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Fluorinated functional materials possessing biological activities: gel formation of novel fluoroalkylated end-capped 2-acrylamido-2-methylpropanesulfonic acid polymers under non-crosslinked conditions

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New fluoroalkylated end-capped 2-acrylamido-2-methylpropanesulfonic acid homopolymers were prepared by reaction of fluoroalkanoyl peroxides with 2-acrylamido-2-methylpropanesulfonic acid (AMPS). Similarly, fluoroalkylated end-capped copolymers were prepared by reaction of fluoroalkanoyl peroxides with AMPS and the comonomers such as trimethylvinylsilane and methyl methacrylate. These thus-obtained fluoroalkylated end-capped AMPS polymers were found to form gels not only in water but also in organic polar solvents such as methanol, ethanol, *N*,*N*-dimethylformamide and dimethyl sulfoxide under non-crosslinked conditions. On the other hand, AMPS polymer containing fluoroalkylene units $\{[\text{-}R_F\text{-}(AMPS)_q]_p\text{-}\}$ could cause no gelation under similar conditions. This suggests that fluoroalkylated end-capped AMPS polymers can cause gelation where strong aggregation of the end-capped fluoroalkyl segments is involved sterically in establishing the physical gel network in these media. Interestingly, these fluoroalkylated end-capped AMPS polymer hydrogels had a strong metal ion binding power. Moreover, it was demonstrated that these fluoroalkylated gelling polymers are potent and selective inhibitors of HIV-1 replication in cell culture. In addition, one of these gelling polymers was found to possess antibacterial activity against *Staphylococcus aureus*. Therefore, these fluorinated gelling polymers are suggested to have high potential for new functional materials through their gelling ability and biological activity.

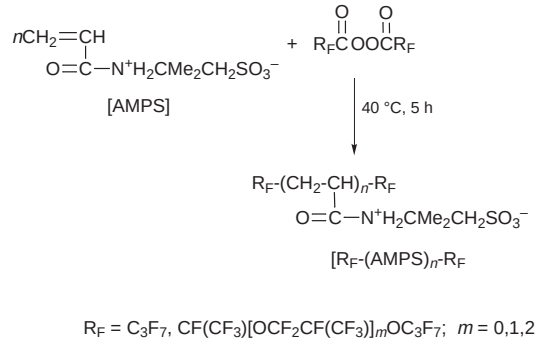
Introduction

Fluorinated polymeric materials exhibit numerous excellent properties which cannot be achieved by the corresponding non-fluorinated materials. However, in general they are very poorly soluble in various solvents.[1] Therefore, it is interesting to search for highly soluble fluorinated polymeric materials with excellent properties imparted by fluorine. We have recently reported that a series of fluoroalkylated end-capped silicon co-oligomers containing carboxy groups, which are prepared by using fluoroalkanoyl peroxides as key intermediates, are highly soluble in various solvents, and are effective in reducing the surface tension of these solvents.[2] These fluorosilicon co-oligomers were also found to be potent and selective inhibitors against HIV-1 (human immunodeficiency virus type 1) replication *in vitro*.[2] Furthermore, we have reported on the synthesis of fluoroalkylated end-capped oligomers containing trimethylammonium segments[3] or sulfo segments[4] by using fluoroalkanoyl peroxides. These fluoroalkylated oligomers containing trimethylammonium or sulfo segments exhibited not only unique properties imparted by fluorine but also biological activities, although they have only two fluoroalkylated end-caps.[3,4] Partially fluoroalkylated polymers were prepared by a variety of anionic polymerizations[5–8] and a fluoroalkylated end-capped moiety was introduced through the ester bond[9–11] to perfluoroalkyl-terminated polymers, and the interesting properties of these polymers have been reported.

In view of the development of new fluoroalkylated end-capped polymeric materials, it is very interesting to explore the fluoroalkylated end-capped polymers containing both cationic and anionic segments by using fluoroalkanoyl peroxides. Hitherto, the synthesis of non-fluorinated zwitterionic (betaine-type) polysoaps has been reported by Laschewsky and Zerbe;[12] however, there has been so far no report on the synthesis of fluoroalkylated end-capped betaine-type polymers. In our continuing effort to design and develop novel fluoroalkylated betaine-type polymers, we discovered that novel fluoroalkylated end-capped 2-acrylamido-2-methylpropanesulfonic acid polymers, which were prepared by the reactions of the corresponding monomer with fluoroalkanoyl peroxides, could lead to gelation not only in water but also in polar organic solvents under non-crosslinking conditions.[13] We now give a full account of the gel formation and properties of these fluoroalkylated end-capped polymers, with emphasis on an application to new fluorinated gelling functional materials possessing biological activities.

Results and Discussion

The reactions of fluoroalkanoyl peroxides with 2-acrylamido-2-methylpropanesulfonic acid (AMPS) were carried out in heterogeneous solvent systems [AK-225 (mixed solvents of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-



Scheme 1

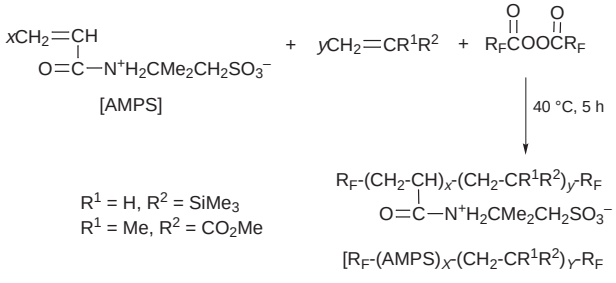
1,2,2,3,3-pentafluoropropane) and water] by stirring vigorously at 40 °C for 5 h under nitrogen. The process is outlined in Scheme 1.

