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Synthesis and surfactant properties of novel acrylic acid co-oligomers containing fluoroalkylated end-groups: a new approach to polymeric inhibitors of human immunodeficiency virus type-1

Hideo Sawada [a,*], Kei-ichi Tanba [a], Nahoko Itoh [a], Chiaki Hosoi [a], Masatoshi Oue [a], Masanori Baba [b], Tokuzo Kawase [c], Motohiro Mitani [d], Hiromitsu Nakajima [d]

[a] *Department of Chemistry, Nara National College of Technology, Yamatokoriyama, Nara 639-11, Japan*
[b] *Division of Human Retroviruses, Center for Chronic Viral Diseases, Faculty of Medicine, Kagoshima University, Kagoshima 890, Japan*
[c] *Faculty of Science of Living, Osaka City University, Sumiyoshi, Osaka 558, Japan*
[d] *Tsukuba Research Laboratory, NOF Corporation, Tsukuba, Ibaraki 300-26, Japan*

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Abstract

Reactions of fluoroalkanoyl peroxides with acrylic acid, and with alkyl methacrylates or trimethylvinylsilane, give a series of new fluoroalkylated acrylic acid/alkyl methacrylate and /trimethylvinylsilane co-oligomers in excellent to moderate yield under very mild conditions. Fluoroalkylated acrylic acid/alkyl methacrylate co-oligomers are soluble in common organic solvents such as methanol, DMSO and tetrahydrofuran, and slightly soluble in non-polar aromatic solvents such as benzene, toluene and xylene. However, these co-oligomers do not have good solubility in both water and aromatic solvents. In contrast, fluoroakylated acrylic acid/trimethylvinylsilane co-oligomers are readily soluble in not only in water but also in common organic solvent such as methanol, ethanol, tetrahydrofuran, carbon tetrachloride, chloroform, DMF, DMSO, benzene, toluene and xylene. This feature is due to the trimethylsilyl side-chains possessing good oleophilic properties. Fluoroalkylated co-oligomers, in particular fluoroalkylated acrylic acid/trimethylvinylsilane co-oligomers, reduce the surface tension of both water and *m*-xylene effectively to around 15–20 mN m^{-1}, the same as for low-molecular weight fluorinated surfactants, though the co-oligomers have high molecular weights. These fluoroalkylated silicon-containing co-oligomers exhibit a clear break point resembling a CMC, which suggest that they form intra- or inter-molecular aggregations in aqueous solutions owing to their unique structure (fluoroalkylated end-capped structure).

The fluoroalkylated acrylic acid co-oligomers inhibit HIV-1 induced cytopathogenesis. Relative to dextran sulfate, superior anti-HIV-1 activity could be obtained with fluoroalkylated acrylic acid/trimethylvinylsilane co-oligomers; however, fluoroalkylated acrylic acid co-oligomers containing hydroxy groups were inactive. An obvious correlation exists between anti-HIV-1 activity and the hydrophilic or lipophilic property of these co-oligomers, i.e. they provide a most adequate HLB value for anti-HIV-1 activity. More hydrophilic or more oleophilic fluoroalkylated co-oligomers were less active (or inactive), suggesting that more hydrophilic or more oleophilic fluoroalkylated co-oligomers have a weaker effect on the interaction between gp/120 (or gp41) in HIV-1 and CD4 receptors. In fluoroalkylated silicon co-oligomers, as the degree of the reduction in surface tension of water becomes higher the anti-HIV-1 activity becomes higher, suggesting that the more adsorbable co-oligomers at the water/air interface have a higher anti-HIV-1 activity. A new correlation between anti-HIV-1 activity and properties of fluoroalkylated acrylic acid co-oligomers is indicated, affording a useful new strategy for exploring potent new polymeric inhibitors of HIV-1.

Keywords: Synthesis; Surfactant properties; Acrylic acid co-oligomers; Fluoroalkylated end-groups; HIV type-1 inhibitors; NMR spectroscopy

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1. Introduction

It is well known that perfluoropolymers such as poly(tetrafluoroethylene) exhibit excellent chemical and thermal stability, low surface energy, and low refractive index and dielectric constant; however, these compounds, in general, exhibit extremely low solubility in organic solvents [1]. In contrast, it has been reported that cyclic fluoropolymers exhibit a solubility in selected fluorinated solvents [2]. Recently, partially protonated ring-containing fluoropolymers have been reported as being soluble in polar aprotic solvents such as DMF, THF, acetone and acetonitrile, though such polymers were insoluble in benzene, chloroform and

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* Corresponding author.

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methanol [3]. On the other hand, acrylated and methacrylated polymers containing long perfluoroalkyl groups exhibit excellent properties imparted by fluorine, including solubility in fluorinated solvents and in polar solvents such as acetone and chloroform. However, the perfluoroalkyl groups are introduced into such polymers through the ester or the amide bond, and so these materials are unstable under acid or alkaline conditions [4].

In general, the introduction of perfluoroalkyl groups is not easy since the usual synthetic methods for alkylation cannot be applied to perfluoroalkylation due to the high electronegativity of perfluoroalkyl groups. Hence, the development of efficient synthetic methodology for the direct introduction of perfluoroalkyl groups into polymeric materials is desirable. In particular, the exploration of fluoroalkylated polymeric compounds leading to relatively high solubility in both water and common organic solvents will open a new route to the development of the field of new functional (new amphiphilic) fluorinated materials.

We have been actively studying the reaction behaviors of a series of fluoroalkanoyl peroxides ($R_FCO_2O_2CR_F$, R_F = perfluoroalkyl, perfluoro-oxaalkyl group) which are useful reagents for the introduction of the corresponding fluoroalkyl group into arenes or olefins via a single-electron transfer or radical process [5]. In particular, we have demonstrated that perfluoro-oxaalkylated compounds cause an extreme decrease in surface tension [6] and exhibit new biological activities which cannot be achieved by the corresponding perfluoroalkylated or alkylated materials [7]. For example, perfluoro-oxaalkylated acrylic acid homo-oligomers [R_F–$(CH_2$–$CHCO_2H)_n$–R_F], which were obtained by the reactions of perfluoro-oxaalkanoyl peroxides with acrylic acid, were shown to be soluble in water and water-soluble polar solvents such as methanol, ethanol and tetrahydrofuran and to be able to reduce the surface tension of water effectively [8].

Recently, polyanionic compounds, such as dextran sulfate [9], heparin [9], pentosan polysulfate [9] and their derivatives [10], were shown to be highly potent and selective inhibitors of HIV-1 (human immunodeficiency virus type-1) replication in vitro. However, a clinical trial with dextran sulfate failed to exhibit a therapeutic effect on AIDS (the acquired immunodeficiency syndrome) patients owing to its low oral bioavailability and rapid degradation in vivo [11]. Therefore, it is strongly desirable to explore novel polymeric inhibitors with high stability, potent antiviral activity and low toxicity. In this respect, our fluoroalkylated acrylic acid oligomers with carbon–carbon bonds derived from fluorinated acyl peroxides could well become highly potent and selective inhibitors of HIV-1 replication with high stability. In a preliminary account, we reported novel fluoroalkylated acrylic acid/silicon co-oligomers which exhibited surface properties typical of amphiphilic compounds, being readily soluble in water and even in non-polar aromatic solvents [12]. Using fluoroalkanoyl peroxides as key materials, we now report a new synthetic approach to amphiphilic fluoroalkylated compounds which are highly soluble in various solvents and, in particular, an application of fluoroalkylated oligomers as a new class of polymeric HIV inhibitors.

2. Results and discussion

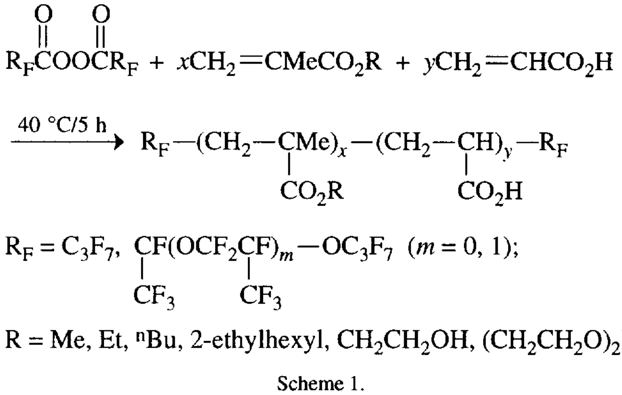
2.1. Synthesis of fluoroalkylated acrylic acid co-oligomers

We were initially interested in a series of alkyl methacrylates (R–MA) as oleophilic segments in fluoroalkylated acrylic acid co-oligomers. Thus, we prepared various fluoroalkylated acrylic acid/alkyl methacrylate co-oligomers by the reactions of fluoralkanoyl peroxides with acrylic acid (ACA) and R–MAs such as methyl, ethyl, butyl, 2-ethylhexyl, 2-hydroxyethyl and 5-hydroxy-3-oxapentyl methacrylates.

As shown in Scheme 1 and listed in Table 1, perfluorobutyryl peroxide and perfluoro-oxaalkanoyl peroxides reacted smoothly with ACA and R–MA to afford the corresponding fluoroalkylated acrylic acid/alkyl methacrylate co-oligomers in excellent to moderate yield under very mild conditions.

The fluoroalkylated acrylic acid/alkyl methacrylate co-oligomers thus obtained were soluble in methanol, dimethyl sulfoxide and tetrahydrofuran. Additionally, they were slightly soluble in non-polar aromatic solvents such as benzene, toluene and xylene. However, the introduction of these hydrocarbon side-chains into the co-oligomers did not lead to good solubility in both water and aromatic solvents such as benzene and toluene.

