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Synthesis of novel fluoroalkyl end-capped *N*-vinyl-2-pyrrolidone–acrylic acid co-oligomers by use of fluoroalkanoyl peroxides, and their properties

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Abstract

The reaction of a fluoroalkanoyl peroxide with *N*-vinyl-2-pyrrolidone was initiated by single electron transfer from the substrate to peroxide to afford the 1:1 adduct (fluoroalkylated *N*-vinyl-2-pyrrolidone); however, in the presence of acrylic acid, this peroxide afforded a fluoroalkylated *N*-vinyl-2-pyrrolidone–acrylic acid co-oligomer via a radical process under very mild conditions. The fluorinated co-oligomers thus obtained were soluble not only in water but also in polar organic solvents such as methanol, ethanol, *N,N'*-dimethylformamide and dimethylsulfoxide, and were able to reduce effectively the surface tension of water. Furthermore, these co-oligomers showed a high calcium binding power compared to common organic chelating agents, and exhibited antibacterial activity to some extent (from 10^8 to 10^6 colony forming units levels) against *Staphylococcus aureus*. © 1997 Elsevier Science S.A.

Keywords: Synthesis; Surfactant properties; *N*-Vinyl-2-pyrrolidone–acrylic acid co-oligomer; Calcium binding; Antibacterial activity

1. Introduction

Recently, there has been interest in the synthesis and applications of partially fluorinated macromolecules because of their unique properties, such as high solubility in common organic solvents, and biological activities which cannot be achieved in the perfluoropolymers [1,2]. From such points of view, it is of particular interest to synthesize partially fluoroalkylated polymeric compounds. In the course of our comprehensive studies on the decomposition behaviour of the fluorinated organic peroxides, we have succeeded in preparing various oligomers containing fluoroalkylated end-groups by using fluoroalkanoyl peroxides as key intermediates [2]. For example, fluoroalkyl end-capped acrylic acid oligomers $\{R_F\text{–}[CH_2\text{–}CH(CO_2H)]_n\text{–}R_F\}$, which are prepared by the reactions of acrylic acid and fluoroalkanoyl peroxides reduce the surface tension of water as well as the usual low-molecular-weight fluorinated surfactants, and are potent and selective inhibitors of human immunodeficiency virus type-1 (HIV-1) in vitro [3], although these compounds are oligomeric (high molecular mass) materials.

On the other hand, much attention has also recently been focused on chelating surfactants such as lauroyl ethylenediaminetriacetate which are both strong surfactants and can chelate multivalent ions [4]. However, the development of fluoroalkylated chelating surfactants via carbon–carbon bond formation has hitherto been limited since the usual alkylation methods cannot be applied to perfluoroalkylation due to the strong electronegativity of fluorine [5]. Therefore, the exploration of these fluoroalkylated compounds, especially partially fluoroalkylated oligomeric-type compounds by using fluoroalkanoyl peroxides is of much interest. In a preliminary communication [6], we reported on the synthesis of fluoroalkyl end-capped *N*-vinyl-2-pyrrolidone–acrylic acid co-oligomers (abbreviated 'Co-oligomer I') by using fluoroalkanoyl peroxides. Now, we would like to give a full account of the synthesis and properties of Co-oligomer I with

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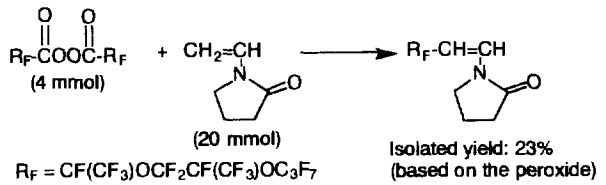
particular emphasis on the application to new fluorinated chelating surfactants.

