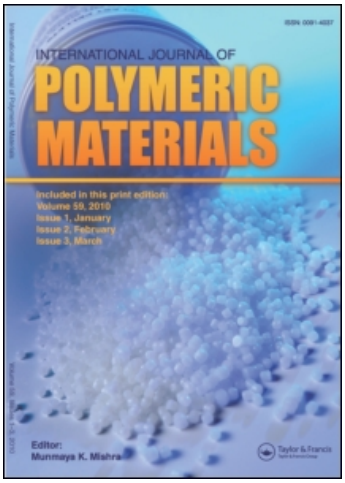

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SYNTHESIS OF FLUOROALKYL END-CAPPED OLIGOMERS CONTAINING PENDANT PHOSPHINIC AND PHOSPHONIC ACID SEGMENTS—APPLICATION TO NOVEL FLUORINATED BIOACTIVE POLYMERS POSSESSING ANTIBACTERIAL AND ANTI-HIV-1 ACTIVITIES

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A variety of fluoroalkyl end-capped homo- and co-oligomers containing pendant phosphinic acid segments were prepared by the reactions of fluoroalkanoyl peroxides with 3-acryloxypropylbutylphosphinic acid (APBPA) [or 3-acryloxypropyloctylphosphinic acid (APOPA)] and comonomers such as N,N-dimethylacrylamide (DMAA) and acrylic acid (ACA). These fluorinated APBPA and APOPA homooligomers thus obtained were insoluble in water but were soluble in common organic solvents, and were able to reduce the surface tension of m-xylene quite effectively. Fluorinated APBPA- and APOPA cooligomers were in general soluble in water and common organic solvents, and exhibited a good surfactant property against water. In addition, PMMA [poly(methyl methacrylate)] surface modified with these fluorinated oligomers containing pendant phosphinic acid segments was found to exhibit a strong oleophobicity imparted by fluorine at the surface. Similarly, fluoroalkyl end-capped homooligomers containing pendant phosphonic acid segments were prepared by the reactions of fluoroalkanoyl peroxides with 3-acryloxypropylphosphonic acid (APPA) under mild conditions. These obtained fluorinated oligomers containing pendant phosphonic acid segments were shown to have no solubility in water and organic solvents; however, these fluorinated oligomers could cause a gelation in water. Of particular interest, fluorinated oligomers containing pendant phosphinic acid segments were found to exhibit strong antibacterial activity against Staphylococcus aureus and Pseudomonas aeruginosa. Moreover, these fluorinated oligomers were also demonstrated to exhibit a potent and selective anti-HIV-1 (human immunodeficiency virus type 1) activity in vitro.

Keywords: end-capped fluoroalkyl, fluorinated oligomer, pendant phosphinic acid, pendant phosphonic acid, fluorinated polymeric biocide, solubility, surfactant property, surface modifier, oleophobicity, antibacterial activity, anti-HIV-1 activity

INTRODUCTION

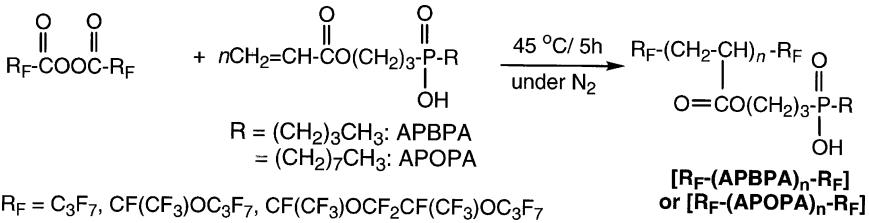
Recently, there has been a considerable interest in organofluorine compounds containing phosphorus atoms from the viewpoints of applications to surfactants, electrolytes, flame-retardant materials, and biological chelating agents [1]. Hitherto, Kotov et al. reported on the synthesis and applications of perfluorocarbon polymers containing phosphonic acid groups [2]. In contrast, partially fluorinated polymers, especially, fluoroalkyl end-capped oligomers, were demonstrated to exhibit a wide variety of unique properties that cannot be achieved

by the perfluorinated polymers [3]. From such a viewpoint, it has already been reported that fluoroalkyl end-capped oligomers containing pendant phosphoric acid groups could exhibit interesting characteristics such as a good surfactant property, surface modification agents on stainless-steel, and gelling property that set them apart from the corresponding perfluorinated polymers and randomly fluoroalkylated polymers [4]. Therefore, it is of particular interest to synthesize new fluoroalkyl end-capped oligomers containing phosphorus segments. This article reports on the synthesis and applications of new fluoroalkyl end-capped oligomers containing pendant phosphinic and phosphonic acid segments. Especially, it has been found that fluoroalkyl end-capped oligomers containing pendant phosphonic acid segments exhibit not only a strong antibacterial activity but also a potent and selective inhibitory effect against HIV-1 replication in vitro, and these results are also described herein.

RESULTS AND DISCUSSION

The reactions of fluoroalkanoyl peroxides with 3-acryloxypropylbutylphosphinic acid (APBPA) [or 3-acryloxypropyloctylphosphinic acid (APOPA)] were carried out at 45°C for 5 h under nitrogen. The reaction scheme and the results are shown in Scheme 1 and Table 1.

