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Fluorinated polymer surfactants bearing an alternating peptide skeleton prepared by three-component polycondensation†

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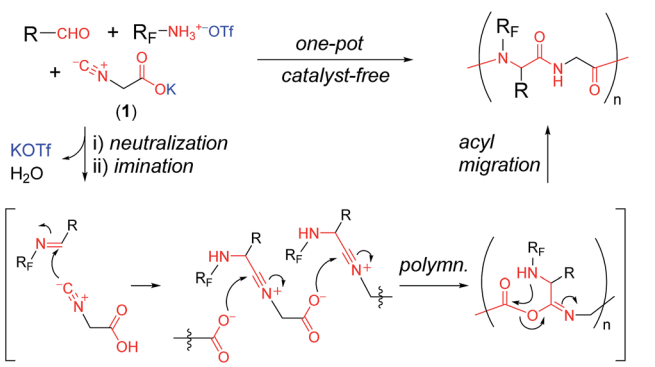
A new species of fluorinated polymer surfactant was developed by three component polycondensation analogous to Ugi four-component condensation. The surfactant exhibited unique surface properties, which made cellulose-based materials hydrophobic and decreased the surface tension of $CHCl_3$. It turned out that the polymer forms micelles in $CHCl_3$.

Fluorinated surfactants constitute an intriguing class of surfactants,[1] which exhibit high surface activity to not only oil–water interfaces but also gas–liquid and solid–liquid interfaces. The surfactants enable the decrease of surface tension even in organic solvents[2] and the fabrication of superhydrophobic surfaces on substrates,[3] which are adopted in various fields for wetting and repellency applications including paints, coatings, lubricants, fire-fighting foams, and mist suppression. Perfluorooctane sulfonic acid and perfluorooctanoic acid are the most popular members in this class.[4] However, the toxicity and bioaccumulation of the surfactants lead to some inevitable limitations on its use.[5] Considering the low biocompatibility of such low-molecular-weight surfactants, our recent efforts have been devoted to the development of new entry for polymeric surfactants. Fluorinated polyethers such as oligo(hexafluoropropylene oxide)[6] and poly(fluorooxetane)[7] are synthesized *via* the ring-opening polymerization of the corresponding monomers. The vinyl polymer-based surfactants can also be prepared by the radical polymerization of fluorinated vinyl monomers and subsequent functionalization of the polymer terminus with a hydrophilic group.[8] Although these polymer surfactants become promising candidates as the substitute of low-molecular-weight fluorinated surfactants, two problems on the synthetic methods that have to be solved arise for practical use. One is the low skeletal diversity of polymer surfactants, because the diversity is strongly dependent on the availability of fluorinated monomers. The other problem is a low reproducibility to give a uniform polymer surfactant with precisely same amphiphilicity, owing to the synthetic challenges on the control of polymerization and polymer reaction. Thus, we became intrigued by the potential possibility of multicomponent polycondensation[9] for the creation of fluorinated polymer surfactants bearing well-defined amphiphilicity.

In a recent publication, we reported a one-pot synthetic technique for synthesizing alternating peptides.[10] The technique involves catalyst-free polymerization analogous to the Ugi four-component condensation (Ugi 4CC) for the synthesis of dipeptides.[11] On the basis of our previous method, we planned three-component polycondensation using an aldehyde, perfluoroammonium triflate, and a potassium salt of glycine-based ambident molecule bearing both isonitrile and carboxylic acid ($CN–CH_2–COOK$, **1**) to give alternating peptides with perfluoroalkyl pendant groups (Scheme 1). Neutral perfluoroalkylamine can be generated *in situ* by the treatment of the ammonium salt with **1**, which smoothly react with an aldehyde to give the corresponding imine. Further reaction of imine ($RC = NR_F$) with the ambident molecule would proceed to polymerization, followed by acyl migration to give the alternating peptides without the need of a catalyst. The peptide main



Scheme 1 One-pot synthesis of amphiphilic alternating peptide.

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chain is expected to serve as the hydrophilic part of surfactant. Because the alternating peptide skeleton consists of the well-defined repeating unit, the amphiphilicity of the polymer would be precisely controlled by the manipulation of R and R_F structures, which could be hardly dependent on the polymerization degree.

