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Synthesis of Oligo-β-Alanine-Based Surfactant via Cobalt-Catalyzed Carbonylation and Surface Activity Study

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Synthesis of a novel surfactant with an oligo-β-alanine hydrophilic headgroup was achieved via the carbonylative oligomerization of aziridine followed by coupling with *n*-octylamine in one pot. The chemical structure of the surfactant was confirmed by NMR and MALDI MS. Preliminary studies on its surface properties, including surface tension measurement and its adsorption on polystyrene latex particles, are reported.

Keywords: Oligo-β-alanine, carbonylation, surfactant.

1 Introduction

Peptide-based surfactants both from natural and synthetic origins have attracted increasing attention (1–4). One important feature of these surfactants is their ability to self-assemble into a range of remarkable supramolecular structures through hydrogen bonding. We have developed the carbonylative polymerization of aziridine as a novel route for the synthesis of poly-β-alanine and poly-β-alanoids (5–10). Because oligo-β-alanines are extraordinarily prone to form β-sheets in the solid state (11–14), but exist in disordered forms in aqueous solution (15), we set out to apply the carbonylative polymerization for the synthesis of oligo-β-alanine-based surfactants. We report here the synthesis and preliminary study of the surface activity of the β-alanine-based surfactant.

2 Experimental

2.1 Materials

All operations were conducted with Schlenk line and glove box techniques under a N_2 environment, except where CO is specified. Hydrocarbon solvents were dried by refluxing over sodium in the presence of benzophenone and distilled before use. Aziridine (**1**) was synthesized following literature procedures (16) and dried by stirring over Na/K alloy at -78°C until the liquid turned blue, at which point, the temperature was allowed to rise, and **1** was immediately vacuum-transferred into a flask containing baked NaOH pellets. *N*-Octylamine (**2**) was purchased from Aldrich, distilled, and dried over CaO before use. The pre-catalyst, $HCo(CO)_3PPh_3$(**3**), was generated in situ using the established method (7). Note that aziridine is highly toxic. All aziridine containers or wastes containing aziridine were treated with concentrated HCl to destroy residual aziridine.

2.2 Measurements

The NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer using hexafluoroisopropanol-d_4 as the solvent. The surface properties of the surfactants were determined using a SensaDyne 6000 bubble tensiometer. Conductivity was measured using a conductivity probe (Vernier Software, CON-DIN), which was calibrated with 100 mg/L sodium chloride and deionized water in 0∼200 μS range. The conductivity probe was connected to a laptop (AST, Ascentia J20). The MALDI MS spectra were obtained using a Bruker Biflex III TOF spectrometer. Dithranol was used as the matrix compound. The samples are prepared by milling the matrix and the analyte together in the solid state (17).

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Table 1. Synthesis of surfactant using $HCo(CO)_3PPh_3$(3) as catalyst[a]

				Water-Soluble Fraction		*Water-Insoluble Fraction*	
Entry	***1*** *(g)*	***1: 2: 3*** *(molar ratio)*	*Reaction Time (h)*	*yield (g)*	n^d	yield (g)	n^d
1	1.37	8 : 1 : 1	16	0.67	9.8	0.70	5.5
2	1.49	8 : 1 : 1	16	0.69	10.5	0.67	5.4
3[b]	1.42	8 : 1 : 1	16 + 7.25	0.71	10.1	0.97	4.9
4[c]	1.19	20 : 1 : 1	10×0.5 + 16	0.54	11.9	0.35	5.3
5[c]	1.20	20 : 1 : 1	10×0.5 + 16	0.58	13.7	0.28	6.0

[a]In 200 mL THF, at 60°C, with a CO pressure of 1000 psi; [b] Aziridine was added in 2 equal portions; [c]Aziridine was added in 10 equal portions, with 30 min between additions and left to react for 16 h after the final addition; [d]Average number of β-alanine units in the hydrophilic segment.

