Synthesis of Amphiphilic Fluoroalkoxyl End-Capped Cooligomers Containing Oxime-Blocked Isocyanato Segments: Architecture and Applications of New Self-Assembled Fluorinated Molecular Aggregates

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ABSTRACT: New fluoroalkoxyl end-capped cooligomers containing oxime-blocked isocyanato segments were prepared by the reactions of fluoroalkanoyl peroxides with isocyanatoethyl methacrylate 2-butanone oxime adduct (IEM-BO) and *N*,*N*-dimethylacrylamide (DMAA). Fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers thus obtained were easily soluble in water and common organic solvents except for hexane. These amphiphilic fluoroalkoxyl end-capped cooligomers were able to reduce the surface tension of water quite effectively around to 18 mN/m levels with a clear break point resembling a cmc (critical micelle concentration). Static and dynamic light scattering measurements showed that fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers are likely to form the self-assembled molecular aggregates in aqueous solutions. In particular, the longest fluoroalkoxyl end-capped IEM-BO−DMAA cooligomer can form the self-assemblies, which are considered to consist of around 100 fluorinated oligomeric molecules with 17−18 nm size even in the lower concentrations of the cooligomer, compared to the other fluoroalkoxylated cooligomers. The molecular assemblies formed by the longest fluoroalkoxyl end-capped IEM-BO−DMAA cooligomer could interact strongly with ethidium bromide (Etd-Br) as a guest molecule to form the host−guest intermolecular complex. Additionally, fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers were found to become useful precooligomers for the introduction of various aromatic segments into the cooligomer chains. In fact, amphiphilic fluoroalkoxyl end-capped cooligomer-bound functional aromatic moieties such as 5-fluorouracil(5-FU) and 9-aminoacridine were prepared in good yields by the reactions of the corresponding fluorinated precooligomers with the parent aromatic compounds. In particular interest, it was demonstrated that fluoroalkoxyl end-capped cooligomer-bound 5-FU could have a remarkably strong interaction with oligoDNA.

Introduction

Partially fluorinated, in particular fluoroalkyl end-capped, polymers are attractive functional materials due to exhibiting various unique properties such as a good solubility in various solvents, surface-active properties, biological activities, and gelling ability which cannot be achieved by the corresponding randomly or block-type fluoroalkylated polymers.[1] Fluoroalkanoyl peroxide is a convenient tool for the preparation of numerous fluoroalkyl end-capped oligomers with carbon−carbon bond formation by the oligomerization of the peroxide with radical polymerizable monomers via a radical process.[2] However, fluoroalkanoyl peroxides are well-known to possess an extremely high reactivities for various aromatic compounds such as benzene, chlorobenzene, and thiophene, and these fluorinated peroxides can suffer a single electron-transfer reaction from aromatic compounds to the peroxides to afford the corresponding fluoroalkylated compounds.[3] Due to their high reactivities, it is in general difficult to synthesize fluoroalkyl end-capped oligomers possessing aromatic segments by the use of fluoroalkanoyl peroxides; however, these compounds have been the subject of considerable research of new fluorinated functional materials. Thus, it is preferential to prepare fluoroalkyl end-capped preoligomers containing the protected reactive segments such as oxime-blocked isocyanato group by using fluoroalkanoyl peroxides as in Scheme 1. These obtained fluoroalkyl end-capped pre-oligomers are expected to become useful key intermediates for the preparation of fluoroalkyl end-capped oligomer-bound various functional aromatic moieties. This strategy is suggested to become very effective for the preparation of fluoroalkyl end-capped oligomers possessing biologically active moieties such as uracils and purines which should show the high reactivity for fluoroalkanoyl peroxide.[4] In a preliminary account, we reported on the synthesis of fluoroalkoxyl end-capped isocyanato cooligomers in which the reactive isocyanato moieties were protected as 2-butanone oxime adduct.[5] In particular interest, it was demonstrated that these fluoroalkoxyl end-capped cooligomers become useful precooligomers for the synthesis of water-soluble fluoroalkoxyl end-capped cooligomer-bound antitumor agents such as 5-fluorouracil. Therefore, it is very important to clarify the fundamental surfactant properties including the architecture of the self-assembled molecular aggregates of these fluorinated precooligomers in view of the development of new fluorinated functional materials. In this paper, we would like to report on the synthesis and properties of fluoroalkoxyl end-capped precooligomers containing oxime-blocked isocyanato segments, with emphasis on the introduction of functional aromatic segments such as 5-fluorouracil into these fluorinated precooligomers

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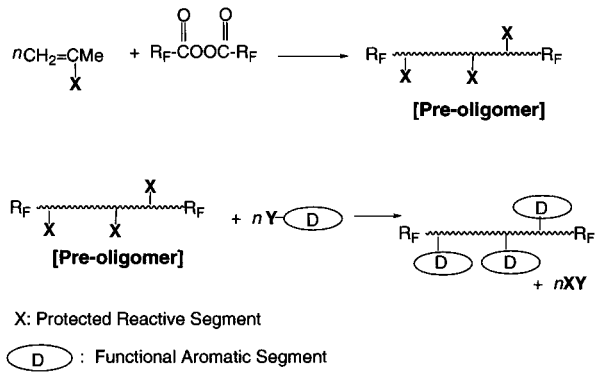
Scheme 1



and application of these obtained fluorinated cooligomer-bound aromatic moieties.

Results and Discussion

Synthesis of Fluoroalkoxyl End-Capped Precooligomers. The reactions of fluoroalkanoyl peroxides with isocyanatoethyl methacrylate 2-butanone oxime adduct (IEM-BO) and *N*,*N*-dimethylacrylamide(DMAA) 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 were carried out at 45 °C for 5 h under nitrogen. The process is outlined in Scheme 2.

IEM-BO and DMAA were found to react with fluoroalkanoyl peroxides under very mild conditions to afford fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers. These results are shown in Table 1.