Building upon this idea, herein, we describe catalyst-free three-component polycondensation to give perfluoroalkyl-containing alternating peptides. The effects of the polymer structure on their surface-active properties were investigated by surface tension and dynamic light scattering (DLS) measurements. We successfully developed a fascinating polymer surfactant, which made cellulose-based materials hydrophobic and decreased the surface tension of $CHCl_3$. It turned out that the polymer forms thermodynamically stable associates, *i.e.*, micelles in $CHCl_3$.

Fig. 1 depicts the structures of alternating peptides with perfluoroalkyl pendant groups (**P1–P6**). We selected three types of aldehydes, two perfluoroalkylammonium salts, and potassium isocyanoacetate (**1**) as the precursor of the ambident molecule. The ammonium salts were freshly prepared in i-PrOH *in situ* before the polymerization. According to the schematic illustration in Scheme 1, the three-component polycondensation began with a combination of isobutyraldehyde, $C_3F_7CH_2NH_3OTf$, and **1**. The three components were stirred in i-PrOH at room temperature for 4 d; then, i-PrOH was removed *in vacuo*. The residue was stirred for an additional 3 d until the magnetic rotator could no longer be stirred, which produced a highly viscous material. After typical workup, a $CHCl_3$ solution of the products was reprecipitated into hexane to give **P1** as a hexane-insoluble part.

The polymer structure of **P1** was confirmed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and IR spectra.[12] The ^{1}H NMR spectrum was found to consist of proton signals from all the three components with an appropriate integral ratio (Fig. S1†). In the ^{13}C NMR spectrum (Fig. S2†), four amide carbon signals were observed at around 170–180 ppm, strongly supporting the formation of amide linkages in the main chain and the presence of *cis–trans* rotamers of the *N*,*N*-disubstituted amide bond. All carbon signals except for the signals attributed to C_3F_7 are very sharp, indicating the formation of a high-molecular-weight polymer. The broadening of C_3F_7 carbons in the range of 100–150 ppm would come from the *N*,*N*-disubstituted amide rotamers and multiple scalar couplings between ^{13}C and ^{19}F nuclei. We also measured the ^{19}F NMR spectrum (Fig. S3†),[12] which clearly provided the direct evidence for the introduction of ^{19}F nuclei to the polymer skeleton. In the IR spectrum, an amide absorption band was observed at around 1660 cm^{-1} (Fig. S5†).[12] These results clearly indicate that the three-component polycondensation formed an alternating peptide polymer, **P1**. In a similar manner, using other reaction components, we also prepared the other polymers, **P2**, **P3**, **P4**, **P5**, and **P6**. The results are summarized in Table 1. The obtained polymers were hardly soluble in water, while the polymers were soluble in various organic solvents. The weight-average molecular weight (M_w) values were estimated by the diffusion coefficients (D) obtained from diffusion-ordered NMR spectroscopy (DOSY) according to the literature.[10,13] The polydispersity indices (M_w/M_n) were estimated by a size exclusion column chromatography. Glass transition temperatures (T_g) were measured by differential scanning calorimetry (DSC) analyses.[12] T_gs of the alternating peptides were found to be dependent on both the rigidity of the pendant groups (R) and the length of perfluoroalkyl chains, implying that the thermal properties of the polymers would be easily tunable by the selection of appropriate aldehyde and amine components.[14]

Next, with six types of perfluoroalkyl group-containing peptides, we investigated the surface modification of the polymers on glass plate, filter paper, and cotton gauze (Fig. 2). A water droplet of 6 μL was deposited on each polymer-modified surface to evaluate the water contact angles (WCA). In the cases of glass plates, WCA for all plates modified by the polymers were <10°, similar to that of the original glass plate (Fig. 2A), mainly because of the interaction of the polymers with water. On the other hand, we found that **P6** efficiently makes highly hydrophobic filter paper or cotton gauze without dissolution in water (Fig. 2B and C),[15] whereas the other polymers hardly change the hydrophilicity of the original materials.