AMPS was found to react with fluoroalkanoyl peroxides under mild conditions to afford fluoroalkylated end-capped AMPS homopolymers [R_F-(AMPS)$_n$-R_F] in 35–58% isolated yields as shown in Table 1.

Similarly, in the copolymerization of AMPS with fluoroalkanoyl peroxides, we succeeded in preparing a series of fluoroalkylated end-capped AMPS copolymers by using comonomers such as trimethylvinylsilane and methyl methacrylate in 30–57% isolated yields as shown in the following Scheme 2 and Table 1.

As shown in Table 1, not only perfluoropropylated but also a series of perfluoro-oxaalkylated end-capped homo- and copolymers were obtained under mild conditions, and the copolymerization ratios of these polymers were determined by ^{1}H NMR analyses. Under our polymerization conditions, in which the concentration of the peroxide was almost the same as that of AMPS (trimethylvinylsilane or methyl methacrylate) as shown in Table 1, mainly polymers with two fluoroalkylated end-groups would be obtained *via* primary radical termination or radical chain transfer to the peroxide. In fact, we have already reported that two fluoroalkylated end-capped acrylic acid oligomers [R_F-(CH_2CHCO_2H)$_n$-R_F] are obtained by the reactions of fluoroalkanoyl peroxides with acrylic acid under similar conditions.[14]

The molecular weights ($\bar{M}$n) of these polymers measured by GPC [gel permeation chromatography calibrated with standard poly(ethylene glycol) by using 0.5 mol dm^{-3} Na_2HPO_4 solution as the eluent] were relatively high (8300–24 500). Considering the fact that water-soluble fluoroalkylated end-capped polymers containing trimethylammonium and sulfo segments easily form molecular aggregates in aqueous solutions,[3,4] this finding suggests that the GPC values indicate the apparent molecular weights. Interestingly, the $\bar{M}$w/$\bar{M}$n values of these fluoroalkylated polymers are extremely high (28–726) compared to that of the corresponding non-fluorinated polymer [-(AMPS)$_n$-: $\bar{M}$n = 5400 ($\bar{M}$w/$\bar{M}$n = 3.25)], which was prepared by using 2,2′-azobis(2-methylpropionamidine) dihydrochloride. This result also suggests that these fluoroalkylated AMPS polymers form aggregates.



Scheme 2

Our fluoroalkylated AMPS polymers were found to be easily soluble not only in water but also in polar organic solvents such as methanol, ethanol, *N*,*N*-dimethylformamide and dimethyl sulfoxide at under dilute conditions (below *ca.* 0.5 g dm^{-3}). In order to clarify the solution properties of our fluoroalkylated polymers, we measured the viscosity of an aqueous solution of fluoroalkylated AMPS polymer [C_3F_7-(AMPS)$_n$-C_3F_7] under dilute conditions (0.1 g dm^{-3}), and the vicosities of aqueous solutions of perfluoropropylated polymers containing trimethylammonium segments [C_3F_7-(AETM)$_n$-C_3F_7] and non-fluorinated AMPS polymer [-(AMPS)$_n$-] were also measured under similar conditions for comparison. These results are shown in Fig. 1.

As shown in Fig. 1, the viscosity of an aqueous solution of C_3F_7-(AMPS)$_n$-C_3F_7 at 5 °C was higher than that of C_3F_7-(AETM)$_n$-C_3F_7 and -(AMPS)$_n$- under dilute conditions (0.1 g dm^{-3}). On the other hand, the viscosities of C_3F_7-(AMPS)$_n$-C_3F_7 including both C_3F_7-(AETM)$_n$-C_3F_7 and -(AMPS)$_n$- were also found to decrease on heating the solutions from 5–50 °C.

However, surprisingly, at concentrations above 1.0 g dm^{-3} all fluoroalkylated end-capped AMPS polymer-solvent systems formed gels. To study this unique gelation, we measured the viscosity of aqueous solutions of these fluoroalkylated end-capped polymers at 30 °C. The results are shown in Fig. 2.

As shown in Fig. 2, the viscosities of -(AMPS)$_n$-, C_3F_7-(AETM)$_n$-C_3F_7 and perfluoropropylated polymer containing sulfo segments [C_3F_7-(MES)$_n$-C_3F_7] increased little with increasing concentrations, and the gel did not form, although these fluoroalkylated polymers were shown to form molecular aggregates like micelles in aqueous solutions.[3,4] On the other hand, the viscosity of our fluoroalkylated end-capped AMPS polymers increased greatly with increasing concentration, and it became impossible to measure their viscosity owing to the gelation at concentrations above 0.5 or 1.0 g dm^{-3}. We also tried to measure the melting temperature of the gel; but, the gel did not melt either in water or in organic solvents even when it was heated to around 95 °C. It is suggested that our fluoroalkylated end-capped AMPS polymers could cause a gelation involving a strong aggregation of fluoroalkyl segments to a physical gel network in water, methanol, ethanol, *N*,*N*-dimethylformamide and dimethyl sulfoxide at higher concen-

