theoretical approach

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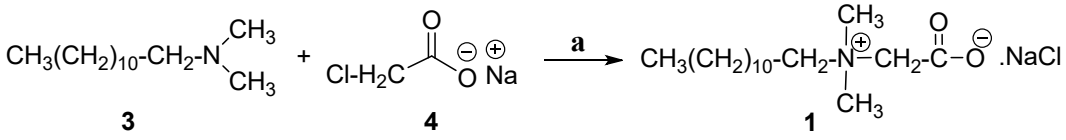
Synthesis and characterization of zwitterionic surfactant: N-Dodecyl-N,N′-dimethyl-2-ammonio-1-ethanecarbonate (1)

8.52 g (0.04 mole, 1 equiv.) of N, N′-Dimethyldodecylamine (**3**) was mixed with 5.1 g (0.044 mole, 1.1 equiv.) of sodium chloroacetate (**4**) in 50 mL methanol/water mixture (1:3, v/v) and was refluxed for overnight at 78-80℃. The solvent was removed in vacuo and the residue was dissolved in dry acetone and filtered to remove unreacted **4** and salt so formed. The filtrate was collected and the acetone was removed in *vacuo* to get the desired product **1** as a highly viscous and colourless liquid (Scheme 1).

Yield: (10.04 g, 93%). IR: 3417 (broad peak), 2919, 2851, 1620 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.90 [t, 3H, *J* 8Hz, **$\underline{CH_3}$**$(CH_2)_{11}$-], 1.27– 1.33 [m, 18H, CH_3**$\underline{(CH_2)_9}$**-CH_2-CH_2-], 1.70 [br s, 2H, $CH_3(CH_2)_9$-**$\underline{CH_2}$**-CH_2-N-], 3.29 (s, 6H, (**$\underline{CH_3)_2}$**N-), 3.56-3.58 (m, 2H, $CH_3(CH_2)_{10}$-**$\underline{CH_2}$**-N-), 4.36 [s, 2H, -N-**$\underline{CH_2}$**-COO-]. ^{13}C NMR (100 MHz) δ (ppm): 14.12, 22.72, 22.88, 26.51, 29.45, 29.74, 29.74, 29.75, 29.81, 31.97, 42.76, 51.32, 57.98, 64.06, 64.36, 167.72.

Scheme 1



Scheme 1. Reaction condition, a: refluxed for overnight at 78-80°C in methanol/water mixture (1:3, v/v).

Synthesis and characterization of zwitterionic gemini surfactant 1,2-Bis[N-methyl-N-carboxymethyltetradecylammonium] ethane (2):

Zwitterionic gemini surfactant 2 was prepared via 2 steps (a & b) as follows:

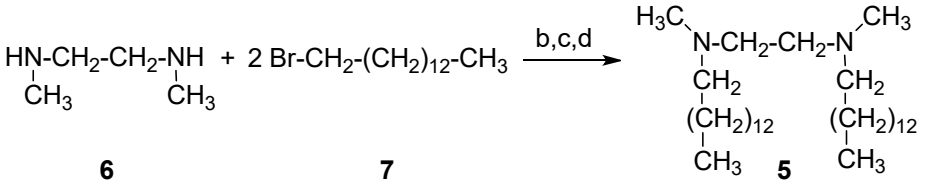
a. Synthesis of N, N$^{/}$-dimethyl-N, N$^{/}$-bis-(tetradecyl)-ethylenediamine (**5**)

To a stirred solution of N, N′-Dimethylethylenediamine (**6**, 0.025 mol, 2.2 g, 1 eq.v.) in 20 mL dry ethanol, 1-bromotetradecane (**7**, 0.055 mol, 16 g, 1.1 equivalent) and 3 g NaOH were added and the resulting mixture was refluxed for overnight at 78°C. The resulting solution was filtered to remove the inorganic salt so formed. The filtrate was quenched with 10 mL conc. hydrochloric acid, yielding hydrochloride salt of N, N′-Dimethyl-N, N′-bis-(tetradecyl)-ethylenediamine (**5**) as a white solid. After washing the solid with chloroform, it was dissolved in 30 mL 10% aqueous NaOH solution at room temperature. The upper organic layer was collected and washed three times with brine. It was then dried in vacuum to get the desired product **5** as a white solid (Scheme 2).

Yield: (11.65 g, 78%). IR: 2955, 2932, 2852, 1470 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.90 [t, 6H, *J* 8 Hz, 2C**H$_3$**$(CH_2)_{11}$-], 1.27- 1.33 [m, 44H, $2CH_3$**$(CH_2)_{11}$**CH_2-], 1.44- 1.48 [m, 4H,

$2CH_3(CH_2)_{11}\underline{\mathbf{CH_2}}CH_2N$-], 2.25 [s, 6H, $2CH_2N\mathbf{CH_3}$], 2.31- 2.34 [t, 4H, *J* 4.5 Hz, $2CH_3(CH_2)_{11}CH_2\mathbf{CH_2}N$] and 2.46 [s, 4H, $N\mathbf{CH_2CH_2}N$].

Scheme 2



Scheme 2. Reaction condition b: NaOH/ refluxed for overnight in dry EtOH at 78°C; c: concentrated HCl; d: 10% NaOH at room temperature.

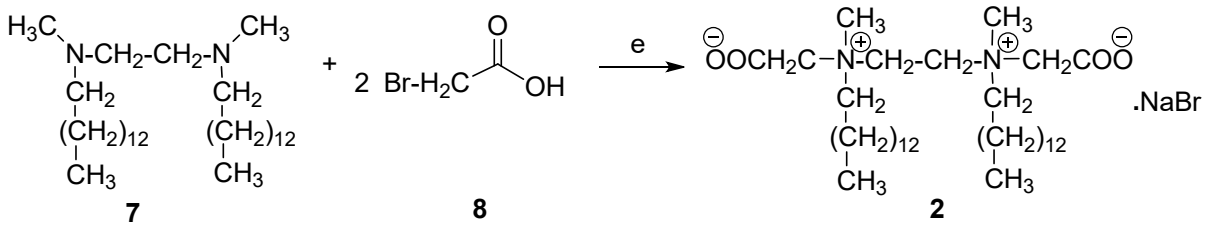
b. Synthesis of 1,2-bis[N-methyl-N-carboxymethyltetradecylammonium] ethane (2)

To a stirred solution of 2-bromoacetic acid (0.05 mol, 7 g) in 50 mL methanol, NaOH (0.05 mol, 2 g) was added in batches under an ice bath. The temperature of the reaction bath was then slowly raised to 50°C and then cooled to room temperature after 30 min. Afterwards, N, N/-dimethyl-N, N/-bis-(tetradecyl)-ethylenediamine (**5**) (0.025 mol, 2 g) and 0.4 g KI were added dropwise to the reaction mixture. The mixture was refluxed for 4 days, then cooled to room temperature and filtered to remove insoluble materials. The filtrate was evaporated under reduced pressure. The residue was then dissolved in 20 mL of 2-propanol and was filtered. The filtrate after crystallization gave the desired product 1,2-bis[N-methyl-N-carboxymethyltetradecyl-ammonium] ethane (**2**) as a colourless solid (Scheme 3).