As shown in Scheme 1 and Table 1, the homooligomerizations of APBPA and APOPA with fluoroalkanoyl peroxides were found to proceed smoothly to afford fluoroalkyl end-capped APBPA and APOPA homooligomers [R_F–$(APBPA)_n$–R_F, R_F–$(APOPA)_n$–R_F and 10–28% isolated yields, respectively. The authors have studied R_F–$(APBPA)_n$–R_F and R_F–$(APOPA)_n$–R_F homooligomers for solubility. R_F–$(APBPA)_n$–R_F homooligomers were insoluble in water, but exhibited a good solubility in common organic solvents. On the other hand, R_F–$(APOPA)_n$–R_F homooligomers had a poor solubility in both water and common organic solvents. However, these APOPA



SCHEME 1

TABLE 1 Reactions of Fluoroalkanoyl Peroxides with **APBPA** (or **APOPA**)

Run	R_F in $(R_FCO_2)_2$ [mmol]	**APBPA** or **APOPA** [mmol]	Product Yield[a] [%]	Product $\overline{Mn}(\overline{MW}/\overline{Mn})$[b]
		APBPA		
1	C_3F_7 [4.4]	22	23	3800 (1.02)
2	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [2.5]	12	28	2900 (1.22)
		APOPA		
3	C_3F_7 [4.3]	21	23	1800 (1.02)
4	$CF(CF_3)OC_3F_7$ [3.3]	17	18	—
5	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [3.0]	15	10	—

[a]The yields are based on the starting materials [**APBPA** or **APOPA**] and the decarboxylated peroxide unit (R_F–R_F).
[b]Molecular weight was determined by GPC using THF as the eleunt.

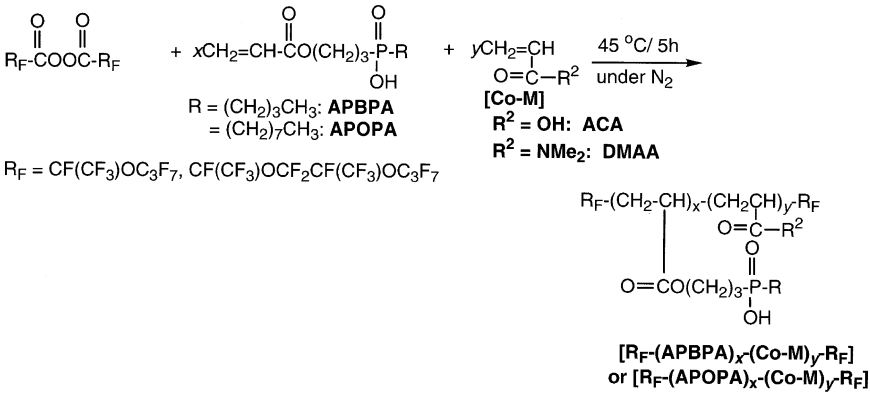
homooligomers exhibited solubility in 0.1 N NaOH and methanol, and perfluoropropylated APOPA homooligomer became soluble in tetrahydrofuran in addition to these solvents.

The molecular weights of $R_F-(APBPA)_n-R_F$ and $R_F-(APOPA)_n-R_F$ homooligomers were measured by GPC (gel permeation chromatography) by using tetrahydrofuran (THF) as the eluent, and the obtained values were of the order of 1000–3000. Due to the poor solubility of $R_F-(APOPA)_n-R_F$ homooligomers in water and organic solvents including THF, the authors were unable to measure the molecular weights of longer fluoroalkylated APOPA homooligomers in Table 1.

In order to develop the amphiphilic fluoroalkyl end-capped oligomers containing phosphinic acid segments, the authors tried to synthesize fluoroalkyl end-capped cooligomers by the cooligomerizations of fluoroalkanoyl peroxides with hydrophilic comonomers such as acrylic acid (ACA) and *N,N*-dimethylacrylamide (DMAA). The reaction scheme and the results are shown in Scheme 2 and Table 2.

As shown in Scheme 2 and Table 2, the cooligomerizations of APBPA (or APOPA) with comonomers by the use of fluoroalkanoyl peroxides were found to proceed under very mild conditions to afford the corresponding fluoroalkyl end-capped APBPA (or APOPA) co-oligomers in 23–72% isolated yields. The molecular weights of fluorinated APBPA and APOPA co-oligomers were measured by GPC by the use of THF as the eluent, and the obtained values are of the order of 1000–2000.

Fluoroalkyl end-capped APBPA co-oligomers thus obtained were found to exhibit amphiphilic characteristics, and these co-oligomers



SCHEME 2

TABLE 2 Reactions of Fluoroalkanoyl Peroxides with **APBPA** (or **APOPA**) with Comonomers (Co-M)

Run	R_F in $(R_FCO_2)_2$ [mmol]	**APBPA** or **APOPA** [mmol]	Co-M [mmol]	Yield[a]%	Product Mn (MW/Mn)[b]	[x : y][c]
		APBPA	$CH_2 = CHCOOH$			
6	$CF(CF_3)OC_3F_7$ [3.3]	6.7	17	38	1460 (1.08)	11 : 89
7	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [2.1]	4.2	21	51	2130 (1.11)	33 : 67
			$CH_2 = CHCONMe_2$			
8	$CF(CF_3)OC_3F_7$ [3.3]	3.3	17	48	1210 (1.07)	22 : 78
9	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [2.1]	4.2	21	72	2450 (1.07)	16 : 84
		APOPA	$CH_2 = CHCOOH$			
10	$CF(CF_3)OC_3F_7$ [3.3]	17	17	23	2820 (1.01)	5 : 95
11	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [2.5]	12	12	28	2000 (1.04)	9 : 91

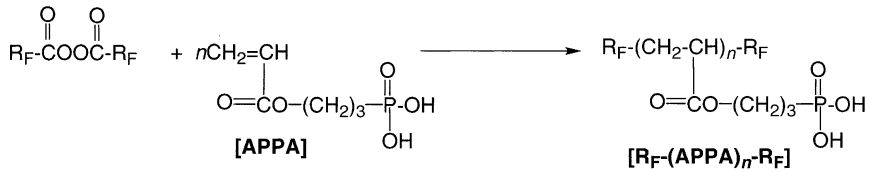
[a]The yields are based on the strating materials [**APBPA** (or **APOPA**) and Co-M], and the decarboxylated peroxide unit (R_F–R_F).
[b]Molecular weight was determined by GPC using THF as the eleunt.
[c]Co-oligomerization ratio was determined by ^{1}H-NMR.

were soluble not only in water but also in common organic solvents. In contrast, fluoroalkyl end-cappped APOPA co-oligomers were not soluble in water; however, these APOPA co-oligomers were shown to have a good solubility in common organic solvent. This is due to the highly oleophilic character of the octyl groups in fluorinated APOPA co-oligomers.