The hydrophobic gauze modified by **P6** was characterized by IR spectra before and after the modification (Fig. S38†).[12] By a careful comparison, we found that the IR spectrum of the

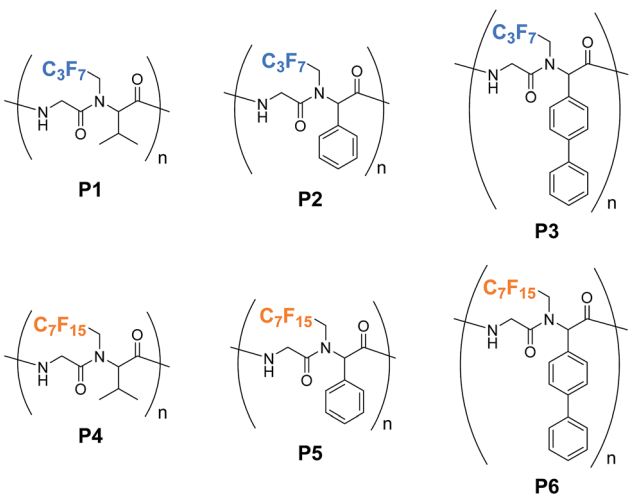

Fig. 1 Alternating peptides with perfluoroalkyl pendant group.

Table 1 Results of alternating copolymerization

Polymer	Yield[a] (%)	M_w[b] (kDa)	M_w/M_n[c]	T_g[d] (°C)
P1	85	7.4	1.5	−23.6
P2	82	7.8	1.8	−13.3
P3	63	7.1	1.5	31.4
P4	43	7.6	1.2	−1.3
P5	67	7.4	1.3	0.7
P6	64	8.8	1.2	45.5

[a] Hexane-insoluble part. [b] Estimated by DOSY spectra (400 MHz, $CDCl_3$, 298 K). [c] Estimated by a size exclusion column chromatography on the basis of polystyrene standards (eluent: DMF). [d] Estimated by a differential scanning calorimetry.

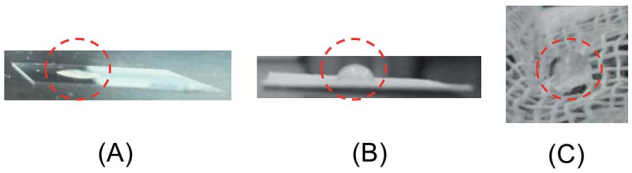

Fig. 2 Photographs of 6 μL water droplet on (A) glass plate, (B) filter paper, and (C) cotton gauze (2 × 2 cm^2) modified by **P6**. Modified glass and filter paper were prepared by uniformly casting a $CHCl_3$ solution of **P6** (0.7 wt%). Modified gauze was prepared by immersing the gauze in 1.0 mL of a $CHCl_3$ solution of **P6** (0.7 wt%) at room temperature for 3 min, wringing the excess solution, and spray-drying.

modified gauze includes a small shoulder at around 1660 cm^{-1}, which perfectly matches the amide C=O absorption of **P6**. The other IR absorption signals of the modified gauze almost match those of the original gauze, suggesting that the high hydrophobicity of the gauze is caused by the trace amount of **P6** immobilized on the surface.

The solutions of **P1**, **P2**, and **P3** are transparent, while the solutions of **P4** and **P5** are slightly opaque (Fig. 3A), because of the low solubility of **P4** and **P5** in $CHCl_3$. On the other hand, the solution of **P6** is transparent. It is noted that the **P6** solution easily made bubbles by shaking, also indicating the interfacial activity between $CHCl_3$ phase and atmosphere. For the evaluation of unique surface modification capability of **P6**, the surface tensions of 1.0 wt% polymer solutions in $CHCl_3$ were measured by the Wilhelmy plate method (Fig. 3B).[16] Compared with the surface tension of pure $CHCl_3$ (26.9 mN m^{-1}), those of all polymers clearly decreased (**P1**: 25.7, **P2**: 25.5, **P3**, 26.7, **P4**: 20.9, **P5**: 20.0, and **P6**: 22.0 mN m^{-1}), suggesting that the polymers serve as a surfactant in $CHCl_3$.[2] The good contrast between the organophobicity of perfluoroalkyl pendant groups and the organophilicity of the main chain would facilitate the interfacial alignment of the polymers in $CHCl_3$. The C_7F_{15}-containing polymers (**P4**, **P5**, and **P6**) exhibit higher surface activity than C_3F_7-containing polymers (**P1**, **P2**, and **P3**).