Yield: (7.55 g, 53%). IR: 3435 (broad peak), 2920, 2851, 1627 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ 0.80 [t, 6H, *J* 8 Hz, $2(\underline{\mathbf{CH_3}}(CH_2)_{13}$-)], 1.19–1.31 [m, 44H, $2(CH_3\underline{\mathbf{(CH_2)_{11}}}$-$CH_2$-$CH_2$-)], 1.70 [m, 4H, $2(CH_3(CH_2)_{11}$-$\underline{\mathbf{CH_2}}$-$CH_2$-N-)], 3.22 [s, 6H, $2(\underline{\mathbf{CH_3}}$N-)], 3.53 [m, 4H, $2(CH_3(CH_2)_{12}$-

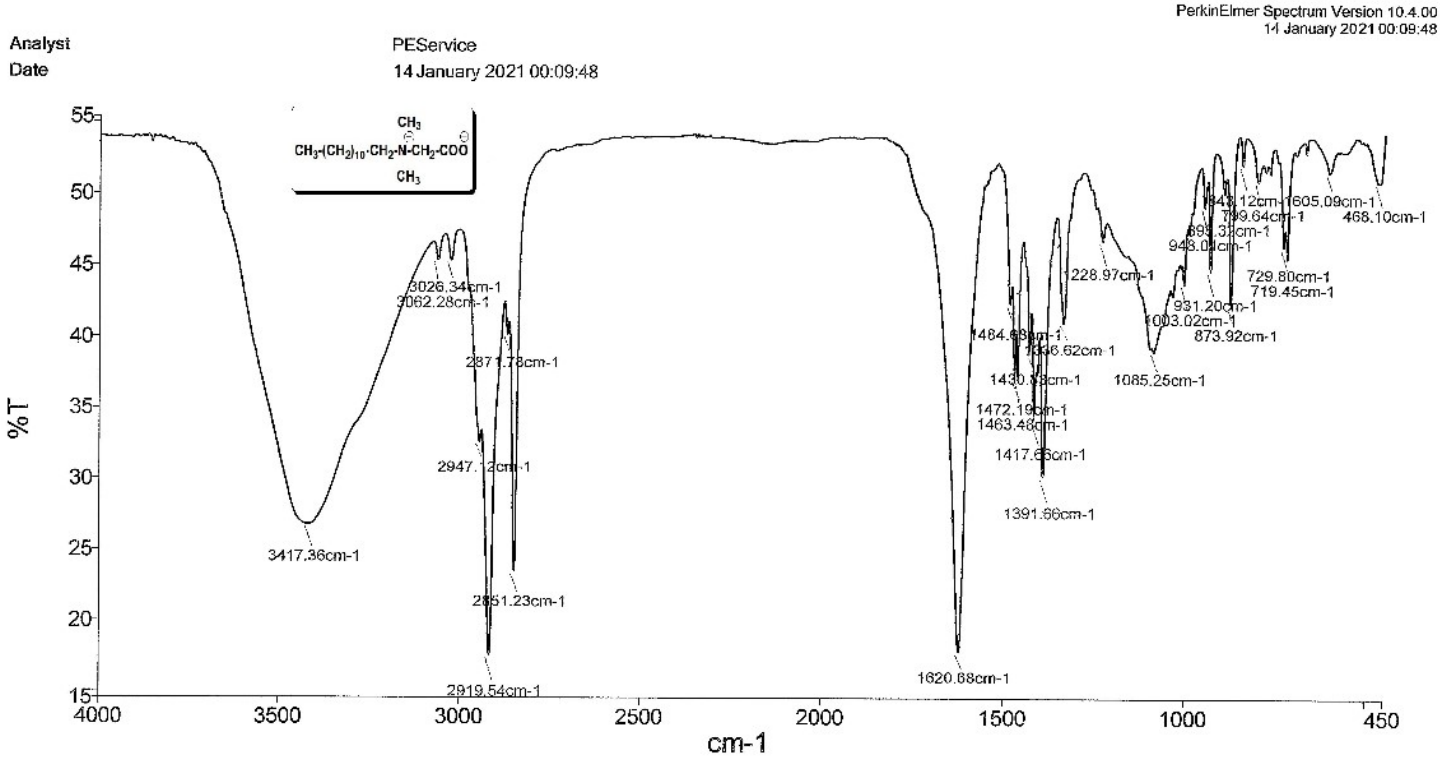
$\underline{CH_2}$-N-)], 3.80 [s, 4H, -N**$\underline{CH_2CH_2}$**N-], 4.19 [s, 4H, 2(-N-**$\underline{CH_2}$**-COO-)]. ^{13}C NMR (100 MHz) δ (ppm): 13.08, 20.87, 22.09, 22.34, 26.01, 28.87, 29.08, 29.21, 29.27, 29.36, 29.40, 31.67, 48.83, 53.09, 61.33, 61.49, 63.76, 167.03.

Scheme 3



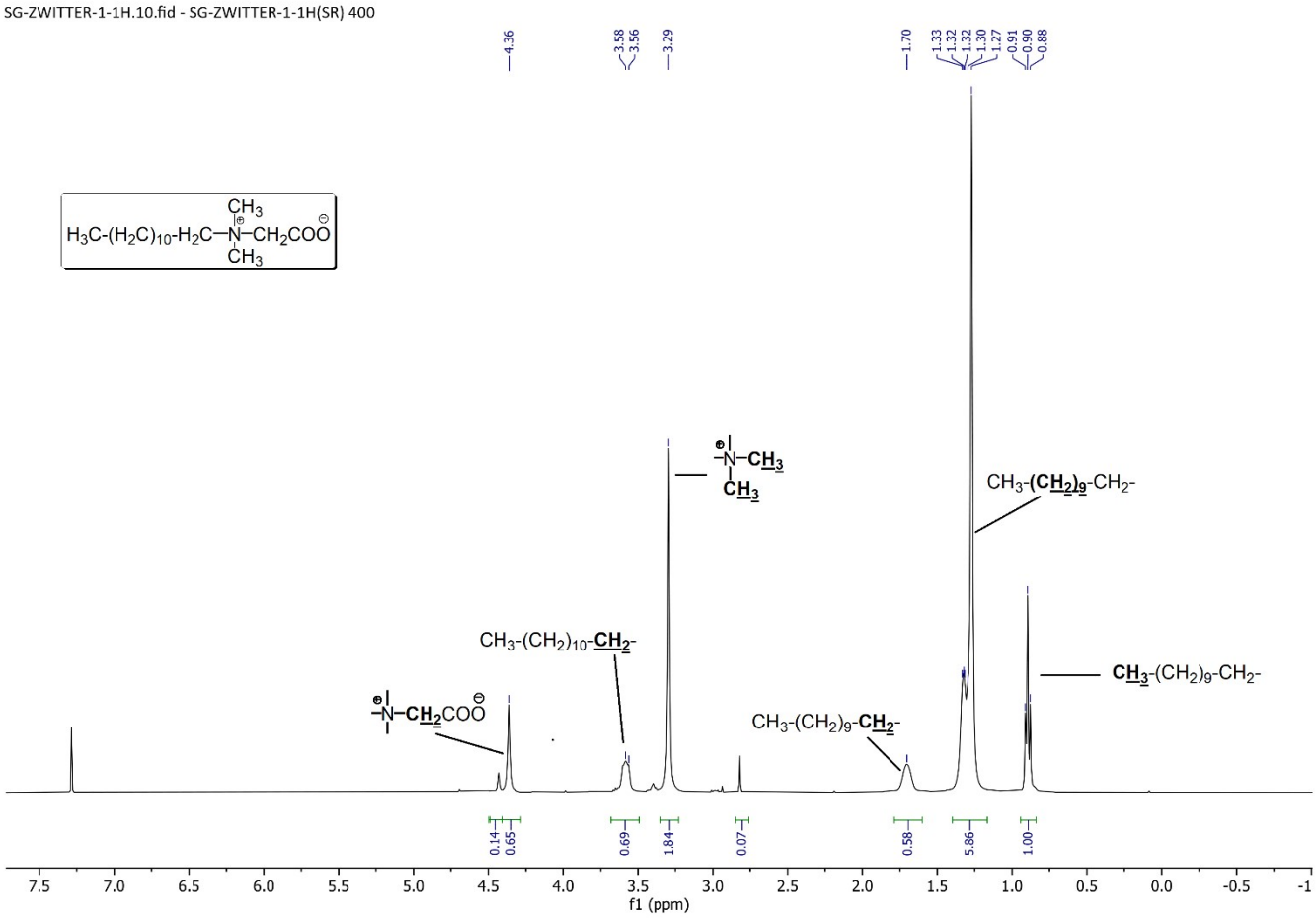
Scheme 3. Reaction condition, e: NaOH & KI/ refluxed for 60 h in MeOH.