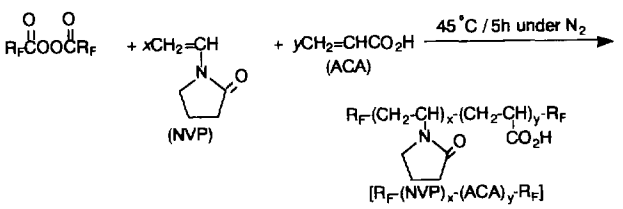
2. Results and discussion

Firstly, we tried to react directly *N*-vinyl-2-pyrrolidone (NVP) with fluoroalkanoyl peroxides to obtain fluoroalkylated *N*-vinyl-2-pyrrolidone oligomers possessing amino and carbonyl moieties as possible fluoroalkylated chelating oligosurfactants, since compounds bearing such moieties could be chelating agents. NVP is well-known to be an excellent radical polymerizable monomer. However, when the reaction of NVP with perfluoro-2,5-dimethyl-3,6-dioxanonanoyl peroxide was carried out at 40 °C for 3 h under nitrogen, the expected oligomer was not isolated. However, we were able to isolate the product of substitution of the perfluoro-1,4-dimethyl-2,5-dioxaoctyl group at the β-carbon of NVP via single electron transfer from NVP to the peroxide as shown in the Scheme 1.

Previously, we reported similar single electron transfer reactions with fluoroalkanoyl peroxides; for example, styrene



Scheme 1.



Scheme 2.

reacts with the peroxide to afford β-fluoroalkylstyrene via single electron transfer [7]. The HOMO energy level of NVP has been calculated using MNDO-PM3 semiempirical MO methods with the MOPAC 5.0 program. NVP was shown to have a high HOMO energy level (−9.004 eV) as for styrene (−9.132 eV). So, a stronger interaction between the HOMO energy level of NVP and LUMO of the peroxide would cause a single electron transfer from NVP to the peroxide.

From these results, it is strongly suggested that lowering of the HOMO energy level of NVP should cause a new interaction between HOMO (NVP) and SOMO of the fluoroalkyl radical ($R_F^{\bullet}$) to afford the oligomerization of NVP with peroxide. Thus, we were interested in using acrylic acid as co-monomer in the above reaction system, and the results on the reactions of fluoroalkanoyl peroxides with NVP and acrylic acid were shown in Scheme 2 and Table 1.

As shown in Table 1, both perfluoropropylated and perfluoro-oxaalkylated *N*-vinyl-2-pyrrolidone-acrylic acid co-oligomers [R_F–(NVP)$_x$–(ACA)$_y$–R_F] were obtained in similar isolated yields under very mild conditions (45 °C/5 h). The products obtained are polydisperse mixtures of co-oligomers ($\overline{Mw}/\overline{Mn} > 1$). The formation of these fluoroalkylated co-oligomers indicates that the basic moiety (>N–) of NVP (in fact, the highest electron density in the HOMO orbital has been found at the nitrogen position) could interact with the acid (acrylic acid) to lower the HOMO energy level of NVP. Hence, the fluoroalkyl radical produced by the homolytic decomposition of the peroxide should add to acrylic acid or NVP. Interestingly, the molecular weights are, in general, lower as compared with those of a series of fluoroalkylated acrylic acid homo-oligomers (R_F–$(CH_2CHCO_2H)_n$–R_F; $\overline{Mn} \approx 12\,800$) which are obtained by the homo-oligomerization of fluoroalkanoyl peroxides with acrylic acid [3a] or NVP–acrylic acid co-oligomer (–(NVP)$_x$–(ACA)$_y$–; $\overline{Mn} = 12\,700$) produced with the usual hydrocarbon azo-initiator (2,2′-azobis(2-methylpropionamidine) dihydrochloride). This finding suggests that addition of the growing radical to acrylic acid or NVP would

Table 1
Reactions of fluoroalkanoyl peroxides with *N*-vinyl-2-pyrrolidone (NVP) and acrylic acid (ACA)