Thus, we were interested in trimethylsilyl segments which could exhibit a stronger oleophilic property than alkyl chains, and hence reacted fluoroalkanoyl peroxides with trimethylvinylsilane (VM–Si) and ACA to afford fluoroalkylated acrylic acid/trimethylvinylsilane co-oligomers, i.e. new fluorinated amphiphilic materials which are easily soluble in both water and non-polar aromatic solvents. As shown in Scheme 2 and listed in Table 2, perfluorobutyryl peroxide and a series of perfluoro-oxaalkanoyl peroxides reacted smoothly with acrylic acid and trimethylvinylsilane to afford the corresponding co-oligomers under very mild conditions.



$$R_F\overset{\overset{O}{\|}}{C}OO\overset{\overset{O}{\|}}{C}R_F + xCH_2{=}CMeCO_2R + yCH_2{=}CHCO_2H$$

$$\xrightarrow{40\ ^{\circ}C/5\ h} R_F{-}(CH_2{-}\underset{\underset{CO_2R}{|}}{C}Me)_x{-}(CH_2{-}\underset{\underset{CO_2H}{|}}{C}H)_y{-}R_F$$

$$R_F = C_3F_7,\ \underset{\underset{CF_3}{|}}{C}F(OCF_2\underset{\underset{CF_3}{|}}{C}F)_m{-}OC_3F_7\ (m = 0, 1);$$

$$R = Me, Et, {}^nBu, 2\text{-ethylhexyl}, CH_2CH_2OH, (CH_2CH_2O)_2H$$

Scheme 1.

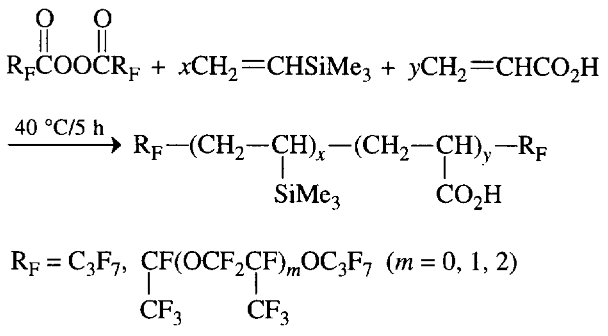
Table 1
Synthesis of fluoroalkylated alkyl methacrylate/acrylic acid co-oligomers: R_F–$(CH_2$–$CMeCO_2R)_x$–$(CH_2CHCO_2H)_y$–R_F

R_F in peroxide (mmol)	R in $CH_2{=}CMeCO_2R$ (mmol)	$CH_2{=}CHCO_2H$ (mmol)	Product	
			Yield (%) [a]	$\bar{M}_n$ ($\bar{M}_w/\bar{M}_n$) (x/y) [b]
C_3F_7				
12	Me (49)	47	54	3910 (2.82) (32:68)
12	Me (24)	47	59	3630 (2.32) (28:72)
12	Me (12)	48	57	3430 (1.77) (17:83)
12	Me (6)	47	55	3270 (1.62) (12:88)
12	Et (24)	47	53	3770 (2.43) (23:77)
12	ⁿBu (24)	48	48	4340 (2.52) (20:80)
12	$CH_2CH(CH_2CH_3)(CH_2)_3CH_3$ (24)	48	49	5540 (2.26) (15:85)
$C_3F_7OCF(CF_3)$				
12	Me (49)	48	45	5180 (3.07) (47:53)
12	Me (24)	48	45	5270 (2.41) (41:59)
12	Me (12)	48	44	5590 (1.93) (23:77)
12	Me (6)	50	42	6130 (1.79) (16:84)
12	Et (24)	47	43	5570 (3.73) (23:77)
12	ⁿBu (25)	48	42	7120 (2.95) (20:80)
12	$CH_2CH(CH_2CH_3)(CH_2)_3CH_3$ (24)	48	42	8970 (3.07) (14:86)
12	CH_2CH_2OH (25)	47	49	4970 (2.74) (16:84)
12	$(CH_2CH_2O)_2H$ (24)	47	53	6060 (2.98) (15:85)
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$				
10	Me (30)	30	30	7270 (1.74) (60:40)

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

The fluoroalkylated acrylic acid/silicon co-oligomers listed in Table 2 were found to be readily soluble not only in water but also in common organic solvents such as methanol, ethanol, tetrahydrofuran, carbon tetrachloride, chloroform, *N,N*-dimethylformamide, dimethyl sulfoxide, benzene, toluene and xylene. In contrast, we have already shown that fluoroalkylated acrylic acid homo-oligomers [R_F–$(CH_2CHCO_2H)_n$–R_F] are only soluble in water and water-soluble polar solvents such as methanol, ethanol and tetrahydrofuran [8]. It is reasonable to suggest that these interesting solubility properties of our fluorinated silicon co-oligomers arise from the presence of trimethylsilyl side-chains. As a result, these fluorinated silicon co-oligomers were studied to indicate the properties typical of the amphiphilic compounds.

As shown in Tables 1 and 2, it is suggested that in our co-oligomerization [in which the concentration of the peroxide was almost the same as that of ACA or VM–Si (or R–MA)],



$$R_F\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}R_F + xCH_2{=}CHSiMe_3 + yCH_2{=}CHCO_2H \xrightarrow{40\ ^\circ C/5\ h} R_F{-}(CH_2{-}\underset{SiMe_3}{\underset{|}{C}}H)_x{-}(CH_2{-}\underset{CO_2H}{\underset{|}{C}}H)_y{-}R_F$$

$$R_F = C_3F_7,\ \underset{CF_3}{\underset{|}{C}}F(OCF_2\underset{CF_3}{\underset{|}{C}}F)_mOC_3F_7\ (m = 0, 1, 2)$$

Scheme 2.

Table 2
Synthesis of fluoroalkylated vinylsilane/acryl acid co-oligomers: R_F–$(CH_2CHSiMe_3)_x$–$(CH_2CHCO_2H)_y$–R_F

R_F in peroxide (mmol)	CH_2=$CHSiMe_3$ (mmol)	CH_2=$CHCO_2H$ (mmol)	Product	
			Yield (%) [a]	$\bar{M}_n$ ($\bar{M}_w$/$\bar{M}_n$) (x/y) [b]
C_3F_7				
35	72	81	28	1480 (1.45) (20:80)
12	24	47	48	1860 (1.83) (13:87)
12	12	47	44	6210 (2.02) (4:96)
12	6	47	49	6600 (1.94) (3:97)
$C_3F_7OCF(CF_3)$				
12	186	51	13	4010 (1.61) (35:65)
12	93	51	21	3300 (1.41) (26:74)
12	46	51	32	2510 (1.25) (24:76)
12	23	51	37	3770 (1.55) (18:82)
12	48	50	28	6070 (2.29) (15:85)
12	12	47	57	7510 (2.10) (4:96)
12	6	47	24	8000 (1.76) (3:97)
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$				
12	23	51	34	5030 (1.39) (15:85)
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$				
3	64	14	33	5670 (1.25) (9:91)

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

mainly co-oligomers with two fluoroalkyl groups, i.e. R_F–$(VM$–$Si)_x$–$(ACA)_y$–R_F [or R_F–$(R$–$MA)_x$–$(ACA)_y$–R_F] were obtained via primary radical termination or radical chain transfer to the peroxide. Fluoroalkanoyl peroxides react with ACA under similar conditions to afford the corresponding fluoroalkylated oligomers with carbon–carbon bond formation [8], and elemental analyses for fluorine showed that these oligomers contain two fluoroalkylated end-groups per oligomeric molecule [R_F–$(CH_2CHCO_2H)_n$–R_F] [13]. Similarly, we succeeded in preparing silicon oligomers with two fluoroalkylated end-groups [R_F–$(CH_2CHSiR_3)_n$–R_F; R_F = fluoroalkyl group] by the reactions of vinylsilanes with fluoralkanoyl peroxides [14].

Interestingly, there was a general tendency for the molecular weight of the fluoroalkylated co-oligomers described in Tables 1 and 2 to be higher in the perfluoro-oxaalkylated oligomers than in the corresponding perfluoropropylated materials under conditions in which the molar ratio of ACA/VM–Si (or R–MA)/peroxide was almost the same though perfluoro-oxaalkanoyl peroxides decompose faster than perfluorobutyryl peroxide [15]. For example, when the molar ratio of ACA/VM–Si/peroxide = 4.0–4.4:2.0–2.8:1, the molecular weights ($\bar{M}_n$) of these co-oligomers [R_F–$(ACA)_x$–$(VM$–$Si)_y$–R_F] increased in the order $R_F = C_3F_7$ (1860) ≪ $CF(CF_3)OC_3F_7$ (3770) < $CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (5030) < $CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (5670). Recently, Scherer et al. reported that the tertiary perfluoroalkyl radical [$(CF_3)_2CF\dot{C}[CF_2CF_3]CF(CF_3)_2$] is extraordinarily stable even at room temperature [16]. Since perfluoro-oxaalkyl radicals are secondary, such radicals would be stabilized to a great extent than perfluoropropyl (primary) radicals. An increase in the molecular weight of perfluoro-oxaalkylated oligomers would therefore be dependent upon retardation of the coupling rates in termination reactions as a direct result of their stabilities.

