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Synthesis and surfactant properties of fluoroalkylated sulfonic acid oligomers as a new class of human immunodeficiency virus inhibitors

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Abstract

New fluoroalkylated 2-(methacryloxy)ethane sulfonic acid homo-oligomers were prepared in excellent to moderate yields by the reactions of fluoroalkanoyl peroxides with 2-(methacryloxy)ethane sulfonic acid (MES) under very mild conditions. These fluoroalkylated oligomers were easily soluble not only in water but also in polar solvents such as methanol, ethanol, *N,N*-dimethylformamide and dimethyl sulfoxide. These oligomers were able to reduce the surface tension of water to around 18 mN m^{-1}, and had a clear breakpoint resembling a CMC (critical micelle concentration). These fluoroalkylated homo-oligomers were also shown to be potent and selective inhibitors of human immunodeficiency virus type 1 (HIV-1) in vitro, and were about 10-times more inhibitory to HIV-1 than dextran sulfate. Furthermore, a series of fluoroalkylated 2-(methacryloxy)ethanesulfonic acid co-oligomers containing dimethylsilicone, trimethylsilyl and alkyl segments were prepared by the reactions of fluoroalkanoyl peroxides with MES and the corresponding monomers. These co-oligomers had a similar solubility and anti-HIV-1 activity to those of the corresponding homo-oligomer.

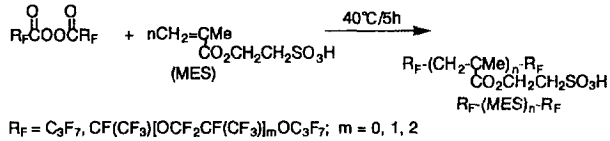
Keywords: Synthesis; Surfactant properties; Fluoroalkylated sulfonic acid oligomers; HIV-1; NMR spectroscopy; IR spectroscopy

1. Introduction

Recently, we have demonstrated that a series of acrylic acid oligomers containing fluoroalkyl groups [1,2] or perfluoro-oxaalkylene groups [3] inhibit selectively human immunodeficiency virus type 1 (HIV-1) in vitro, though it has been already reported that poly(acrylic acid) does not exhibit appreciable activity against HIV-1 [4]. In addition, it was clarified that these fluoroalkylated acrylic acid oligomers possess a similar activity against HIV-1 as that of dextran sulfate, which has been considered to be a potent and selective polymeric inhibitor of HIV-1 replication in cell culture to date [5]. The mechanism of action of these fluoroalkylated acrylic acid oligomers against HIV-1 has been attributed to the inhibition of virus adsorption/fusion to the cells, resulting from the interaction of the compounds with the viral glycoprotein positively charged gp120 [1]. This finding suggests that more anionic polymers could interact more strongly with gp120 to suppress virus adsorption to the cell membrane. From the viewpoint of the development of the attractive anti-HIV-1 agents, we were interested in preparing more acidic oligomers than the corresponding fluoroalkylated oligomers containing carboxy groups. In this paper, we would like to report on the synthesis and surfactant properties of novel fluoroalkylated sulfonic acid oligomers, with particular emphasis on the anti-HIV-1 activity of these oligomers.

2. Results and discussion

Fluoroalkylated sulfonic acid homo-oligomers were prepared by the reactions of 2-(methacryloxy)ethanesulfonic acid (MES) with various fluoroalkanoyl peroxides under very mild conditions (40 °C/5 h) as in Scheme 1:



$R_F = C_3F_7$, $CF(CF_3)[OCF_2CF(CF_3)]_mOC_3F_7$; m = 0, 1, 2

Scheme 1.

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Table 1
Reactions of MES with fluoroalkanoyl peroxides

R_F in peroxide (mmol)	MES (mmol)	R^F–(MES)$_n$–R_F	
		Yield (%) [a]	$\overline{M_n}$ [b]
C_3F_7 (6)	30	46	15300
C_3F_7 (3)	30	72	21500
$CFOC_3F_7$ (6) CF_3	30	61	13700
$CFOC_3F_7$ (3) CF_3	30	74	32100
$CFOCF_2CFOC_3F_7$ (6) CF_3 CF_3	29	51	12300
$CFOCF_2CFOC_3F_7$ (3) CF_3 CF_3	27	58	7800
$CFOCF_2CFOCF_3CFOC_3F_7$ (6) CF_3 CF_3 CF_3	30	53	12000
$CFOCF_2CFOCF_2CFOC_3F_7$ (3) CF_3 CF_3 CF_3	30	11	37400

[a] Yields based on starting materials: MES and the decarboxylated peroxide unit (R_F–R_F).
[b] $\overline{M_n}$ indicates the number average molecular weight.