As shown in Table 1, fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers were obtained in good yields. The cooligomerization ratios and the molecular weights of these cooligomers were determined by ^{1}H NMR and gel permeation chromatography (GPC) (calibrated with standard polystyrene by using THF as the eluent) analyses, respectively, and the obtained molecular weights (M_n) were in oligomeric regions (1150−2040). A similar cooligomerization ratio was obtained in each reaction. This finding suggests that fluoroalkoxyl radical could possess a similar reactivity toward IEM-BO and DMAA. The concentrations of fluoroalkanoyl peroxides used were higher than that of IEM-BO or DMAA [molar ratio of IEM-BO (or DMAA)/peroxide = 1.0 or 10], in contrast to the usual case for radical polymerization. Under these conditions, mainly IEM-BO−DMAA cooligomers with two fluoroalkoxyl end groups would be obtained via primary radical termination or radical chain transfer to the peroxide, as well as by our previously reported method for the synthesis of acrylic acid oligomers having two fluoroalkyl end groups in one oligomeric molecule [R_F−$(CH_2CHCOOH)_n$−R_F; R_F = fluoroalkyl group].[6,7] In particular, two fluoroalkyl end-capped acrylic acid oligomers were obtained in excellent to moderate isolated yields under these conditions [molar ratios of monomer/peroxide = 1−10].[6,7]

Surfactant Properties of Fluoroalkoxyl End-Capped Precooligomers. Fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers thus obtained were easily soluble in water and common organic solvents except for hexane. Thus, these fluoroalkoxyl end-capped cooligomers are applicable to new fluorinated oligo-surfactants. In fact, we have measured the surface tension of their aqueous solutions with the Wilhelmy plate methods at 30 °C. These results were shown in Figure 1.

As shown in Figure 1, fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers were effective for reducing the surface tension of water, to around 18 mN/m levels with a clear break point resembling a cmc (critical micelle concentration). This finding suggests that our present fluoroalkoxyl end-capped cooligomers should form the intermolecular aggregates in aqueous solutions.

Architecture of Self-Assembled Molecular Aggregates Formed by Fluoroalkoxyl End-Capped Precooligomers in Aqueous Solutions. We have measured the molecular weights of fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers in Table 1 by GPC analyses by using 5 mmol/dm^3 tris(hydroxymethyl)-aminomethane (Tris) −HCl buffer solution (pH 7.4) as the eluent, and the results are shown in Table 2.

The molecular weights (M_n = 9150−21500) of fluorinatd cooligomers determined by GPC (eluent: Tris−HCl buffer) are considerably higher compared to the values [M_n = 1150−2040 (see Table 1)] determined by GPC with THF as the eluent. On the other hand, the molecular weight of nonfluorinated −$(IEM\text{-}BO)_x$−$(DMAA)_y$− cooligomer was a similar value to the case in which THF was used as the eluent. These findings indicate that fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers are likely to form the self-assembled molecular aggregates in aqueous solutions.

We have conducted static light scattering measurements to confirm the formation of molecular assemblies in aqueous solutions of R_F−$(IEM\text{-}BO)_x$−$(DMAA)_y$−R_F; R_F = $CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$; M_n = 2040], including the corresponding nonfluorinated cooligomer [−$(IEM\text{-}BO)_x$−$(DMAA)_y$−] for comparison. These results are shown in Figure 2.

As shown in Figure 2, the ratio of the strength of the scattered light from the fluorinated cooligomer solution to that from benzene (standard substance) was small at lower cooligomer concentrations (below 0.01%), and it increased abruptly above a certain fluorinated cooligomer concentration (ca. 0.02%). In contrast, in the corresponding nonfluorinated cooligomer, the ratio of the strength of the scattered light did not increase significantly at 0.05 or 0.1%. This finding suggests the formation of molecular assemblies of fluoroalkoxyl end-capped IEM-BO−DMAA cooligomer above this concentration because the strength of the scattered light depends on the number and size of particles in the medium. Interestingly, the value of this concentration (0.02%) was almost the same as that of a break point resembling a cmc in the surface tension measurements as in Figure 1.

The molecular weights of the aggregates formed by the fluorinated cooligomers [R_F−$(IEM\text{-}BO)_x$−$(DMAA)_y$−R_F; R_F = $CF(CF_3)O[CF_2CF(CF_3)O]_mC_3F_7$] determined by the static light scattering measurements were as follows:

	mol wt
R_F = $CF(CF_3)OC_3F_7$	25 200
R_F = $CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	102 000
R_F = $CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	198 000

The longer fluoroalkoxyl end-capped cooligomers are effective in increasing the molecular weights of cooligomers. This finding suggests that longer fluoroalkoxyl end-capped cooligomers are likely to form the self-assembled molecular aggregates. For example, the self-assemblies formed by the longest fluoroalkoxyl (m = 2) end-capped IEM-BO−DMAA cooligomer is considered

Scheme 2

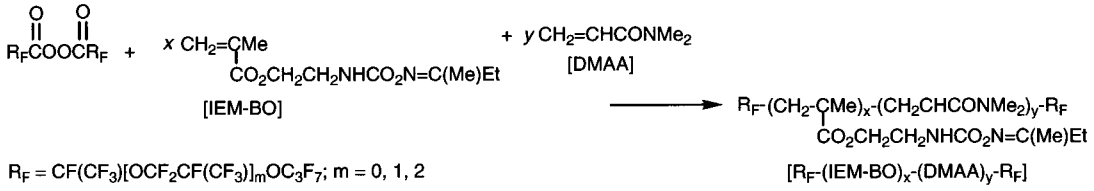


Table 1. Reactions of Fluoroalkanoyl Peroxides with IEM-BO and DMAA

run	R_F	$(R_FCO_2)_2$ (mmol)	IEM-BO (mmol)	DMAA (mmol)	yield[a] (%)	M_n (M_w/M_n)[b]	[x:y][c]
1	$CF(CF_3)OCF_3F_7$	5.0	5.0	50	87	1150 (1.21)	7:93
2	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	2.5	2.5	25	68	1640 (1.07)	7:93
3	$CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	5.0	5.0	50	70	2040 (1.05)	10:90

[a] The yields are based on the starting materials (IEM-BO and DMAA and the decarboxylated peroxide unit $[R_F-R_F]$. [b] Molecular weight was determined by GPC (eluent:THF). [c] Co-oligomerization ratio was determined ^1H-NMR.