R_F in peroxide	NVP	ACA	R_F–(NVP)$_x$–(ACA)$_y$–R_F	
(mmol)	(mmol)	(mmol)	Yield (%) [a]	$\overline{Mn}(\overline{Mw}/\overline{Mn})$ [x:y] [b]
C_3F_7				
7	37	37	24	1130(1.05) [37:63]
7	22	27	36	2000(1.84) [74:26]
$CF(CF_3)OC_3F_7$				
5	24	24	46	1080(1.05) [65:35]
5	14	24	52	1070(1.09) [47:53]
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$				
3	13	13	24	2190(2.16) [65:35]
3	8	13	44	2230(2.27) [53:47]

[a] The yields are based on the starting materials [NVP, ACA, and the decarboxylated peroxide unit (R_F–R_F)].
[b] Co-oligomerization was determined by ^{1}H NMR.

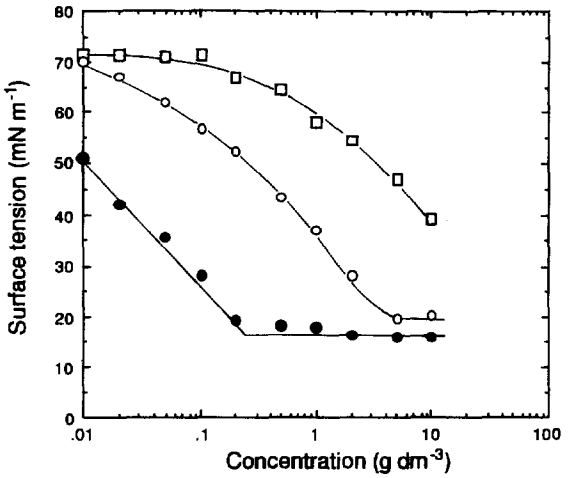


Fig. 1. Surface tension of aqueous solutions of R_F–(NVP)$_x$–(ACA)$_y$–R_F at 30 °C: □, $R_F = C_3F_7$ ($\overline{Mn} \approx 2000$); ○, $R_F = CF(CF_3)OC_3F_7$ ($\overline{Mn} \approx 1080$); ●, $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ ($\overline{Mn} \approx 2230$).

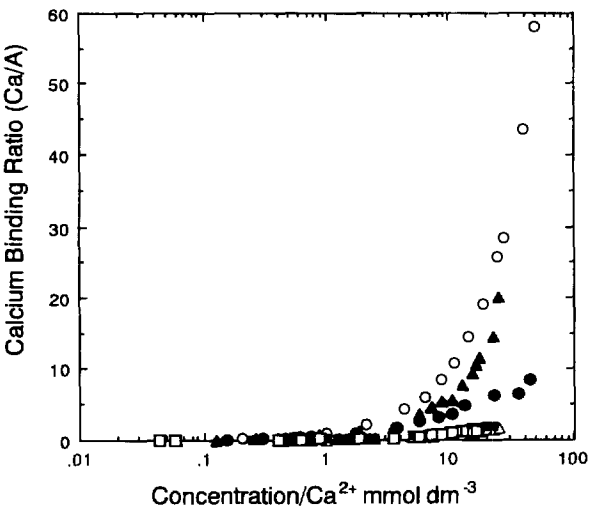


Fig. 2. Ca^{2+} binding isotherms of R_F–(NVP)$_x$–(ACA)$_y$–R_F (0.5 g dm^{-3}): ●, $R_F = C_3F_7$ ($\overline{Mn} = 2000$); △, $R_F = CF(CF_3)OC_3F_7$ ($\overline{Mn} = 1080$); ○, $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ ($\overline{Mn} = 2230$); △, –(CH_2CHCO_2H)$_n$–($\overline{Mn} = 2000$); ■, R_F–(CH_2CHCO_2H)$_n$–R_F; $R_F = CF(CF_3)OC_3F_7$ ($\overline{Mn} = 6700$); □, –(NVP)$_x$–(ACA)$_y$– ($x:y = 62:38$; $\overline{Mn} = 12\,700$).

be suppressed in part by the interaction of acid (acrylic acid) and basic moiety (>N–) of NVP.