As shown in Table 1, fluoroalkylated sulfonic acid oligomers were obtained in excellent to moderate isolated yields. In general, both the yields and molecular weights of the oligomers obtained were markedly dependent upon the molar ratios of MES and peroxides employed, increasing with greater molar ratios of MES in MES/peroxides as is usual for radical oligomerization. The molecular weights of the oligomers listed in Table 1 were determined by GPC (gel permeation chromatography) calibrated with standard pullulan using 0.2 M Na_2HPO_4 solution as the eluent, and the molecular weights of the oligomers obtained were relatively high (7800–37 400). This finding suggests that since these fluoroalkylated sulfonic acid oligomers are likely to form molecular aggregation in aqueous solutions, the values obtained by GPC indicate only apparent molecular weights. In fact, it was shown that the molecular weights of oligomers obtained by GPC analyses decreased remarkably on adding salts to the eluent.

A series of fluoroalkylated sulfonic acid oligomers prepared using fluoroalkanoyl peroxides were shown to be easily soluble not only in water but also in polar solvents such as methanol, ethanol, *N,N*-dimethylformamide and dimethyl sulfoxide. In general, it is well known that fluorinated polymers exhibit extremely low solubility in organic solvents [6]. In contrast, the relatively high solubility of our fluoroalkylated sulfonic acid homo-oligomers should open a new route to the development of the field of new functional fluorinated materials.

The surface properties of our fluoroalkylated sulfonic acid homo-oligomers were evaluated by measuring the reduction in surface tension of aqueous solutions by these oligomers using the Wilhelmy plate method at 30 °C. These results are shown in Fig. 1.

As Fig. 1 shows, a significant decrease in the surface tension of water, to around 18 mN m^{-1}, was found for perfluoro-oxaalkylated sulfonic acid oligomers compared to non-fluorinated sulfonic acid oligomers [–(MES)$_n$–: –(CH$_2$–CMeCO$_2$CH$_2$CH$_2$SO$_3$H)$_n$–; $\overline{M_n}$ = 11 500]. Previously, we reported that low-molecular fluorinated surfactants such as sodium *m*-perfluorooctylbenzene sulfonate are able to reduce the surface tension of water to 15 mN m^{-1} levels [7]. Thus, our fluoroalkylated sulfonic acid oligomers are novel high-molecular mass surfactants which can reduce the surface tension of water as effectively as the low-molecular ones. This interesting feature could be attributable to their unique structure, i.e., the fluoroalkyl groups in these oligomers are an end-capped structure and are likely to be arranged more regularly above the water surface, similar to the fluoroalkyl groups of usual low-molecular weight fluorinated surfactants. Unexpectedly, the shorter perfluoro-oxaalkyl chains in these oligomers were more effective in reducing the surface tension of water. This finding suggests that longer perfluoro-oxaalkyl chains in oligomers are not likely to be arranged more closely above the water surface owing to the steric hindrance of the fluoroalkyl group. More interestingly, as shown in Fig. 1, our fluoroalkylated sulfonic acid oligomers exhibited quite similar curves (plots of surface tensions versus log[C]: [C] is the concentration of the oligomers) typical of monomeric surfactants, and had a clear breakpoint resembling a CMC (critical micelle concentration) for each oligomer. Normally, no CMC or breakpoint resembling a CMC is observed in non-fluorinated polymeric surfactants [8]. Hence, our fluoroalkylated sulfonic acid oligomers probably undergo intra- or inter-molecular aggregation in aqueous solutions.