2.3 Synthetic Procedure for Addition of Aziridine at Once

In a typical experiment, the *in situ* generated solution of **3** in THF (25 mL) was transferred into a 300-mL Parr high-pressure reactor under CO flow with a syringe. A subsequent aliquot of THF (125 mL) was also added to the reactor under CO flow with a syringe. Aziridine **1** (1.51 g, 34.9 mmol) was vacuum-transferred from a storage flask into a graduated tube. *n*-Octylamine **2** (0.268 g, 4.37 mmol) was then syringed from a storage flask. Both were added under N_2 flow to a Schlenk flask containing 50 mL of THF. The solution of **1** and **2** was transferred into the autoclave with a syringe under CO flow. The autoclave was immediately closed, pressurized with CO, and placed in an oil-bath at 60°C. After the reaction lasted for the amount of time specified in Table 1, the pressure was released and the reactor was opened. The solid product was collected after filtration and dried in air. The filtered solid product was then fractionated by stirring the product over 100 mL of distilled water for 30 min followed by filtration. The water-insoluble fraction was washed by a small amount of distilled water and left to dry. Water was removed from the aqueous filtrate to yield the solid water-soluble product. The product was dried under vacuum at room temperature. The yields of the individual fractions are listed in Table 1.

2.4 Synthetic Procedure for Graduate Addition of Aziridine

In these experiments, the catalyst was generated in a Parr reactor stirred by a magnetic stirrer. The reactor was connected to a HPLC pump, which was used for addition of reactants under high pressure. Typically, sodium cobaltate (0.324 g, 1.67 mmol), *N*,*N*-dimethylanalinium chloride (0.219 g, 1.39 mmol), and triphenyl phosphine (0.364 g, 1.39

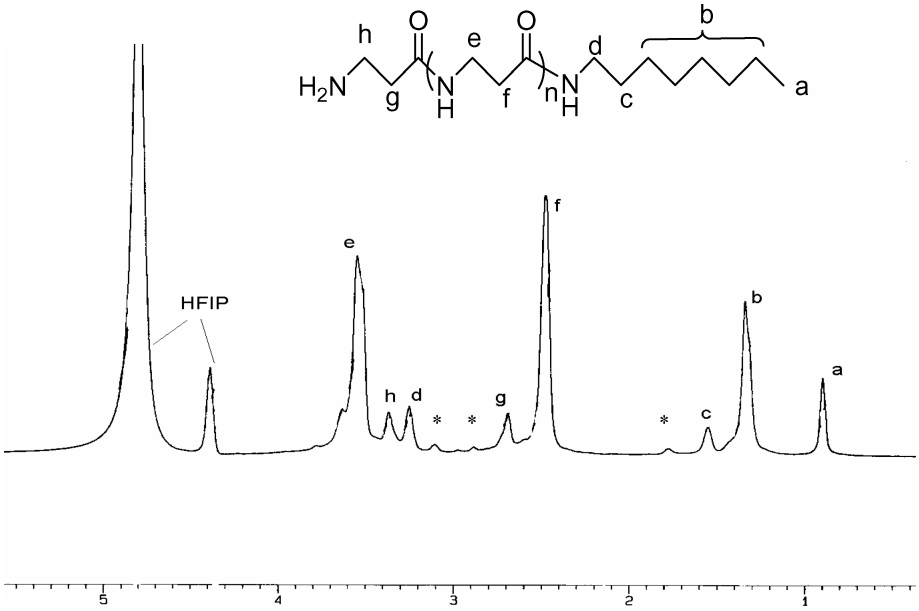


Fig. 1. ^{1}H-NMR spectrum (500 MHz in HFIP-d_4) of surfactant product (entry 1, **Table 1**). Small peaks labeled with asterisks are due to the presence of amine units.

mmol) was loaded into the 300 mL reactor under in a glove box. The reactor was closed, taken out of the glove box, and placed in a 0°C ice bath. THF (50 mL) was injected into the reactor under 1 atm of CO. The mixture was then stirred for 20 min at 0°C. While the catalyst solution was being stirred, **1** (1.20 g, 27.9 mmol) was vacuum-transferred from a storage flask into a graduated tube, and **2** (0.181 g or 1.39 mmol) was then syringed from a storage flask. Both were added to a Schlenk flask containing 50 mL of THF. After *in situ* generation of **1**, the reactor was removed from the ice bath and 75 mL of additional THF was injected into the autoclave. The THF solution of **1** and **2** was then added to the solvent reservoir of the HPLC pump under N_2 flow. The reactor was pressurized with CO and was placed into a preheated oil bath at 60°C. The THF solution of **1** and **2** was added to the reactor through the HPLC pump according to the time schedule defined in Table 1. After the final addition, a small amount of THF was pumped into the autoclave to flush any residual reactants from the pump system. The contents were then stirred for the amount of time specified in Table 1. Then, CO was released into the hood, and the autoclave was opened. The product was fractionated and collected as described above. The yields of the individual fractions are listed in Table 1.