FT-IR spectrum of zwitterionic surfactant: N-Dodecyl-N,N-dimethyl-2-ammonio-1-ethanecarbonate (1)

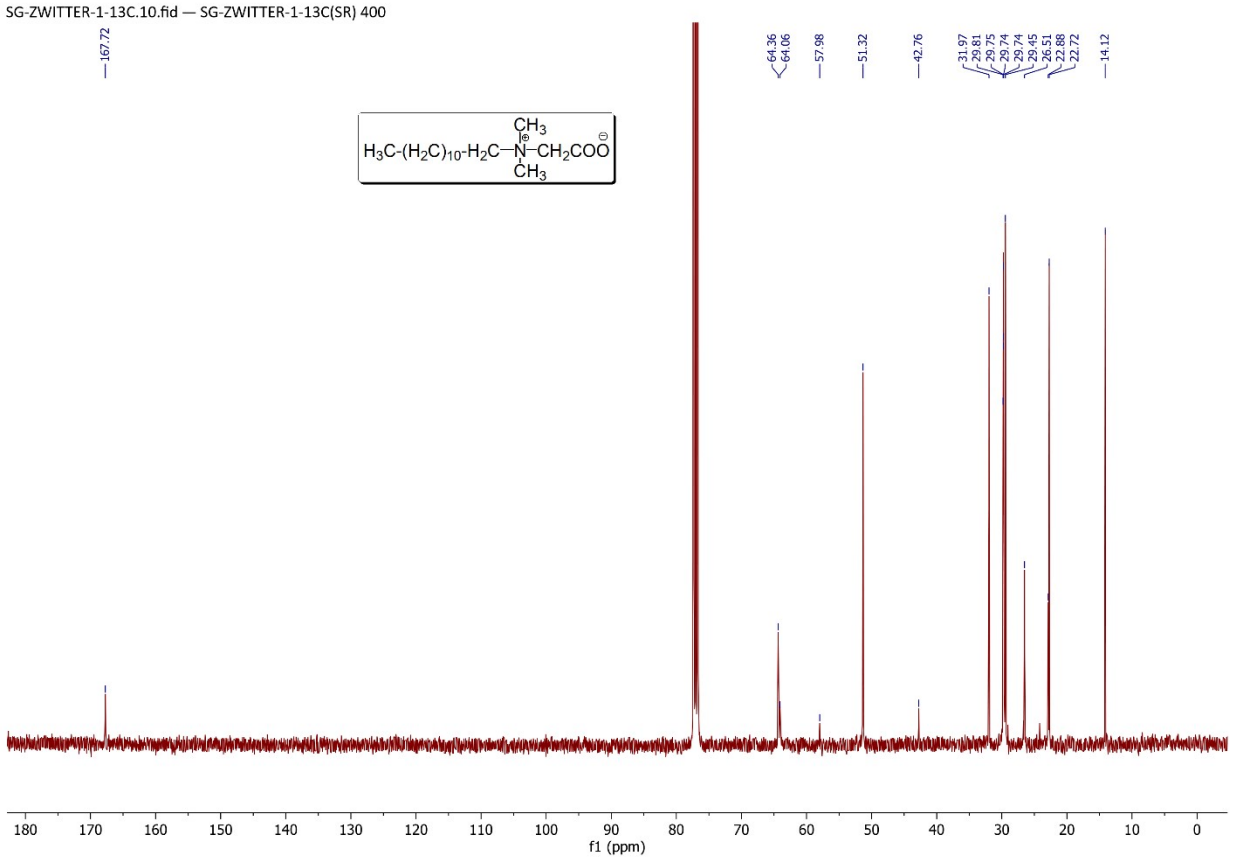


FT-IR Spectrum of N-Dodecyl-N,N-dimethyl-2-ammonio-1-ethanecarbonate

^{1}H-NMR spectrum of zwitterionic surfactant: N-Dodecyl-N,N-dimethyl-2-ammonio-1-ethanecarbonate (1)

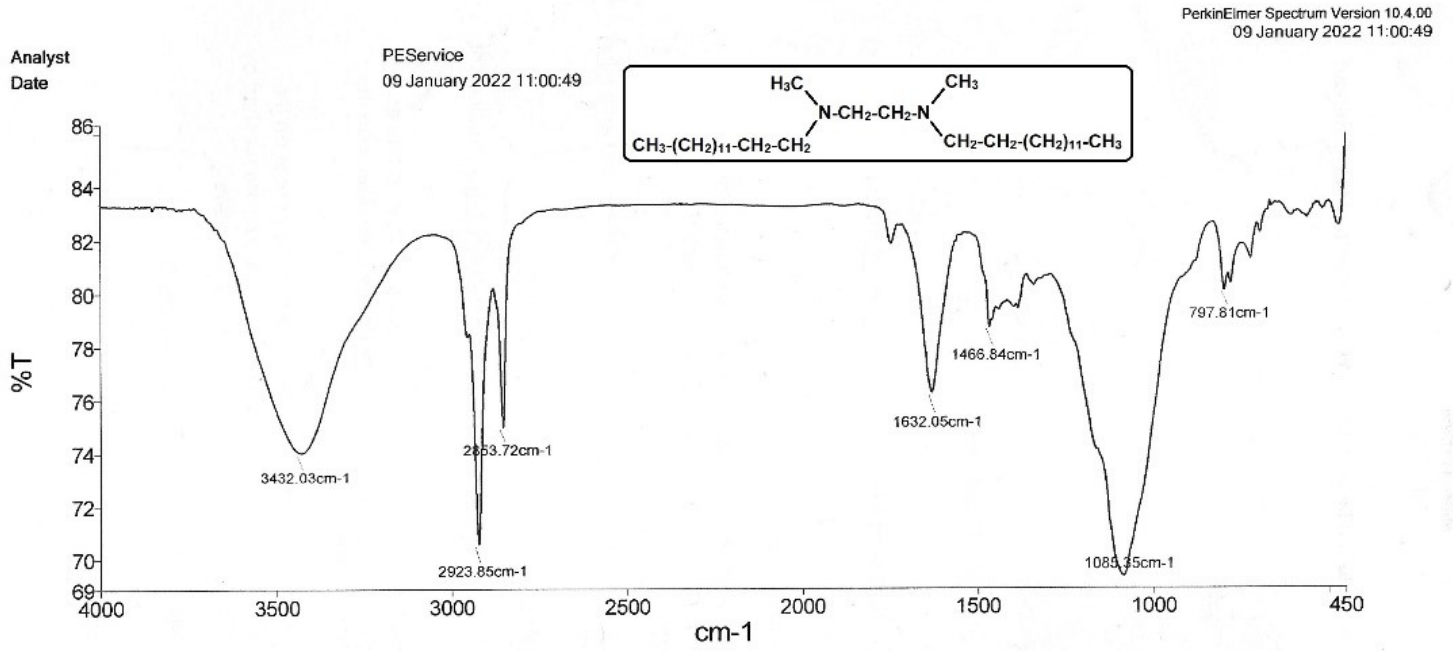


^{13}C-NMR spectrum of zwitterionic surfactant: N-Dodecyl-N,N-dimethyl-2-ammonio-1-ethanecarbonate (1)