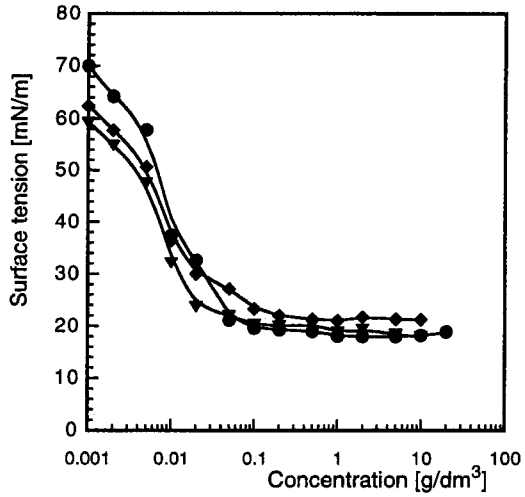


Figure 1. Surface tension of aqueous solutions of $R_F-(IEM-BO)_x-(DMAA)_y-R_F$. Key: (●) $R_F = CF(CF_3)OC_3F_7$; (♦) $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$; (▼) $R_F = CF(CF_3)OCF_2CF(CF_3)-OCF_2CF(CF_3)OC_3F_7$.

Table 2. Molecular Weights of $R_F-(IEM-BO)_x-(DMAA)-R_F$ Cooligomers Determined by GPC Analyses with Tris−HCl Buffer as the Eluent

R_F in $R_F-(IEM-BO)_x-(DMAA)_y-R_F$	M_n (M_w/M_n)
m in R_F [$R_F = CF(CF_3)O[CF_2CF(CF_3)O]_mC_3F_7$]	
$m = 0$	9150 (1.64)[a]
$m = 1$	16400 (1.23)
$m = 2$	21500 (1.24)
$-(IEM-BO)_x-(DMAA)_y-$ ($x:y$ = 13:87)	3620 (3.46) [1300 (1.02)[b]]

[a] Eluent: Tris−HCl buffer. [b] Eluent: THF.

to consist of around 100 fluorinated oligomeric molecules since the molecular weight of the aggregates formed by the fluorinated IEM-BO−DMAA cooligomer determined by the static light scattering measurements and the molecular weight of the cooligomer determined by GPC measurements (eluent: THF) are 198 000 and 2040, respectively.

From this point of view, it is very interesting to estimate the size of molecular assemblies formed in aqueous solutions of the fluoroalkoxyl end-capped co-oligomers. In fact, we have studied on the size of molecular assemblies formed in 0.1 mol/dm^3 $NaNO_3$ solutions of a series of fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers and the corresponding non-fluorinated cooligomer by the dynamic light scattering measurements, and the results are shown in Table 3.

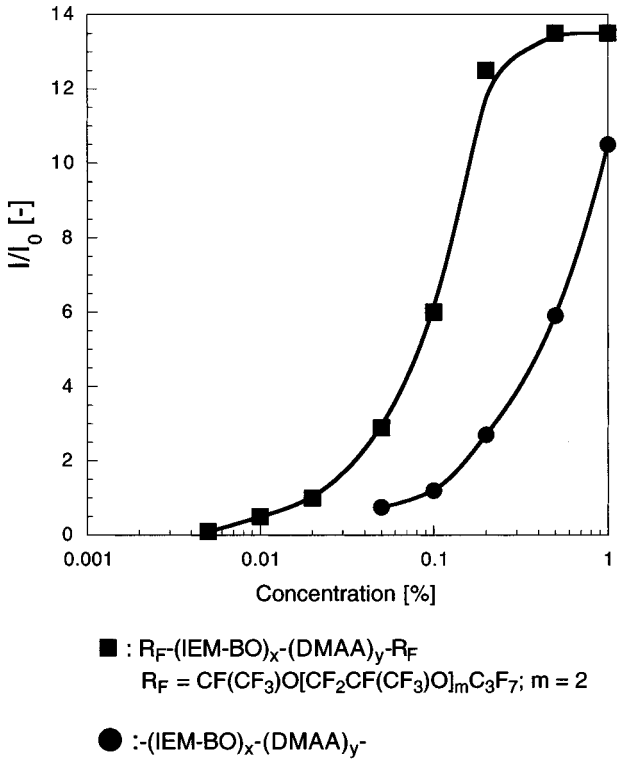


Figure 2. Relationship between relative scattered light intensity [I/I_0(PhH)] and concentration of $R_F-(IEM-BO)_x-(DMAA)_y-R_F$ solutions at 25 °C.

As shown in Table 3, the size of molecular assemblies was found to increase with an increase in the length of the R_F chain in the cooligomers. In particular, the longest fluoroalkoxyl ($m = 2$) end-capped cooligomers can form the molecular assemblies with 17−18 nm size even in the lower concentration of 0.02% compared to the other cooligomers. The value of this concentration (0.02%) was almost the same as that of a break point resembling a cmc in the surface tension measurements in Figure 1. On the other hand, other fluoroalkoxyl ($m = 0$, 1) end-capped cooligomers and nonfluorinated cooligomers are not likely to form molecular assemblies at this concentration. Moderate longer fluoroalkoxyl ($m = 1$) end-capped cooligomer can form the molecular assemblies with 10 nm size levels above the concentration of 0.1%, and in the case of shorter fluoroalkoxyl (*m*

Table 3. Size of the Molecular Aggregates Formed by $R_F-(IEM\text{-}BO)_x-(DMAA)_y-R_F$[a] in 0.1 M $NaNO_3$ Solutions Determined by the Dynamic Light Scattering Measurements

	size of the molecular aggregates (nm)			
	R_F in oligomer			
concn (%)	$m = 0$	$m = 1$	$m = 2$	non-fluorinated
0.005			10.7	
0.010			11.2	
0.020	3.10	4.30	17.3	
0.050	6.20	5.90	16.8	6.00
0.100	5.70	11.1	17.4	7.20
0.200	5.70	12.8	17.4	8.70
0.500	13.3	15.4	18.1	12.0
1.000	10.8	16.8	18.4	10.5

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

$= 0$) end-capped cooligomer or nonfluorinated cooligomers, the molecular assemblies with 10 nm size levels were formed above the concentration of 0.5%. Thus, it was clarified that the longest ($m = 2$) fluoroalkoxyl end-capped cooligomers can form molecular aggregates with 17 nm size levels in aqueous solutions. Previously, we reported that molecular assemblies formed in aqueous solutions of the fluoroalkyl end-capped acrylic acid−trimethylvinylsilane cooligomers have an ellipsoidal shape with the aggregations of terminal fluoroalkyl segments.[8,9] Therefore, our present fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers should form similar molecular aggregates imparted by the aggregations of end-capped fluoroalkoxyl segments. In particular, it is suggested that the longest fluoroalkoxyl end-capped cooligomers are likely to form the molecular assemblies due to the stronger association through the aggregation of longer fluoroalkoxyl segments in cooligomers.