2.5 Surfactant Purification for Surface Property Study

The water-soluble fraction was dissolved in hexafluoroisoproanol. The solution was filtered through a 0.45 μm filter to remove any inorganic particles such as decomposed catalyst and NaCl from *in situ* generation of **3**. The solvent was then removed under vacuum. The remaining off-white solid was washed with diethyl ether and dried in air.

2.6 Surfactant Adsorption on Latex Particles

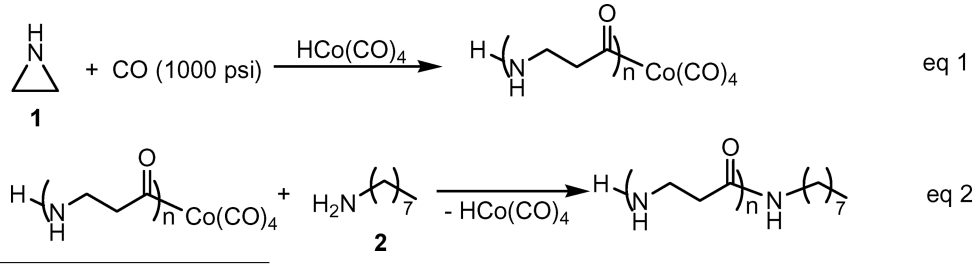
A monodisperse polystyrene latex suspension (Dow Chemical Co., D = 357 ± 5.6 nm, wt% = 44.65%) was used for surfactant adsorption tests. The latex particles were cleaned by analytical grade Bio-Rad anionic and cationic ion-exchange resins. The polystyrene latex was first diluted to 5 wt%. Then, the diluted latex was stirred with an excess amount of anionic (7.5 g) and cationic (7.5 g) ion-exchange resins. Old resins was replaced with new resins every 3 h. This was repeated 5 times. The conductivity of the diluted latex was recorded after each resin treatment and was 0.39 μs after the fifth cycle. The final solid content of the polystyrene latex suspension was 2.98%.

The polystyrene latex dispersion (8.5 mL) was added into a 16.5 cm long dialysis membrane tubing (Spectrum Laboratories, Inc, molecular porous membrane tubing, molecular weight cut-off = 12,000∼14,000). Two of the above dialysis tubes were placed in a 50 mL glass tube containing 26.8 g of the surfactant solution (0.0733 wt%). The conductivity of the solution outside of the dialysis membrane was recorded every 2 min at room temperature while the solution was magnetically stirred. To account the conductivity drop caused by dilution and other effects, a background control experiment was carried out. An identical amount of deionized water was added into the same dialysis membrane tubing in place of the polystyrene latex suspension.

3 Results and Discussion

3.1 Synthesis and Characterization of Surfactant

The synthesis of the hydrophilic segment of the target surfactant utilizes the cobalt-catalyzed copolymerization of aziridine (**1**) and CO, which we previously developed (Equation 1). The hydrophobic end of the surfactant was introduced by including *n*-octylamine (**2**) in the reaction mixture (Equation 2).



The carbonylative oligomerization of **1** and the coupling of the oligo-β-alanine segment with **2** can be achieved in one pot. The solid product was isolated by filtration. The results of the preparation of the amphiphilic oligomers are summarized in Table 1.