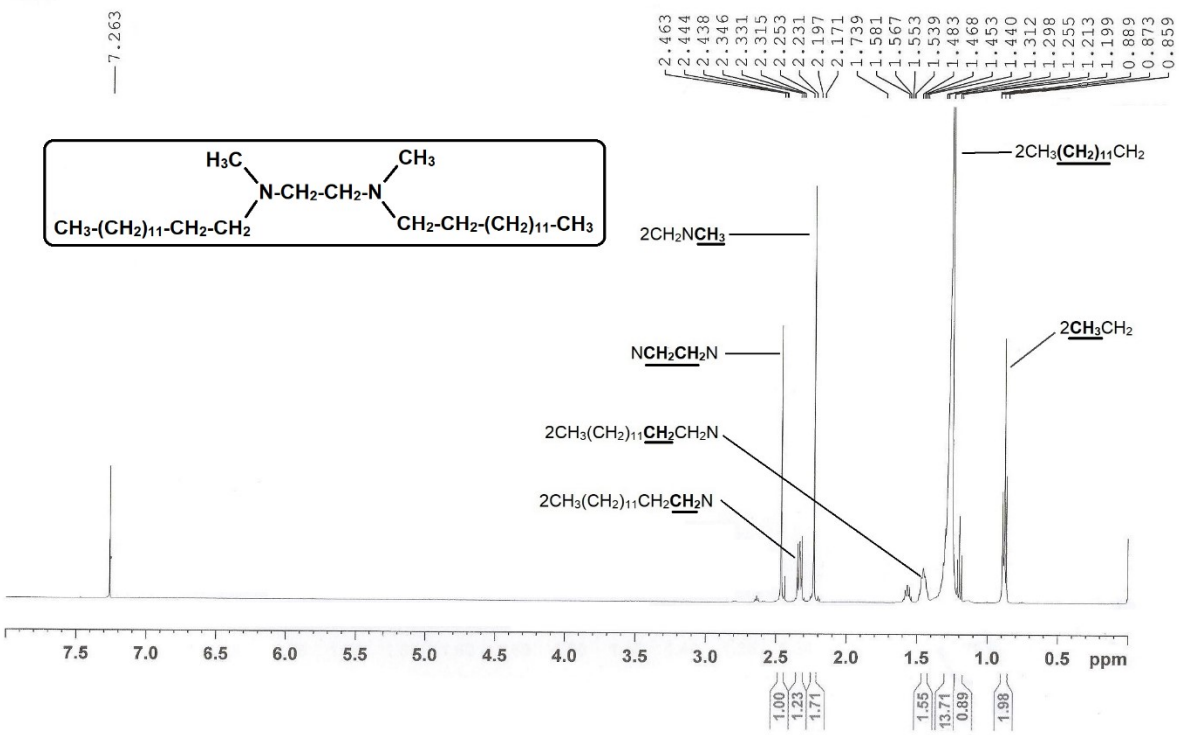


Synthesis and characterization of zwitterionic gemini surfactant 1,2-Bis[N-methyl-N-carboxymethyltetradecylammonium] ethane (2):

FT-IR spectrum of N, N/-dimethyl-N, N/-bis-(tetradecyl)-ethylenediamine (5)

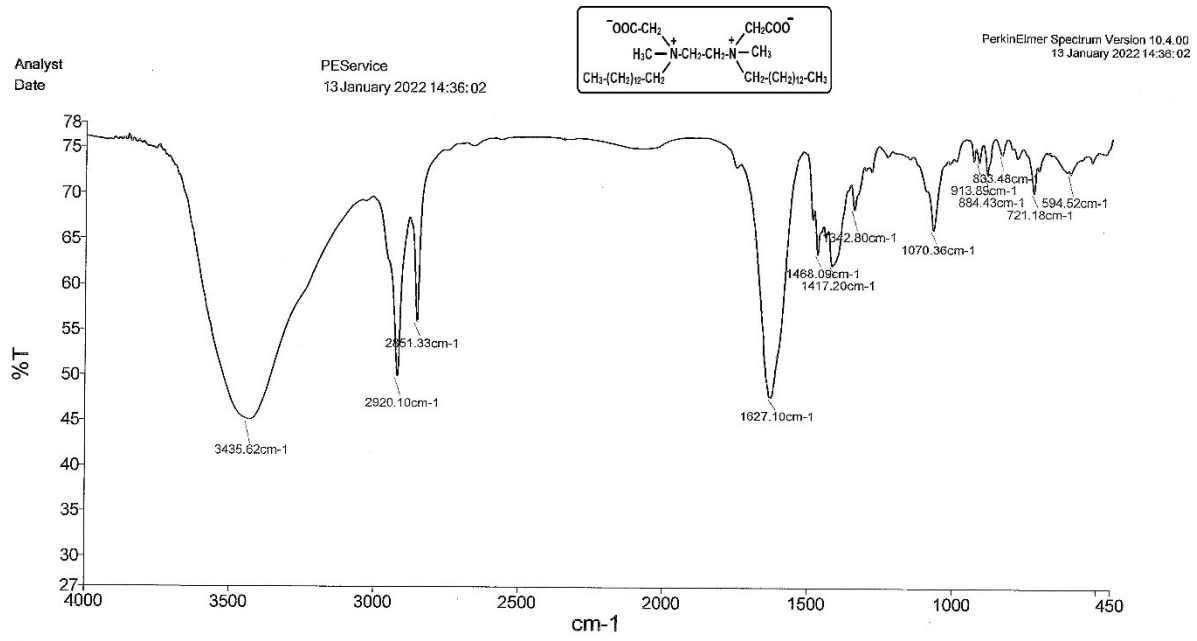


^{1}H-NMR spectrum of N, N$^{/}$-dimethyl-N, N$^{/}$-bis-(tetradecyl)-ethylenediamine (5)



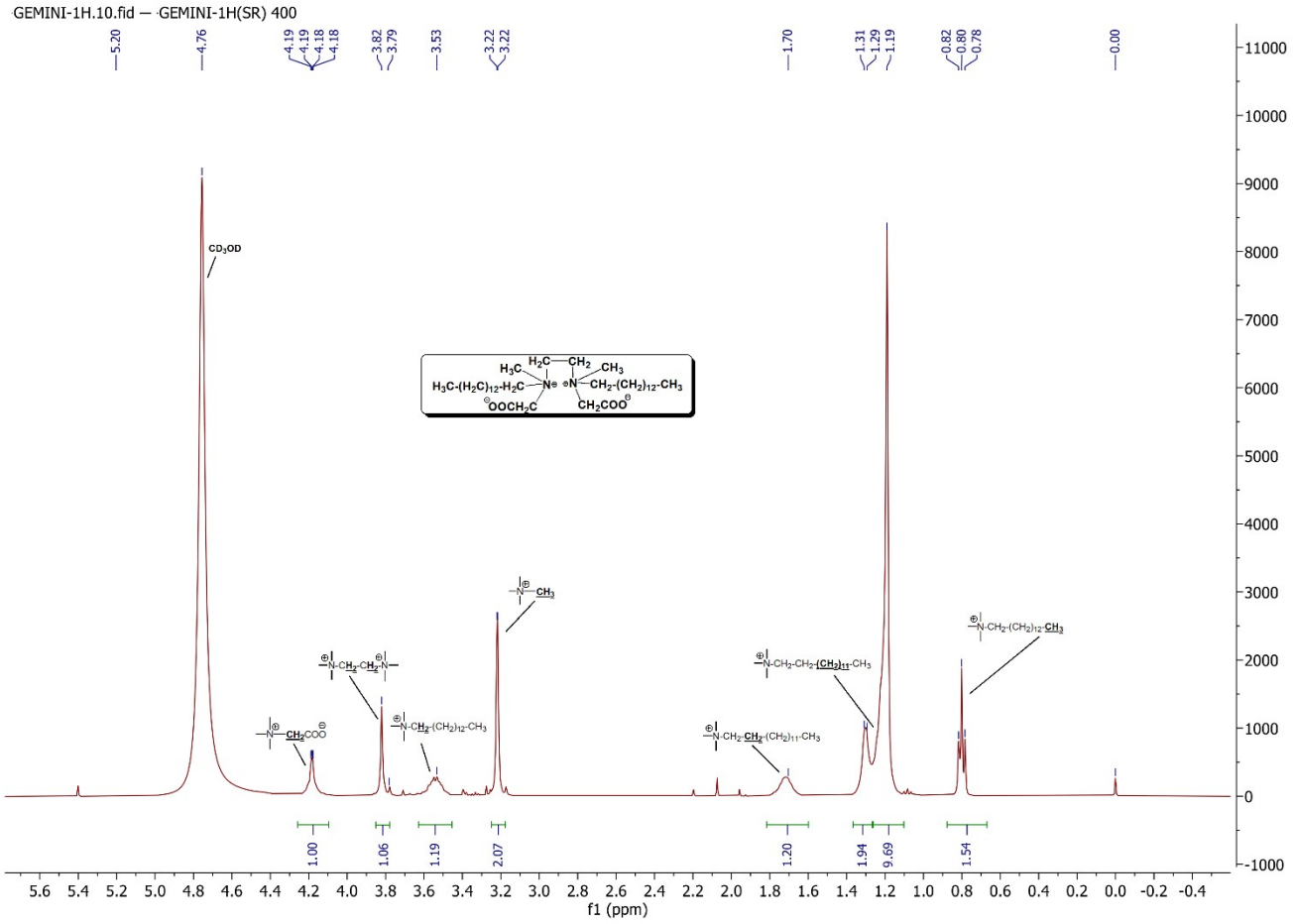
b. Synthesis of 1,2-bis[N-methyl-N-carboxymethyltetradecylammonium] ethane (2)