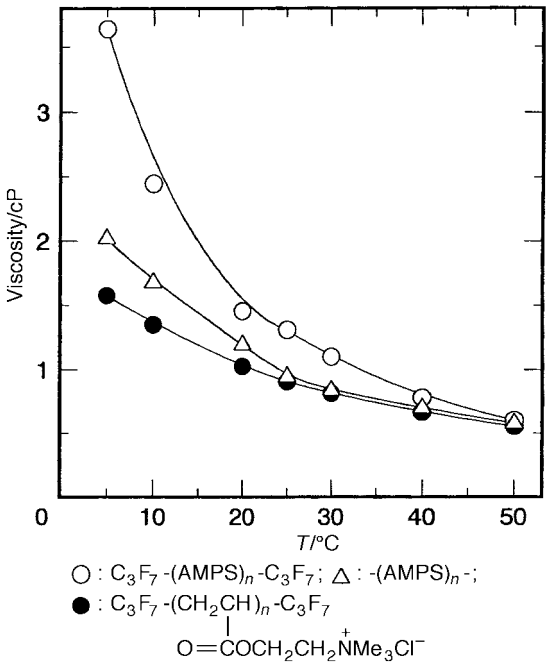


Fig. 1 Effect of temperature on viscosity of aqueous polymer solutions

Table 1 Homo- and co-polymerizations of AMPS with fluoroalkanoyl peroxides

R_F in peroxide (amt, mmol)	AMPS (mmol)	comonomer (amt, mmol)	product; yield (%)[a]	$\bar{M}$n($\bar{M}$w/$\bar{M}$n)[b]	[x:y][c]
C_3F_7 (3)	9	—	R_F-(AMPS)$_n$-R_F; 39	24 500 (28)	
$CF(CF_3)OC_3F_7$ (3)	9	—	R_F-(AMPS)$_n$-R_F; 58	20 500 (131)	
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (3)	9	—	R_F-(AMPS)$_n$-R_F; 38	12 000 (282)	
$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (2)	6	—	R_F-(AMPS)$_n$-R_F; 35	24 000 (76)	
C_3F_7 (3)	9	$CH_2=CHSiMe_3$ (9)	R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; 57	11 000 (291)	[90:10]
$CF(CF_3)OC_3F_7$ (3)	9	$CH_2=CHSiMe_3$ (9)	R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; 38	10 000 (400)	[78:22]
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (3)	9	$CH_2=CHSiMe_3$ (9)	R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; 30	17 400 (166)	[98:2]
C_3F_7 (3)	9	$CH_2=CMeCO_2Me$ (9)	R_F-(AMPS)$_x$-(CH_2-$CMeCO_2Me$)$_y$-R_F; 52	11 300 (216)	[93:7]
$CF(CF_3)OC_3F_7$ (3)	9	$CH_2=CMeCO_2Me$ (9)	R_F-(AMPS)$_x$-(CH_2-$CMeCO_2Me$)$_y$-R_F; 41	14 300 (211)	[94:6]
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (3)	9	$CH_2=CMeCO_2Me$ (9)	R_F-(AMPS)$_x$-(CH_2-$CMeCO_2Me$)$_y$-R_F; 41	8300 (726)	[92:8]

[a]The yields are based on the starting materials [AMPS, comonomer and the decarboxylated peroxide unit (R_F-R_F]. [b]The molecular weight of each polymer was determined by GPC; however, it is suggested that the obtained values by GPC indicate the apparent molecular weights owing to the strong aggregations of fluoroalkyl segments in aqueous solutions. [c]Copolymerization ratio was determined by ^{1}H NMR analysis.

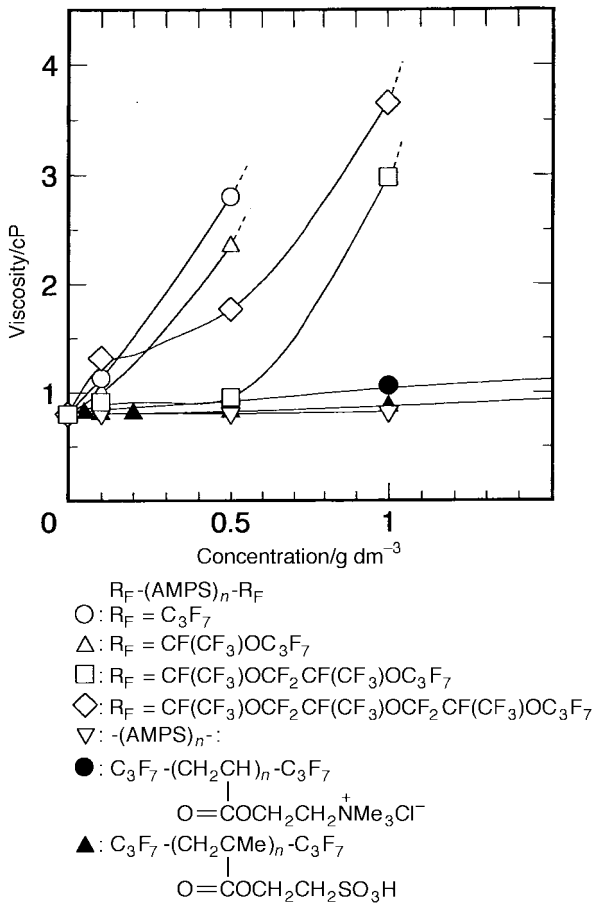


Fig. 2 Effect of concentration on viscosity of fluoroalkylated end-capped polymers measured at 30 °C by using a falling-sphere viscometer

trations. By contrast, non-fluorinated AMPS polymers were completely soluble in these media, and no gel formed.