Interaction of Self-Assemblies Formed by Fluoroalkoxyl End-Capped Precooligomers with Ethidium Bromide (Etd-Br). Fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers were demonstrated to form the self-assembled molecular aggregates in aqueous solutions. Therefore, it is very interesting to investigate the potential of fluoroalkoxyl end-capped IEM-BO−DMAA cooliogomers as a host system for a hydrophilic guest molecule. Thus, it is strongly suggested that fluorescent dyes such as ethidium bromide (Etd-Br) could act as a suitable guest molecule for these fluorinated self-assembled molecular aggregates. We have measured the fluorescence spectrum of Etd-Br in the presence of fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers, and the results are shown in Figure 3.

As shown in Figure 3, when fluoroalkoxyl ($m = 0, 1$) end-capped IEM-BO−DMAA cooligomers and nonfluorinated IEM-BO−DMAA cooligomer were added into Etd-Br solution, the fluorescence intensity of Etd-Br did not change with increasing the concentrations of these cooligomers. On the other hand, very interestingly, when the longest fluoroalkoxyl ($m = 2$) end-capped

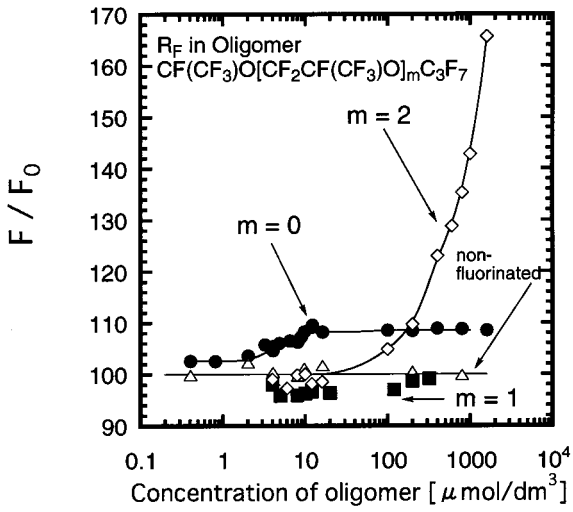


Figure 3. Relative fluorescent intensity (F/F_0) of Etd-Br in the presence of $R_F-(IEM\text{-}BO)_x-(DMAA)_y-R_F$ at 36 °C. Samples were excited at 540nm. Experiments were conducted in 5 mmol/dm^3 tris(hydroxymethyl) aminomethane−HCl buffer (pH 7.4) containing 20 mmol/dm^3 NaCl.

IEM-BO−DMAA cooligomer was added into Etd-Br solution, the fluorescence intensity of Etd-Br was found to increase drastically with increasing amounts of the fluorinated cooligomer. In particular, its intensity increased abruptly above a certain cooligomer concentration [ca. 100 μmol/dm^3 (0.02%)], which value is almost the same as that of a break point resembling a cmc in the surface tension measurements in Figure 1 or that of the concentration for the formation of molecular assemblies of fluorinated cooligomer as in Figure 2 and Table 3. Hitherto, the interaction of the self-assemblies of macromolecules with fluorescence probes has been investigated in detail, and it is well-known that fluorescence intensity drastically increases with increasing concentration of the macromolecular aggregates, and the probe molecules are incorporated in the hydrophobic domain of the macromolecular aggregates.[10,11] Thus, our present results suggest that the longest fluoroalkoxyl ($m = 2$) end-capped cooligomer should form the suitable molecular assemblies imparted by the aggregations of the end-capped fluoroalkoxyl segments for a guest molecule, and Etd-Br could interact as a guest molecule for these fluorinated host moieties.

UV−vis spectra of Tris−HCl buffer solutions of Etd-Br in the presence of fluorinated cooligomers are shown in Figure 4. We can observe that the spectra ($\lambda_{max} = 480$ nm) of Etd-Br in the presence of the longest fluoroalkoxyl ($m = 2$) end-capped cooligomer are slightly red-shifted with increasing concentration (1000 and 1600 μM) of the cooligomer, although the other fluoroalkoxyl ($m = 0$ and 1) end-capped cooligomers could not shift the wavelength of the maximum absorbance as shown in Figure 4. In particu-

Table 4. Reactions of $R_F-(IEM\text{-}BO)_x-(DMAA)_y-R_F$ with 5-FU

R_F in cooligomer	$R_F-(IEM\text{-}BO)_x-(DMAA)_y-R_F$ (mmol)	5-FU (mmol)	yield[a] (%)	product M_n (M_w/M_n)[b]	[x:y][c]
$R_F = CF(CF_3)OC_3F_7$	0.9	1.6	65	1240 (1.04)	7:93
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	0.6	1.2	89	1510 (1.13)	7:93
$R_F = CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	0.5	1.0	65	2320 (1.00)	10:90

[a] The yields (mol/mol) are based on $R_F-(IEM\text{-}BO)_x-(DMAA)_y-R_F$. [b] Molecular weight was determined by GPC (eluent:THF). [c] The cooligomerization ratio was determined by ^1H−NMR.