The effects of alkyl groups (R) in both C_3F_7- and C_7F_{15}-containing polymer series on the surface activity appear to exhibit a similar trend as follows; phenyl > i-propyl > biphenyl.

Micellization affects interfacial properties such as reduction of surface tension. It is therefore, very important to characterize the surfactants in term of micellization behavior. Quite reasonably, the critical micelle concentration (CMC), *i.e.*, onset concentration to form micelle is an important parameter. Thus, on the assumption, we measured UV-vis spectra of **P6** in $CHCl_3$ at various concentrations. The UV-vis spectra include the characteristic absorption to biphenyl structures in the polymer.[12] We plotted the relationship between polymer concentration and absorbance at 340 nm normalized by the concentration (Fig. 4). The plots clearly include the intersection point at around 0.6 wt%, indicating the CMC for the surfactant. To our best knowledge, the studies on micelle formation in $CHCl_3$ has not been sufficiently investigated, while there are several reports about surface activities of fluorinated surfactants in organic solvents. The numerical magnitude of CMC of **P6** in $CHCl_3$ might be comparable with those of typical hydrocarbon- and fluorocarbon-based low-molecular-weight surfactants in water (*e.g.* $C_8H_{17}COONH_4$: 7.0 wt% and $C_8F_{17}COONH_4$: 0.4 wt%),[2d] suggesting that the perfluoroalkyl pendant groups of **P6** would play an important role on the decrease of surface tension even in $CHCl_3$.

To know the size of micelles, we performed the DLS measurements above the CMC (1.0 wt%) of the polymer solutions in $CHCl_3$. In the profile of **P6** solution (Fig. 5), we observed

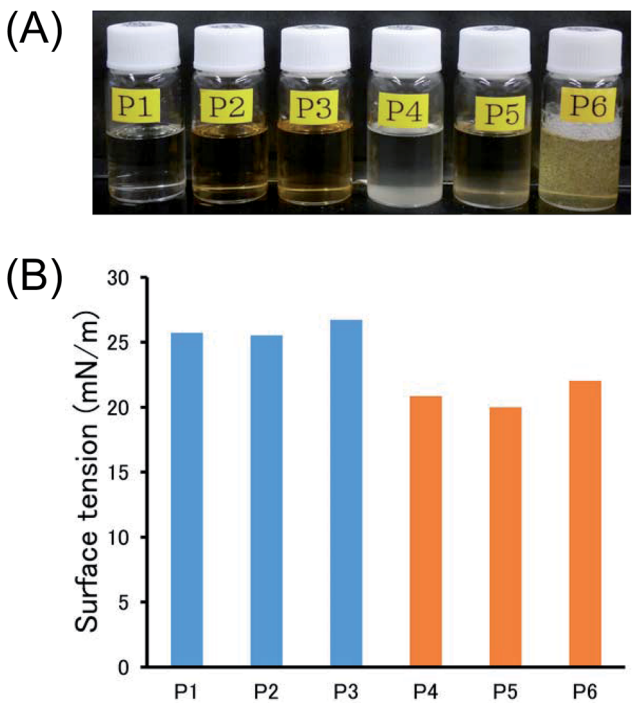

Fig. 3 (A) Photographs and (B) surface tension of 1.0 wt% polymer solutions in $CHCl_3$ at room temperature.

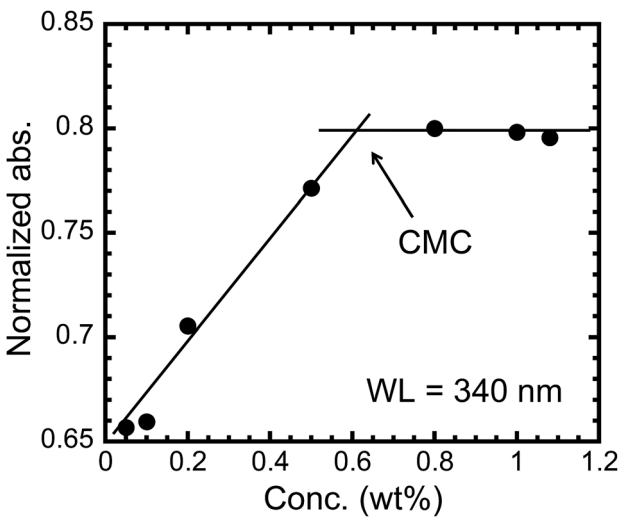

Fig. 4 Normalized absorbance of **P6** at 340 nm ($CHCl_3$, room temperature) as a function of concentration (wt%).