The gelation abilities of some fluoroalkylated end-capped AMPS polymers were also studied by measuring the minimum concentrations of these polymers necessary for gelation according to the method reported of Hanabusa *et al.*[15,16] The minimum concentrations for gelation (C_{min}) in water and dimethyl sulfoxide (DMSO) at 30 °C are listed in Table 2.

As shown in Table 2, the gelling ability of fluoroalkylated end-capped copolymers is somewhat superior to that of the homopolymers, with C_{min} 2–9 g dm^{-3} for copolymers and 11–33 g dm^{-3} for homopolymers. This result is in fair agreement with the values of $\bar{M}w/\bar{M}n$ of polymers in Table 1, and the more polydisperse polymers exhibited the higher gelling ability. These findings would suggest that the copolymers are likely to promote the gelation sterically compared to the corresponding homopolymers.

These fluoroalkylated polymers also exhibited a quite similar property to the common water-swollen crosslinked polymeric hydrogels. That is, these fluoroalkylated AMPS polymers in water exhibited extremely high water adsorption, with the weight of adsorbed water by fluoroalkylated gelling copolymers: C_3F_7-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-C_3F_7 and C_3F_7-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-C_3F_7 201 and 213 times the weight of the dry gel, respectively. These values are similar to that of AMPS polymer hydrogel prepared by radical polymerization of AMPS and *N*,*N*′-methylenebisacrylamide initiated by H_2O_2.[17]

The striking characteristic of our AMPS polymers is their gelation both in water and in organic polar solvents under non-crosslinking conditions. This is because fluoroalkyl segments are solvophobic and aggregate in aqueous and organic media. In fact, it was reported that the solvophobic fluorocarbon tails in fluorinated amphiphiles are responsible for the formation of stable bilayer membrances in water and organic solvents.[18–22] Semifluorinated alkanes, such as $F(CF_2)_{10}(CH_2)_{12}H$, are also known to exhibit gel-like characteristics in hydrocarbon solvents [$H(CH_2)_pH$; p=8, 10, 12, 14].[23] Such aggregation of fluoroalkyl segments in these media should be enhanced due to the self-organization of polymers which causes gelation in these media.

Our AMPS polymers can form gels in both water and organic media due to the synergistic interaction between the aggregations of fluoroalkyl units, and the ionic interactions of the amide cations and the sulfonate anions as shown in the following schematic illustration.

On the other hand, in the case of the corresponding non-fluorinated polymer [-(AMPS)$_n$-], only the ionic interactions would operate and the gelation would not occur. Furthermore,

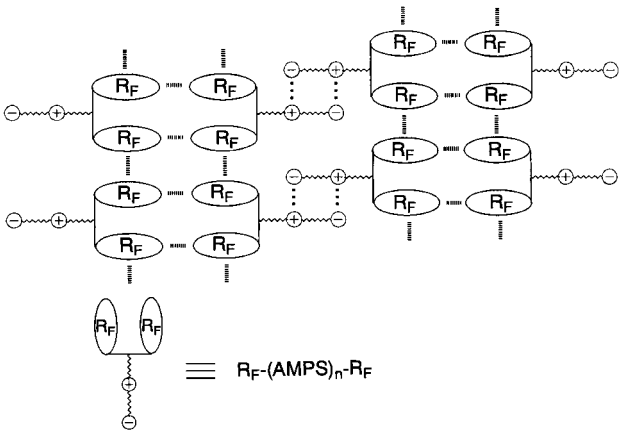


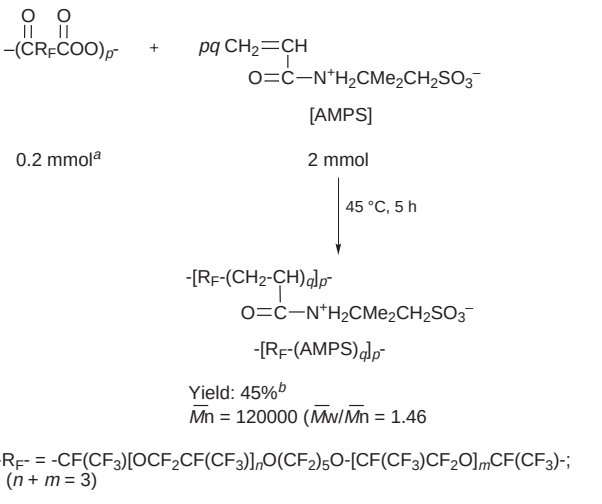
Fig. 3 Schematic illustration for gelation of R_F-(AMPS)$_n$-R_F

Table 2 Minimum concentrations for gelation (C_{min}) of fluoroalkylated AMPS homo- and co-polymers (in g dm^{-3} solvent) necessary for gelation at 30 °C

polymer	C_{min}/g dm^{-3} (gelator/medium)	
	water	DMSO
R_F-(AMPS)$_n$-R_F; R_F=C_3F_7	25	13
R_F-(AMPS)$_n$-R_F; R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	31	11
R_F-(AMPS)$_n$-R_F; R_F=$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	33	21
R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; R_F=C_3F_7	6	6
R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; R_F=$CF(CF_3)OC_3F_7$	6	8
R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	7	9
R_F-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-R_F; R_F=C_3F_7	2	5
R_F-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-R_F; R_F=$CF(CF_3)OC_3F_7$	9	7
R_F-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-R_F; R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	5	5

in the case of C_3F_7-(AETM)$_n$-C_3F_7 or C_3F_7-(MES)$_n$-C_3F_7, only the aggregation of the end-capped fluoroalkyl segments would operate, owing to the electrostatic repulsion of cationic segments (AETM) or anionic segments (MES) between the central polymer chains, and these polymers could not form gels.