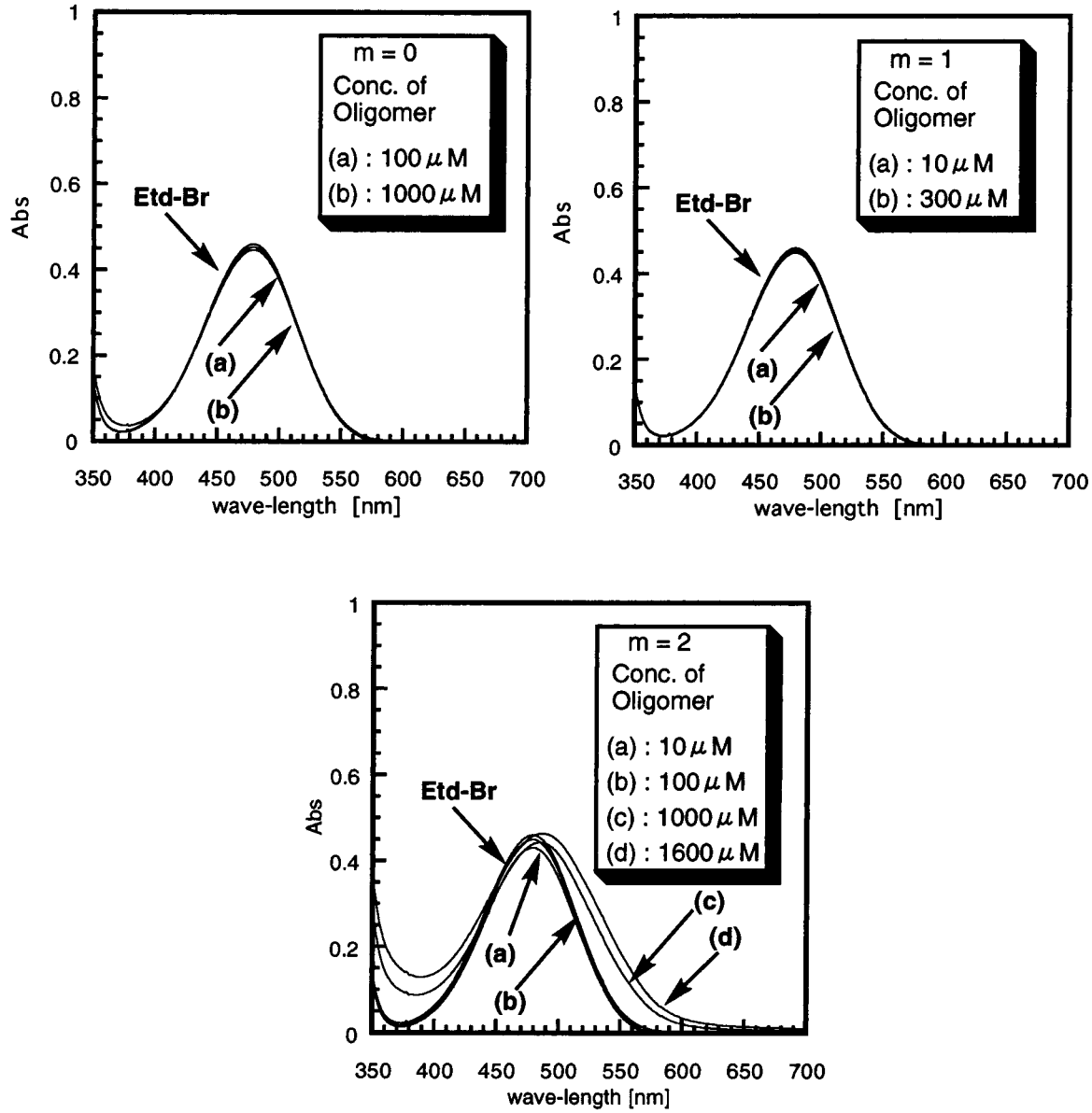


Figure 4. UV−visible spectra of buffer solutions of Etd-Br (80 μmol/dm^3) in the presence of R_F−(IEM-BO)$_x$−(DMAA)$_y$−R_F. Experiments were conducted in 5mmol/dm^3 tris(hydroxymethyl)aminomethane−HCl buffer (pH 7.4) containing 20 mmol/dm^3 NaCl.

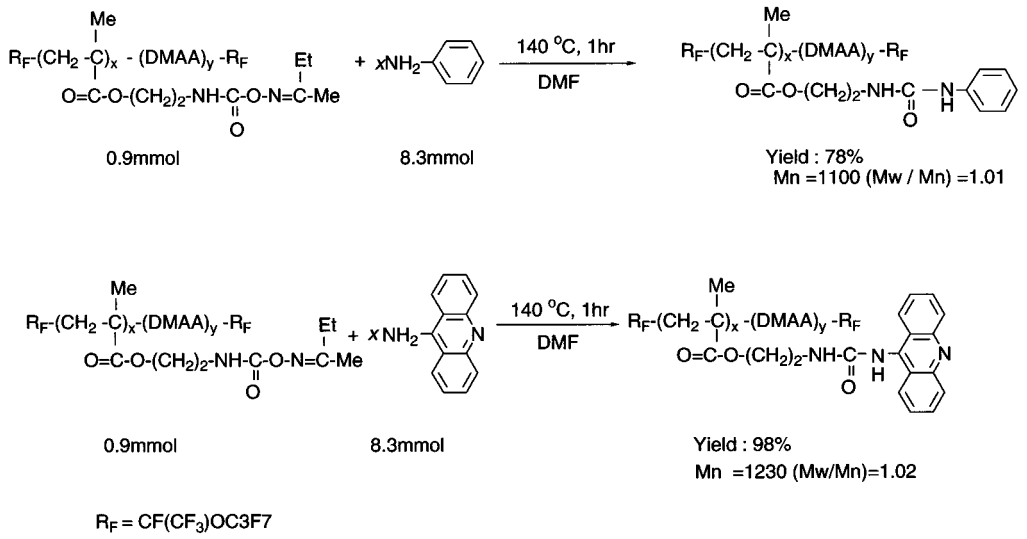
lar, this concentration (1000 or 1600 μM) of the cooligomer is fairly consistent with that for which the fluorescence intensity as in Figure 3 remarkably increases. This finding suggests that molecular assemblies formed by the longest fluoroalkoxyl ($m = 2$) end-capped cooligomer could interact strongly with Etd-Br as a guest molecular to form the host−guest intermolecular complex.