Similarly, the authors succeeded in preparing fluoroalkyl end-capped oligomers containing pendant phosphonic acid segments by the use of fluoroalkanoyl peroxide as a key intermediate as shown in Scheme 3.

As shown in Scheme 3, the reactions of fluoroalkanoyl peroxides with 3-acryloxypropylphosphonic acid (APPA) proceeded in heterogeneous solvent systems [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 and water] by stirring vigorously at 45°C for 5 h under nitrogen to give fluoroalkyl end-capped APPA homooligomers. However, the isolated yields of the expected products were extremely low (5–7%) compared to those of fluorinated APBPA and APOPA oligomers (see Table 3). The low product yields in Table 3 resulted from the heterogeneous reaction system. Fluorinated APPA homooligomers thus obtained were found to cause a gelation in water, and had no solubility in common organic solvents. The gelation abilities of fluorinated APPA homooligomers were studied by measuring the minimum concentration (C_{min}) of these homooligomers necessary for gelation in water at 30°C according to the method by Hanabusa et al. [5], and the results were as follows;

$R_F-(APPA)_n-R_F$	$C_{min}(g/dm^3)$
$R_F = CF(CF_3)OC_3F_7$	33
$= CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	50
$= CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	33



$R_F = CF(CF_3)O[CF_2CF(CF_3)O]_mC_3F_7$, m = 0, 1, 2

SCHEME 3

TABLE 3 Reactions of Fluoroalkanoyl Peroxides with **APPA**

Run	R_F in $(R_FCO_2)_2$ [mmol]	**APPA** [mmol]	Product Yield[a] [%]
13	$CF(CF_3)OC_3F_7$ [2.5]	26	7
14	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [2.1]	21	5
15	$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [1.8]	18	5

[a]The yields are based on the starting material [**APPPA**] and the decarboxylated peroxide unit (R_F-R_F).

The present authors previously reported that fluoroalkyl end-capped oligomers containing triol segments [$R_F-[CH_2CHC(=O)NHC(CH_2OH)_3)_n-R_F$: $R_F-(NAT)_n-R_F$] can cause a gelation in water, and the C_{min} value of this oligomer [R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$] is 42 g/dm^3 [6]. Thus, the gelation ability of the present APPA homooligomers is the same as that of $R_F-(NAT)_n-R_F$ homooligomer. The gelling characteristics of fluorinated APPA homooligomer are governed by the synergistical interactions of the aggregations of fluoroalkyl segments within oligomers and intermolecular hydrogen bonding between the hydroxyl segments in the pendant phosphonic acids segments. On the other hand, such gelling behavior could not be observed in fluorinated APBPA and APOPA oligomers due to the weaker hydrogen bonding interaction between hydroxyl segments in the phosphinic acid groups in comparison with those of the phosphonic acid groups. Thus, the intermolecular hydrogen bonding interaction between the hydroxyl segments in the phosphonic acids can participate strongly in the gel formation with the aggregation of end-capped fluoroalkyl groups because the hydroxyl groups in fluoroalkyl end-capped oligomers containing the phosphonic acid groups were introduced into the main oligomer chains through the ester spacer. In contrast, the authors previously reported that fluoroalkyl end-capped vinylphosphonic acid cooligomers [$R_F-[CH_2CHP(=O)(OH)_2]_x-(Co-M)_y-R_F$; Co–M: comonomers] were completely soluble in water and polar organic solvents, and cause no gelation in these solvents [4b]. It is suggested that the intermolecular hydrogen bonding interaction between hydroxyl segments in fluorinated vinylphosphonic acid cooligomers cannot participate strongly in the gelation that is caused by the aggregation of the end-capped fluoroalkyl segments because hydroxyl segments in fluorinated vinylphosphonic acid cooligomers are directly introduced into the main oligomer chains. The authors tried to measure the molecular weights of fluorinated APPA homooligomers by using

GPC analyses; however, they failed to measure the molecular weights owing to the gel formation.

Due to the development of the present fluoroalkyl end-capped oligomers containing pendant phosphinic acid groups as new fluorinated functional materials containing phosphorus segments, it is important to evaluate the surface properties of organic and aqueous media of fluorinated oligomers. The authors have measured the reduction of surface tension of *m*-xylene by $R_F-(APBPA)_n-R_F$ homooligomers with the Wilhelmy plate method at 30°C. The results are shown in Figure 1.

As shown in Figure 1, a significant decrease in the surface tension of *m*-xylene, to around 15 mN/m, was found for longer perfluorooxaalkyl end-capped APBPA homooligomers. Of particular interest, it was shown that $R_F-(APBPA)_n-R_F$ homooligomers are surface active against oleophilic solvents, though these oligomers possess a highly oleophilic butyl group.