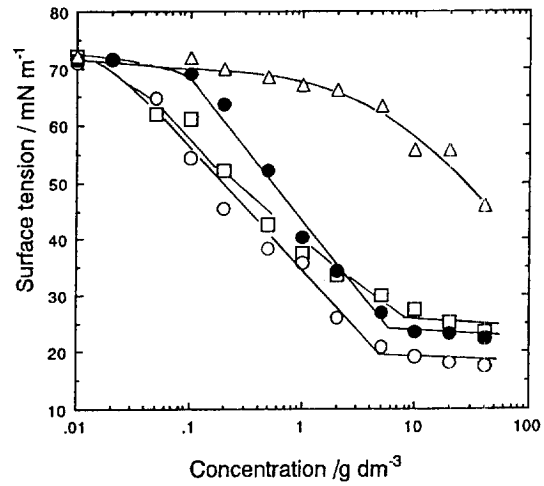


Fig. 1. Surface tension of aqueous solutions of R_F–(MES)$_n$–R_F. ○: R_F = CF(CF$_3$)OC$_3$F$_7$, $\overline{M_n}$ = 32 100; ●: R_F = CF(CF$_3$)OCF$_2$CF(CF$_3$)OC$_3$F$_7$, $\overline{M_n}$ = 7800; □: R_F = C$_3$F$_7$, $\overline{M_n}$ = 21 500; △ –(MES)$_n$–, $\overline{M_n}$ = 11 500.

Table 2
Inhibitory effect of R_F–(MES)$_n$–R_F on the replication of HIV-1 in MT-4 cells

	$\overline{M_n}$	EC_{50} ($\mu g\ ml^{-1}$) [a]	CC_{50} ($\mu g\ ml^{-1}$) [b]
R_F–(MES)$_n$–R_F			
$R_F = C_3F_7$	21500	0.44	> 100
$R_F = CF(CF_3)OC_3F_7$	13700	0.42	> 100
$R_F = CF(CF_3)OC_3F_7$	32100	0.38	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	12300	0.50	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	7800	0.48	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	12000	1.7	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	37400	1.6	> 100
R_F–(CH_2CHCO_2H)$_n$–R_F			
$R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [c]	8800	6.2	> 100
Dextran sulfate (MW = 5000)		3.5	> 100

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

Fluoroalkylated sulfonic acid oligomers prepared using fluoroalkanoyl peroxides possess unique segments such as sulfo and fluoroalkyl groups. Furthermore, these oligomers have been demonstrated to be easily soluble in water and to be capable of reducing the surface tension of water effectively. Hence, we would expect our fluoroalkylated sulfonic acid oligomers to behave as novel poly(anionic) inhibitors of HIV-1 and for this reason such fluoroalkylated sulfonic acid homo-oligomers have been evaluated for activity against HIV-1 replication in MT-4 cells (see Table 2).

As shown in Table 2, a series of fluoroalkylated sulfonic acid oligomers tested were observed to inhibit HIV-1-induced cytopathogenesis. The concentrations required to mediate the anti-HIV-1 effect were significantly lower than the concentrations required to inhibit the growth of MT-4 cells. Relative to dextran sulfate ($EC_{50} = 3.5\ \mu g\ ml^{-1}$) or fluoroalkylated oligomers containing carboxy groups ($EC_{50} = 6.2\ \mu g\ ml^{-1}$) superior EC_{50} values could be obtained with fluoroalkylated sulfonic acid oligomers. Of particular interest, in a series of fluoroalkylated oligomers, were perfluoro-1-methyl-2-oxapentylated sulfonic acid oligomers which have a clear breakpoint resembling a CMC in aqueous solutions and can reduce the surface tension of water more effectively [R_F–(MES)$_n$–R_F; $R_F = CF(CF_3)OC_3F_7$; $EC_{50} = 0.38$ or $0.42\ \mu g\ ml^{-1}$, which were the most active being about 10-times more inhibitory to HIV-1 than dextran sulfate which is considered at present to be a potent and selective polymeric inhibitor [5]. Thus, it can be considered that the intra- or inter-molecular aggregation of fluoroalkylated sulfonic acid oligomers could interact in part with HIV-1 to suppress virus adsorption to the cell membrane.

As described previously for fluoroalkylated acrylic acid oligomers [1], the mechanism of action of these fluoroalkylated sulfonic acid oligomers is considered to be primarily attributed to an inhibition of virus adsorption to the cell membrane. Anionic polymers such as dextran sulfate which possess anti-HIV-1 activity are known to interact with positively charged gp120 [9]. Due to the presence of both sulfo and fluoroalkyl groups, our fluoroalkylated sulfonic acid homo-oligomers are suggested to be more acidic than fluoroalkylated acrylic acid oligomers. In fact, the pH values of fluoroalkylated sulfonic acid oligomers are as listed in Table 3.