It was shown that our new Co-oligomer I was soluble not only in water but also in polar solvents such as methanol, ethanol, *N,N'*-dimethylformamide and dimethyl sulfoxide. Therefore, Co-oligomer I is expected to behave as a new fluorinated oligosurfactant containing both pyrrolidonyl and carboxyl segments. In order to clarify the surfactant properties of our Co-oligomer I, we have measured the surface tension of their aqueous solutions with the Wilhelmy plate method at 30 °C. These results are listed in Fig. 1.

In hydrocarbon polysoaps, it is well-known that their aqueous solutions exhibit a continuous decrease of surface tension with increasing concentration, as do the low-molecular-weight surfactants; however no critical micelle concentration (CMC) or a break point resembling a CMC is observed in these polymers [8]. Additionally, for polysoaps with fluorocarbon hydrophobic chains, which are prepared by random co-polymerization of 1,1,2,2-tetrahydroperfluorooctyl methacrylate, the surface tensions of aqueous solutions are not reduced with increasing content of hydrophobic chains in the co-polymers, reaching a minimum of about 50 mN m^{-1} [9]. In contrast, as shown in Fig. 1, our present Co-oligomer I was found to reduce the surface tension of water effectively. The degree of reduction in surface tension of water depends on the length of fluoroalkyl groups in the co-oligomers for the usual low-molecular-weight fluorinated surfactants. The longer-chain perfluoro-oxaalkylated co-oligomer (abbreviated 'Co-oligomer II') was more effective for reducing the surface tension of water to around 15 mN m^{-1} than the perfluoropropylated one. In addition, Co-oligomer II exhibited a clear break point resembling a CMC near 0.2 g dm^{-3} [10].[1] On the other hand, the corresponding non-fluorinated co-oligomer [–(NVP)$_x$–(ACA)$_y$–] decreased the surface tension of water to a minimum of about 50 mN m^{-1}, and this co-oligomer had no break point. This finding is an interesting feature in the fluoroalkyl series, especially with perfluoro-oxaalkyl end-capped oligomeric surfactants, and also suggests strongly that these oligomers could form the intra- or inter-molecular aggregates in aqueous solutions.

From these results, it is interesting to develop Co-oligomer I as a new fluorinated oligomeric chelating surfactant. Thus, we tried to measure the equilibrium calcium ion concentrations in the presence of R_F–(NVP)$_x$–(ACA)$_y$–R_F (concentration of each oligomer is 0.5 g dm^{-3}; $R_F = C_3F_7$ (0.25 mmol dm^{-3}), $CF(CF_3)OC_3F_7$ (0.46 mmol dm^{-3}), $CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (0.22 mmol dm^{-3})) by using a calcium ion electrode and a digital pH/ion meter (HORIBA F-23). These results are shown in Fig. 2.

As shown in Fig. 2, our Co-oligomer I was found to have an extraordinarily high calcium ion binding power as compared to those of the corresponding non-fluorinated co-oligomer, –(NVP)$_x$–(ACA)$_y$–, non-fluorinated acrylic acid oligomer, –(CH_2CHCO_2H)$_n$– and fluoroalkyl end-capped acrylic acid homo-oligomers, R_F–(CH_2CHCO_2H)$_n$–R_F. In the case of poly(*N*-vinylpyrrolidone) (–(NVP)$_n$–; $\overline{Mn} = 10\,000$), this polymer did not bind calcium ions. It is known that poly(acrylic acid) is effective in removing free calcium ions from solution, and the binding ratio under lower concentrations is slightly higher than the theoretical binding ratio (Ca/A: the average number of bound calcium ions per carboxylate group in the oligomers) of poly(acrylic acid) due to the electrostatic effect [4b]. Furthermore, the chelat-

[1] Recently, not only our fluoroalkyl end-capped oligomers but also water soluble hydrocarbon block co-polymers, such as a poly(ethylene oxide)–block-poly(propylene oxide)–block-poly(ethylene oxide) co-polymer, were reported to form an aggregate of these high molecular weight compounds at a CMC.