FT-IR spectrum of 1,2-bis[N-methyl-N-carboxymethyltetradecylammonium] ethane (2)



FT-IR of N,N′-Dimethyl-N,N′-bis-(tetradecyl)-ethylenediamine

^{1}H-NMR spectrum of 1,2-bis[N-methyl-N-carboxymethyltetradecylammonium] ethane (2)



^{13}C-NMR spectrum of 1,2-bis[N-methyl-N-carboxymethyltetradecylammonium] ethane (2)

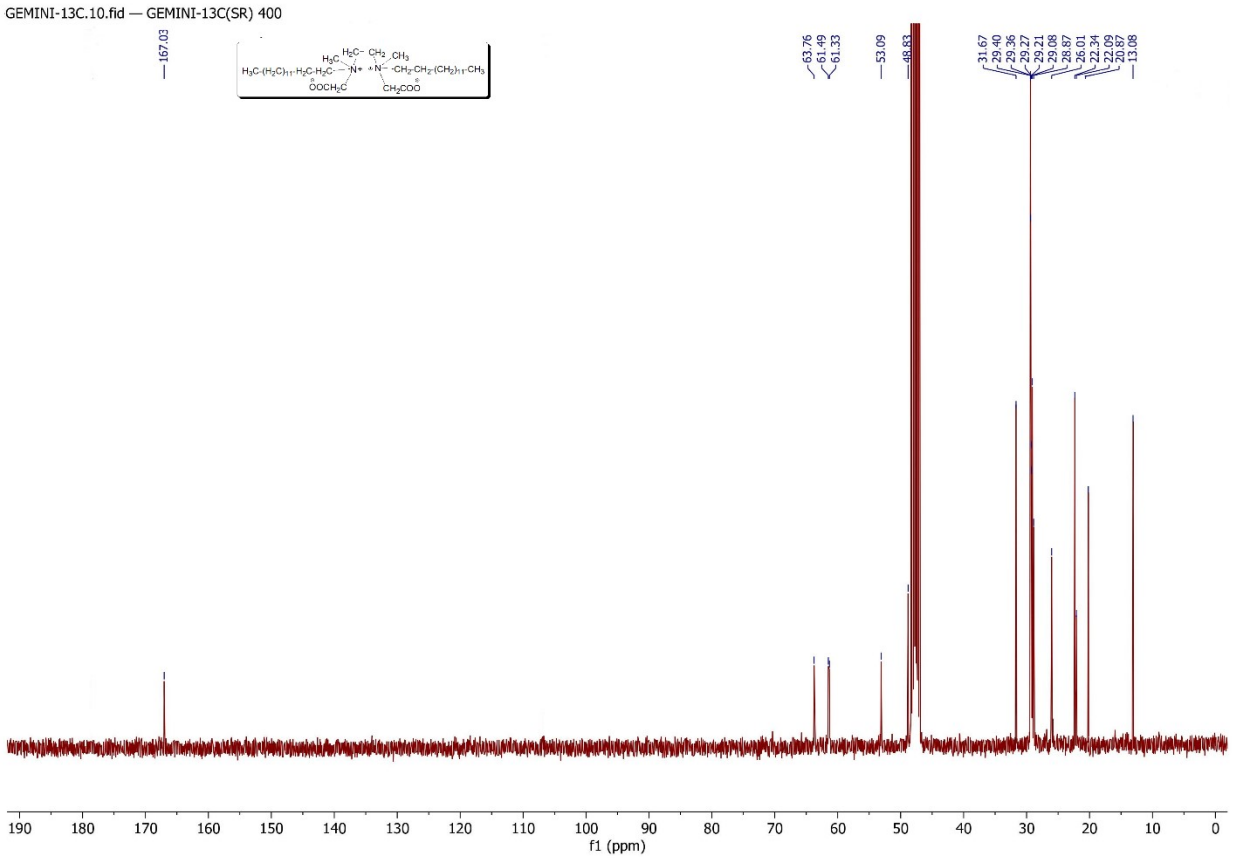
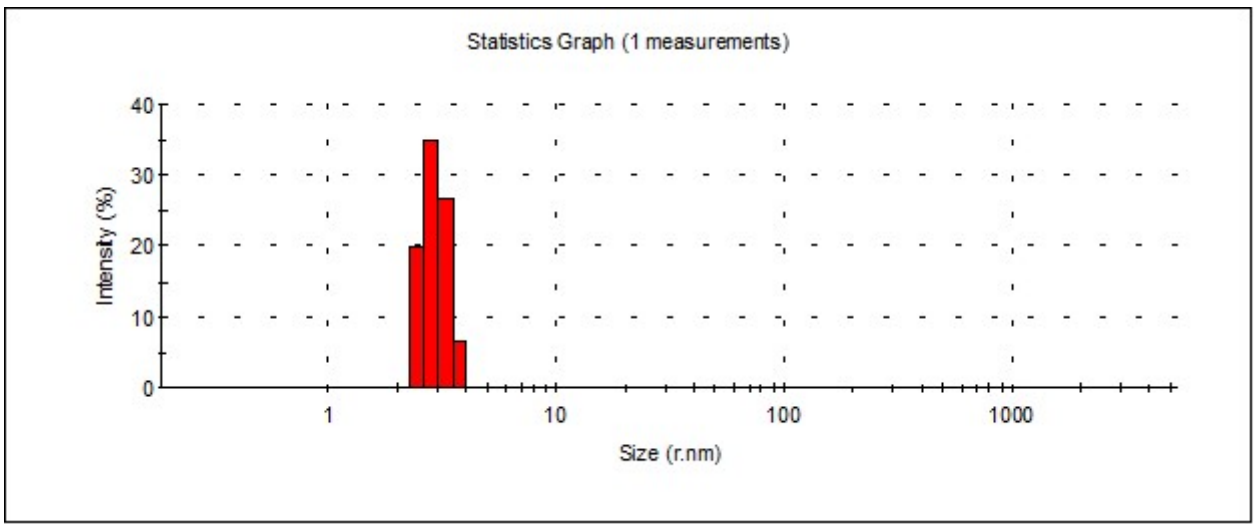


Table S1. Detailed calculation of Packing Parameter.