Fluoroalkyl end-capped APBPA and APOPA cooligomers exhibit hydrophilic characteristics. Thus, these cooligomers are expected to

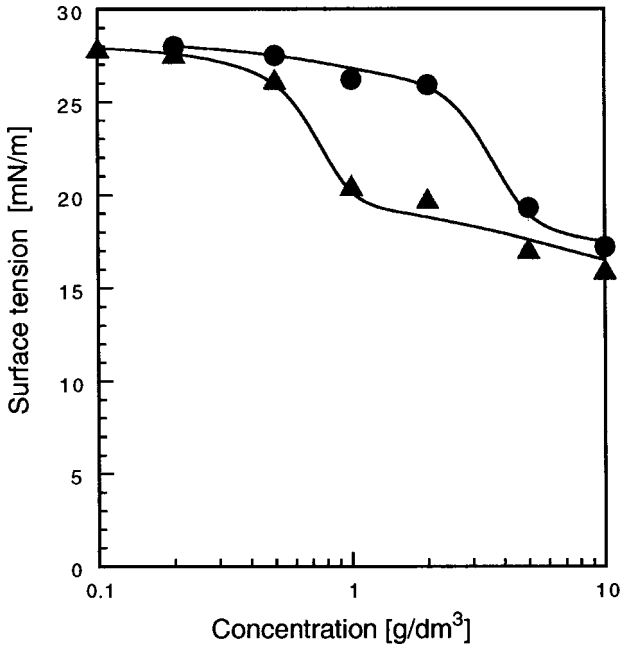


FIGURE 1 Surface tension of *m*-xylene solutions of $R_F-(APBPA)_n-R_F$ at 30°C. ●: R_F=CF(CF_3)OC_3F_7 (Run 1 in Table 1) ▲: R_F=CF(CF_3)OCF_2CF(CF_3)OC_3F_7 (Run 2 in Table 1).

apply to new hydrophilic oligosurfactants. In fact, as shown in Figures 2 and 3, these fluorinated cooligomers were able to reduce the surface tension of water (or 0.1 N NaOH) effectively with a clear breakpoint resembling a CMC (critical micelle concentration) to around 20 mN/m. In this respect, the fluorinated APBPA and APOPA oligomers could develop as new fluorinated polymeric surface active materials containing phosphorus residues.

Fluorinated APBPA homooligomers, APBPA co-oligomers and APOPA co-oligomers were found to exhibit a surface active property imparted by fluorine with a good oleophilicity toward organic media. Therefore, these oligomers are expected to develop into new fluorinated surface active compounds for common polymeric materials such as PMMA [poly(methyl methacrylate)]. These fluorinated oligomers were tested for surface activity as a new type of surface modification agents, and the results are shown in Table 4.

As shown in Table 4, the contact angle of dodecane on cast film of PMMA treated with fluorinated oligomers showed a significantly large value (28–56°) compared with that of non-treated PMMA (0°). Especially, in these homo- and co-oligomers, longer fluoroalkylated

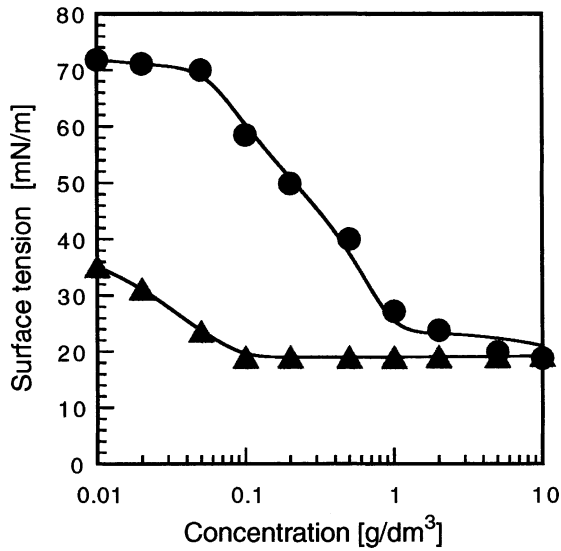


FIGURE 2 Surface tension of aqueous solutions of fluorinated APBPA cooligomers at 30°C. ●: R_F–$(APBPA)_x$–$(ACA)_y$–R_F; R_F=$CF(CF_3)OC_3F_7$ (Run 6 in Table 2) ▲: R_F–$(APBPA)_x$–$(DMAA)_y$–R_F; R_F=$CF(CF_3)OC_3F_7$ (Run 8 in Table 2).

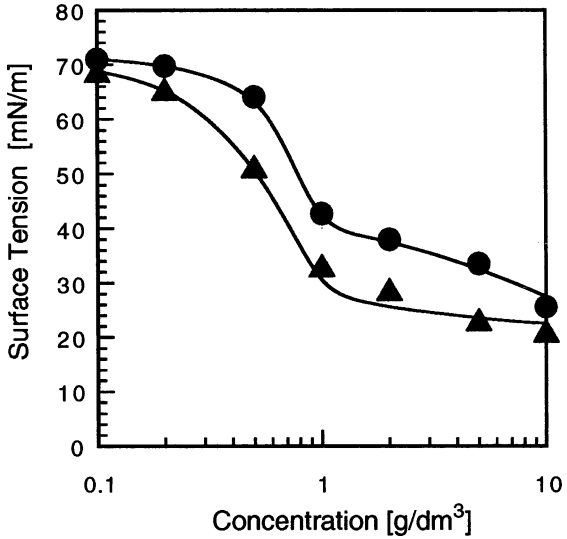


FIGURE 3 Surface tension of 0.1 N NaOH solutions of R_F–$(APOPA)_x$–$(ACA)_y$–R_F at 30°C. ●: $R_F = CF(CF_3)OC_3F_7$ (Run 10 in Table 2) ▲: $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (Run 11 in Table 2).