ing ability of surfactants is, in general, not so high (for example, the maximum calcium chelating ratio of sodium lauroyl ethylenediaminotriacetate is 190 mg $CaCO_3$ g^{-1}) [4a]. On the other hand, the calcium binding ratio of R_F–$(NVP)_x$–$(ACA)_y$–R_F (R_F=$CF(CF_3)OC_3F_7$; $\overline{Mn}$ = 1030; concentration, 0.5 g dm^{-3}) was maximally 20, and the higher calcium binding ratios were obtained in Co-oligomer II. This finding may arise because Co-oligomer II is likely to form an aggregate as shown in Fig. 1, and this aggregate should interact strongly with calcium ions. Fluoroalkyl segments in these co-oligomers are solvophobic in aqueous solutions, and enhance the aggregation due to the strong interaction between fluoroalkyl segments. Therefore, the synergistical interaction (one is the aggregations of fluoroalkyl segments, and the other is the hydrogen bonding between pyrrolidonyl (or carboxy) segments and water) could provide strong aggregation in aqueous solutions, and calcium ions should act as guest molecules for these aggregates. Especially, pyrrolidonyl segments in aqueous solutions would act as suitable host moieties in these aggregates, and interact strongly with calcium ions.

Fluoroalkyl end-capped acrylic acid oligomers, especially fluoroalkyl end-capped acrylic acid-trimethylvinylsilane (or alkyl methacrylates) co-oligomers, have recently been demonstrated to act as potent and selective inhibitors against HIV-1 [11]. The co-oligomers in Table 1 have been evaluated for their inhibitory effects on HIV-1 replication in MT-4 cells. However, each co-oligomer was found to be inactive against HIV-1 replication. Previously, we reported that fluoroalkyl end-capped acrylic acid co-oligomers containing poly(oxyethylene) units are inactive against HIV-1 [11]. Furthermore, it was demonstrated that the activity against HIV-1 is sensitive to the oleophilic property of these co-oligomers, and as the co-oligomers become more hydrophilic, the activity is, in general, not shown [11]. Hence, the fact that our present co-oligomers possess no anti-HIV-1 activity would be due to these co-oligomers having hydrophilic pyrrolidonyl segments.

Very recently, we have demonstrated that fluoroalkyl end-capped oligomers containing trimethylammonium [12] or allylammonium [13] segments possess not only unique properties imparted by fluorine but also antibacterial activity. Therefore, our present co-oligomers are also possible antibacterial materials, having amido segments. Co-oligomer I shown in Table 1 has been evaluated for their antibacterial activity against *Staphylococcus aureus* by a viable cell counting method as already reported [12]. These results are shown in Table 2.

As shown in Table 2, Co-oligomer I was found to exhibit anti-bacterial activity to some extent ($\sim 10^6$ colony forming units levels) against *Staphylococcus aureus*. Of these, perfluoro-1,4-dimethyl-2,5-dioxaoctylated co-oligomer was the most active, with a 3.7×10^6 c.f.u., and this co-oligomer was also effective for reducing the surface tension of water as shown in Fig. 2.

In this way, our present Co-oligomer I, in particular, and Co-oligomer II, exhibit not only the well known properties imparted by fluorine such as surface activity, but also chelating surfactant property and some antibacterial activity. Therefore, these new fluorinated oligomeric compounds may develop as novel functional polymeric materials possessing various unique properties imparted by fluorine.

Table 2
Antibacterial activity of R_F–$(NVP)_x$–$(ACA)_y$–R_F against *Staphylococcus aureus* [a]

R_F in oligomer	$\overline{Mn}$ (x:y)	*Staphlyococcus aureus*
none		1.5×10^8 c.f.u. ml^{-1} [b]
C_3F_7		
	1130 (37:63)	4.9×10^7
	2000 (74:26)	3.3×10^7
$CF(CF_3)OC_3F_7$		
	1080 (65:35)	1.1×10^8
	1070 (47:53)	6.5×10^7
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$		
	2190 (65:35)	8.8×10^7
	2230 (53:47)	3.7×10^6

[a] Concentration of each oligomer was 1 mg ml^{-1}.
[b] c.f.u. indicates colony forming units.