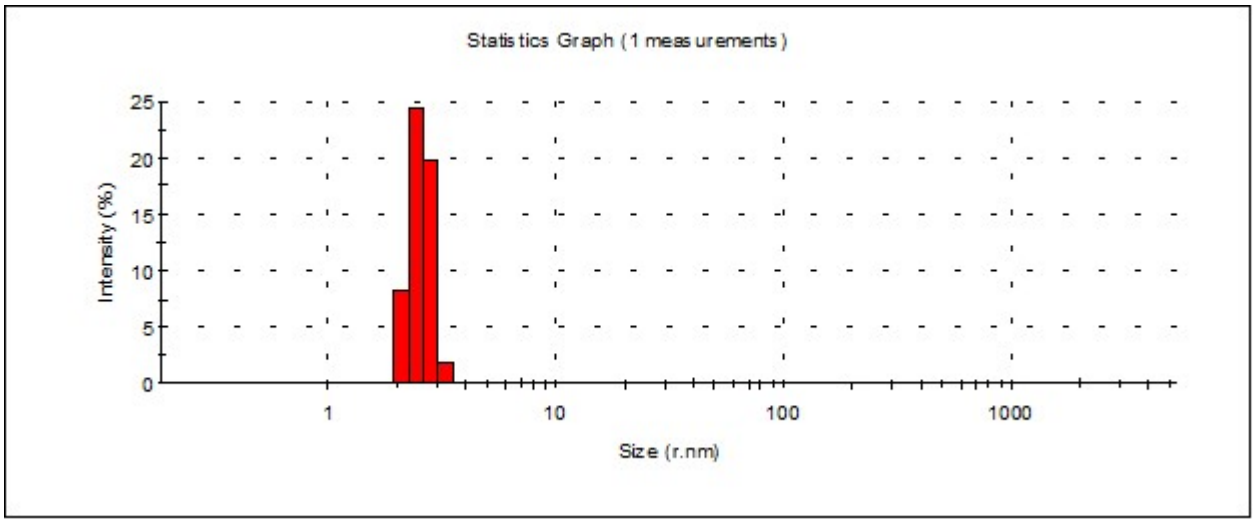
α_{CPZ}	$l_c \leq l_{max}$	v	A_{min}	P
CPZ/C_{12}DmCB				
0.0	1.672	0.350	0.42	0.50
0.2	1.672	0.377	0.49	0.45
0.4	1.672	0.404	0.53	0.46
0.6	1.672	0.431	1.03	0.25
0.8	1.672	0.458	2.09	0.13
1.0	1.039	0.485	2.14	0.21
CPZ/C_{14}Ab				
0.0	1.925	0.404	0.23	0.92
0.2	1.925	0.420	0.33	0.66
0.4	1.925	0.436	0.47	0.48
0.6	1.925	0.452	0.46	0.51
0.8	1.925	0.468	0.58	0.42
1.0	1.039	0.484	2.14	0.21

Dynamic light scattering (DLS) size distribution plots of CPZ/C_{12}DmCB system

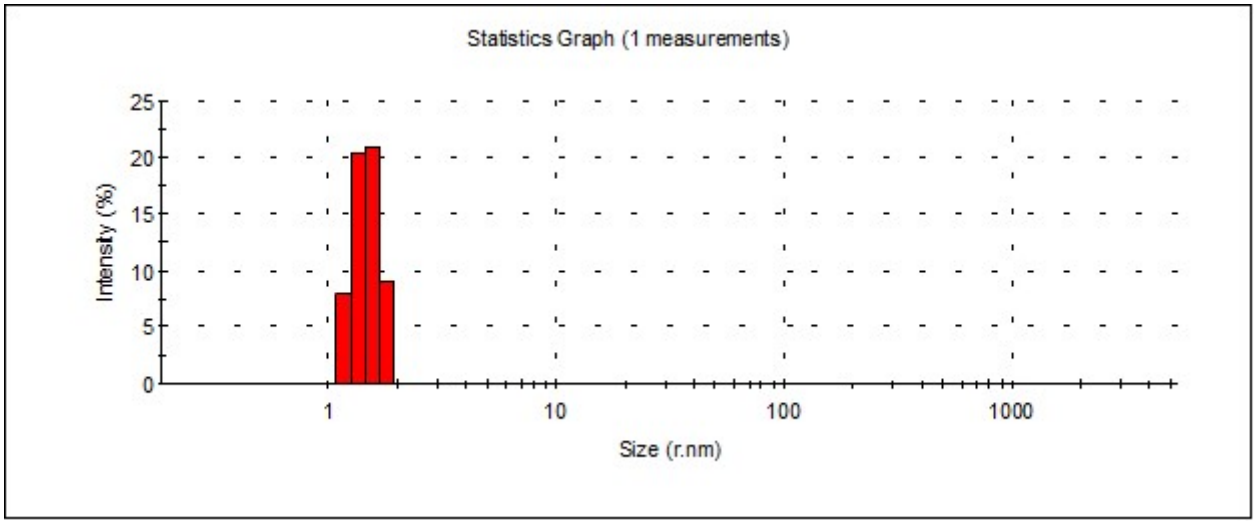


$\alpha_{CPZ} = 0$

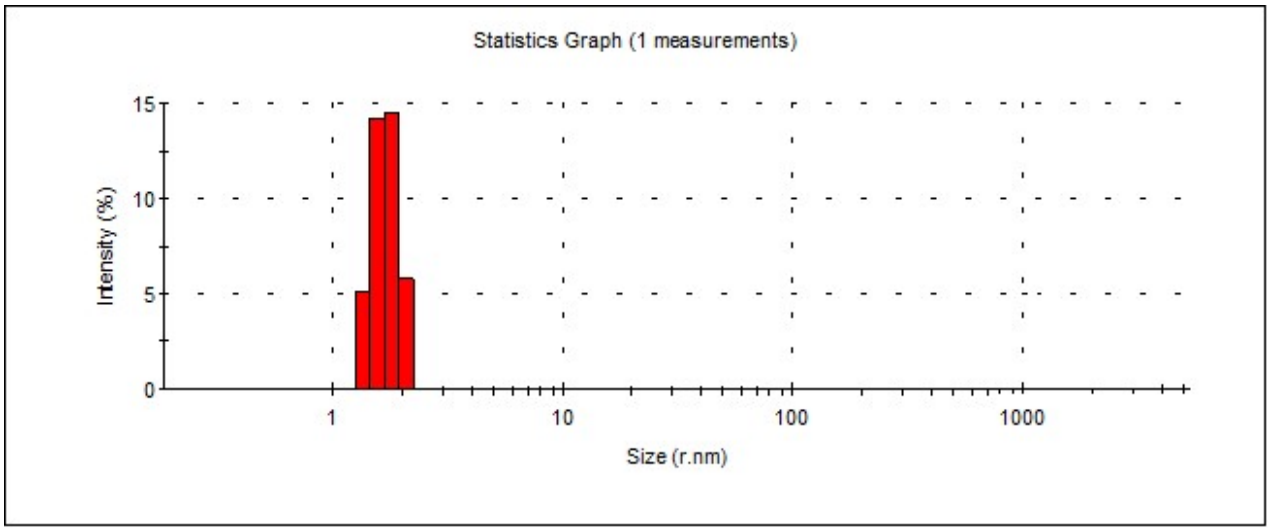
$\alpha_{CPZ} = 0.2$



$\alpha_{CPZ} = 0.6$

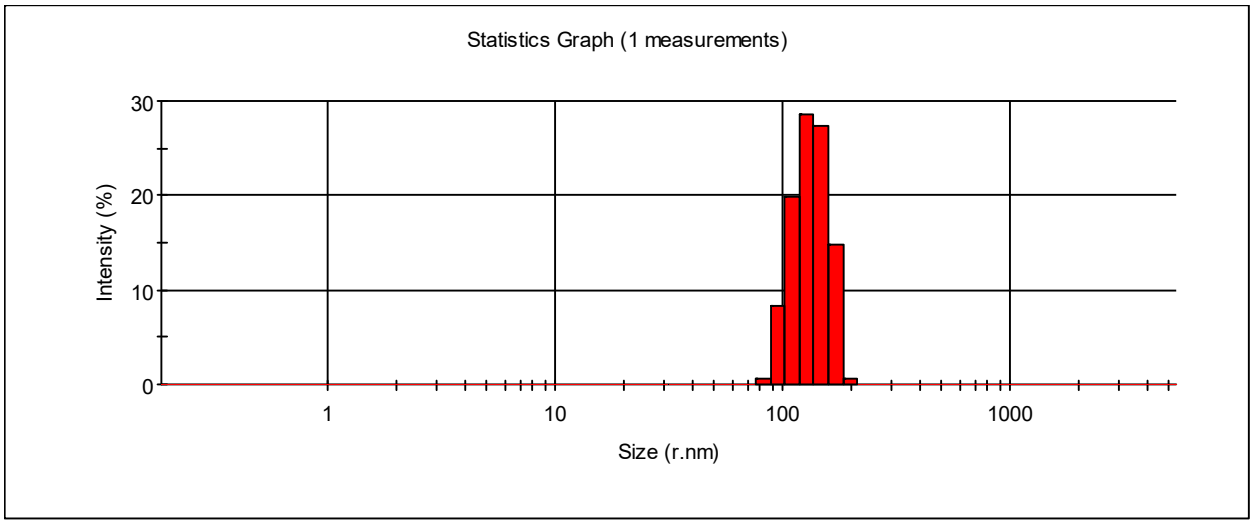


$\alpha_{CPZ} = 0.8$



Dynamic light scattering (DLS) size distribution plots of CPZ/C_{14}Ab system

$\alpha_{CPZ} = 0$


Statistics Graph (1 measurements)
Intensity (%)
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20
10
0
1
10
100
1000
Size (r.nm)