The solid product was further fractionated into water-soluble and water-insoluble fractions. The water-soluble fraction is the desired surface-active species. The presence of both the hydrophilic β-alanine unit and the hydrophobic *n*-octyl group in the water-soluble fraction is clearly shown by the ^{1}H-NMR spectrum (Figure 1). The assignments of the peaks are confirmed by the ^{13}C, COSY and HMQC NMR experiments (see Supporting Information). Based on ^{1}H-NMR integration, the average number of hydrophilic β-alanine repeating units in the water-soluble product is about 10 when the feed molar ratio of **1**:**2** was 8:1 in the catalytic reaction (entries 1–3, Table 1). Matrix Assisted Laser Desorption Mass Spectrometry (MALDI MS) of the water-soluble surfactant further confirmed that both the hydrophilic and hydrophobic segments were present in each water-soluble molecule. The peak with mass/charge ratio m/z = (71n + 129 + 1) and (71n + 129 + 23) can be assigned to the protonated and sodium complex of **A**,

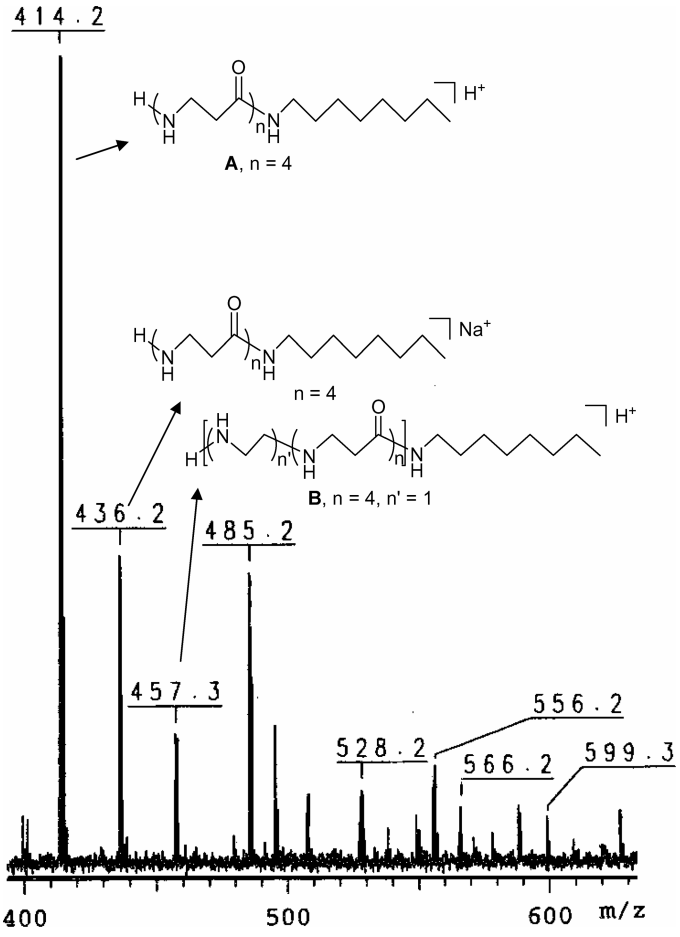


Fig. 2. MALDI-MS spectrum of surfactant product (entry 1, Table 1).

where n is the number of β-alanine units in the molecule (Figure 2). The strong bias toward the low molecule weight species with short β-alanine segments is likely due to the strong propensity of oligo-β-alanine to form the β-sheet secondary structure in the solid state (11–14). A minor peak with $m/z = (71n + 129 + 1 - 28)$ is also assignable to correspond to the protonated **B**. The structure **B** is the result of non-alternating enchainment of **1** and CO, which we have observed previously (7). The presence of a small amount of molecules of the type **B** in the product is consistent with the presence of small peaks labeled with asterisks (*) in the ^{1}H-NMR (Figure 1).

The water-insoluble fraction and the water-soluble fraction have almost identical chemical structures except that the average number of β-alanine units in the water-insoluble fraction is lower than in the water-soluble fraction ($n \leq 6$). This observation prompted us to try to increase the length of the β-alanine segment in order to increase the water-solubility of the surfactant. When the molar feed ratio of **1**:**2** was increased from 8:1 to 20:1, the average number of the β-alanine units in the hydrophilic segment increased to $n = 12.9$ and 13.7 in two separate runs (entries 4 and 5, Table 1). In these runs, **1** was added in several portions in order to maintain a low concentration of **1** throughout the reaction to avoid introduction of a high level of amine units into the hydrophilic segment.