Introduction of Aromatic Segments into Fluoroalkoxyl End-Capped Precooligomers and Surfactant Properties of These Fluorinated Cooligomers-Bound Aromatic Segments. First, we were interested in reacting fluoroalkoxyl end-capped precooligomers [R_F−(IEM-BO)$_x$−(DMAA)$_y$−R_F] with some aromatic amino compounds such as aniline and 9-aminoacridine, and the results are shown in Scheme 3. The reactions of R_F−(IEM-BO)$_x$−(DMAA)$_y$−R_F with amino compounds were found to proceed under mild conditions in *N*,*N*-dimethylformamide(DMF) to afford fluoroalkoxyl end-capped cooligomers containing the corresponding aromatic segments. These fluorinated cooligomer-bound aromatic segments thus obtained were easily soluble in water and common organic solvents except for hexane. Therefore, these cooligomers are applicable to new fluorinated polymeric surfactants.

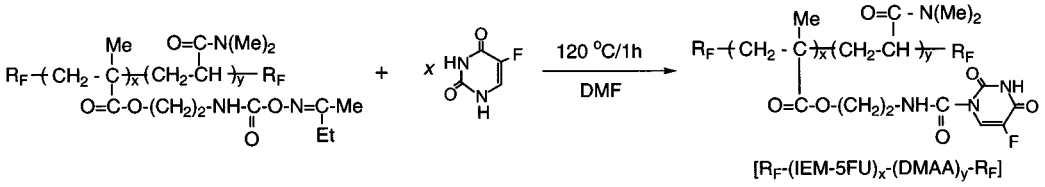
Furthermore, we tried to react R_F−(IEM-BO)$_x$−(DMAA)$_y$−R_F with powerful antitumor agents such as 5-fluorouracil (5-FU). These results are shown in Scheme 4.

Scheme 4 shows that fluoroalkoxyl end-capped cooligomer-bound 5-FU [R_F−(IEM-5FU)$_x$−(DMAA)$_y$−R_F] were easily obtained in good yields under mild conditions by the use of R_F−(IEM-BO)$_x$−(DMAA)$_y$−R_F. Usually, it is not favorable to synthesize fluoroalkoxyl end-capped cooligomer-bound 5-FU or 9-aminoacridine by the direct cooligomerizations of the corresponding monomers with fluoroalkanoyl peroxides since the reactivity of fluoroalkanoyl peroxide for 5-FU or 9-aminoacridine is very high, and the preparations of such bioactive monomers are in general not easy and their solubility

Scheme 3



Scheme 4



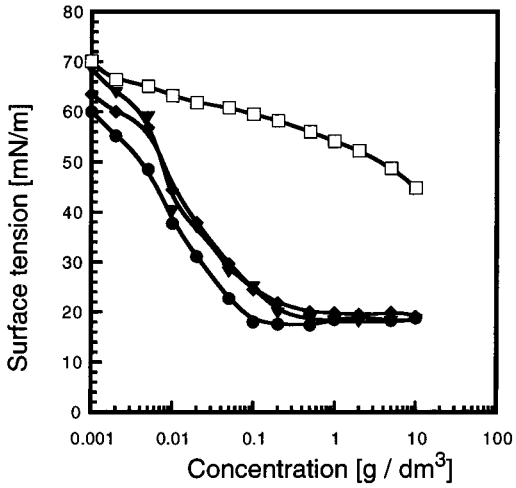


Figure 5. Surface tension of aqueous solutions of $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$. Key: (●) $R_F = CF(CF_3)OC_3F_7$; (♦) $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$; (▼) $R_F = CF(CF_3)OCF_2CF(CF_3)$-$OCF_2CF(CF_3)OC_3F_7$; (□) non-fluorinated.

is poor.[12] Thus, this synthetic strategy is very convenient for the preparation of various fluoroalkoxyl end-capped oligomer-bound antitumor and antiviral agents. In particular, $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ were easily soluble not only in water but also in common organic solvents such as MeOH, EtOH, THF, chloroform, acetone DMSO, DMF, and benzene. Therefore, these fluorinated cooligomers are expected to become surface-active compounds.

In fact, we have measured the surface tension of aqueous solutions of $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ with the Wilhelmy plate methods at 30 °C. These results are shown in Figure 5.

As shown in Figure 5, a significant decrease in the surface tension of water, to around 20 mN/m, was found for $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ compared to the corresponding nonfluorinated cooligomer. Unexpectedly, the shorter fluoroalkoxyl ($m = 0$) end-capped cooligomer-bound 5-FU was more effective in reducing the surface tension of water with a lower cmc. This finding suggests that the shorter fluoroalkoxyl chains in cooligomers are likely to be arranged more closely above the water surface owing to the presence of relatively bulky 5-FU moieties in cooligomers. This result indicates that our present $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ should form the self-assemblies in aqueous solutions.

Interaction of Self-Assembled Molecular Aggregates of $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ with Etd-Br in the Presence of OligoDNA. It is very interesting to apply fluoroalkoxyl end-capped cooligomer-bound antitumor agents into pharmacologically active polymers (polymer drug). It is well-known that fluorescent dyes such as Etd-Br can intercalate into the double helix chains of DNA and greatly enhance the intensity of fluorescence, and, in general, when the compounds possessing good antitumor and antiviral activities are added to the Etd-Br/DNA fluorescence system, the fluorescence intensity will be decreased.[13] To evaluate the interaction of our present $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ with DNA, we have measured the fluorescence spectrum of Etd-Br in the presence of DNA [oligoDNA:-d$(ACGT)_{21}$] and the cooligomers, and the results are shown in Figure 6.