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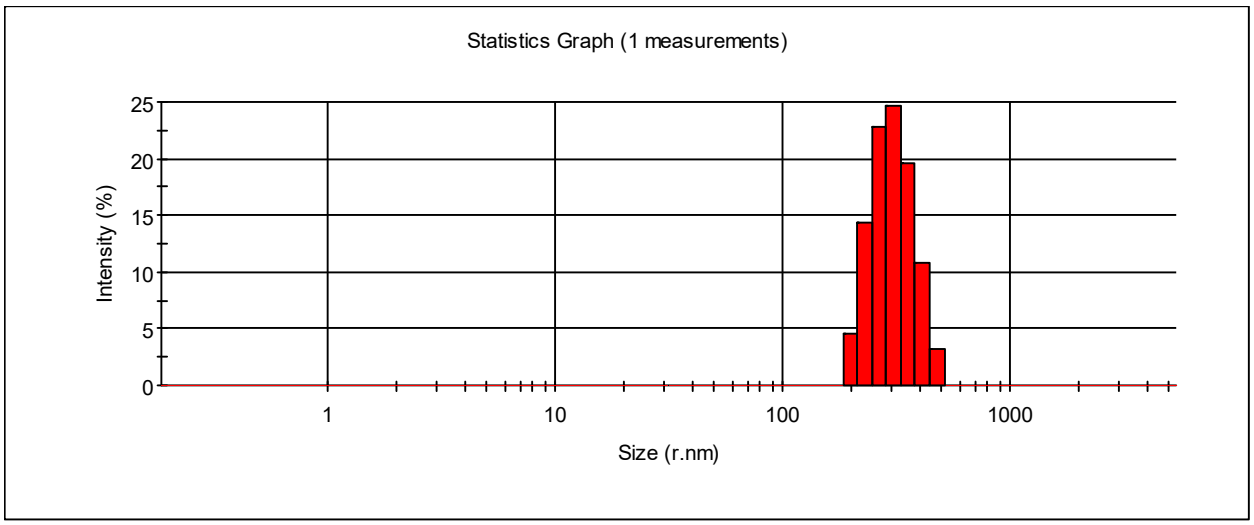
Statistics Graph (1 measurements)
Intensity (%)
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20
15
10
5
0
1
10
100
1000
Size (r.nm)

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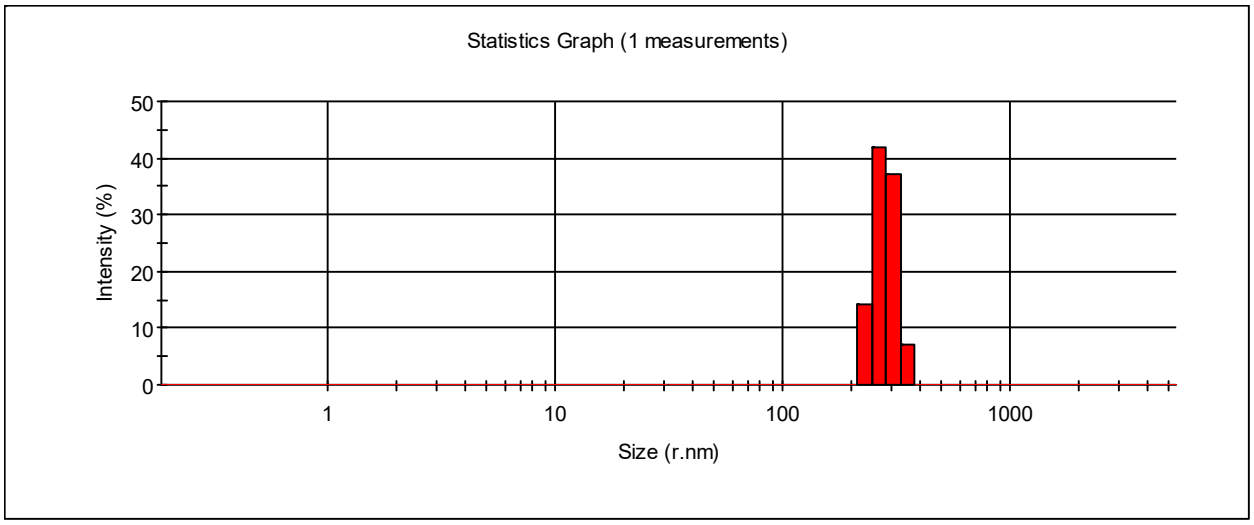

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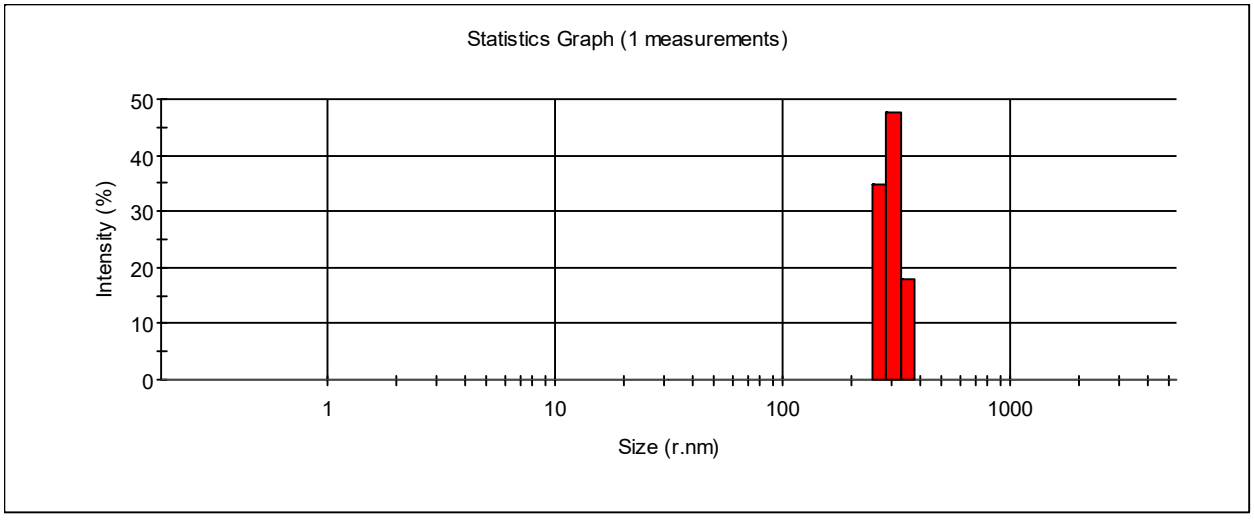