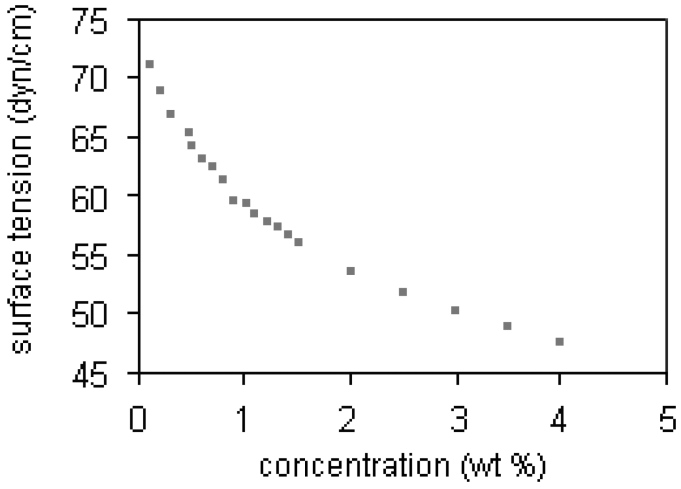


Fig. 3. Surface Activity data acquired using aqueous solutions of water-soluble surfactant products of known concentration and a SensaDyne 6000 bubble tensiometer.

3.2 Surface Activity Studies

Preliminary tests of the surface activity of the β-alanine-based surfactant were carried out. The water-soluble products from entries 4 and 5 in Table 1 were combined for the tests. The average number of β-alanine units is 13.5 in the combined surfactant (**S-13**). The surface tensions of aqueous solutions of **S-13** were measured using a SensaDyne 6000 bubble tensiometer at various concentrations. A decrease in surface tension with the increase of **S-13** concentration was clearly observed (Figure 3). The highest **S-13** concentration that we could reach before precipitation

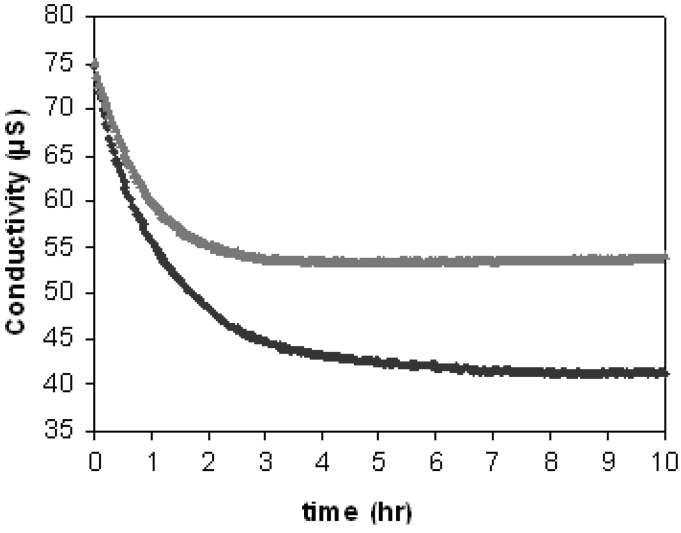


Fig. 4. Conductivity vs. adsorption time. The dark curve describes the conductivity drop when polystyrene latex particles are used. The gray curve describes the control experiment where deionized water instead of polystyrene latex dispersion was used.

was 4 wt%. The data do seem to indicate the existence of a critical micelle concentration, which can be extrapolated to be ~1.15 wt% (10.6 mM) at $\gamma = 56.2$ dyn/cm. However, the low solubility of the surfactant limits the accuracy of the extrapolation. The critical micelle concentration and the corresponding surface tension should be taken as approximate values. Again, the low solubility of **S-13** can likely be attributed to the propensity of oligo-β-alanine to form β-sheets.

To further confirm the observed surface activity, we studied the adsorption of **S-13** onto polystyrene latex particles. In this experiment, dialysis membrane containers filled with polystyrene latex suspensions were placed in a solution of **S-13**. The molecular weight cut-off of the membrane (12,000–14,000 g.mol) is such that **S-13** can diffuse through the membrane but the polystyrene particles can not. The adsorption of **S-13** onto the polystyrene particles will decrease the concentration of **S-13** outside of the dialysis membrane. Because the amino end group of **S-13** exists in the ionic form at neutral pH, the decrease of the **S-13** concentration is monitored by continuous measurement of the electric conductivity of the **S-13** solution. A blank experiment was also carried out, where the polystyrene latex suspension was replaced by deionized water, to take into account of the conductivity change due to dilution and other factors such as adsorption on the dialysis membrane. As shown in Figure 4, the decrease of conductivity in the presence of polystyrene latex is considerably greater than in the absence of polystyrene latex. The adsorption of **S-13** onto the polystyrene latex reaches the saturation point within 10 h and is responsible for ~12 μS of the conductivity decrease.