Table 3
Fluoroalkylated sulfonic acid oligomers – pH values

	pH
R_F–(MES)$_n$–R_F	
$R_F = C_3F_7$	2.5
$R_F = CF(CF_3)OC_3F_7$	2.5
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	2.6
R_F–(CH_2CHCO_2H)$_n$–R_F	
$R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3(OC_3F_7$	3.4
–(MES)$_n$–	2.5

Since the pH values listed show that our fluoroalkylated sulfonic acid homo-oligomers are more anionic than the corresponding acrylic acid oligomers, our present oligomers are suggested to interact more strongly with gp120 to suppress virus adsorption to the cell membrane. On the other hand, –(MES)$_n$– was more acidic than fluoroalkylated acrylic acid oligomers as listed in Table 2 above, though –(MES)$_n$– had a similar pH value to those of fluoroalkylated sulfonic acid homo-oligomers. Hitherto, sulfonic acid polymers such as poly(vinylsulfonic acid) sodium salt and poly(4-styrenesulfonic acid) sodium salt [9–11], and sulfated polymers such as dextran sulfate and sulfated poly(vinyl alcohol) [12] are well known as exhibiting potent inhibition of HIV-1 replication. Thus, –(MES)$_n$– is expected to possess a similar anti-HIV-1 activity as fluoroalkylated acrylic acid oligomers, and in fact this oligomers was demonstrated to possess a similar anti-HIV-1 activity ($EC_{50} = 1.6\ \mu g\ ml^{-1}$; $CC_{50} > 100\ \mu g\ ml^{-1}$) as those of the usual sulfonic acid and sulfated polymers. However, our present fluoroalkylated sulfonic acid

Table 4
Reactions of fluoroalkanoyl peroxides with MES and VP-Si or MP-Si

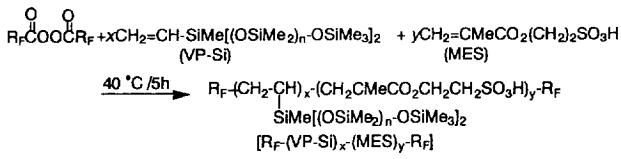
R_F in peroxide (mmol)	VP-Si or MP-Si (mmol)	MES (mmol)	Product	
			Yield (%) [a]	$\overline{M_n}$ (x/y) [b]
	VP-Si		R_F–(*VP-Si*)$_x$–(*MES*)$_y$–R_F	
C_3F_7 (9)	0.5	18	23	14800 (8:92)
C_3F_7 (9)	1	9	12	8600 (38:62)
$CF(CF_3)OC_3F_7$ (9)	0.5	18	24	17400 (7:93)
$CF(CF_3)OC_3F_7$ (9)	1	9	6	20200 (5:95)
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (9)	0.5	18	20	16900 (10:90)
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (9)	0.5	9	6	16300 (4:96)
$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (9)	0.5	18	10	30400 (12:88)
	MP-Si		R_F–(*MP-Si*)$_x$–(*MES*)$_y$–R_F	
C_3F_7 (9)	1	36	50	18200 (2:98)
C_3F_7 (9)	3	18	36	10800 (4:96)
C_3F_7 (9)	5	9	8	8000 (3:97)
$CF(CF_3)OC_3F_7$ (9)	1	35	54	9500 (1:99)
$CF(CF_3)OC_3F_7$ (9)	5	18	23	16400 (1:99)
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (9)	1	35	37	6810 (0.1:99.9)
$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (9)	3	18	18	16600 (4:96)
$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (9)	1	35	26	20600 (3:97)
$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (9)	3	18	20	23400 (4:96)
$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (9)	5	18	17	11600 (6:94)

[a] Yields based on starting materials: VP-Si (or MP-Si), MES and the decarboxylated peroxide unit (R_F–R_F).
[b] Co-oligomerization determined by ^{1}H NMR spectroscopy.

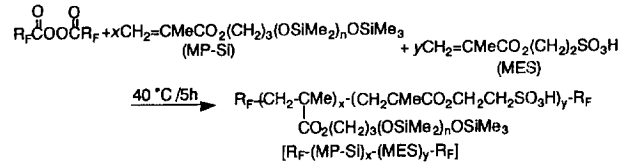
homo-oligomers were more active (about four-times) against HIV-1 than the corresponding non-fluorinated ones. This interesting result may be attributed to the fact that only the more anionic sulfo groups near to the fluoroalkyl units in oligomers interact strongly with positively charged gp120.