TABLE 4 Contact Angles of Dodecane on PMMA Films Treated with Fluoroalkyl End-Capped Phosphinic Acid Oligomers

No.	R_F in oligomer	Contact angles (degree) Dodecane
1	R_F–$(APBPA)_n$–R_F R_F=C_3F_7	28
2	R_F–$(APBPA)_n$–R_F R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	56
6	R_F–$(APBPA)_x$–$(ACA)_y$–R_F R_F=$CF(CF_3)OC_3F_7$	32
8	R_F–$(APBPA)_x$–$(DMAA)_y$–R_F R_F=$CF(CF_3)OC_3F_7$	37
10	R_F–$(APBPA)_x$–$(ACA)_y$–R_F R_F=$CF(CF_3)OC_3F_7$	28
11	R_F–$(APOPA)_x$–$(ACA)_y$–R_F R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	56
	Non-treated	0

[a]Concentration of oligomer based on PMMA is 1% (m/m).

oligomers exhibited large values for contact angle of dodecane. In particular interest, it was found that these oligomers exhibited a remarkably strong oleophobicity above the PMMA surface, although these oligomers possess highly oleophilic moieties such as butyl and octyl groups. From these results, it is suggested that longer fluoroalkyl segments in oligomers are likely to be arranged regularly above the PMMA surface.

Previously, the authors demonstrated that fluoroalkyl end-capped *N*-1,1-dimethyl-3-oxobutylacrylamide homooligomers [R_F–$(DOBAA)_n$–R_F] can form self-assembled molecular aggregates with the aggregations of the end-capped fluoroalkyl segments in organic media [7]. These fluorinated self-assemblies could recognize the hydrophilic amino and *N*,*N*-dimethylamino compounds as guest molecules. The present fluorinated APBPA and APOPA homo- and co-oligomers can exhibit a good surface active property as shown in Figures 1–3. Therefore, these fluorinated oligomers are suggested to form the self-assembled molecular aggregates in aqueous and organic media as well as R_F–$(DOBAA)_n$–R_F oligomers. The authors have studied the interactions of fluorinated APBPA homo- and co-oligomers, and APOPA co-oligomers with hydrophilic vinyltriphenylphosphonium bromide (VTPBr) as a guest molecule. These results are shown in Table 5.

Fluorinated APBA homo- and APBPA–DMAA co-oligomers were able to transfer VTPBr in 84 and 93% extractability from aqueous solution into 1,2-dichloroethane by the liquid-liquid extraction. Fluori-

TABLE 5 Solvent Extraction of $CH_2=CHP^+Ph_3\ Br^-$ (VTPBr) by Fluoroalkyl End-Capped Oligomers Containing Pendant Phosphinic Acid Segments

Run[a] R_F	Oligomer	Extractability (%)[b]
2	R_F–$(APBPA)_x$–R_F R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	84
9	R_F–$(APBPA)_x$–$(DMAA)_y$–R_F R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	93
11	R_F–$(APOPA)_x$–$(ACA)_y$–R_F R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	86

[a]Different from those in Tables 1 and 2.

[b]Org. layer (dichloroethane): [oligomer] = 2.0 g/dm^3; Aq. layer [VTPBr] = 0.05 mmol/dm^3; Extractability = $([VTPBr]_0 - [VTPBr]_{aq}/[VPBr]_0 \times 100$; $[VTPBr]_0$ = initial concentration of VTPBr in the aqueous layer; $[VTPBr]_{aq}$ = concentration of VTPBr in the aqueous layer as equilibrium.

nated APOPA-ACA co-oligomer had an extraction ability toward VTPBr (86%) under similar conditions. On the other hand, the extractability toward VTPBr by the corresponding nonfluorinated APBPA homooligomers [$-(APBPA)_n-$] and monomer (APBPA) became extremely lower: 41 and 0%, respectively. These findings suggest that fluorinated APBPA and APOPA oligomers should form self-assemblies in organic media to interact with VTPBr as a guest molecule, whereas the corresponding nonfluorinated APBPA oligomers would not form such self-assembled molecular aggregates in organic media. Therefore, these fluorinated aggregates–VTPBr (guest molecule) complexes exemplify new fluorinated functional materials imparted by phosphorus atoms.

It is well known that cationic polymers could in general show antibacterial activity, and numerous polycationic biocides have been reported so far [8]. Therefore, it is very interesting to synthesize novel fluorinated polymeric biocides from the point of the exploration of polymeric biocides possessing surface active properties imparted by fluorine. In fact, the authors have already reported on a variety of fluoroalkyl end-capped oligomers containing cationic segments such as ammonium and phosphonium groups [9]. These fluorinated cationic oligomers were shown to have a good antibacterial activity with a surface active property imparted by fluorine [10]. The present fluorinated APBPA and APOPA oligomers do not possess the cationic segments, but the hydroxyl segments in these oligomers would interact with each other through hydrogen bonding with the aggregation of the end-capped fluoroalkyl groups to form the self-assembled molecular aggregates. These fluorinated aggregates are expected to act as host moieties toward bacterial cells to exhibit antibacterial activity. The authors have investigated the antibacterial activity of fluorinated APBPA and APOPA oligomers against *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) by the viable cell counting method. About 10^8 cells/ml of *S. aureus* and *P. aeruginosa* were exposed to 1000 μg/ml of the oligomers in saline solution and Table 6 shows the colony forming units (cfu) versus exposure of these co-oligomers against *S. aureus* and *P. aeruginosa*.

As shown in Table 6, fluorinated APBPA and APOPA homo- and co-oligomers were found to exhibit extremely high antibacterial activity against *S. aureus* and these oligomers are capable of killing the bacterial cells from 10^8 to below 10^3 cfu except for $R_F-(APOPA)_x-(DMAA)_y-R_F$ [R_F=$CF(CF_3)OC_3F_7$]: 3.8×10^5 cfu. In general, the compounds, which are capable of killing bacterial cells from 10^8 to 10^5 cfu, are considered to possess antibacterial activity. These fluorinated co-oligomers were also active against *P. aeruginosa*.