As shown in Figure 6, when $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ [$R_F = CF(CF_3)OC_3F_7$], $-(IEM\text{-}BO)_x-(DMAA)_y-$, and 5-FU were added into the Etd-Br/DNA system, respectively, each fluorescence intensity of the Etd-Br/DNA system was found to decrease with increasing amounts of fluoroalkoxyl end-capped cooligomer, nonfluorinated cooligomer and 5-FU. In particular, $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ was able to decrease the fluorescence intensity of Etd-Br/DNA system more effec-

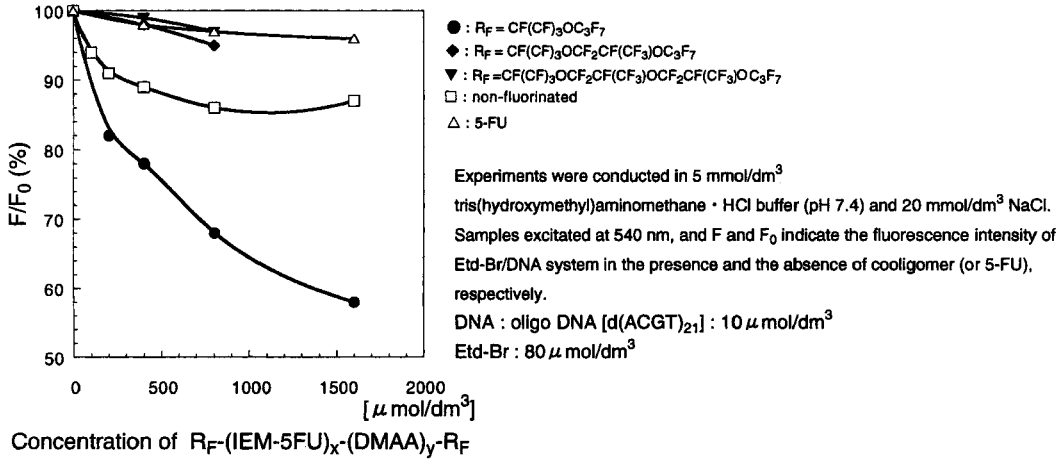


Figure 6. Relative fluorescent intensity (F) of the ethidium bromide/DNA system in the presence of $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$.

tively compared to that of the corresponding nonfluorinated cooligomer or 5-FU. Therefore, this fluorinated cooligomer could interact strongly with DNA to decrease the fluorescence intensity. This finding suggests that the self-assembled molecular aggregates of $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ imparted by the aggregations of end-capped fluoroalkoxyl segments can recognize DNA as a guest molecule. On the other hand, the corresponding nonfluorinated cooligomer $[-(IEM\text{-}5FU)_x-(DMAA)_y-]$ could not form such molecular aggregates, and only the polymer matrix effect would derive a slightly strong interaction with DNA compared to monomeric 5-FU. Additionally, we have measured the fluorescence spectra of Etd-Br/DNA system in the presence of the other fluoroalkoxyl (m = 1, 2) end-capped cooligomer $[R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F]$ under similar conditions. However, the fluorescence intensities did not change with increasing amounts of these fluorinated cooligomers, compared to that of the corresponding $R_F-(IEM\text{-}5FU)_x-(DMAA)_y-R_F$ [$R_F = CF(CF_3)OC_3F_7$] as in Figure 6. This suggests that the self-assembled molecular aggregates formed by longer fluoroalkoxyl (m = 1, 2) end-capped IEM-5FU−DMAA cooligomers cannot interact with DNA as a guest molecule to decrease the fluorescence intensity of Etd-Br. Thus, it was clarified that oligoDNA can interact selectively with the self-assembled molecular aggregates, especially with the self-assemblies formed by shorter fluoroalkoxyl (m = 0) end-capped IEM-5FU−DMAA cooligomer.

Conclusions

New fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers were obtained under very mild conditions by the use of fluoroalkanoyl peroxide as a key intermediate. These obtained fluoroalkoxylated cooligomers exhibited a good solubility in water and common organic solvents and were able to reduce the surface tension of water quite effectively around to 18 mN/m levels with a clear break point resembling a cmc. This finding suggests that these amphiphilic fluorinated cooligomers are likely to form the self-assembled molecular aggregates in aqueous solutions. In fact, static and dynamic light scattering measurements showed that these fluorinated cooligomers can form the self-assemblies in aqueous solutions; in particular, the longest fluoroalkoxylated cooligomer is easy to form the molecular aggregates. Fluoroalkoxylated IEM-BO−DMAA cooligomers were also demonstrated to become useful precooligomers for the introduction of functional aromatic units such as 9-aminoacridine and 5-FU into the cooligomer chains. Fluoroalkoxylated cooligomers −bound 5-FU are suggested to form the molecular aggregates in aqueous solutions and were able to have a remarkably strong interaction with oligoDNA.

Experimental Section

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 (pomp) and Shodex RI-71 (detector) gel permeation chromatography (GPC) calibrated with standard polystyrene using THF as the eluent [or 5 mmol dm^{-3} tris(hydroxymethyl)aminomethane−HCl buffer (pH 7.4) solution as the eluent], respectively. The surface tensions of aqueous solutions of the fluoroalkoxyl end-capped cooligomers were measured at 30 °C using a Wilhelmy-type surface tensiometer (ST-1, Shimadzu Co.) with a glass plate. UV−visible spectra and fluorescence spectra of cooligomer solutions were obtained using a Shimadzu UV-1600 spectrophotometer and a Shimazdu RF-5700 PC spectrophotometer, respectively. Static and dynamic light scattering of cooligomer solutions were measured using Wyatt DAWN DSP and NICOMP 380ZSL particle sizing systems, respectively. Average diameters (R_D) of the samples listed in Table 3 were calculated by the following equation

$$R_D = \frac{kT}{3\pi\eta D}$$

where k is the Boltzmann constant, T is the absolute temperature (303 K), η is the viscosity of the disperse system, and D is the diffusion constant.

Materials. Isocyanatoethyl methacrylate 2-butanone oxime adduct (IEM-BO), *N*,*N*-dimethylacrylamide (DMAA), and oligDNA were used as received from Showa Denko K.K. (Tokyo, Japan), Kohjin Co., Ltd. (Tokyo, Japan), and Yuki Gosei Kogyo (Tokyo, Japan), respectively. Etidium bromide, aniline and 5-fluorouracil were purchased from Tokyo Kasei Kogyou Co., Ltd. (Tokyo, Japan). 9-Aminoacridine was purchased from Sigma-Aldrich Japan Corp. (Tokyo, Japan). A series of fluoroalkanoyl peroxides [$(R_FCOO)_2$] were prepared by the method described in the literature.[14,15]

General Procedure for the Synthesis of Fluoroalkoxyl End-Capped IEM-BO−DMAA Cooligomers. Perfluoro-2-methyl-3-oxahexanoyl peroxide (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 (30 g) was added to a

mixture of IEM-BO(6 mmol), DMAA(50 mmol), and AK-225 (100 g). The solution was stirred at 45 °C for 5 h under nitrogen. After the solvent was evaporated off, the obtained crude products were reprecipitated from the methanol−hexane system to give an α, ω-bis(perfluoro-1-methyl-2-oxapentylated) IEM-BO−DMAA cooligomer (7.38 g). This cooligomer exhibited the following spectra characteristics: IR(ν/cm^{-1}) 1730, 1625 (CO), 1320 (CF_3), 1242 (CF_2);^{1}H NMR ($CDCl_3$) δ 0.80−3.20 (CH_3, CH_2, CH), 3.38−3.62 (CH_2), 3.92−4.38 (CH_2);^{19}F NMR ($CDCl_3$, external CF_3COOH) δ −4.78 to −7.37 (16F), −54.20 (6F).