3. Experimental details

3.1. Measurements

NMR spectra were measured with a Varian Unity-plus 500 (500 MHz) spectrometer while IR spectra were recorded on a HORIBA FT-IR spectrophotometer. Molecular weights were calculated by using a JASCO 830-RI gel permeation chromatograph calibrated with standard pullulan using 0.2 mol dm^{-3} sodium phosphate dibasic as the eluent.

3.2. Materials

A series of fluoroalkanoyl peroxides ($(R_FCOO)_2$) were prepared from the corresponding acyl halides and hydrogen peroxides in the presence of aqueous sodium hydroxide according to our previously reported method [14].

3.3. Reaction of fluoroalkanoyl peroxide with NVP

A solution containing 4 mmol of perfluoro-2,5-dimethyl-3,6-dioxanonanoyl peroxide and 20 mmol of NVP in 1:1 mixed solvents (AK-225) of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane (50 g) was stirred under nitrogen at 40 °C for 3 h. The solution was then washed well with 100 ml of water. The organic layer was dried over magnesium sulphate. After the removal of the solvent, the crude product was chromatographed on silica gel (Wakogel C-200) using ethyl acetate and hexane (5:2) as the eluent to give the colorless oily

substituted product of perfluoro-1,4-dimethyl-2,5-dioxaoctyl group to the β-carbon of NVP which exhibits the following spectral characteristics; IR (cm^{-1}) 1729, 1662 (C=O), 1342 (CF_3), 1240 (CF_2); ^{1}H-NMR ($CDCl_3$) δ 2.26 (CH_2), 2.64 (CH_2), 3.68 (CH_2), 5.78 (d, J=14 Hz, 1H), 8.39 (d, J=14Hz, 1H); ^{19}F-NMR ($CDCl_3$, ext. CF_3CO_2H) δ −1.71 (CF_3), −5.30 (CF_2), −6.13 (CF_2), −50.88 (CF), −52.72 (CF_2), −65.32 (CF).

3.4. General procedure for the synthesis of fluoroalkyl end-capped co-oligomers

A solution containing perfluoro-2,5-dimethyl-3,6-dioxanonanoyl peroxide (3 mmol), NVP (8 mmol) and acrylic acid (13 mmol) in AK-225 (100 g) was stirred at 45 °C for 5 h. The resulting white powder was washed with hexane and dialyzed to give a bis(perfluoro-1,4-dimethyl-2,5-dioxaoctylated) *N*-vinyl-2-pyrrolidone–acrylic acid co-oligomer (1.99 g). This product showed the following spectral data: IR (cm^{-1}) 3417 (OH), 1642 (C=O), 1315 (CF_3), 1241 (CF_2); ^{1}H-NMR (D_2O) δ 1.62–2.71 (CH_2, CH), 3.36–3.75 (CH_2); ^{19}F-NMR (D_2O, ext. CF_3CO_2H) δ −7.03 to −10.94 (26F), −57.53 to −55.24 (8F); average molar mass ($\overline{Mn}$) = 2230, $\overline{Mw}/\overline{Mn}$ = 1.48 (x:y = 53:47).

Other fluoroalkyl end-capped co-oligomers were obtained under similarly mild conditions. The following spectral data were obtained for the other products studied.

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$–(NVP)$_x$–(ACA)$_y$–$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: $\overline{Mn}$ = 2190, $\overline{Mw}/\overline{Mn}$ = 1.18 (x:y = 65:35). IR (cm^{-1}) 3459 (OH), 1646 (C=O), 1302 (CF_3), 1244 (CF_2); ^{1}H-NMR (D_2O) δ 1.55–2.18 (CH_2), 2.28–2.89 (CH, CH_2), 3.28–3.78 (CH_2); ^{19}F-NMR (D_2O, ext. CF_3CO_2H) δ −7.25 to −10.94 (26F), −57.53 to −55.25 (8F).