TABLE 6 Antibacterial Activity of Fluoroalkylated End-Capped Oligomers against *Staphylococcus aureus* and *Pseudomonas aeruginosa*

Run[a]	Oligomer	*Staphylococcus aureus* (cfu/ml)[b]	*Pseudomonas aeruginosa* (cfu/ml)[b]
	Control	1.9×10^8	1.9×10^8
1	$[R_F-(APBPA)_x-R_F]$ C_3F_7	$<1 \times 10^3$	$<1 \times 10^3$
2	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ $[R_F-(APOPA)_x-R_F]$	$<1 \times 10^3$	1.3×10^6
3	C_3F_7 $[R_F-(APBPA)_x-(ACA)_y-R_F]$	$<1 \times 10^3$	$<1 \times 10^3$
6	$CF(CF_3)OC_3F_7$	$<1 \times 10^3$	$<1 \times 10^3$
7	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ $[R_F-(APBPA)_x-(DMAA)_y-R_F]$	$<1 \times 10^3$	1.2×10^5
8	$CF(CF_3)OC_3F_7$	3.8×10^5	1.3×10^7
9	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ $[R_F-(APOPA)_x-(ACA)_y-R_F]$	$<1 \times 10^3$	3.6×10^7
10	$CF(CF_3)OC_3F_7$	$<1 \times 10^3$	2.2×10^5
11	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	$< 1 \times 10^3$	$<1 \times 10^3$

[a]Different from those in Tables 1 and 2.
[b]cfu indicates colony-forming units.

In particular, fluorinated APOPA homooligomers and APOPA co-oligomers were found to exhibit higher antibacterial activity against *S. aureus* and *P. aeruginosa*. The reason why the present fluorinated oligomers containing pendant phosphinic acid segments exhibit strong antibacterial activity is not understood at present; however one thought is that the pendant phosphinic acid segments in these fluorinated oligomers could interact with bacterial cells by the adsorption of the fluorinated oligomers on the bacterial cell surface.

The present fluorinated oligomers possess pendant acidic moieties (phosphinic acids) in oligomer chains. Previously, the authors reported that fluoroalkyl end-capped acrylic acid and sulfonic acid oligomers possess a potent and selective anti-HIV-1 (human immunodeficiency virus type 1) activity in vitro [11]. From this viewpoint, the fluorinated APBPA and APOPA oligomers were strongly expected to exhibit anti-HIV-1 activity. A series of fluorinated APBPA and APOPA oligomers were evaluated for activity against HIV-1 replication in MT-4 cells, and the results are shown in Table 7.

As shown in Table 7, perfluorooxaalkylated APBPA homooligomers, perfluorooxaalkylated APBPA–ACA, and APOPA–ACA co-oligomers have proved to inhibit HIV-1 replication in cell cultures. However,

TABLE 7 Inhibitory Effect of Various Fluoroalkyl End-Capped Phosphinic Acid Oligomers on the Replication of HIV-1 in MT-4 Cells

Run	Oligomer	EC_{50} (μg/ml)[a]	CC_{50} (μg/ml)[b]
	$R_F-(APBPA)_n-R_F$		
1	$R_F=C_3F_7$	>100	>100
2	$=CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	7.8	>100
	$R_F-(APBPA)_x-(ACA)_y-R_F$		
6	$R_F=CF(CF_3)OC_3F_7$	3.2	>100
7	$=CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	6.6	>100
	$R_F-(APOPA)_x-(ACA)_y-R_F$		
10	$R_F=CF(CF_3)OC_3F_7$	1.0	>100
11	$=CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	1.4	>100
	Dextran Sulfate	1.6	>100

[a]Fifty percent effective concentration, based on the inhibition of HIV-1-induced cytopathicity in MT-4 cells.

[b]Fifty percent cytotoxic concentration, based on the reduction of viability of mock-infected MT-4 cells.

perfluoropropylated APBPA homooligomer was inactive against HIV-1 replication. Fluorinated APBPA-ACA and APOPA-ACA co-oligomers exhibited more potent and selective HIV-1 activity than that of the corresponding fluorinated APBPA homooligomer, and EC_{50} values were 1.0–6.6 μg/ml, whereas the 50% cytotoxic concentration (CC_{50}) was >100 μg/ml in each case. Of these, $R_F-(APOPA)_x-(ACA)_y-R_F$ [$R_F=CF(CF_3)OC_3F_7$] was the most active, with a 50% effective concentration (EC_{50}) of 1.0, a value similar to that of dextran sulfate, which has been considered to date to be a potent and selective polymeric inhibitor of HIV-1 replication in cell culture [12]. These results suggest that longer fluoroalkylated molecular aggregates containing pendant phosphinic acid and carboxyl segments could interact strongly with positively charged HIV-1 virus to exhibit anti-HIV-1 activity.