In general, it is well-known that acrylated and methacrylated polymers containing longer perfluoroalkyl groups are strongly repelled by water or hydrocarbons owing to the strong electronegativity of fluorine. In contrast, the characteristics of our present fluoroalkylated end-capped AMPS polymers are to cause gelation under non-crosslinking conditions. This feature would be due to their unique structure (fluoroalkylated end-capped structure), and the end-capped fluoroalkyl segments in polymers could strongly aggregate rather than being repelled by aqueous or organic media. Therefore, it is suggested that AMPS polymers containing fluoroalkylene units but no fluoroalkyl end-cap units, {[-R_F-(AMPS)$_q$]$_p$-}, could not gel since the interaction between the aggregation of internal fluoroalkylene units in the polymers should become weaker than that of the aggregation of end-capped fluoroalkyl units in polymers. Previously, we reported that a polymeric perfluoro-oxaalkane diacyl peroxide {[-(O=C)R_FC(=O)OO]$_p$-} is a useful tool for the introduction of the perfluoro-oxaalkylene unit (-R_F-) into acrylic acid polymers.[24,25] Thus, we tried to prepare fluoroalkylene unit-containing AMPS polymers by using a polymeric perfluoro-oxaalkane diacyl peroxide. The result is shown in Scheme 3.



-R_F- = -CF(CF$_3$)[OCF$_2$CF(CF$_3$)]$_n$O(CF$_2$)$_5$O-[CF(CF$_3$)CF$_2$O]$_m$CF(CF$_3$)-; ($n + m = 3$)

Scheme 3 [a]Calculated on the basis of the peroxide monomer unit. [b]Yield based on AMPS and decarboxylated peroxide unit (R_F-)

As shown in Scheme 3, the reaction of AMPS with a polymeric perfluoro-oxaalkane diacyl peroxide proceeded smoothly to give AMPS polymer containing perfluoro-oxaalkylene units {-[R_F-(AMPS)$_q$]$_p$-}. The AMPS polymer containing fluoroalkylene units thus obtained was found to be easily soluble not only in water but also in methanol, ethanol, *N*,*N*-dimethylformamide and dimethyl sulfoxide even at higher concentrations above 1.0 g dm^{-3}, and the gel could not form in any of these media. This finding suggests that the internal fluoroalkylene units in the polymer are not likely to aggregate sterically with each other compared to the end-capped fluoroalkyl units. Therefore, it is concluded that fluoroalkylated end-capped AMPS polymers can cause gelation where strong aggregation of the end-capped fluoroalkyl segments is involved sterically in establishing the physical gel network in aqueous and organic media.

Hitherto, the synthesis of chemically-cross-linked AMPS polymer gels has been reported by Osada *et al.*, and this polymer hydrogel crosslinked by *N*,*N*′-methylenebisacrylamide has a high adsorptive property towards various metal ions.[17] Therefore, it is interesting to study the adsorptive property towards metal ions on the swelling equilibrium of our fluoroalkylated end-capped AMPS polymer hydrogel.

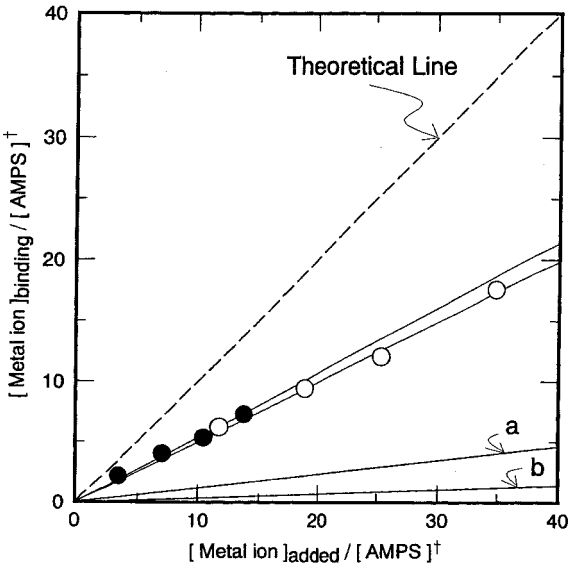


Fig. 4 Relationship between relative amount of metal ions binding to [R_F-(AMPS)$_x$-(CH$_2$CMeCO$_2$Me)$_y$-R_F; R_F=CF(CF$_3$)OCF$_2$CF-(CF$_3$)OC$_3$F$_7$] and relative amount of initial metal ions: (○) Co^{2+}; (●) Cr^{3+}; (– – –) theoretical line (corresponds to a 100% binding ratio); (*a*) Cr^{3+} ion (AMPS polymer curved by *N*,*N*′-methylenebisacrylamide–H_2O_2 system) (see ref. 17); (*b*) Co^{2+} ion (AMPS polymer cured by *N*,*N*′-methylenebisacrylamide–AIBN system) (see ref. 17). †[AMPS] indicates calculated concentration (mol dm^{-3}) based on polymer monomer unit.