The molecular weights of the co-oligomers obtained are markedly dependent upon the molar ratios of VM–Si and ACA, decreasing with greater molar ratios of VM–Si. This may be due to VM–Si being less capable of polymerization compared with acrylic acid. The monomer reactivity ratios r_1

(VM–Si) and r_2 (ACA) in the co-oligomerizations with $(C_3F_7CO_2)_2$ listed in Table 2 were determined by the Fineman–Ross method [17] to give $r_1=0.51$ and $r_2=4.09$, respectively. This finding indicates that a radical reactivity of the fluoroalkyl radical towards trimethylvinylsilane compared to acrylic acid is not so high as with the more usual alkyl radical [for example, $r_1=0.02$ (VM–Si), $r_2=34$ (methyl methacrylate); $r_1=0.07$ (VM–Si), $r_2=3.9$ (acrylonitrile) [18]. However, the higher reactivity towards VM–Si (r_1) of a fluoroalkyl radical relative to an alkyl radical would be dependent upon primary radical termination or radical chain transfer to the peroxide under our oligomeric conditions. On the other hand, r_1 (methyl methacrylate) and r_2 (ACA) in the co-oligomerization with $[C_3F_7OCF(CF_3)COO]_2$ listed in Table 1 gave $r_1=0.31$ and $r_2=0.44$, respectively. The similar reactivity of the fluoroalkyl radical towards methyl methacrylate and acrylic acid is due to the strong electrophilic nature of the fluoroalkyl radical. For an alkyl radical, values of $r_1=2.64$ (methyl methacrylate) and $r_2=0.12$ (ACA) have been reported [19].

2.2. Surfactant properties of fluoroalkylated acrylic acid co-oligomers

In general, fluorinated surfactants such as perfluoroalkanoic and perfluoroalkane sulfonic acids, and perfluoroalkyl acrylate polymers, are known to give poor solubility in various solvents except for selected fluorinated ones. However, the dramatic improvement in solubility of our fluoroalkylated acrylic acid/silicon co-oligomers in various solvents is suggested to be derived from their unique oligomeric structure. Namely, our fluorinated compounds are fluoroalkylated end-capped hydrocarbon oligomers in which fluoroalkyl segments have been introduced only into the two end-sites in one oligomeric molecule. In order to clarify the effect of the unique structure of our fluoroalkylated co-oligomers, we have measured the surface tensions of their aqueous and *m*-xylene solutions with the Wilhelmy plate method at 30 °C.

As shown in Figs. 1–5, a significant decrease in the surface tension (γ) of water, to ca. 18–20 mN m^{-1}, was found for all fluoroalkylated acrylic acid/trimethylvinylsilane, /alkyl methacrylate co-oligomers and the corresponding sodium

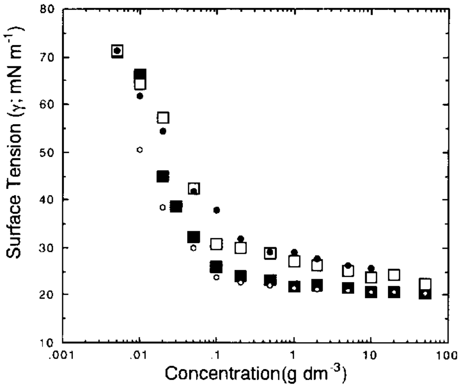


Fig. 1. Surface tensions of aqueous solutions of R_F–$(CH_2CHSiMe_3)_x$–$(CH_2CHCO_2H)_y$–R_F. ■, R_F = C_3F_7 [$\bar{M}_n$ = 1860 (*x*/*y* = 8:92)]; ○, R_F = $CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 3770 (*x*/*y* = 18:82)]; □, R_F = $CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 5030 (*x*/*y* = 15:85)]; and ●, R_F = $CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 5670 (*x*/*y* = 9:91)].

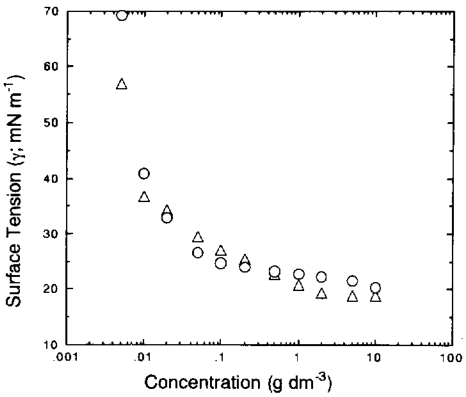


Fig. 2. Surface tensions of aqueous solutions of R_F–$(CH_2CHSiMe_3)_x$–$(CH_2CHCO_2H)_y$–R_F (○) and R_F–$(CH_2CHSiMe_3)_x$–$(CH_2CHCO_2Na)_y$–R_F (△): R_F = $CF(CF_3)OC_3F_7$; $\bar{M}_n$ = 2510 (*x*/*y* = 24:76).

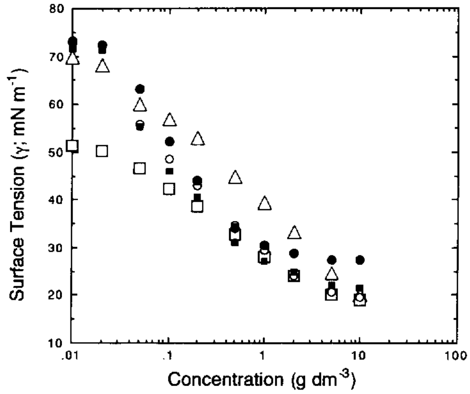


Fig. 3. Surface tensions of aqueous solutions of R_F–$(CH_2CMeCO_2R)_x$–$(CH_2CHCO_2Na)_y$–R_F. $R_F=C_3F_7$: R = Me, △ $\bar{M}_n=3430$ (*x*/*y* = 17:83), □ $\bar{M}_n=3630$ (*x*/*y* = 28:72); R = Et, ○ $\bar{M}_n=3770$ (*x*/*y* = 23:77); R = Bu, ■ $\bar{M}_n=4340$ (*x*/*y* = 20:80); R = 2-ethylhexyl, ● $\bar{M}_n=5540$ (*x*/*y* = 15:85).

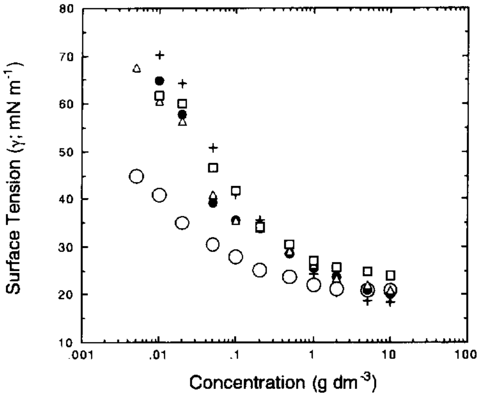


Fig. 4. Surface tensions of aqueous solutions of R_F–$(CH_2CMeCO_2R)_x$–$(CH_2CHCO_2Na)_y$–R_F. $R_F=CF(CF_3)OC_3F_7$: R = Me, + $\bar{M}_n=5270$ (*x*/*y* = 41:59); R = Me, ○ $\bar{M}_n=5180$ (*x*/*y* = 47:53); R = Et, ● $\bar{M}_n=5570$ (*x*/*y* = 23:77); R = Bu, △ $\bar{M}_n=7120$ (*x*/*y* = 20:80); R = 2-ethylhexyl, □ $\bar{M}_n=8970$ (*x*/*y* = 14:86).

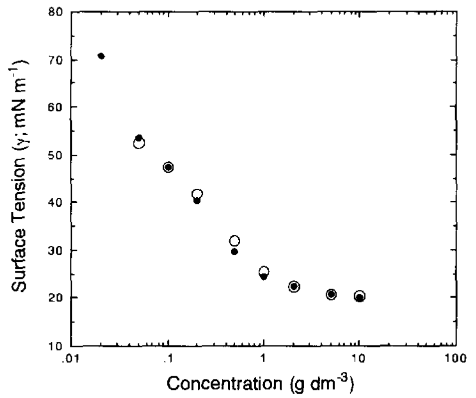


Fig. 5. Suface tensions of aqueous solutions of R_F–$(CH_2CMeCO_2R)_x$–$(CH_2CHCO_2Na)_y$–R_F. $R_F = CF(CF_3)OC_3F_7$: $R = CH_2CH_2OH$, ○ $\bar{M}_n = 4970$ ($x/y = 16:84$); $R = (CH_2CH_2O)_2H$, ● $\bar{M}_n = 6060$ ($x/y = 15:85$).

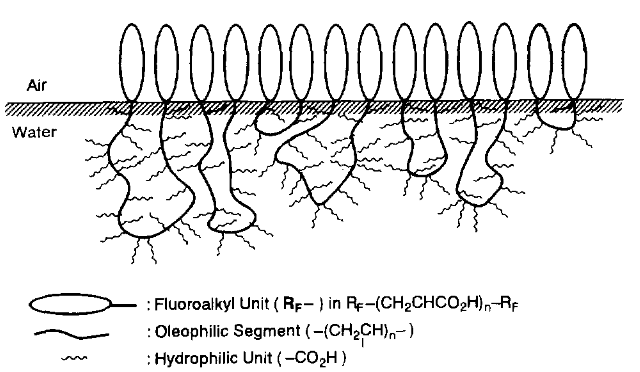


Fig. 6. Schematic illustration of the surface arrangement of fluoroalkyl units in aqueous solutions of fluoroalkylated acrylic acid oligomers.

salts, despite the fact that these co-oligomers are high molecular weight compounds. To data, hydrophobically-modified polyelectrolytes have been characterized as 'polysoaps' [20], and polysoap solutions are known to exhibit a continuous decrease in surface tension with increasing concentration as do low molecular weight surfactants; however, no critical micelle concentration (CMC) or breakpoint resembling a CMC is observed in these polymers [21]. Interestingly, as shown in Figs. 1–5, plots of γ versus log[C] (concentration of co-oligomer) are similar to the curves typical of monomeric surfactants, i.e. our fluorinated acrylic acid co-oligomers, especially the silicon co-oligomers, exhibit a clear breakpoint resembling a CMC. This is a unique and interesting feature of our oligomeric-type surfactants.