In this way, fluoroalkyl end-capped homo- and co-oligomers containing pendant phosphinic acid segments were prepared under very mild conditions by the use of fluoroalkanoyl peroxide as a key intermediate. These fluorinated homooligomers thus obtained, in general became soluble in organic media, and were able to reduce the surface tension of *m*-xylene quite effectively. Fluoroalkyl end-capped co-oligomers containing pendant phosphinic acid segments became soluble in water and common organic solvents, and were able to reduce the surface tension of water effectively. Additionally, these fluorinated oligomers containing phosphinic acid segments were applied as surface modification agents for common polymeric materials such as

PMMA, and the modified PMMA surface with these oligomers was shown to have a strong oleophobicity imparted by fluorine. Liquid-liquid extraction analyses showed that self-assembled molecular aggregates formed by fluorinated oligomers containing phosphinic acid segments in organic media could interact with hydrophilic vinyltriphenylphosphonium bromide as a guest molecule. Fluoroalkyl end-capped homooligomers containing pendant phosphonic acid segments were also prepared by using fluoroalkanoyl peroxide under similar conditions. These fluorinated homooligomers had no solubility in water and common organic media; however, these oligomers were found to cause a gelation in water. Of particular interest, it was shown that fluoroalkyl end-capped oligomers containing pendant phosphinic acid segments exhibited not only good antibacterial activity but also a potent and selective anti-HIV-1 activity in vitro. Therefore, these fluorinated oligomers have high potential for new fluorinated functional polymeric materials through not only the surface active property imparted by fluorine, but also good biological activities such as antibacterial activity and anti-HIV-1 activity imparted by phosphorus segments.

EXPERIMENTAL

Measurements

Fourier-transform infrared (FTIR) spectra were measured using a HORIBA FT-300 FT-IR spectrophotometer. NMR spectra and molecular weights were measured using a Varian Unity-plus 500 (500 MHz) spectrometer and a Shodex DS-4 (pump) and Shodex RI-71 (Detector) gel permeation chromatography (GPC) calibrated with polystyrene standards using tetrahydrofuran as the eluent, respectively. 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. Contact angles were measured by the use of the goniometer type contact angle meter (ERMA G-1-1000) according to the authors' previously reported method [13].

Materials

3-Acryloxypropylbutylphosphinic acid (APBPA), 3-acryloxypropyloctylphosphinic acid (APOPA), and 3-acryloxypropylphosphonic acid (APPA) were used as received from Nippon Chemical Industrial Co., Ltd. (Tokyo, Japan). Acrylic acid and vinyltriphenylphosphonium

bromide (VTPBr) were purchased from Wako Chemicals (Osaka, Japan) and Sigma-Aldrich Japan Inc. (Tokyo, Japan), respectively. *N*,*N*-Dimethylacrylamide (DMAA) was used as received from Kohjin Co., Ltd. (Tokyo, Japan). A series of fluoroalkanoyl peroxides [$(R_FCOO)_2$] were prepared by the method described in the literatures [14].

General Procedure for the Synthesis of Fluoroalkyl End-Capped Oligomers Containing Pendant Phosphinic Acid Segments

Perfluoro-2,5-dimethyl-3,6-dioxanonanoyl peroxide (2.5 mmol) 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 (130 g) was added to APBPA (17 mmol). The homogeneous solution was stirred at 45°C for 5 h under nitrogen. After evaporating the solvent, the crude products obtained were dialyzed with methanol to give a α, ω−bis(perfluoro-1-methyl-2-oxanonanoyl) APBPA homooligomer (1.44 g). This homooligomer exhibited the following spectra characteristics:

IR (ν/cm^{-1}) 3359 (OH), 1734 [C(=O)], 1305 (CF_3), 1241 (CF_2);
^{1}H NMR ($CDCl_3$) δ 0.83−0.95 (CH_3), 0.90−2.83 (CH_2, CH), 3.61−3.82 (CH_2), 3.95−4.25 (CH_2);
^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −4.34−−7.83 (26F), −54.02 (6F), −55.61 (2F).

Similarly, a series of fluoroalkyl end-capped oligomers containing pendant phosphinic acid segments were prepared by reactions with fluoroalkanoyl peroxides. These exhibited the following spectral characteristics:

R_F−(APBPA)$_n$−R_F [R_F=C_3F_7]
IR(ν/cm^{-1}) 3381 (OH), 1728 [C(=O)], 1303 (CF_3), 1242 (CF_2);
^{1}H NMR ($CDCl_3$) δ 0.83−1.00 (CH_3), 1.20−2.65 (CH_2, CH), 3.55−3.75 (CH_2), 3.90−4.35 (CH_2);
^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −5.64 (6F), −43.18 (4F), −54.65 (4F).

R_F−(APOPA)$_n$−R_F [R_F=C_3F_7]
IR (ν/cm^{-1}) 3381 (OH), 1728 [C(=O)], 1303 (CF_3), 1242 (CF_2);
^{1}H NMR ($CDCl_3$) δ 0.83−0.92 (CH_3), 1.20−2.72 (CH_2, CH), 3.40−3.90 (CH_2), 3.92−5.10 (CH_2);
^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −5.66−−6.65 (6F), −44.19 (4F), −54.21 (4F).

$R_F-(APOPA)_n-R_F$ [R_F=$CF(CF_3)OC_3F_7$]
IR (ν/cm^{-1}) 3426 (OH), 1736 [C(=O)], 1335 (CF_3), 1241 (CF_2);
^{1}H NMR (CD_3OD) δ 0.72–0.92 (CH_3), 1.00–2.85 (CH_2, CH), 3.18–3.62 (CH_2), 3.98–5.32 (CH_2);
^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ −5.22–−9.06 (16F), −55.07–−55.69 (6F).

$R_F-(APOPA)_n-R_F$ [R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$]
IR (ν/cm^{-1}) 3426 (OH), 1711 [C(=O)], 1310 (CF_3), 1242 (CF_2);
^{1}H NMR (CD_3OD) δ 0.82–0.93 (CH_3), 1.00–2.91 (CH_2, CH), 3.19–3.80 (CH_2), 3.92–5.21 (CH_2);
^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ −3.22–−9.06 (26F), −55.25–−55.69 (6F), −70.37 (2F).