$C_3F_7OCF(CF_3)$–(NVP)$_x$–(ACA)$_y$–$CF(CF_3)OC_3F_7$: $\overline{Mn}$ = 1070, $\overline{Mw}/\overline{Mn}$ = 1.47 (x:y = 47:53). IR (cm^{-1}) 3448 (OH), 1646 (C=O), 1300 (CF_3), 1238 (CF_2); ^{1}H-NMR (D_2O) δ 1.58–2.19 (CH_2), 2.25–2.86 (CH, CH_2), 3.21–3.68(CH_2); ^{19}F-NMR (D_2O, ext. CF_3CO_2H) δ −5.88 to −10.74 (16F), −57.54 (6F).

$C_3F_7OCF(CF_3)$–(NVP)$_x$–(ACA)$_y$–$CF(CF_3)OC_3F_7$: $\overline{Mn}$ = 1080, $\overline{Mw}/\overline{Mn}$ = 1.52 (x:y = 65:35). IR (cm^{-1}) 3454 (OH), 1650 (C=O), 1284 (CF_3), 1228 (CF_2); ^{1}H-NMR (D_2O) δ 1.56–2.18 (CH_2), 2.27–2.82 (CH, CH_2), 3.22–3.68 (CH_2); ^{19}F-NMR (D_2O, ext. CF_3CO_2H) δ −5.32 to −9.67 (16F), −51.01 (6F).

C_3F_7–(NVP)$_x$–(ACA)$_y$–C_3F_7: $\overline{Mn}$ = 2000, $\overline{Mw}/\overline{Mn}$ = 1.42 (x:y = 74:26). IR (cm^{-1}) 3442 (OH), 1650 (C=O), 1284 (CF_3), 1228 (CF_2); ^{1}H-NMR (D_2O) δ 1.52–2.32 (CH_2), 2.33–2.84 (CH, CH_2), 3.22–3.68 (CH_2); ^{19}F-NMR (D_2O, ext. CF_3CO_2H) δ −5.71 (CF_3), −45.59 (CF_2), −55.30 (CF_2).

C_3F_7–(NVP)$_x$–(ACA)$_y$–C_3F_7: $\overline{Mn}$ = 1130, $\overline{Mw}/\overline{Mn}$ = 1.80 (x:y = 37:63). IR (cm^{-1}) 3446 (OH), 1646 (C=O), 1275 (CF_3), 1245 (CF_2); ^{1}H-NMR (D_2O) δ 1.57–1.96 (CH_2), 2.23–2.68 (CH, CH_2), 3.23–3.78 (CH_2); ^{19}F-NMR (D_2O, ext. CF_3CO_2H) δ −5.69 (CF_3), −45.58 (CF_2), −55.25 (CF_2).

3.5. Surface tension measurements

The surface tensions of aqueous solutions of the fluoroalkyl end-capped co-oligomers were measured at 30 °C using a Wilhelmy-type surface tensiometer (ST-1, Shimadzu Co.) with a glass plate.

3.6. Measurements of the equilibrium calcium ion concentrations

A calcium ion electrode and a digital pH/ion meter (HORIBA F-23) were used to measure the equilibrium calcium ion concentrations. All of the titration procedures were carried out in a KCl solution for the Ca^{2+}-ion binding study. Each co-oligomer sample was added to a 0.1 mol dm^{-3} KCl solution. After 30 min of stirring, the mixture solution was titrated with a $CaCl_2$ solution.

3.7. Antibacterial assessment

The antibacterial activity of the oligomers was evaluated against *Staphylococcus aureus* by viable cell counting method as described previously [12].

3.8. Antiviral assays

Antiviral activity of the compounds against HIV-1 (HTLB-IIIb starin) replication was based on the inhibition of the virus-induced cytopathic effect in MT-4 cells as described previously [3c].

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