Previously, we reported that acrylic acid homo-oligomers with two fluoroalkylated end-groups [R_F–$(CH_2$–CH–$CO_2H)_n$–R_F] are capable of reducing the surface tension of water to ca. 10 mN m^{-1}, which is almost the same level as that achieved by the usual low molecular weight fluorinated surfactants {for example, monolayers of perfluorolauric acid adsorbed onto platinum have been recently reported to have an energy of ca. 10 mN m^{-1}, the lowest value known (an older reference value of 6 mN m^{-1} has been reported [22])} [23]. This finding suggests that the fluoroalkyl groups in our co-oligomers are likely to be arranged regularly above the water surface as illustrated in Fig. 6, where all the fluoroalkyl groups are parallel to each other similar to the fluoroalkyl groups of usual low molecular weight fluorinated surfactants. On the other hand, the carboxy groups of the co-oligomers would be directed randomly under the water surface.

Using the plots of γ versus log[C] depicted in Figs. 1, 3 and 5, we can determine the adsorption parameters Γ (surface excess: mol m^{-2}) and A (area occupied by one molecule: Å^2 per molecule) of these fluoroalkylated co-oligomers at the air/water interface, based on the slope of the linear portion of each curve just below the breakpoint, from the Gibbs adsorption isotherm [24]:

$$\Gamma = \frac{-1}{RT} (\delta\gamma / \delta \ln [C])$$

$$A\ (\text{Å}^2) = 10^{20}/(N_A \Gamma)$$

where $\delta\gamma/\delta \ln[C]$ is the slope of the γ versus ln[C] plot (just before the breakpoint) at constant (absolute) temperature, T (K) and pressure; $R = 8.314$ J mol^{-1} K^{-1} and N_A is Avogadro's number.

The values of Γ and A for typical fluoroalkylated and alkyl methacrylate co-oligomers are listed in Table 3.

Table 3
Values of the surface excess and area occupied per molecule for typical fluoroalkylated trimethylvinylsilane and alkyl methacrylate co-oligomers

(a) R_F–$(CH_2$–$CHSiMe_3)_x$–$(CH_2CHCHCO_2H)_y$–R_F

R_F ($\bar{M}_n$)	Γ (mol m^{-2}) × 10^6	A (Å^2)
C_3F_7 (1860)	6.6	25
$C_3F_7OCF(CF_3)$ (3770)	6.8	24
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$ (5030)	5.4	31
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$ (5670)	4.2	40

(b) R_F–$(CH_2$–$CMeCO_2R)_x$–$(CH_2CHCO_2H)_y$–R_F

R_F ($\bar{M}_n$)	R	Γ (mol m^{-2}) × 10^6	A (Å^2)
C_3F_7 (5540)	$CH_2CH(CH_2CH_3)(CH_2)_3CH_3$	4.8	35
$C_3F_7OCF(CF_3)$ (4970)	CH_2CH_2OH	3.6	46

Judging from the values of A (24–46 Å^2), the two fluoroalkylated end-groups in our co-oligomers are arranged in parallel and distance as close as the fluoroalkyl groups in the low molecular weight fluoroalkylated compounds {recently, it has been reported that low molecular weight perfluoroalkyl oxyethylene non-ionic compounds have similar A values (35–46 Å^2) [25]}.

Very recently, we have prepared acrylic acid oligomers containing a perfluoro-oxaalkylene unit $-\{R_F-[CH_2-CH(CO_2H)]_q\}_p-$ using a polymeric perfluoro-oxaalkane diacyl peroxide $-[C(:O)R_FC(:O)OO]_p-$ [26]. However, such acrylic acid oligomers containing a perfluoro-oxaalkylene unit were not as effective in reducing the surface tension of water as acrylic acid oligomers with two fluoroalkylated end-groups (for example, the surface tensions of aqueous solutions of $-[R_F-(CH_2CHCO_2H)_q]_p-\{-R_F-=-(CF_3)CF[OCF_2(CF_3)CF]_n-O[CF_2]_5O-[CF(CF_3)CF_2O]_mCF(CF_3)-$; $n+m=3$; $\bar{M}_n=12\,000\}$ and $R_F-(CH_2CHCO_2H)-R_F$ $[R_F=CF(CF_3)OC_3F_7$; $\bar{M}_n=12\,000]$ are 33.5 mN m^{-1} (1 g dm^{-3}) and 20.3 mN m^{-1} (1 g dm^{-3}), respectively) [26]. This result suggests that the perfluoro-oxaalkylene chains in $-\{R_F-[CH_2-CH(CO_2H)]_q\}_p-$ are unlikely to be arranged regularly above the water surface relative to the fluoroalkyl chains in $[R_F-(CH_2-CHCO_2H)_n-R_F]$ as illustrated in Fig. 7. Therefore, it can be concluded that the unique properties exhibited by our fluoroalkylated oligomers are very dependent upon the mode of arrangement of the fluoroalkyl chains above the water surface.

More interestingly, as shown in Fig. 1, in the case of aqueous solutions of fluoroalkylated acrylic acid/trimethylvinylsilane co-oligomers the degree of reduction in surface tension of water does not depend upon the length of the fluoroalkyl groups in the co-oligomers, differing from the usual fluoroalkylated surfactants [6]. Shorter perfluoro-oxaalkyl chains were more effective in reducing the surface tension of water to 20.4 mN m^{-1} than longer chains. This unique result suggests that the longer perfluoro-oxaalkyl chains in these fluoroakylated co-oligomers are unlikely to be arranged more closely above the water surface owing to the presence of trimethylsilyl segment (steric hindrance).

It is known that a particular feature of polysoaps is their intramolecular hydrophobic aggregation, which is explained both by the close proximity of the surface side-chain within one macromolecule [21] and by polymeric micelles. The latter are classified into three major models: 'local micelle', 'regional micelle' and 'molecular micelle' [21g], which can be formed from one polymer chain (unimer) or even from parts of chains [27]. For example, aqueous Nafion, i.e. $-[CF_2CF_2CF(OCF_2CF(CF_3)OCF_2CF_2SO_3H)]_n-$, is considered to form regions of local hydrophobic aggregation that lead to intramolecular micelles [28] or rod-like micelles [29]. Thus, because of the presence of a clear breakpoint resembling a CMC, our fluoroalkylated oligomers are also suggested to undergo intra- or inter-molecular aggregation in aqueous solutions. Details are now under investigation.

On the other hand, as shown in Figs. 8 and 9, the degree of reduction in surface tension of m-xylene depends on the length of the fluoroalkyl groups in a series of co-oligomers as for the usual fluoroalkylated surfactants. Thus, longer fluoroalkyl chains, especially, longer perfluoro-oxaalkyl chains containing silicon co-oligomers reduce the surface tension of

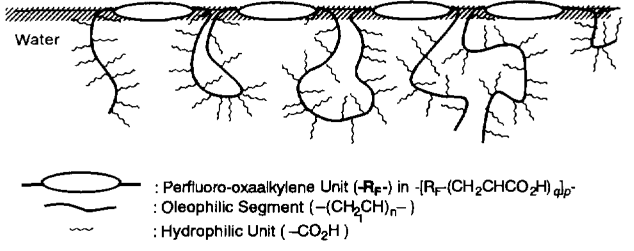


Fig. 7. Schematic illustration of the surface arrangement of perfluoro-oxaalkylene units in aqueous solutions of acrylic acid oligomers containing perfluoro-oxaalkylene units.

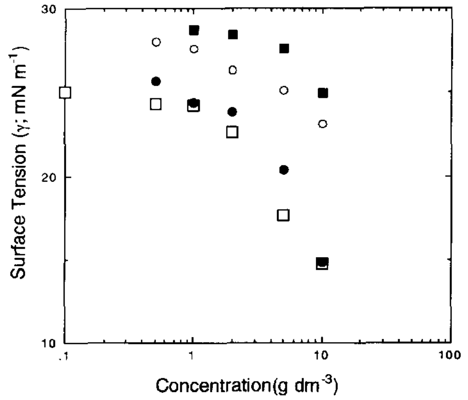


Fig. 8. Surface tensions of m-xylene solutions of $R_F-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-R_F$. ■ R_F = C_3F_7 [$\bar{M}_n$ = 1860 (x/y = 8:92)]; ○ R_F = $CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 3770 (x/y = 18:82)]; □ R_F = $CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 5030 (x/y = 15:85)]; ● R_F = $CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 5670 (x/y = 9:91)].