4 Conclusion

We have synthesized an oligo-β-alanine-based surfactant using our recently developed CO-aziridine copolymerization catalyzed by the cobalt catalyst. The structure of the surfactant was characterized using a combination of NMR and MALDI MS techniques. Surface tension measurement and surface adsorption study show that the amphiphilic molecule is indeed surface active. Its limited solubility suggests that it can be used as a co-surfactant but is not sufficient to function alone in applications such as emulsion polymerization.

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Supporting Information

Carbon-13 and two dimensional NMR spectra.

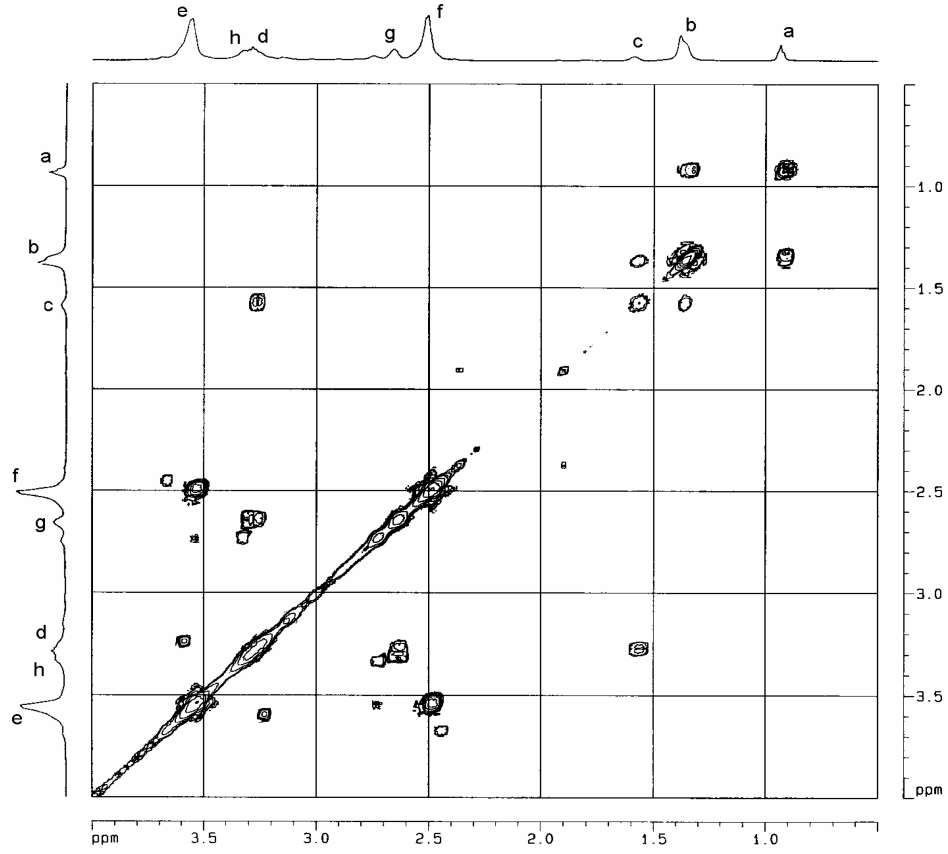

Fig. S1. ^{1}H-^{1}H COSY NMR spectrum 500 MHz, 27°C, in d_4-HFIP. of water-soluble surfactant product entry 8, Table 1.