The swelling equilibrium of R_F-(AMPS)$_x$-(CH$_2$CMeCO$_2$Me)$_y$-R_F[R_F=CF(CF$_3$)OCF$_2$CF(CF$_3$)OC$_3$F$_7$] hydrogel was studied in aqueous solutions of metal ions (Cr^{3+} and Co^{2+}). The metal-ion concentrations of the supernatant liquid after incubation (at 25 °C for 24 h) was spectrophotometrically determined from absorbance at 580 nm (Cr^{3+}) or 510 nm (Co^{2+}). The binding of the metal ions by this fluorinated gel was studied for a wide range of metal-ion concentrations, and the results are shown in Fig. 4.

We found a remarkable decrease in the absorbance of Cr^{3+} or Co^{2+} after the addition of the fluoroalkylated hydrogel to each metal ion solution. As shown in Fig. 4, the Cr^{3+} and Co^{2+} ion bindings increased linearly with an increase in the initial concentration of Cr^{3+} or Co^{2+} with *ca.* 60% binding ratio {based on the relative amount of Cr^{3+} (or Co^{2+}) binding to gel ([Metal ion]$_{binding}$/[AMPS]) and relative amount of initial metal ion ([Metal ion]$_{add}$/[AMPS])}. Furthermore, this fluoroalkylated hydrogel was found to have a similar adsorptive property towards Co^{2+} and Cr^{3+} ions. This finding would mean that these metal ions bind ionically to the anionic parts of the oligomer networks in the fluorinated gel, and this ionic interaction is not affected by the gel structure. On the other hand, bound Co^{2+} or Cr^{3+} ion was not released from the fluoroalkylated gel into water. This result also suggests that the interaction for the binding of the metal ions to the hydrogel is not coordination but ionic.

Interestingly, the fluoroalkylated end-capped AMPS polymer hydrogel was shown to have a higher metal ion binding power than the corresponding AMPS polymer hydrogels crosslinked by *N*,*N*′-methylenebisacrylamide–H_2O_2 or AIBN (azobisisobutyronitrile) system[17] as in Fig. 4. As a result, it can be said that the metal ions should interact in part with not only the anionic parts of the fluorinated hydrogel but also the fluoroalkyl segments in the fluorinated AMPS hydrogel possessing strong electron-withdrawing properties.

In this way, it was verified that the aggregation of fluoroalkyl segments in water and in organic media becomes a new driving

Table 3 Inhibitory effect of fluoroalkylated 2-acrylamido-2-methylpropanesulfonic polymers on the replication of HIV-1 in MT-4 cells

polymer	$\bar{M}n$	EC_{50}[a]/μg ml^{-1}	CC_{50}[b]/μg ml^{-1}
R_F-(AMPS)$_n$-R_F; $R_F = C_3F_7$	24 500	1.6	>100
R_F-(AMPS)$_n$-R_F; $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	12 000	1.6	>100
R_F-(AMPS)$_n$-R_F; $R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	24 000	1.7	>100
R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; $R_F = C_3F_7$	11 000	0.6	>100
R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; $R_F = CF(CF_3)OC_3F_7$	10 000	2.3	>100
R_F-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-R_F; $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	17 400	1.7	>100
R_F-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-R_F; $R_F = R_F = C_3F_7$	11 300	1.9	>100
R_F-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-R_F; $R_F = CF(CF_3)OC_3F_7$	14 300	0.23	>100
-(AMPS)$_n$-	5400	1.6	36
dextran sulfate (MW = 5000)		3.5	>100

[a]Fifty percent effective concentration, based on the inhibition of HIV-1 induced cytopathic effects in MT-4 cell. [b]Fifty percent cytotoxic concentration, based on the impairment of viability of mock-infected MT-4 cells.

factor for gelation as well as the well-known interactions such as hydrogen bonding and ionic interaction. Furthermore, it was clarified that the hydrogels which are built up through the aggregation of the fluoroalkyl segments have similar metal ion adsorptive properties to the well-known chemically crosslinked polymer hydrogels.

Because our fluoroalkylated AMPS polymers are gelling, it is of particular interest to investigate their potential as biologically active materials. Thus, a series of fluoroalkylated end-capped AMPS polymers have been evaluated for activity against HIV-1 replication in MT-4 cells (see Table 3).

As shown in Table 3, the 50% effective concentrations of the oligomers were 0.23–2.3 μg ml^{-1} in MT-4 cells, whereas they were not toxic at concentrations up to 100 μg ml^{-1}. These values are superior to those of dextran sulfate, which has been considered to be a potent and selective polymeric inhibitor of HIV-1 replication in cell culture to date.[26] On the other hand, non-fluorinated polymers were toxic to the host cells. The mechanism of action of the gelling polymers may also explain the inhibition of virus adsorption, as previously demonstrated for fluoroalkylated acrylic acid oligomers.[27–29] Interestingly, there is some correlation between the activity against HIV-1 and the C_{min} values (medium: water). As the activity against HIV-1 shown in Table 3 becomes higher, the C_{min} values (see Table 2) become in general smaller. Thus, fluoroalkylated end-capped AMPS copolymers such as C_3F_7-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-C_3F_7, $C_3F_7OCF(CF_3)$-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-$CF(CF_3)OC_3F_7$ exhibit a higher anti-HIV-1 activity than the corresponding homopolymers, and these copolymers possess in general a higher gelling ability. Therefore, it is suggested that the polymers possessing a higher gelling ability (that is, the oligomers which are more adsorbable) would interact strongly with the virus leading to more potent inhibitory effects against HIV-1 replication.