Recently, we have found that fluoroalkylated acrylic acid co-oligomers containing dimethylsilicone segments are more potent and selective inhibitors than the corresponding fluoroalkylated acrylic acid homo-oligomers [2]. Therefore, in our present fluoroalkylated sulfonic acid homo-oligomers, the co-oligomerization of MES with fluoroalkanoyl peroxide is expected to become a useful strategy for the development of the compounds possessing more potent anti-HIV-1 activity. From such points of view, we tried to prepare a series of fluoroalkylated sulfonic acid co-oligomers containing dimethylsilicones possessing one vinyl end-group (VP-Si: average molecular weight, 4900) or one methacryloxypropyl group (MP-Si: average molecular weight, 1000). The reaction schemes are as follows (Schemes 2 and 3).

A series of fluoroalkanoyl peroxides were treated with MES and VP-Si or MP-Si as shown in Schemes 2 and 3. These results were summarized in Table 4.



Scheme 2.



Scheme 3.

As shown in Table 4, both perfluoropropylated and perfluoro-oxaalkylated sulfonic acid/dimethylsilicone co-oligomers [R_F–(VP-Si)$_x$–(MES)$_y$–R_F, R_F–(MP-Si)$_x$–(MES)$_y$–R_F] were obtained in excellent to moderate yield under very mild conditions. The molecular weights of the co-oligomers were obtained by GPC analyses in the same manner as with those of the fluoroalkylated sulfonic acid homo-oligomers. GPC analyses showed that these co-oligomers are likely to undergo molecular aggregation in aqueous solutions in the same well as the homo-oligomers. and again the obtained values are suggested as being apparent molecular weights. In co-oligomerizations with VP-Si or MP-Si, the content of silicone segments in co-oligomers obtained was in general higher in the case of VP-Si (x=4–13). On the other hand, R_F–(MP-Si)$_x$–(MES)$_y$–R_F in which the co-oligomerization ratio (x) of dimethylsilicone segments was not so high (x=0.1–9) were obtained as listed in Table 4. However, the content of silicone segments in one of the co-oligomers was relatively high [i.e., the content of silicone segment in C_3F_7–(MP-Si)$_x$–(MES)$_y$–C_3F_7 (x=2) in Table 4 is ca. 10 mol%] since the silicone segments MP-Si is a macromonomer.

Table 5
Inhibitory effect of fluoroalkylated sulfonic acid co-oligomers containing dimethylsilicone segments on the replication of HIV-1 in MT-4 cells

Co-oligomer	$\overline{M_n}(x/y)$	EC_{50}[a] ($\mu g\ ml^{-1}$)	CC_{50}[b] ($\mu g\ ml^{-1}$)
R_F–(*VP-Si*)$_x$–(*MES*)$_y$–R_F			
$R_F = C_3F_7$	14800 (8:92)	1.1	> 100
$R_F = CF(CF_3)OC_3F_7$	17400 (7:93)	0.49	> 100
$R_F = CF(CF_3)OC_3F_7$	20200 (5:95	0.45	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	16900 (10:90)	1.5	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	16300 (4:96)	1.4	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	30400 (12:88)	1.6	> 100
R_F–(*MP-Si*)$_x$–(*MES*)$_y$–R_F			
$R_F = C_3F_7$	18200 (2:98)	0.39	> 100
$R_F = C_3F_7$	10800 (4:96)	0.45	> 100
$R_F = CF(CF_3)OC_3F_7$	9500 (1:99)	0.56	> 100
$R_F = CF(CF_3)OC_3F_7$	16400 (1:99)	0.38	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	6800 (0.1:99.9)	1.3	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	16600 (4:96)	1.2	> 100
$R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	20600 (3:97)	1.6	> 100

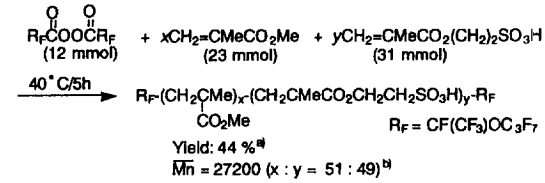
[a] Fifty per cent effective concentration, based on the inhibition of HIV-1 induced cytopathic effects in MT-4 cells.
[b] Fifty per cent cytotoxic concentration, based on the impairment of viability of mock-infected MT-4 cells.

The series of fluoroalkylated sulfonic acid co-oligomers containing dimethylsilicone segments thus obtained were tested for solubility. These co-oligomers were found to be soluble not only in water but also in polar solvents such as methanol, ethanol, dimethyl sulfoxide and *N,N*-dimethylformamide. Thus, co-oligomerization with dimethylsilicone segments did not lead to an improvement in solubility in common organic solvents compared with the corresponding fluoroalkylated homo-oligomers. On the other hand, the corresponding co-oligomerization of acrylic acid with dimethylsilicone segments led to a drastic improvement in solubility in common non-polar organic solvents [2].