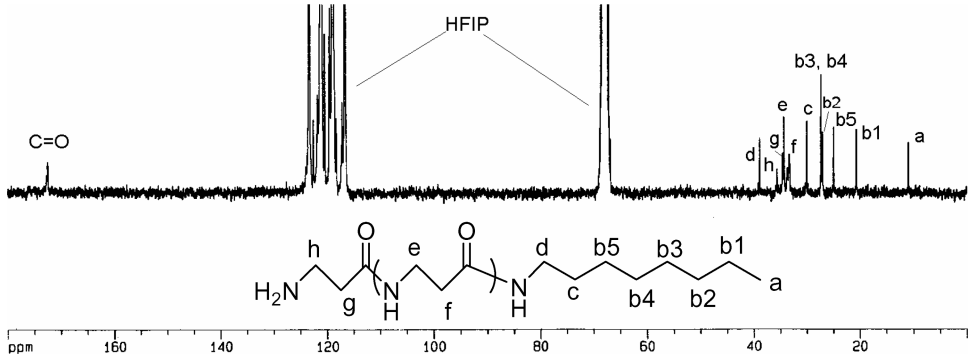

Fig. S2. ^{13}C-NMR spectrum 500 MHz, 27°C, in d_4-HFIP. of water-soluble surfactant product entry 9, Table 1.

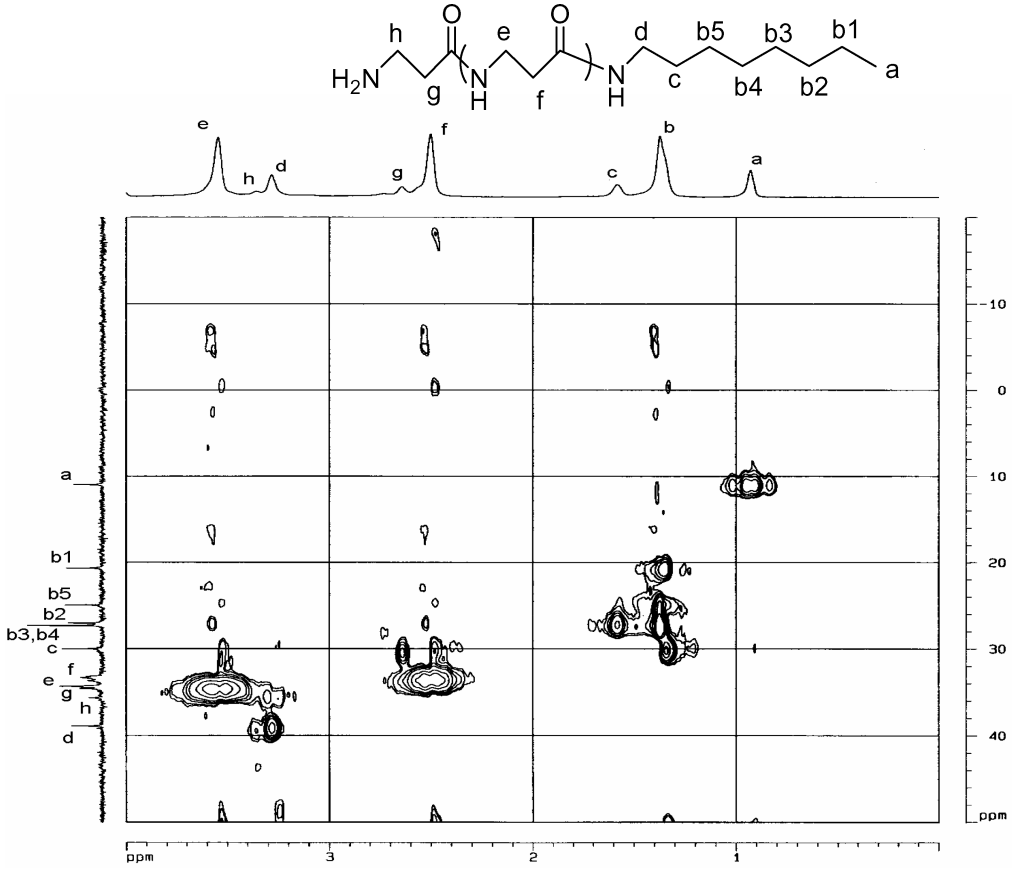

Fig. S3. ^{1}H-^{13}C HMQC NMR spectrum 500 MHz, 27°C, in d_4-HFIP. of water-soluble surfactant product.

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