Very recently, we have reported that fluoroalkylated end-capped oligomers containing trimethylammonium segments possess antibacterial activity against *Staphylococcus aureus*.[3] Hence, our present fluoroalkylated end-capped AMPS polymers are also expected to show antibacterial activity since these polymers contain the amide segments. These AMPS polymers have been evaluated for their antibacterial activity against *S. aureus* by viable cell counting method as already reported.[3] About 10^8 cells per ml of *S. aureus* were exposed to 1 mg ml^{-1} of the oligomers in saline.

Fluoroalkylated end-capped AMPS homo- and co-polymers were in general inactive. However, of these AMPS polymers, perfluoropropylated AMPS–trimethylvinylsilane copolymer [C_3F_7-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-C_3F_7] was found to show bacterial activity (from 2.2×10^8 to 2×10^2 colony forming units levels). In addition, this copolymer was shown to possess a higher anti-HIV-1 activity (see Table 3).

Hitherto, the development of antibacterial cationic materials possessing fluoroalkyl segments has been limited.[30,31] However, C_3F_7-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-C_3F_7 was able to exhibit effectively not only anti-HIV-1 activity but also antibacterial activity.

In this way, it was demonstrated that our fluorinated AMPS oligomers have not only a gelling ability but also anti-HIV-1 activity or antibacterial activity, although these compounds are high molecular mass materials containing only fluoroalkylated end-groups in one oligomeric molecule. Hence, these new fluorinated compounds are expected to be widely applicable in various fields as new attractive fluorinated gelling functional materials possessing biological activities.

Experimental

NMR spectra were measured using a Varian Unity-plus 500 (500 MHz) spectrometer, while IR spectra were recorded on a HORIBA FT-300 FT-IR spectrophotometer. Molecular weights were calculated by using a JASCO-PU-980-Shodex-SE-11 gel permeation chromatography calibrated with standard poly(ethylene glycol) by using 0.5 mol dm^{-3} Na_2HPO_4 solution as the eluent. Absorption spectra were recorded on a Shimadzu UV-240 spectrophotometer. Solution viscosities were measured by using a falling-sphere Haake Viscometer D1-G.

Materials

A series of fluoroalkanoyl peroxides [($R_FCOO)_2$] and a polymeric perfluoro-oxaalkane diacyl peroxide were prepared by the method described in the literature.[24,25,32] 2-Acrylamido-2-methylpropanesulfonic acid was purchased from Tokyo Kasei Kogyo Co., Ltd. Trimethylvinylsilane was purchased from Shin-Etsu Co., Ltd. Chromium(III) nitrate and cobalt(II) chloride were purchased from Wako Chemicals.

General procedure for the synthesis of fluoroalkylated end-capped AMPS oligomers

Perfluorobutyryl peroxide (3 mmol) in a 1:1 mixture (AK-225) of 1,1-dichloro-2,2,3,3,3-pentafluoropropane and 1,3-dichloro-1,2,2,3,3-pentafluoropropane (110 g) was added to an aqueous solution (50%, w/w) of AMPS (9 mmol). The heterogeneous mixture was stirred vigorously at 40 °C for 5 h under nitrogen. After evaporation of the solvent, the crude product obtained was reprecipitated from water–tetrahydrofuran to give an α,ω-bis(perfluoropropylated) 2-acrylamido-2-methylpropanesulfonic acid polymer (1.13 g). This polymer exhibited the following spectral characteristics: IR (cm^{-1}) 3448 (OH, NH), 1641 [C(=O)N$^+$H$_2$-], 1310 (CF_3), 1259 (SO_3^-), 1228 (CF_2), 1101 (SO_3^-); ^{1}H NMR (D_2O) δ 1.51–2.12 (CH_2), 1.60 (CH_3), 2.29–2.71(CH), 3.65–4.22 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −3.45 (6F), −40.60 (4F), −50.20 (4F).

The other products obtained exhibited the following spectral characteristics.

$C_3F_7OCF(CF_3)$-(AMPS)$_n$-$CF(CF_3)OC_3F_7$. IR (cm^{-1}) 3469 (OH, NH), 1647 [C(=O)N^+H_2-], 1304 (CF_3), 1228 (CF_2); ^1H NMR (D_2O) δ 1.49–2.11 (CH_2), 1.60 (CH_3), 2.31–2.69 (CH), 3.61–4.15 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −1.56 to −5.10 (16F), −48.00 (4F).

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$-(AMPS)$_n$-$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$. IR ($cm^{-1}$) 3370 (OH, NH), 1647 [C(=O)N^+H_2-], 1303 (CF_3), 1255 (SO_3^-), 1226 (CF_2), 1101 (SO_3^-); ^1H NMR (D_2O) δ 1.38–1.83 (CH_2), 1.53 (CH_3), 1.97–2.30 (CH), 3.19–3.57 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −4.42 to −8.42 (26F), −54.0 to −56.26 (6F), −66.78 (2F).

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$-(AMPS)$_n$-$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$. IR ($cm^{-1}$) 3465 (OH, NH), 1641 [C(=O)N^+H_2-], 1238 (CF_2); ^1H NMR (D_2O) δ 1.51–2.12 (CH_2), 1.54 (CH_3), 2.35–2.71 (CH), 3.65–4.17 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −0.98 to −5.50 (36F), −49.10 (6F), −69.10 (4F).