$R_F-(APBPA)_x-(ACA)_y-R_F$ [R_F=$CF(CF_3)OC_3F_7$]
IR (ν/cm^{-1}) 3397 (OH), 1738 [C(=O)], 1303 (CF_3), 1240 (CF_2);
^{1}H NMR ($CDCl_3$) δ 0.86–0.94 (CH_3), 1.10–2.95 (CH_2, CH), 3.35–3.80 (CH_2), 3.90–4.60 (CH_2);
^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −3.84–−7.40 (16F), −54.00–−54.18 (6F).

$R_F-(APBPA)_x-(ACA)_y-R_F$ [R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$]
IR (ν/cm^{-1}) 3396 (OH), 1741 [C(=O)], 1385 (CF_3), 1236 (CF_2);
^{1}H NMR (CD_3OD) δ 0.60–0.88 (CH_3), 0.95–2.40 (CH_2, CH), 3.05–3.71 (CH_2), 3.56–4.45 (CH_2);
^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −3.60–−6.69 (26F), −554.21 (6F), −76.12 (2F).

$R_F-(APBPA)_x-(DMAA)_y-R_F$ [R_F=$CF(CF_3)OC_3F_7$]
IR (ν/cm^{-1}) 3398 (OH), 1732, 1634 [C(=O)], 1302 (CF_3), 1234 (CF_2);
^{1}H NMR ($CDCl_3$) δ 0.83–0.96 (CH_3), 1.10–2.11 (CH_2, CH), 2.31–3.20 (CH_2), 3.28–3.82 (CH_2); 4.00–4.46 (CH_2);
^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −5.53–−8.15 (16F), −53.97–−54.23 (6F).

$R_F-(APBPA)_x-(DMAA)_y-R_F$ [R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$]
IR (ν/cm^{-1}) 3451 (OH), 1732, 1671 [C(=O)], 1341 (CF_3), 1246 (CF_2);
^{1}H NMR ($CDCl_3$) δ 0.79–0.91 (CH_3), 1.05–2.05 (CH_2, CH), 2.45–3.23 (CH_2, CH_3), 3.45–3.80 (CH_2), 3.90–4.42 (CH_2);
^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ −3.48–−7.44 (26F), −53.05 (6F), −69.47 (2F).

$R_F-(APOPA)_x-(ACA)_y-R_F$ [R_F=$CF(CF_3)OC_3F_7$]
IR (ν/cm^{-1}) 3454 (OH), 1726, [C(=O)], 1310 (CF_3), 1242 (CF_2);
^{1}H NMR (CD_3OD) δ 0.75–0.94 (CH_3), 1.00–2.82 (CH_2, CH), 3.19–3.79 (CH_2), 3.82–5.18 (CH_2);

^{19}F NMR (CD_3OD, ext. CF_3CO_2H) $\delta -5.40 - -9.04$ (16F), $-53.64 - -55.12$ (6F).
$R_F-(APOPA)_x-(ACA)_y-R_F$ [R_F=$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$]
IR (ν/cm^{-1}) 3453 (OH), 1734 [C(=O)], 1305 (CF_3), 1242 (CF_2);
^{1}H NMR (CD_3OD) δ 0.62–0.90 (CH_3), 0.98–2.84 (CH_2, CH), 3.08–3.73 (CH_2), 3.83–5.22 (CH_2);
^{19}F NMR (CD_3OD, ext. CF_3CO_2H) $\delta -5.40 - -8.36$ (26F), $-55.33 - -55.66$ (6F), $-70.43 - -70.85$ (2F).

General Procedure for the Synthesis of Fluoroalkyl End-Capped Oligomers Containing Pendant Phosphonic Acid Segments

Perfluoro-2-methyl-3-oxahexanoyl peroxide (2.5 mmol) 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 (120 g) was added to an aqueous solution (50%, w/w) of APPA (26 mmol). The heterogeneous solution was stirred vigorously at 45°C for 5 h under nitrogen. The crude product obtained was washed well with methanol to remove the unreacted APPA monomer, and dried in vacuo to give a bis(perfluoro-1-methyl-2-oxapentylated) APPA homooligomer (0.44 g). This oligomer exhibited the following spectral characteristics:

IR (cm^{-1}) 3483 (OH), 1637 [C(=O)], 1308 (CF_3), 1281 (CF_2).

Similarly, a series of fluoroalkyl end-capped APPA homooligomers were prepared by homooligomerizations with fluoroalkanoyl peroxides. These exhibited the following spectral characteristics:

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)-(APPA)_n-CF(CF_3)OCF_2CF(CF_3)$-$OC_3F_7$:
IR (cm^{-1}) 3467 (OH), 1635 [C(=O)], 1310 (CF_3), 1240 (CF_2).
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)-(APPA)_n-$
$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$:
IR (cm^{-1}) 3453 (OH), 1633 [C(=O)], 1310 (CF_3), 1243 (CF_2).

NMR spectra were not measured due to gelling (highly viscoelastic) of these APPH homooligomers.

A Typical Procedure for Gelation Test

A procedure for studying the gel-formation ability was based on a method reported by Hanabusa et al. [5]. Briefly, weighted fluoroalkyl end-capped APPA homooligomer was mixed with water in a tube. The mixture was treated under ultrasonic conditions until the solid was dissolved. The resulting solution was kept at 30°C for 1 h, and gelation

was checked visually. The gel was stable and the tube could be inverted without changing the shape of the gel.

Antiviral Assays

Antiviral activity of the compounds against HIV-1 (HTLB-IIIb strain) replication was based on the inhibition of the virus-induced cytopathic effect in MT-4 cells as described previously [15].

Antibacterial Assessment

The antibacterial activity of the polymers was evaluated against *Staphylococcus aureus* and *Escherichia coli* by viable cell counting method as described previously [9d].

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