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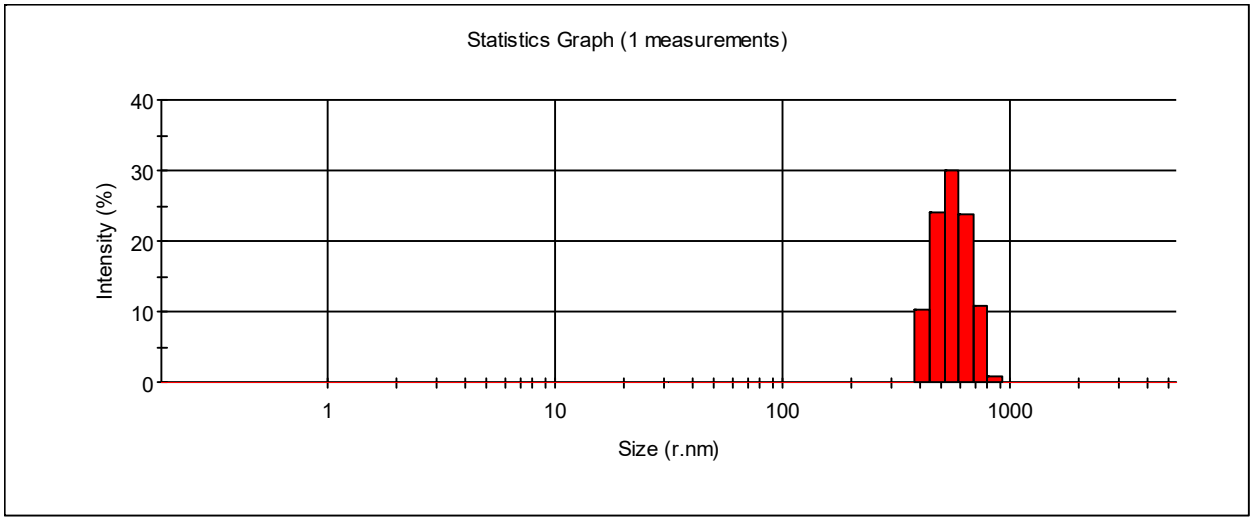

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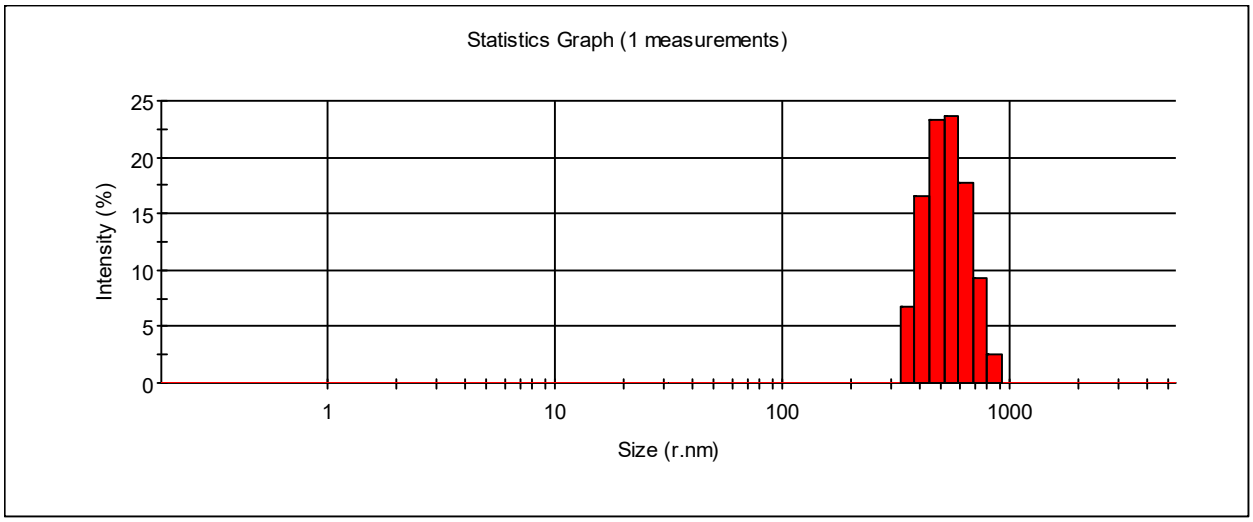

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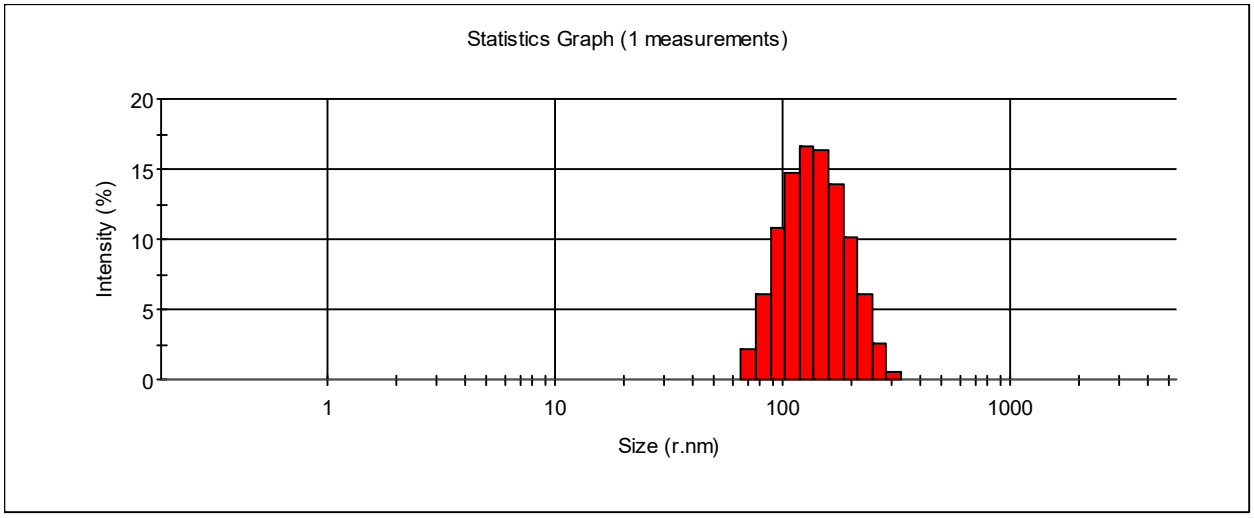
Statistics Graph (1 measurements)
Intensity (%)
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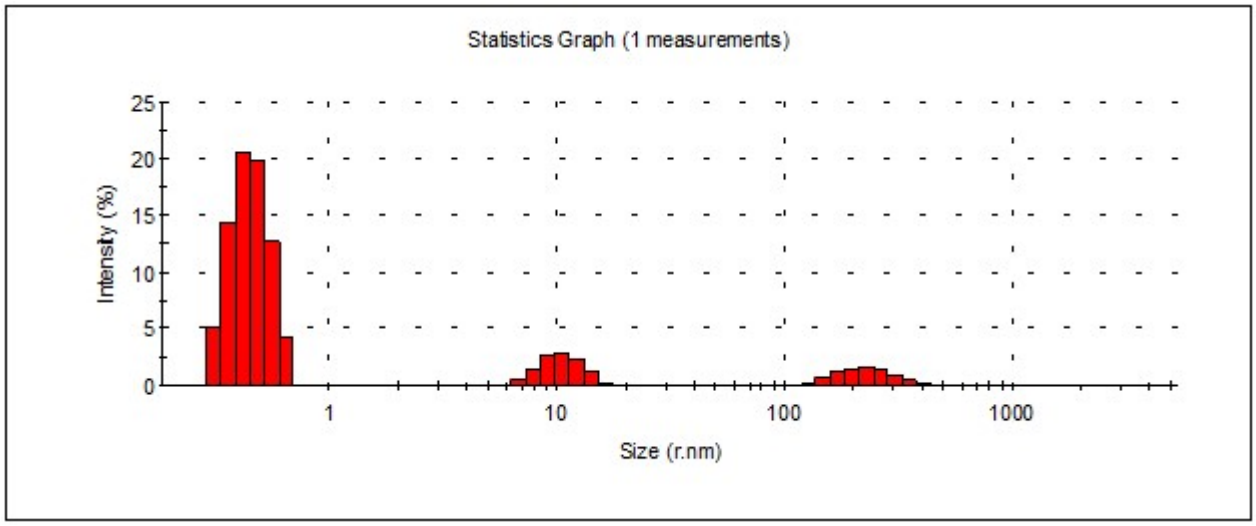
15
10
5
0
1
10
100
1000
Size (r.nm)


Statistics Graph (1 measurements)
Intensity (%)
25
20
15
10
5
0
1
10
100
1000
Size (r.nm)

$\alpha_{CPZ} = 1.0$