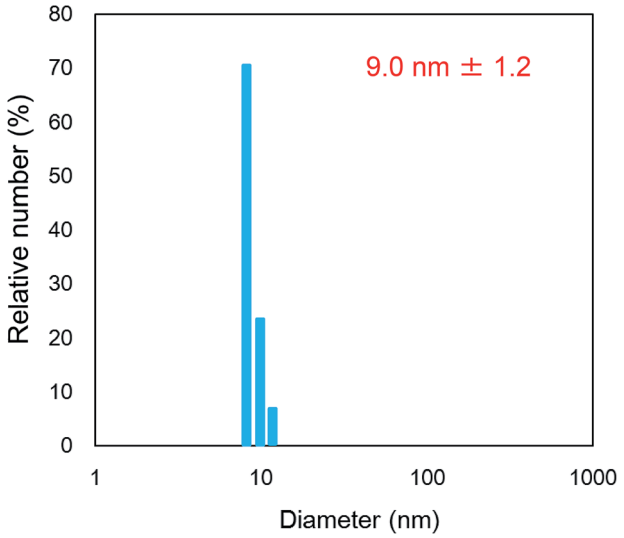

Fig. 5 DLS profile of **P6** in $CHCl_3$ (1.0 wt%) at room temperature.

scattered light signals enough for fitting the auto-correlate function, which reveals the existence of associates in the solution. The size of associates was found to be 9.0 ± 1.2 nm. On the other hand, the other polymers didn't exhibit any association, which was confirmed by the DLS analyses. It is interesting that **P6** forms micelles in $CHCl_3$, which is a good contrast to the results of **P4** and **P5** with the same C_7F_{15} groups.

The differences in the micellization result directly from the bulkiness of the substituents in the peptide main chain, since more bulky groups in the surfactants can stabilize the micelle structure. Probably, the organophobic C_7F_{15} groups would self-associate in $CHCl_3$, which could form micelles projecting the organophilic peptide main chain outside. The bulky biphenyl substituents in **P6** at the outer face could prevent the aggregation of micelles, probably due to the kinetic suppression of interchain interactions such as hydrogen bondings and fluorous–fluorous interactions. In the cases of **P4** and **P5**, lack of appropriate bulkiness could result in the formation of the unstable aggregated structure, leading to the opaque solution as shown in Fig. 3A. The other factors may also play a role for the formation of superstructure. The micelles in the solution of **P6** in $CHCl_3$ would recognize and coat the hydrophilic cellulose surface, which could make the surface hydrophobic. The biphenyl groups in **P6** are also expected to suppress the approach of water not only to the cellulose scaffold but also to the polypeptide main chain of **P6** on a molecular scale, which could remarkably decrease the dissolution rate of **P6** in a water droplet on the **P6**-modified surface.

Conclusions

In conclusion, we state that we have developed a new three-component polycondensation technique to synthesize well-defined fluorinated polymer surfactants, where aldehyde, ammonium salt, and potassium salt **1** work as the reaction components. The reaction not only enables the one-pot synthesis of alternating peptides but also enables easy introduction of the perfluoroalkyl group to the polypeptide skeleton at a regular interval. Since the synthesis of alternating copolymers is still difficult,[17] the present method might provide a new insight into the control of polymer sequence. The rigidity of the side group attributed to the aldehyde strongly influences the T_gs of the polymers. In all polymers, **P6** particularly exhibited unique surface activity, which made the cellulose-based materials hydrophobic and decreased the surface tensions of $CHCl_3$. It was indicated that **P6** forms micelle even in $CHCl_3$, which was confirmed by both UV-vis spectra and DLS measurements. Our finding about micelle formation in organic solvent might open a new field of surfactant chemistry. The effects of polymer structure, solvent, and temperature on the CMC are currently investigating in detail.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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