Similarly, a series of fluoroalkoxyl end-capped IEM-BO−DMAA cooligomers were prepared by the reactions with fluoroalkanoyl peroxides. These exhibited the following spectral characteristics for R_F−(IEM-BO)$_x$−(DMAA)$_y$−R_F.

R_F = $CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: IR($\nu$/cm^{-1}) 1729, 1650 (CO), 1315 (CF_3), 1246 (CF_2); ^{1}H NMR ($CDCl_3$) δ 0.73−3.28 (CH_3, CH_2, CH), 3.22−3.62 (CH_2), 3.80−4.31 (CH_2); ^{19}F NMR (D_2O, external CF_3COOH) δ −4.33 to −7.74 (26F), −54.31 to −56.47 (6F).

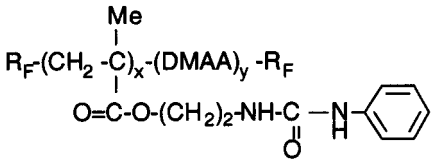
R_F = $CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: IR($\nu$/cm^{-1}) 1729, 1630 (CO), 1301 (CF_3), 1245 (CF_2); ^{1}H NMR ($CDCl_3$) δ 0.80−3.27 (CH_3, CH_2, CH), 3.30−3.61 (CH_2), 3.79−4.32 (CH_2); ^{19}F NMR ($CDCl_3$, external CF_3COOH) δ −4.96 to −7.54 (36F), −54.21 (6F), −70.43 (4F).

General Procedure for the Introduction of Aromatic Segments into Cooligomer Chains. A solution of R_F−(IEM-BO)$_x$−(DMAA)$_y$−R_F [R_F = $CF(CF_3)OC_3F_7$; 0.8 mmol (1.00 g)] and 5-FU (1.6 mmol) in DMF(10 g) was stirred at 120 °C for 1 h. After the solvent was evaporated off under reduced pressure, the crude products were reprecipitated from methanol-hexane and then dialyzed against 50% methanol solution to give R_F−(IM-5FU)$_x$−(DMAA)$_y$−R_F [R_F = $CF(CF_3)OC_3F_7$: 0.67 g]. This cooligomer showed the following spectral data: IR (ν/cm^{-1}) 1722, 1625 (CO), 1350 (CF_3), 1240 (CF_2); ^{1}H NMR ($CDCl_3$) δ 0.80−3.78 (CH_2, CH, CH_3), 3.80−4.39 (CH_2), 8.02 (1H); ^{19}F NMR ($CDCl_3$, ext. CF_3COOH) δ −4.21 ∼ −7.71 (16F), −54.09 (6F), −93.20 (1F).

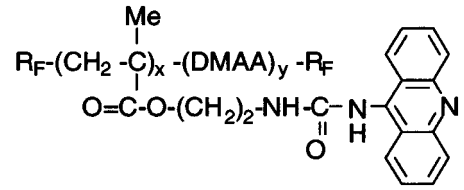
Similarly, fluoroalkoxyl end-capped cooligomer-bound aromatic segments were prepared by the use of R_F−(IEM-BO)$_x$−(DMAA)$_y$−R_F. These exhibited the following spectral characteristics for R_F−(IEM-5FU)$_x$−(DMAA)$_y$−R_F.

R_F = $CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: IR ($\nu$/cm^{-1}) 1722, 1625 (CO), 1308 (CF_3), 1248 (CF_2);^{1}H NMR (DMSO-d_6) δ 0.78−3.67 (CH_2, CH, CH_3), 3.79−4.38 (CH_2), 8.00 (1H);^{19}F NMR ((DMSO-d_6, external CF_3COOH) δ −4.10 to −7.69 (26F), −53.95 (6F), -69.60 (2F), −95.18 (1F).

R_F = $CF(CF_3)OCF_2CF(CF_3)OCF_2CF(CF_3)OC_3F_7$: IR ($\nu$/cm^{-1}) 1723, 1630 (CO), 1315 (CF_3), 1248 (CF_2); ^{1}H NMR (DMSO, d_6) δ 0.70−3.42 (CH_2, CH, CH_3), 3.71−4.38 (CH_2), 8.00 (1H);^{19}F NMR (DMSO-d_6, ext. CF_3COOH) δ −4.36 to −7.67 (36F), −53.98 to −55.66 (6F), −69.84 (4F), −95.88 (1F).



R_F = $CF(CF_3)OC_3F_7$: IR (ν/cm^{-1}) 1630 (CO), 1325 (CF_3), 1246 (CF_2); ^{1}H NMR (DMSO, d_6) δ 0.79−2.01 (CH_2, CH_3), 2.22−3.21 (CH, CH_3), 3.25−3.66 (CH_2), 3.81−4.38 (CH_2), 6.78−7.55 (5H); ^{19}F NMR (DMSO-d_6, ext. CF_3COOH) δ −5.61 to −7.71 (36F), −54.05 (6F).



R_F = $CF(CF_3)OC_3F_7$: IR (ν/cm^{-1}) 1639 (C═O), 1350 (CF_3), 1250 (CF_2); ^{1}H NMR ($CDCl_3$) δ 0.83−3.42 (CH_3, CH_2, CH), 3.60−4.22 (CH_2), 6.61−7.83 (8H); ^{19}F NMR($CDCl_3$, ext. CF_3COOH) δ −4.32 to −8.21 (16F), −55.20 (6F).

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