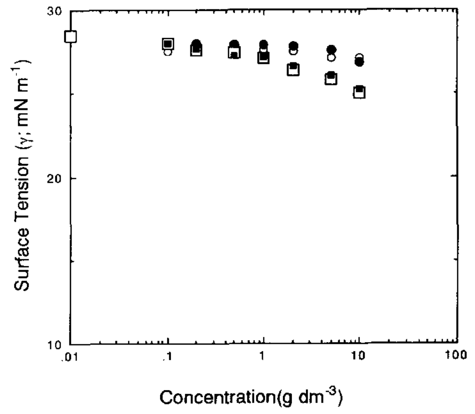


Fig. 9. Surface tensions of m-xylene solutions of $R_F-(CH_2CMeCO_2R)_x-(CH_2CHCO_2H)_y-R_F$. ○ R = Me, R_F = C_3F_7 [$\bar{M}_n$ = 3630 (x/y = 28:73)]; ● R = Et, R_F = C_3F_7 [$\bar{M}_n$ = 3770 (x/y = 23:77)]; □ R = Me, R_F = $CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 5270 (x/y = 41:59)]; ■ R = Et, R_F = $CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 5570 (x/y = 23:77)].

m-xylene quite effectively. This finding should result from the strong action of the oleophobic fluoroalkyl groups aligned on the surface, the trimethylsilyl or alkyl ester moiety being, in general, oleophilic so that such segments would not lie on the *m*-xylene surface.

Furthermore, the silicon co-oligomers were more effective in reducing the surface tension of *m*-xylene than the alkyl methacrylate co-oligomers, though silicon segments are oleophilic. This probably depends, in part, upon the higher solubility of these materials in non-polar aromatic solvents. Thus, these novel fluoroalkylated oligomers in particular, fluorosilicon oligomers, will attract much attention as useful functional materials in the various fields since there has been a great need for the development of new functional materials possessing excellent properties imparted by both silicon and fluorine.

2.3. Anti-HIV-1 activity of fluoroalkylated acrylic acid co-oligomers towards MT-4 cells

Our new fluoroalkylated co-oligomers are possible potent polymeric inhibitors of HIV-1 exhibiting high stability and low toxicity. Fluoroalkylated co-oligomers prepared using fluoroalkanoyl peroxides have been evaluated for their inhibitory effects on HIV-1 (III_B) replication in MT-4 cells. These results are listed in Table 4.

Table 4
Anti-HIV activity of $R_F–(CH_2–CHSiMe_3)_x–(CH_2CHCO_2H)_y–R_F$ and $R_F–(CH_2–CMeCO_2R)_x–(CH_2CHCO_2H)_y–R_F$ in MT-4 cells

	$\bar{M}_n$ ($\bar{M}_w/\bar{M}_n$) [*x*/*y*]	EC_{50} [a] (μg ml^{-1})	CC_{50} [b] (μg ml^{-1})
$R_F–(CH_2–CHSiMe_3)_x–(CH_2CHCO_2H)_y–R_F$			
$R_F = C_3F_7$			
	1480 (1.45) [20:80]	3.9	> 100
	1860 (1.83) [13:87]	2.2	> 100
	6210 (2.02) [4:96]	42	> 100
	6600 (1.94) [3:97]	67	> 100
	5100 (1.47) [0:100]	> 100	> 100 [c]
$R_F = C_3F_7OCF(CF_3)$			
	4180 (1.65) [44:56]	> 100	> 100
	4010 (1.61) [35:65]	16	> 100
	3500 (1.45) [35:65]	42	> 100
	3300 (1.41) [26:74]	12	> 100
	2510 (1.25) [24:76]	5.5	> 100
	3770 (1.55) [18:82]	1.8	> 100
	6070 (2.29) [15:85]	2.2	> 100
	4240 (1.23) [13:87]	2.1	> 100
	7510 (2.10) [4:96]	7.2	> 100
	8000 (1.76) [3:97]	12	> 100
	12000 (1.54) [0:100]	> 100	> 100 [c]
$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)$			
	5030 (1.39) [15:85]	8.3	> 100
	9200 (2.10) [0:100]	29	> 100 [c]
$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$			
	5670 (1.25) [9:91]	8.9	> 100
	6300 (1.80) [0:100]	8.5	> 100 [c]
$R_F–(CH_2–CMeCO_2R)_x–(CH_2CHCO_2H)_y–R_F$			
$R_F = C_3F_7$			
R = Me	3910 (2.82) [32:68]	10	> 100
= Me	3630 (2.32) [28:72]	39	> 100
$= CH_2CH(CH_2CH_3)(CH_2)_3CH_3$	5540 (2.26) [15:85]	7.3	> 100
$R_F = C_3F_7OCF(CF_3)$			
R = Me	5180 (3.07) [47:53]	5.6	> 100
= Me	5590 (1.93) [23:77]	12	> 100
= Me	6130 (1.79) [16:84]	12	> 100
= Et	5570 (3.73) [23:77]	5.2	> 100
= ^{n}Bu	7120 (2.95) [20:80]	6.4	> 100
$= CH_2CH_2OH$	4970 (2.74) [16:84]	> 100	> 100
$= (CH_2CH_2O)_2H$	6060 (2.98) [15:85]	> 100	> 100
$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)$			
R = Me	7270 (1.74) [60:40]	7.7	> 100
Dextran sulfate	5000	3.5	> 100

[a] 50% effective concentration, based on the inhibition of HIV-1-induced cytopathic effects in MT-4 cells.

[b] 50% cytotoxic concentration, based on the impairment of viability of mock-infected MT-4 cells.

[c] See Ref. [30].

As shown in Table 4, fluoroalkylated co-oligomers containing both trimethylvinylsilane and alkyl methacrylate, were observed to inhibit HIV-1-induced cytopathogenesis. The concentrations 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, in the fluoroalkylated acrylic acid/silicon co-oligomers, an obvious direct correlation between the co-oligomerization ratio (x/y) in the co-oligomers and the anti-HIV-1 activity was observed. Relative to dextran sulfate [$EC_{50}=3.5\ \mu\ \mathrm{ml}^{-1}$], superior EC_{50} values could be obtained with fluoroalkylated acrylic acid/silicon co-oligomers. Notable examples were $R_F-(VM-Si)_x-(ACA)_y-R_F$; $R_F=CF(CF_3)OC_3F_7$, $x=18\%$ [$EC_{50}=1.8\ \mu g\ \mathrm{ml}^{-1}$], $x=15\%$ [$EC_{50}=2.2\ \mu g\ \mathrm{ml}^{-1}$], $x=13\%$ [$EC_{50}=2.1\ \mu g\ \mathrm{ml}^{-1}$]. In contrast, silicon co-oligomers possessing the higher content of silicon segments ($x=44\%$) and hydroxy group-containing acrylic acid co-oligomers were respectively inactive. Previously, we have reported that fluoroalkylated acrylic acid homo-oligomers [$R_F-(CH_2CHCO_2H)_n-R_F$], especially those containing longer perfluoro-oxaalkyl chains, are effective against HIV-1 replication in MT-4 cells, though these compounds are not so potent compared to dextran sulfate as shown partly in Table 4 [30]. However, with our present fluoroalkylated acrylic acid/trimethylvinylsilane or /alkyl methacrylate co-oligomers, compounds containing shorter fluoroalkyl chains such as C_3F_7 and $C_3F_7OCF(CF_3)$ are more effective against HIV-1 replication in MT-4 cells.

Interestingly, as shown in Table 4, there is some correlation between the anti-HIV-1 activity (EC_{50}) of fluoroalkylated [C_3F_7- and $C_3F_7OCF(CF_3)-$] acrylic acid/trimethylvinylsilane co-oligomers and the co-oligomerization ratio (x) of the trimethylsilyl segments. Thus, in the perfluoropropylated (C_3F_7) acrylic acid/trimethylvinylsilane co-oligomers, as the ratio (x) increases (from 0 to 13), the activity against HIV-1 also increases, with EC_{50} of >100 to 2.2 or 3.9 $\mu g\ \mathrm{ml}^{-1}$. In contrast, in the perfluoro-1-methyl-2-oxapentylated [$CF(CF_3)OC_3F_7$] acrylic acid/trimethylvinylsilane co-oligomers, the highest value for the activity against HIV-1 was observed in the case of $x=18\%$; when the ratio (x) was higher (or lower) than 18%, the activity against HIV-1 was lower, with EC_{50} values of 5.5 to $>100\ \mu g\ \mathrm{ml}^{-1}$ or EC_{50} values of 2.2 to $>100\ \mu g\ \mathrm{ml}^{-1}$ as illustrated in Fig. 10.

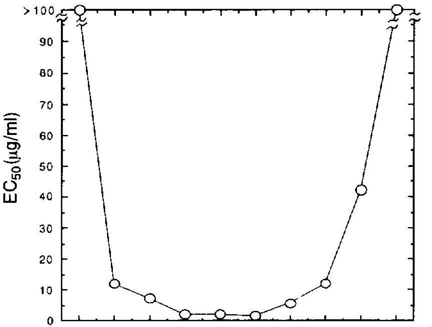


Fig. 10. Relationship of EC_{50} value to content of trimethylsilyl segment in $R_F-(CH_2-CHSiMe_3)_x-(CH_2CHCO_2H)_y-R_F$; $R_F=C_3F_7OCF(CF_3)$.