Our new fluoroalkylated sulfonic acid co-oligomers were readily soluble in water. Hence, these co-oligomers are expected to possess anti-HIV-1 activity as well as the corresponding homo-oligomers. In fact, a series of fluoroalkylated sulfonic acid co-oligomers containing dimethylsilicone segments have been evaluated for their anti-HIV-1 activity in MT-4 cells. The results obtained are listed in Table 5.

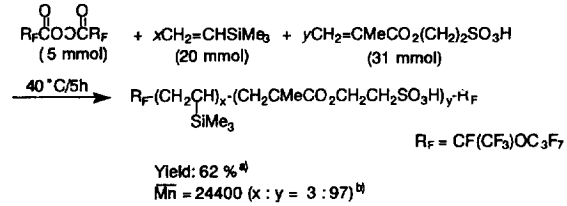
As shown in Table 5, a series of fluoroalkylated sulfonic acid co-oligomers containing dimethylsilicone segments inhibited HIV-1-induced cytopathogenesis as well as the corresponding fluoroalkylated homo-oligomers. The concentration required to exert the anti−HIV-1 effect were significantly lower than the concentrations required to inhibit the growth of MT-4 cells. In particular, perfluoro-1-methyl-2-oxapentylated co-oligomers proved to be the most active against HIV-1 replication in MT-4 cells with EC_{50} values of 0.38–0.49 $\mu g\ ml^{-1}$. However, these values are almost the same as with those of the fluoroalkylated sulfonic acid homo-oligomers as shown in Table 2.

Similarly, we prepared fluoroalkylated 2-(methacryloxy)ethanesulfonic acid/methyl methacrylate or trimethylvinylsilane co-oligomers by using fluoroalkanoyl peroxides as shown in Schemes 4 and 5.



[a] Yields based on starting materials: MES, methyl methacrylate and the decarboxylated peroxide unit (R_F–R_F).
[b] Co-oligomerization determined by ^1H NMR spectroscopy.

Scheme 4.



[a] Yields based on starting materials: MES, trimethylvinylsilane and the decarboxylated peroxide unit (R_F–R_F).
[b] Co-oligomerization determined by ^1H NMR spectroscopy.

Scheme 5.

However, these fluoroalkylated co-oligomers were shown to possess a similar solubility (soluble in water and water-soluble polar solvents such as methanol, ethanol, *N,N*-dimethylformamide and dimethyl sulfoxide) to that of fluoroalkylated sulfonic acid co-oligomers containing dimethylsilicone segments. Furthermore, these fluoroalkylated oligomers exhibited a similar anti-HIV-1 activity in MT-4 cells as fluoroalkylated sulfonic acid homo-oligomers and the

corresponding co-oligomers containing dimethylsilicone segments:

R_F–$(CH_2CR^1R^2)_x$–$(CH_2CMeCO_2CH_2CH_2SO_3H)_y$–$R_F$
[R_F = $CF(CF_3)OC_3F_7$]

R^1	R^2	EC_{50} ($\mu g\ ml^{-1}$)	CC_{50} ($\mu g\ ml^{-1}$)
Me	CO_2Me	1.7	>100
H	$SiMe_3$	1.4	>100

Thus, it was shown that a higher anti-HIV-1 activity in these fluoroalkylated sulfonic acid oligomers was not developed by co-oligomerization, in contrast to the case of the corresponding fluoroalkylated acrylic acid homo- and co-oligomers [2,13]. This finding could, in part, depend on the fact that co-oligomerization of the sulfonic acid oligomers did not lead to an improvement in solubility, in contrast to the corresponding acrylic acid oligomers. It has been reported that activity against HIV-1 is sensitive to the oleophilic property of fluoroalkylated oligomers, the more hydrophilic or more oleophilic fluoroalkylated oligomers having a weaker effect on the interaction between gp120 in HIV-1 and CD4 receptors [13].

3. Experimental details

3.1. Measurements

NMR spectra were measured with a JEOL-EX-270 FT-NMR (270 MHz) and 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 830-RI gel permeation chromatograph containing two columns filled with Shodex-A-80M, calibration being based on pullulan standards.

