Synthesis and Gelation of Novel Fluoroalkyl End-Capped *N*-(1,1-Dimethyl-3-oxobutyl)acrylamide Copolymers Containing Triol Segments—Interaction of These Fluorinated Gels with Various Hydrophilic Compounds

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ABSTRACT: Fluoroalkyl end-capped *N*-(1,1-dimethyl-3-oxobutyl)acrylamide (DOBAA) copolymers containing triol segments were prepared by the reactions of fluoroalkanoyl peroxide with the corresponding monomer and *N*-tris(hydroxymethyl)methylacrylamide (NAT). These obtained fluorinated copolymers [R_F-$(DOBAA)_x$-$(NAT)_y$-R_F] were found to cause gelation in water, dimethyl sulfoxide, and *N*,*N*-dimethylformamide under the non-crosslinked conditions, although the corresponding nonfluorinated DOBAA–NAT copolymer [-$(DOBAA)_x$-$(NAT)_y$-] could cause no gelation in these solvents. This gelation is governed by the synergistic interaction of strong aggregations of end-capped fluoroalkyl segments and intermolecular hydrogen bonding between triol segments. We also studied the uptake and release of a variety of hydrophilic compounds such as methylene blue, methyl orange, 4-hydroxyazobenzene-4′-sulfonic acid sodium salt, 2,4-dihydroxyazobenzene-4′-sulfonic acid sodium salt, acriflavine hydrochloride, acridine hydrochloride, lucigenin, and fluorescein by this fluorinated copolymer gel and fluoroalkyl end-capped NAT homopolymer gel [R_F-$(NAT)_n$-RF] for comparison. It was demonstrated that the uptake and release ratios of these hydrophilic compounds by R_F-$(DOBAA)_x$-$(NAT)_y$-R_F gel become generally lower than those of R_F-$(NAT)_n$-R_F gel. Interestingly, R_F-$(DOBAA)_x$-$(NAT)_y$-R_F gel has no releasing power toward methylene blue, acridine hydrochloride, lucigenin, and fluorescein, although R_F-$(NAT)_n$-R_F gel has a good releasing power toward these compounds. Additionally, R_F-$(DOBAA)_x$-$(NAT)_y$-R_F gel was applied to the controlled release of anticancer drugs such as methotrexate (MTX), and the releasing ratios of MTX became higher with increasing pH values (from pH 4.3 to 9.1). © 2003 Wiley Periodicals, Inc. J Appl Polym Sci 88: 3212–3217, 2003

Key words: fluoropolymers; gelation; hydrogels; drug delivery systems

INTRODUCTION

Recently, we reported that water-soluble fluoroalkyl end-capped cooligomer-bound antitumor agents such as 5-fluorouracil could be prepared by the reaction of the corresponding isocyanate-blocked cooligomers with the parent antitumor agents.[1] Additionally, it was demonstrated that fluoroalkyl end-capped cooligomer-bound 5-fluorouracil thus obtained can form the self-assembled molecular aggregates imparted by the aggregations of the end-capped fluoroalkyl segments to have a remarkably strong interaction with oligo-DNA.[2] In contrast, there has been a great interest in the application of dendrimers[3] and polymer hydrogels[4] to drug delivery systems owing to their interior being capable of encapsulating various guest molecules. From such a point of view, it is very interesting to synthesize novel fluoroalkyl end-capped polymer gels containing numerous guest molecules and to apply these fluorinated polymer gels to drug carriers. Although the preparation and application of these novel fluorinated polymer gels to biomaterials have hitherto been very limited, these polymers have been the subject of considerable research of a fundamental and an applied nature. In this article, we report on the synthesis and gelation of novel fluoroalkyl end-capped copolymers and interactions of these fluorinated gels with a variety of hydrophilic compounds, with emphasis on the applications to drug carriers.

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EXPERIMENTAL

Measurements

Fourier transform infrared (FTIR) spectra were measured by using a Shimadzu FTIR-8400 spectrophotometer (Kyoto, Japan). NMR spectra and molecular

weights were measured by using a Varian Unity-plus 500 (500 MHz) spectrometer (Palo Alto, CA) and a Shodex DS-4 (pump) and Shodex RI-71 (Detector) gel permeation chromatograph (GPC, Tokyo, Japan), respectively. UV-visible spectra were obtained by using a Shimadzu UV-1600 spectrophotometer (Kyoto, Japan).

Materials

Isocyanatoethyl methacrylate 2-butanone oxime adduct (IEM-BO) was used as received from Showa Denko K.K. (Tokyo, Japan). Methylene blue, 4-hydroxyazobenzene-4′-sulfonic acid sodium salt, 2,4-dihydroxyazobenzene-4′-sulfonic acid sodium salt, acriflavine hydrochloride, acridine hydrochloride, and lucigenin were purchased from Tokyo Kasei Kogyou Co., Ltd. (Tokyo, Japan). Methyl orange and fluorescein were purchased from Wako Pure Chemical Industries Ltd. (Osaka, Japan). *N*-tris(hydroxymethyl)-methylacrylamide (NAT) and methotrexate (MTX) were purchased from Sigma-Aldrich Japan Corp. (Tokyo, Japan). *N*-(1,1-dimethyl-3-oxobutyl)acrylamide (DOBAA) was used as received from Kyowa Hakko Kogyou Co., Ltd. (Tokyo, Japan). Fluoroalkanoyl peroxides [$(R_F\text{-}COO)_2$] were prepared by the method described in the literature.[9,10]

Procedure for the synthesis of fluoroalkoxyl end-capped IEM-BO–NAT copolymer

Perfluoro-2-methyl-3-oxahexanoyl peroxide (4.6 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 (160 g) were added to a mixture of IEM-BO (4.6 mmol) and an aqueous solution (50%, w/w) of NAT (28 mmol). The heterogeneous solution was stirred vigorously at 45°C for 5 h under nitrogen. The crude product obtained was washed well with methanol to remove the unreacted IEM-BO and NAT monomers and dried *in vacuo* to give a bis(perfluoro-1-methyl-2-oxapentylated) IEM-BO–NAT copolymer (4.70 g). This cooligomer exhibited the following IR spectra characteristics:

IR (ν/cm^{-1}) 3306 (OH), 1651 (CO), 1310 (CF_3), 1246 (CF_2)

Molecular weight by GPC analyses and NMR spectra of this copolymer were not measured due to its insolubility in various solvents.