Similarly, a series of fluoroalkylated end-capped AMPS copolymers were prepared by copolymerizations with fluoroalkanoyl peroxides. These exhibited the following spectral characteristics.

C_3F_7-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-C_3F_7. IR (cm^{-1}) 3409 (OH, NH), 1649 [C(=O)N^+H_2-], 1304 (CF_3), 1227 (CF_2); ^1H NMR (D_2O) δ −0.20–0.46 (CH_3), 1.51–2.12 (CH_2), 1.54 (CH_3), 2.29–2.71 (CH), 3.65–4.22 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO2H) δ −3.50 (6F), −40.60 (4F), −50.20 (4F).

$C_3F_7OCF(CF_3)$-(AMPS)$_y$-($CH_2CHSiMe_3$)$_y$-$CF(CF_3)OC_3F_7$. IR (cm^{-1}) 3453 (OH, NH), 1645 [C(=O)N^+H_2-], 1304 (CF_3), 1232 (CF_2); ^1H NMR (D_2O) δ −0.23–0.36 (CH_3), 1.49–2.11 (CH_2), 1.54 (CH_3), 2.31–2.69 (CH), 3.61–4.15 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −1.58 to −5.12 (16F), −48.00 (4F).

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$-(AMPS)$_x$-($CH_2CHSiMe_3$)$_y$-$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$. IR ($cm^{-1}$) 1647 [C(=O)$N^+H_2$-], 1227 ($CF_2$); ^1H NMR (D_2O) δ −0.18–0.33 (CH_3), 1.61–2.31 (CH_2), 1.44 (CH_3), 2.33–2.72 (CH), 3.59–4.08 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −3.64 to −7.10 (26F), −48.91 (6F), −67.48 (2F).

C_3F_7-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-C_3F_7. IR (cm^{-1}) 3452 (OH, NH), 1641 [C(=O)N^+H_2-], 1228 (CF_2); ^1H NMR (D_2O) δ 1.51–2.13 (CH_2, CH_3), 2.29–2.58 (CH), 3.65–4.20 (CH_2, CH_3); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −3.50 (6F), −40.65 (4F), −50.20 (4F).

$C_3F_7OCF(CF_3)$-(AMPS)$_x$-(CH_2CMeCO_2Me)$_y$-$CF(CF_3)OC_3F_7$. IR (cm^{-1}) 1645 [C(=O)N^+H_2-], 1315 (CF_3), 1238 (CF_2); ^1H NMR (D_2O) δ 1.49–2.11 (CH_2, CH_3), 2.33–2.70 (CH), 3.60–4.15 (CH_2, CH_3) ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −1.62 to −5.00 (16F), −48.30 (4F).

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$-(AMPS)$_x$-[$CH_2CMeCO_2CH_3$]$_y$-$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$. IR ($cm^{-1}$) 1642 [C(=O)$N^+H_2$-], 1236 ($CF_2$); ^1H NMR (D_2O) δ 1.52–2.26 (CH_2, CH_3), 2.33–2.78 (CH), 3.59–4.08 (CH_2, CH_3); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −3.60 to −7.10 (26F), −48.96 (6F), −67.48 (2F).

Similarly, fluoroalkylene unit-containing AMPS polymer {-[R_F-(AMPS)$_q$]$_p$-} was prepared by reaction of a polymeric perfluoro-oxaalkane diacyl peroxide with AMPS. This exhibited the following spectral characteristics.

-[$CF(CF_3)[OCF_2CF(CF_3)]_nO(CF_2)_5O$-[$CF(CF_3)CF_2O$]$_m$-$CF(CF_3)$-(AMPS)$_q$]$_p$-; $n+m=3$. IR (cm^{-1}) 3492 (OH, NH), 1643 [C(=O)N^+H_2-], 1226 (CF_2); ^1H NMR (D_2O) δ 0.82–1.80 (CH_2), 1.35 (CH_3), 1.82–2.23 (CH), 2.97–3.76 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −5.06 to −10.70 (21F), −48.24 (2F), −51.38 (10F), −71.11 (3F).

Viscosity measurements

The viscosities of aqueous solutions of fluoroalkylated end-capped AMPS polymers were measured at 5–50 °C using a falling-sphere viscometer (Haake Viscometer D1-G).

Typical procedure for gelation test

A procedure for studying the gel-formation ability was based on a method reported by Hanabusa *et al.*[15] Briefly, weighed fluoroalkylated end-capped AMPS polymer was mixed with water or organic fluid in a tube. The mixture was treated under ultrasonic conditions until the solid dissolved. The resulting solution was kept at 30 °C for 1 h, and then the gelation was assessed visually. When it was formed, the gel was stable and the tube was able to be inverted without changing the shape of the gel.

Metal ion binding by fluorinated AMPS oligomer hydrogel

Fluoroalkylated end-capped AMPS copolymer hydrogel was swelled with water in a measuring flask. After the addition of the required amount of aqueous metal ion solution into the flask, the flask was allowed to stand for 1 day at 25 °C. The metal-ion concentration of supernatant liquid after the incubation was spectrophotometrically determined.

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.[27]

Antibacterial assessment

The antibacterial activity of the oligomers was evaluated against *Staphylococcus aureus* by a viable cell counting method as described previously.[3]

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