In particular, both co-oligomers containing CH_2CH_2OH and $CH_2CH_2OCH_2CH_2OH$ groups and acrylic acid homo-oligomers containing shorter fluoroalkyl groups, respectively, were found to be inactive. This result strongly suggests that the activity against HIV-1 is sensitive to the oleophilic property of these co-oligomers. Hence, we became interested in the hydrophilic/lipophilic balance (HLB) in these co-oligomers. HLB values may be estimated from empirical calculations [31] which depend on some fundamental property of the molecule. Griffin's method which is defined for non-ionic surfactants as $\mathrm{HLB}=[H/(H+L)]\times 20$, where H = molar mass of the hydrophilic head group; L = molar mass of the lipophilic chain, was adapted for estimating the HLB values of our fluoroalkylated co-oligomers [31] [1]. Thus, the HLB can be calculated as follows: hydrophilic moiety (H) = $(CO_2H)_x$, $(CH_2CH_2OH)_x$ or $(CH_2CH_2OCH_2CH_2OH)_x$; lipophilic moieties (L) = $R_F-(CH_2-CHSiMe_3)_x-(CH_2-CH)_y-R_F$ or $R_F-(CH_2-CMeCO_2R)_x-(CH_2-CH)_y-R_F$, where the values of x and y can be derived from $\bar{M}_n$ for the co-oligomers and the co-oligomerization ratio (x/y), provided R does not correspond to CH_2CH_2OH or $CH_2CH_2OCH_2CH_2OH$. The results obtained are listed in Table 5.

There is an obvious correlation between the HLB values quoted in Table 5 and the activity against HIV-1. As the HLB values become higher (9.8–11.9) (i.e. greater hydrophilicity), activity against HIV-1 is in general not shown. On the other hand, when the HLB values for these co-oligomers are lower (9.1–7.6), these compounds exhibit anti-HIV-1 activity. However, the compound possessing the lowest HLB value (5.2) was not active against HIV-1. Compounds possessing moderate HLB values of ca. 8 showed the highest activities against HIV-1. Thus, the more hydrophilic co-oligomers, $R_F-(CH_2-CMeCO_2R)_x-(CH_2-CHCO_2H)_y-R_F$ ($R=CH_2CH_2OH$, $CH_2CH_2OCH_2CH_2OH$ and homo-oligomers $R_F-(CH_2-CHCO_2H)_x-R_F$, respectively, were shown to be inactive. In addition, the more oleophilic fluoroalkylated acrylic acid trimethylvinylsilane co-oligomers ($x=44\%$) were also shown to be inactive. As described previously for fluoroalkylated acrylic acid homo-oligomers [30], the mechanism of action of these fluoroalkylated acrylic acid co-oligomers is considered to be primarily the inhibition of virus adsorption onto the cell membrane. Hence, the more hydrophilic or more oleophilic fluoroalkylated co-oligomers would have a weaker effect on the interaction between gp/120 (or gp41) and CD4 receptors on host lymphoid cells.

The interaction between gp 120 of persistently HIV-1-infected cells and the CD4 receptor of uninfected cells leads to the formation of multinucleated giant cells [9a,d]. This giant cell (syncytium) formation is assumed to play an

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[1] Recently, HLB values {$\mathrm{HLB}=[H/(H+L)]\times 20$} have been applied to perfluoroalkyl oxyethylene non-ionic compounds [$CF_3(CF_2)_pCH_2O-(C_2H_4O)_qCH_3$; $p=6, 7$, $q=2$–6]; see Ref. [25].

Table 5
Values of hydrophilic/lipophilic balance and EC_{50} for fluoroalkylated co-oligomers studied

	$\bar{M}_n$; x/y	HLB	EC_{50} (μg ml^{-1})
R_F–$(CH_2$–$CHSiMe_3)_x$–$(CH_2$–$CHCO_2H)_y$–R_F			
$R_F = C_3F_7$			
	1860; 13:87	8.5	2.2
	5100; 0:100	11.7	> 100
$R_F = C_3F_7OCF(CF_3)$			
	12000; 0:100	11.9	> 100
	3770; 18:82	8.1	1.8
	6070; 15:85	9.1	2.2
	4180; 44:56	5.2	> 100
$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)$			
	5030; 15:85	8.2	8.3
	9200; 0:100	11.3	> 100
R_F–$(CH_2$–$CMeCO_2R)_x$–$(CH_2$–$CHCO_2H)_y$–R_F			
$R_F = C_3F_7OCF(CF_3)$			
R = Et	5570; 23:77	7.6	5.2
= ^{n}Bu	7120; 20:80	7.7	6.4
= CH_2CH_2OH	4970; 16:84	9.8	> 100
= $CH_2CH_2OCH_2CH_2OH$	6060; 15:85	10.9	> 100

Table 6
Anti-HIV activity and pH of fluoroalkylated trimethylvinylsilane/acrylic acid co-oligomers: R_F–$(CH_2$–$CHSiMe_3)_x$–$(CH_2CHCO_2H)_y$–R_F

	x/y	$\bar{M}_n$	EC_{50} (μg ml^{-1})	pH
$R_F = C_3F_7$				
	13:87	1480	3.9	3.5
	0:100	5100	> 100	3.5
$R_F = C_3F_7OCF(CF_3)$				
	44:56	4180	> 100	3.6
	18:82	3770	1.8	3.5
	0:100	12000	> 100	3.1
$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)$				
	15:85	5030	8.3	3.6
	0:100	9200	> 100	3.1
$R_F = C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$				
	9:91	5670	8.9	3.9
	0:100	6300	8.5	3.4
$-(CH_2CHCO_2H)_n-$		2000		3.5

important role in the depletion of CD4$^+$ T-lymphocytes in AIDS patients [32]. Azidothymidine (AZT) and other dideoxynucleoside analogs, which are potent inhibitors of HIV-1 reverse transcriptase, do not block such giant cell formation [9a]. Since fluoroalkylated acrylic acid homo-oligomers have been shown to be capable of suppressing giant cell formation [30], our fluoroalkylated acrylic acid co-oligomers would also be expected to inhibit syncytium formation.

Non-fluorinated poly(acrylic acid) [$-(CH_2$–CH-$CO_2H)_n-$] has been reported to be inactive against HIV-1 replication [33]. In general, anionic polymers such as dextran sulfate which possesses anti-HIV-1 activity are known to interact with positively charged gp 120 [34]. More anionic compounds are suggested to interact more strongly with gp 120 to suppress virus adsorption onto the cell membrane. Our fluoroalkylated co-oligomers should be more acidic than the corresponding non-fluorinated poly(acrylic acid) due to the strong electronegativity of the fluoroalkyl groups. Therefore, we have measured the pH values of a series of fluoroalkylated acrylic acid oligomers and non-fluorinated acrylic acid oligomer, and the results are listed in Table 6.

As shown in Table 6, no obvious direct correlation between the pH of these oligomers and their anti-HIV-1 activity was observed, and pH values of the fluoroalkylated oligomers were almost the same as that of the non-fluorinated acrylic acid oligomer. This finding indicates that since our oligomers have only two-fluoroalkylated end-caps, most carboxy groups are not affected by the strong inductive effect of the fluoroalkyl groups. Hence, only the anionic carboxy groups near to the fluoroalkyl units in the oligomers would interact strongly with the positively charged gp 120.

As mentioned before, fluoroalkylated silicon co-oligomers were more effective in reducing the surface tension of water. In particular, as shown in Figs. 1 and 2, each silicon co-

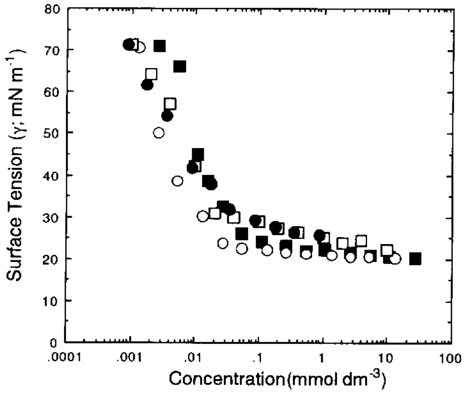

Fig. 11. Surface tensions of aqueous solutions of R_F–$(CH_2CHSiMe_3)_x$–$(CH_2CHCO_2H)_y$–R_F. ■ $R_F = C_3F_7$ [$\bar{M}_n$ = 1860 (x/y = 8:92)]; ○ $R_F = CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 3770 (x/y = 18:82)]; □ $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 5030 (x/y = 15:85)]; ● $R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ [$\bar{M}_n$ = 5670 (x/y = 9:91)].

oligomer exhibited a clear breakpoint resembling a CMC. More interestingly, in these co-oligomers, as the degree of reduction in the surface tension of water increased, the anti-HIV-1 activity also increased as shown in Fig. 1 and Table 4. A similar tendency to that of Fig. 1 was also obtained in the case of molar concentrations (calculated on the basis of $\bar{M}_n$) of these co-oligomers as shown in Fig. 11. Thus, as shown in Fig. 1, a silicon co-oligomer with a higher anti-HIV-1 activity is likely to exhibit a breakpoint at ca. 0.1 mg ml^{-1}, which is a little higher than its EC_{50} value (1.8 μg ml^{-1}). Hence, it is possible that intra- or inter-molecular aggregation of fluoroalkylated acrylic acid co-oligomers would interact in part with gp 120 leading to more potent inhibitory effects against HIV-1 replication.

Moreover, there is some correlation between Γ and EC_{50}, and it was shown that as the Γ values increased the EC_{50} values decreased as shown in Table 7.

Thus, fluoralkylated co-oligomers which are more adsorbable at the water/air interface would lead to the greater surface interaction with gp 120 and hence exhibit a higher anti-HIV-1 activity.