3.2. Materials

A series of fluoroalkanoyl peroxides [$(R_FCOO)_2$] were prepared by the reactions of the corresponding acyl halides and hydrogen peroxides in the presence of aqueous sodium hydroxide according to our previously reported method [14]. MES and VP-Si (or MP-Si) were supplied by the NOF Corporation and Chisso Corporation, respectively.

3.3. General procedure for the synthesis of fluoroalkylated 2-(methacryloxy)ethanesulfonic acid oligomers

Perfluorobutyryl peroxide (6 mmol) in Freon-113 ($CF_2ClCFCl_2$) solution (80 g) was added to the aqueous solution (50%, w/w) of MES (30 mmol). The heterogeneous solution was stirred vigorously at 40 °C for 5 h under nitrogen. Methanol was added to the reaction mixture and the solvent evaporated under reduced pressure. The crude product obtained was reprecipitated from methanol/ethyl acetate to give bis(perfluoropropylated) 2-(methacryloxy)ethanesulfonic acid oligomers (3.62 g).

C_3F_7–$(CH_2$–$CMeCO_2CH_2CH_2SO_3H)_n$–C_3F_7: IR (ν/cm^{-1}): 3270 (OH); 1726 (C=O); 1268 (CF_3); 1232 (CF_2); 1165 (SO_3). ^1H NMR (D_2O) δ: 0.57–1.25 (CH_3); 1.68–2.11 (CH_2); 3.00–3.32 (CH_2); 4.07–4.43 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −3.19 (6F); −37.2 (4F); −51.3 (4F) ppm.

The other products obtained exhibited the following spectral characteristics:

$C_3F_7OCF(CF_3)$–$(CH_2$–$CMeCO_2CH_2CH_2SO_3H)_n$–$CF(CF_3)OC_3F_7$: IR (ν/cm^{-1}): 3285 (OH); 1720 (C=O); 1260 (CF_3); 1225 (CF_2); 1165 (SO_3). ^1H NMR (D_2O) δ: 0.40–1.14 (CH_3); 1.20–2.09 (CH_2); 3.14–3.40 (CH_2); 4.05–4.54 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −3.75 to −8.13 (16F); −51.3 to −55.0 (6F) ppm.

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$–$(CH_2$–$CMeCO_2CH_2CH_2SO_3H)_n$–$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: IR ($\nu$/$cm^{-1}$): 3390 (OH); 1726 (C=O); 1298 (CF_3); 1240 (CF_2); 1263 (SO_3). ^1H NMR (D_2O) δ: 0.90–1.47 (CH_3); 1.82–2.27 (CH_2); 3.24–3.47 (CH_2); 4.25–4.50 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −4.28 to −7.25 (26F); −58.20 (6F); −68.70 (2F) ppm.

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$–$(CH_2$–$CMeCO_2CH_2CH_2SO_3H)_n$–$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: IR ($\nu$/$cm^{-1}$): 3265 (OH); 1726 (C=O); 1302 (CF_3); 1242 (CF_2); 1155 (SO_3). ^1H NMR (D_2O) δ: 0.60–1.13 (CH_3); 1.68–2.11 (CH_2); 3.10–3.33 (CH_2); 4.00–4.49 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −1.0 to −5.5 (36F); −52.5 (6F); −68.0 (4F) ppm.

Similarly, a series of fluoroalkylated 2-(methacryloxy)ethanesulfonic acid co-oligomers were prepared by co-oligomerizations with fluoroalkanoyl peroxides. These exhibited the following spectral characteristics:

R_F–$[CH_2$–$CMeCO_2(CH_2)_3(SiMe_2O)_nSiMe_3]_x$–$(CH_2$–$CMeCO_2CH_2CH_2SO_3H)_y$–$R_F$:

$R_F = C_3F_7$: IR (ν/cm^{-1}): 3265 (OH); 1724 (C=O); 1260 (CF_3); 1227 (CF_2); 1167 (SO_3, Si–OSi). ^1H NMR (D_2O) δ: 0.60–1.10 (CH_3); 1.64–2.11 (CH_2); 3.05–3.33 (CH_2); 4.00–4.44 (CH_2) pp. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −0.90 (6F); −36.0 (4F); −48.7 (4F) ppm.

$R_F = C_3F_7OCF(CF_3)$: IR (ν/cm^{-1}): 3270 (OH); 1720 (C=O); 1276 (CF_3); 1230 (CF_2); 1165 (SO_3, Si–OSi). ^1H NMR (D_2O) δ: 0.60–1.10 (CH_3); 1.68–2.08 (CH_2); 3.08–3.31 (CH_2); 4.00–4.40 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −2.0 (16F); −51.0 (6F) ppm.