Sulfonic acid and sulfate moieties are well known as being necessary for highly potent inhibition to be exhibited in HIV-1 replication [9,35–40]. However, it has been reported that hydroxy and carboxy moieties are not effective against HIV-1 replication [32]. To our knowledge, the present is the first example which shows that compounds containing carboxy groups possess highly potent inhibitory properties against HIV-1 replication. On this basis, our fluoroalkylated acrylic acid co-oligomers seem to be more attractive than dextran sulfate because of their high level of stability. Further applications to new polymeric inhibition of HIV are expected.

3. Experimental details

3.1. Measurements

NMR spectra were measured with a JEOL-EX-270 FT-NMR (270 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 filled with Shodex KF-800P, KF-804 and KF-8025 columns (calibration based on polystyrene standards).

3.2. Materials

A series of fluoroalkanoyl peroxides {$(R_FCO_2)_2$; $R_F = C_3F_7$, $C_3F_7O[CF(CF_3)CF_2O]_mCF(CF_3)$, m = 0, 1, 2} were prepared from the corresponding acyl halides and hydrogen peroxides in the presence of aqueous sodium hydroxide in 1,1,2-trichloro-1,2,2-trifluoroethane (Freon-113) according to our previously reported method [15a,41]. Trimethylvinylsilane, acrylic acid and other monomers were used after distillation.

3.3. General procedure for the synthesis of fluoroalkylated acrylic acid co-oligomers

A solution containing perfluorobutyryl peroxide (12 mmol), trimethylvinylsilane (24 mmol) and acrylic acid (47

Table 7
Values of the surface excess and EC_{50} for typical fluoroalkylated and alkyl methacrylate co-oligomers

(a) R_F–$(CH_2$–$CHSiMe_3)_x$–$(CH_2CHCO_2H)_y$–R_F

R_F ($\bar{M}_n$)	Γ (mol m^{-2}) × 10^6	EC_{50} (μg ml^{-1})
C_3F_7 (1860)	6.6	2.2
$C_3F_7OCF(CF_3)$ (3770)	6.8	1.8
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$ (5030)	5.4	8.3
$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)$ (5670)	4.2	8.9

(b) R_F–$(CH_2$–$CMeCO_2R)_x$–$(CH_2CHCO_2H)_y$–R_F

R_F ($\bar{M}_n$)	R	Γ (mol m^{-2}) × 10^6	EC_{50} (μg ml^{-1})
C_3F_7 (5540)	$CH_2CH(CH_2CH_3)(CH_2)_3CH_3$	4.8	7.3
$C_3F_7OCF(CF_3)$ (4970)	CH_2CH_2OH	3.6	> 100

mmol) in Freon-113 (1,1,2-trichlorotrifluoroethane: 200 g) was stirred at 40 °C for 5 h under nitrogen, and the resulting white powder reprecipitated from methanol ethyl acetate to give a bis(perfluoropropylated) acrylic acid trimethylvinylsilane co-oligomer $C_3F_7-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-C_3F_7$ (4.67 g). This co-oligomer exhibited the following spectral characteristics. IR (cm^{-1}): 3130 (OH); 1712 (CO); 1350 (CF_3); 1226 (CF_2); 840 (Si–Me). ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.3 (6F); −36.6 (4F); −51.9 (4F) ppm. ^{1}H NMR (CD_3OD) δ: −0.10 to 0.11 (CH_3); 0.33–0.69 (CH); 1.28–2.08 (CH_2); 2.18–2.63 (CH) ppm. Co-oligomerization ratio, x/y = 13:87; average molar mass ($\bar{M}_n$) = 1860, $\bar{M}_w/\bar{M}_n$ = 1.83 (determined by gel permeation chromatography calibrated with standard polystyrene). Other fluoroalkylated co-oligomers not listed in Tables 1 and 2 were isolated by repeated reprecipitation of the corresponding co-oligomers.

$C_3F_7-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-C_3F_7$: x/y = 20:80. IR (cm^{-1}): 3115 (OH); 1712 (CO); 1350 (CF_3); 1226 (CF_2); 840 (Si–Me). ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.0 (6F); −37.8 (4F); −52.2 (4F) ppm. ^{1}H NMR (CD_3OD) δ: −0.09 to 0.13 (CH_3); 0.32–0.68 (CH); 1.31–2.01 (CH_2); 2.18–2.62 (CH) ppm.

$C_3F_7-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-C_3F_7$: x/y = 4:96. IR (cm^{-1}): 3455 (OH); 1724 (CO); 1353 (CF_3); 1228 (CF_2); 847 (Si–Me) ppm. ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −6.0 (6F); −38.5 (4F); −52.0 (4F) ppm. ^{1}H NMR (CD_3OD) δ: 0.03–0.30 (CH_3); 0.38–0.64 (CH); 1.49–2.17 (CH_2); 2.36–2.89 (CH) ppm.

$C_3F_7-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-C_3H_7$: x/y = 3:97. IR (cm^{-1}): 3452 (OH); 1722 (CO); 1351 (CF_3); 1228 (CF_2); 846 (Si–Me) ppm. ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.5 (6F); −8.5 (4F); −51.8 (4F) ppm. ^{1}H NMR (CD_3OD) δ: −0.07 to 0.21 (CH_3); 0.34–0.80 (CH); 1.43–2.11 (CH_2); 2.25–2.79 (CH) ppm.

$C_3F_7OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: x/y = 35:65. IR (cm^{-1}): 3109 (OH); 1712 (CO); 1329 (CF_3); 1246 (CF_2); 841 (Si–Me) ppm. ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.7 to −7.6 (16F); −53.6 (6F) ppm. ^{1}H NMR (CD_3OD) δ: 0.04–0.23 (CH_3); 0.58–0.82 (CH); 1.18–2.16 (CH_2); 2.30–2.81 (CH) ppm.

$C_3F_7OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: x/y = 26:74. IR (cm^{-1}): 3423 (OH); 1714 (CO); 1397 (CF_3); 1250 (CF_2); 840 (Si–Me). ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.8 to −7.6 (16F); −53.7 (6F) ppm. ^{1}H NMR (CD_3OD) δ: 0.08–0.40 (CH_3); 0.48–0.82 (CH); 1.18–2.09 (CH_2); 2.32–2.81 (CH) ppm.

$C_3F_7OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: x/y = 24:76. IR (cm^{-1}): 3103 (OH); 1714 (CO); 1397 (CF_3); 1250 (CF_2); 840 (Si–Me). ^{19}F NMR (CD_3OD, ext. CF_3OD, ext. CF_3CO_2H) δ: −5.8 to −7.6 (16F); −53.7 (6F) ppm. ^{1}H NMR (CD_3OD) δ: 0.08–0.40 (CH_3); 0.48–0.82 (CH); 1.18–2.09 (CH_2); 2.32–2.81 (CH) ppm.

$C_3F_7OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: x/y = 18:82. IR (cm^{-1}): 3150 (OH); 1712 (CO); 1330 (CF_3); 1241 (CF_2); 840 (Si–Me) ppm. ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.1 to −8.4 (16F); −53.8 (6F) ppm. ^{1}H NMR (CD_3OD) δ: 0.10–0.26 (CH_3); 0.48–0.83 (CH); 1.17–2.18 (CH_2); 2.33–2.97 (CH) ppm.

$C_3F_7OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: x/y = 15:85. IR (cm^{-1}): 3260 (OH); 1701 (CO); 1331 (CF_3); 1248 (CF_2); 841 (Si–Me) ppm. ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.5 to −8.1 (16F); −53.8 (6F) ppm. ^{1}H NMR (CD_3OD) δ: −0.03 to 0.34 (CH_3); 0.44–0.81 (CH); 1.45–2.11 (CH_2); 2.30–2.75 (CH) ppm.

$C_3F_7OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: x/y = 4:96. IR (cm^{-1}): 3141 (OH); 1716 (CO); 1331 (CF_3); 1240 (CF_2); 844 (Si–Me). ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.4 to −8.4 (16F); −53.9 (6F) ppm. ^{1}H NMR (CD_3OD) δ: 0.06–0.26 (CH_3); 0.42–0.81 (CH); 1.57–2.14 (CH_2); 2.37–2.69 (CH) ppm.

$C_3F_7OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: x/y = 3:97. IR (cm^{-1}): 3145 (OH); 1718 (CO); 1332 (CF_3); 1242 (CF_2); 844 (Si–Me). ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.4 to −8.4 (16F); −54.1 (6F) ppm. ^{1}H NMR (CD_3OD) δ: −0.01 to 0.27 (CH_3); 0.38–0.78 (CH); 1.51–2.14 (CH_2); 2.39–2.77 (CH) ppm.

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: x/y = 15:85. IR (cm^{-1}): 3465 (OH); 1718 (CO); 1352 (CF_3); 1246 (CF_2); 846 (Si–Me) ppm. ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −4.0 to −8.9 (26F); −53.8 (6F); −68.7 (2F) ppm. ^{1}H NMR (CD_3OD) δ: −0.10 to 0.26 (CH_3); 0.41–0.84 (CH); 1.19–2.13 (CH_2); 2.28–2.83 (CH) ppm.

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)CF_2OCF(CF_3)-(CH_2CHSiMe_3)_x-(CH_2CHCO_2H)_y-CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: x/y = 9:91. IR (cm^{-1}): 3463 (OH); 1718 (CO); 1329 (CF_3); 1242 (CF_2); 846 (Si–Me). ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −3.4 to −8.6 (36F); −54.0 (6F); −69.2 (4F) ppm. ^{1}H NMR (CD_3OD) δ: −0.01 to 0.28 (CH_3); 0.43–0.82 (CH); 1.10–2.16 (CH_2); 2.30–2.90 (CH) ppm.

$C_3F_7-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-C_3F_7$: x/y = 32:68. IR (cm^{-1}): 3456 (OH); 1726 (CO); 1350 (CF_3); 1228 (CF_2). ^{1}H NMR (CD_3OD) δ: 0.82–2.93 (CH_3, CH_2, CH); 3.56–3.83 (CH_3) ppm.

$C_3F_7-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-C_3F_7$: x/y = 28:72. IR (cm^{-1}): 3450 (OH); 1731 (CO); 1346 (CF_3); 1232 (CF_2). ^{19}F NMR (CD_3OD, ext. CF_3CO_2H) δ: −5.1 (6F); −38.3 (4F); −52.3 (4F) ppm. ^{1}H NMR (CD_3OD) δ: 0.95–3.07 (CH_3, CH_2, CH); 3.63–3.89 (CH_3) ppm.

$C_3F_7-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-C_3F_7$: x/y = 17:83. IR (cm^{-1}): 3161 (OH); 1720 (CO); 1350 (CF_3); 1230 (CF_2). ^{1}H NMR (CD_3OD) δ: 0.83–2.89 (CH_3, CH_2, CH); 3.54–3.86 (CH_3) ppm.

$C_3F_7-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-C_3F_7$: x/y = 12:88. IR (cm^{-1}): 3448 (OH); 1720 (CO); 1350 (CF_3); 1230 (CF_2). ^{1}H NMR (CD_3OD) δ: 0.83–2.87 (CH_3, CH_2, CH); 3.57–3.80 (CH_3) ppm.

$C_3F_7-(CH_2CMeCO_2Et)_x-(CH_2CHCO_2H)_y-C_3F_7$: $x/y=23:77$. IR (cm^{-1}): 3419 (OH); 1722 (CO); 1354 (CF_3); 1228 (CF_2). ^{19}F NMR (DMSO-d_6, ext. CF_3CO_2H) δ: −2.8 (6F); −36.3 (4F); −50.8 (4F) ppm. ^{1}H NMR (DMSO-d_6) δ: 0.77–2.74 (CH_3, CH_2, CH); 3.81–4.26 (CH_2) ppm.

$C_3F_7-(CH_2CMeCO_2Bu)_x-(CH_2CHCO_2H)_y-C_3F_7$: $x/y=20:80$. IR (cm^{-1}): 3169 (OH); 1720 (CO); 1350 (CF_3); 1228 (CF_2). ^{19}F NMR (DMSO-d_6, ext. CF_3CO_2H) δ: −2.7 (6F); −36.3 (4F); −50.2 (4F) ppm. ^{1}H NMR (DMSO-d_6) δ: 0.67–2.72 (CH_3, CH_2, CH); 3.79–4.17 (CH_2) ppm.

$C_3F_7-[CH_2CMeCO_2CH_2CH(CH_2CH_3)(CH_2)_3CH_3]_x-(CH_2CHCO_2H)_y-C_3F_7$: $x/y=15:85$. IR (cm^{-1}): 3456 (OH); 1720 (CO); 1350 (CF_3); 1228 (CF_2). ^{19}F NMR (DMSO-d_6, ext. CF_3CO_2H) δ: −2.8 (6F); −36.2 (4F); −50.3 (4F) ppm. ^{1}H NMR (DMSO-d_6) δ: 0.68–2.40 (CH_3, CH_2, CH); 3.73–4.07 (CH_2) ppm.

$C_3F_7OCF(CF_3)-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: $x/y=47:53$. IR (cm^{-1}): 3446 (OH); 1726 (CO); 1321 (CF_3); 1240 (CF_2) ppm. ^{1}H NMR (CD_3OD) δ: 0.93–2.97 (CH_3, CH_2, CH); 3.53–3.80 (CH_3) ppm.

$C_3F_7OCF(CF_3)-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-CF(CCF_3)OC_3F_7$: $x/y=41:59$. IR (cm^{-1}): 3122 (OH); 1726 (CO); 1327 (CF_3); 1240 (CF_2). ^{19}F NMR (DMSO-d_6, ext. CF_3CO_2H) δ: −3.5 to −5.5 (16F); −51.9 (6F) ppm. ^{1}H NMR (DMSO-d_6) δ: 0.74–2.95 (CH_3, CH_2, CH); 3.48–3.65 (CH_3) ppm.

$C_3F_7OCF(CF_3)-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: $x/y=23:77$. IR (cm^{-1}): 3126 (OH); 1720 (CO); 1326 (CF_3); 1240 (CF_2). ^{1}H NMR (CD_3OD) δ: 0.80–2.83 (CH_3, CH_2, CH); 3.50–3.83 (CH_3) ppm.

$C_3F_7OCF(CF_3)-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: $x/y=16:84$. IR (cm^{-1}): 3116 (OH); 1720 (CO); 1327 (CF_3); 1240 (CF_2). ^{1}H NMR (CD_3OD) δ: 0.73–2.85 (CH_3, CH_2, CH); 3.52–3.93 (CH_3) ppm.

$C_3F_7OCF(CF_3)-(CH_2CMeCO_2Et)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: $x/y=23:77$. IR (cm^{-1}): 3460 (OH); 1720 (CO); 1327 (CF_3); 1240 (CF_2). ^{19}F NMR (DMSO-d_6, ext. CF_3CO_2H) δ: −3.5 to −5.2 (16F); −51.9 (6F) ppm. ^{1}H NMR (DMSO-d_6) δ: 0.75–2.88 (CH_3, CH_2, CH); 3.87–4.27 (CH_2) ppm.

$C_3F_7OCF(CF_3)-(CH_2CMeCO_2Bu)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: $x/y=20:80$. IR (cm^{-1}): 3120 (OH); 1720 (CO); 1327 (CF_3); 1240 (CF_2). ^{19}F NMR (DMSO-d_6, ext. CF_3CO_2H) δ: −3.5 to −5.2 (16F); −51.9 (6F) ppm. ^{1}H NMR (DMSO-d_6) δ: 0.73–2.80 (CH_3, CH_2, CH); 3.79–4.20 (CH_2) ppm.

$C_3F_7OCF(CF_3)-[CH_2CMeCO_2CH_2CH(CH_2CH_3)-(CH_2)_3CH_3]_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: $x/y=14:86$. IR (cm^{-1}): 3452 (OH); 1720 (CO); 1327 (CF_3); 1240 (CF_2) ppm. ^{19}F NMR (DMSO-d_6, ext. CF_3CO_2H) δ: −3.5 to −5.6 (16F); −52.0 (6F) ppm. ^{1}H NMR (DMSO-d_6) δ: 0.73–2.79 (CH_3, CH_2, CH); 3.67–4.23 (CH_2) ppm.

$C_3F_7OCF(CF_3)-(CH_2CMeCO_2CH_2CH_2OH)_x-(CH_2-CHCO_2H)_y-CF(CF_3)OC_3F_7$: $x/y=16:84$. IR (cm^{-1}): 3218 (OH); 1728 (CO); 1330 (CF_3); 1240 (CF_2). ^{1}H NMR (CD_3OD) δ: 0.71–2.75 (CH_3, CH_2, CH); 3.47–4.74 (CH_2) ppm.

$C_3F_7OCF(CF_3)-(CH_2CMeCO_2CH_2CH_2OCH_2CH_2OH)_x-(CH_2CHCO_2H)_y-CF(CF_3)OC_3F_7$: $x/y = 15:85$. IR (cm^{-1}): 3230 (OH); 1726 (CO); 1329 (CF_3); 1240 (CF_2). ^{1}H NMR (CD_3OD) δ: 0.66–2.84 (CH_3, CH_2, CH); 3.53–4.58 (CH_2) ppm.

$C_3F_7OCF(CF_3)CF_2OCF(CF_3)-(CH_2CMeCO_2Me)_x-(CH_2CHCO_2H)_y-CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: $x/y=60:40$. IR (cm^{-1}): 3150 (OH); 1720 (CO); 1330 (CF_3); 1240 (CF_2). ^{19}F NMR ($CDCl_3$, ext. CF_3CO_2H) δ: −3.0 to −7.1 (26F); −50.3 to −58.2 (6F); −74.1 to −78.2 (2F) ppm. ^{1}H NMR ($CDCl_3$) δ: 0.75–3.20 (CH_3, CH_2, CH); 3.75 (CH_3) ppm.

3.4. Surface tension measurements

The surface tensions of aqueous and *m*-xylene solutions of the fluoroalkylated co-oligomers were measured at 30 °C using a Wilhelmy-type surface tensiometer (ST-1, Shimadzu Co.) with a glass plate. For the measurement of the surface tension of aqueous solutions of fluoroalkylated alkyl methacrylate/acrylic acid co-oligomers, these co-oligomers were neutralized and converted into the corresponding sodium salts by adding 0.1 M NaOH.

3.5. Antiviral assays

The antiviral activity of the compounds against HIV-1 (HTLV-III$_B$ strain) replication was based on the inhibition of virus-induced cytopathic effect in MT-4 cells as previously described [30]. Briefly, MT-4 cells were suspended in a culture medium at 1×10^5 cells ml^{-1} and infected with HIV-1 at a multiplicity of infection of 0.02. Immediately after virus infection, the cell suspension (100 μl) was added to each well of a microtitre tray containing various concentrations of test compounds. After a 4-d incubation period at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method [42].

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