$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)$: IR ($\nu$/$cm^{-1}$): 3270 (OH); 1724 (C=O); 1270 (CF_3); 1234 (CF_2); 1163 (SO_3, Si–OSi). ^1H NMR (D_2O) δ: 0.63–1.14 (CH_3); 1.71–2.08 (CH_2); 3.11–3.37 (CH_2); 4.08–4.45 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −2.0 to −3.0 (26F); −49.5 to −51.5 (6F) ppm.

$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$: IR ($\nu$/$cm^{-1}$): 3260 (OH); 1722 (C=O); 1238 (CF_2); 1163 (SO_3, Si–OSi). ^1H NMR (D_2O) δ: 0.65–1.16 (CH_3); 1.69–

2.05 (CH_2); 3.12–3.35 (CH_2); 4.02–4.48 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −2.6 to −4.0 (36F); −51.8 (6F) ppm.

R_F–[CH_2–CHSiMe[$(OSiMe_2)_n$–$OSiMe_3]_2]_x$–(CH_2–C-MeCH$_2$CH$_2$$SO_3H)_y$–$R_F$:

$R_F = C_3F_7$: IR (ν/cm^{-1}): 3270 (OH); 1722 (C=O); 1275 (CF_3); 1224 (CF_2); 1167 (SO_3, Si–OSi). ^1H NMR (D_2O) δ: 0.60–1.29 (CH_3); 1.40–2.20 (CH_2); 3.11–3.38 (CH_2); 4.00–4.49 (CH_2) ppm.

$R_F = C_3F_7OCF(CF_3)$: IR (ν/cm^{-1}): 3280 (OH); 1720 (C=O); 1260 (CF_3); 1224 (CF_2); 1164 (SO_3, Si–OSi). ^1H NMR (D_2O) δ: 0.44–0.92 (CH_3); 1.41–1.81 (CH_2); 2.82–3.05 (CH_2); 3.83–4.15 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −2.6 to −6.6 (16F); −51 (6F) ppm.

$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)$: IR ($\nu$/cm^{-1}): 3265 (OH); 1722 (C=O); 1255 (CF_3); 1226 (CF_2); 1168 (SO_3, Si–OSi). ^1H NMR (D_2O) δ: 0.52–1.11 (CH_3); 1.65–2.11 (CH_2); 3.08–3.33 (CH_2); 4.00–4.44 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −1.2 to −4.6 (26F); −50.0 to −52.0 (6F); −65.5 to −67.1 (2F) ppm.

$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$: IR ($\nu$/cm^{-1}): 3265 (OH); 1724 (C=O); 1290 (CF_3); 1240 (CF_2); 1161 (SO_3, Si–OSi). ^1H NMR (D_2O) δ: 0.65–1.16 (CH_3); 1.68–2.16 (CH_2); 3.11–3.40 (CH_2); 4.00–4.47 (CH_2) ppm. ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ: −2.1 to −4.8 (36F); −52.0 (6F); −66.5 (4F) ppm.

$C_3F_7OCF(CF_3)$–($CH_2CMeCO_2Me)_x$–(CH_2–$CMeCO_2$-$CH_2CH_2SO_3H)_n$–$CF(CF_3)OC_3F_7$: IR (ν/cm^{-1}): 3113 (OH); 1728 (C=O); 1394 (CF_3); 1267 (CF_2). ^1H NMR (CD_3OD) δ: 0.91–1.32 (CH_3); 0.83–2.24 (CH_2); 4.32–4.53 (CH_2) ppm. ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.8 to −7.3 (16F); −53.8 (6F) ppm.

$C_3F_7OCF(CF_3)$–($CH_2CHSiMe_3)_x$–(CH_2–$CMeCO_2CH_2$-$CH_2SO_3H)_n$–$CF(CF_3)OC_3F_7$: IR (ν/cm^{-1}): 3140 (OH); 1720 (C=O); 1315 (CF_3); 1236 (CF_2); 747 (SiMe). ^1H NMR (CD_3OD) δ: 0.10–0.25 (SiMe); 0.94–1.25 (CH_3); 1.42–2.23 (CH_2); 2.30–2.50 (CH); 3.28–3.40 (CH_2); 4.38–4.53 (CH_2) ppm. ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.8 to −7.2 (16F); −53.6 (6F) ppm.

3.4. Surface tension measurements

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

3.5. 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 [1].

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