Similarly, fluoroalkyl end-capped DOBAA–NAT copolymers were prepared by copolymerization with perfluoro-2-methyl-3-oxahexanoyl peroxide and exhibited the following IR spectra characteristics:

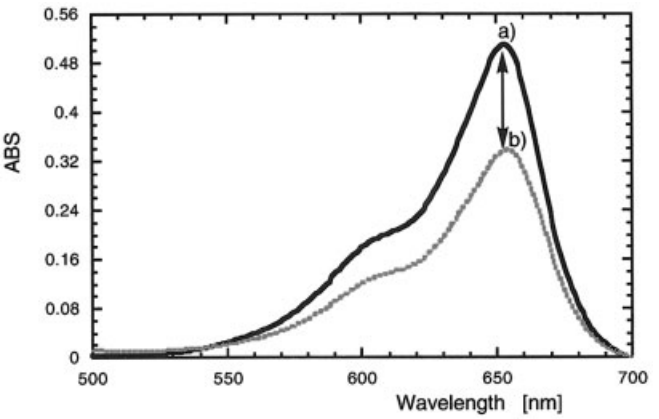


Figure 1 The UV-visible spectra of methanol solutions of methylene blue in the presence (b) and absence (a) of R_F-$(DOBAA)_x$-$(NAT)_y$-R_F gel. (a) Methylene blue: 3.33 μmol/dm^3; (b) methylene blue binding to R_F-$(DOBAA)_x$-$(NAT)_y$-RF gel.

IR (ν/cm^{-1}) 3406 (OH), 1651 (CO), 1305 (CF_3), 1245 (CF_2) [(I) in Scheme 2]

IR (ν/cm^{-1}) 3387 (OH), 1643 (CO), 1302 (CF_3), 1245 (CF_2) [(II) in Scheme 2]

Molecular weight by GPC analyses and NMR spectra were not measured because of the gelling of these samples.

A typical procedure for gelation test

A procedure for studying the gel-formation ability was based on a method reported by Hanabusa et al.[7] Briefly, weighted fluoroalkyl end-capped DOBAA–NAT copolymer was mixed with water in a tube. The mixture was treated under ultrasonic conditions until the solid was dissolved. The resulting solution was kept at 30°C for 1 h, and gelation was checked visually. The gel was stable and the tube could be inverted without changing the shape of the gel.

Methylene blue uptake by R_F-$(DOBAA)_x$-$(NAT)_y$-R_F

R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel (20 mg) was swelled with dimethyl sulfoxide (DMSO; 300 μL) in a 10-mL vial. After the addition of methylene blue (3.3 μmol/dm^3) methanol solution (6 mL) into the vial, the vial was allowed to stand for 1 day at room temperature. The methylene blue concentration of supernatant liquid after the incubation was spectrophotometrically (λ_{max}: 653 nm) determined, and the result is shown in Figure 1. Furthermore, the uptake ratios of methylene

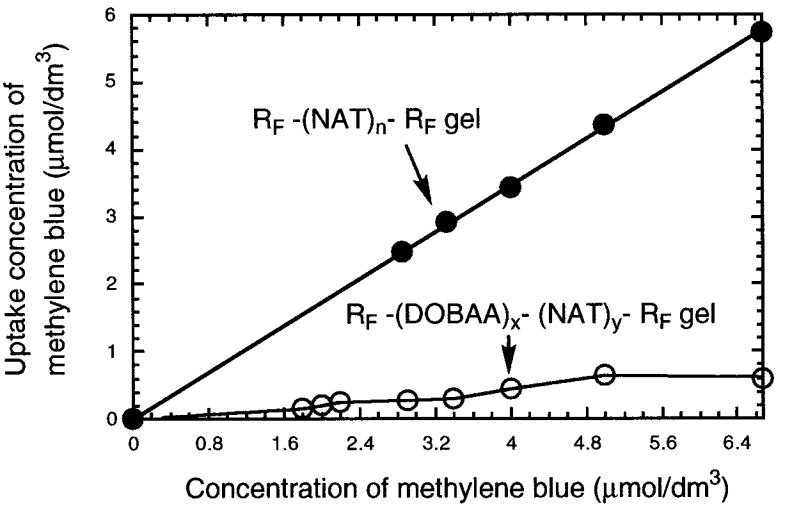


Figure 2 Relationship between concentration of methylene blue and uptake concentration of methylene blue by R_F-$(NAT)_n$-R_F gel and R_F-$(DOBAA)_x$-$(NAT)_y$-R_F.

blue ({[concentration of initial methylene blue] − [concentration of the supernatant solution after the incubation]}/[concentration of initial methylene blue]) by this fluorinated gel and R_F-$(NAT)_n$-R_F gel were measured for a wide range of methylene blue concentrations under similar conditions, and the results are shown in Figure 2.

Hydrophilic compounds binding or releasing by R_F-$(DOBAA)_x$-$(NAT)_y$-R_F and R_F-$(NAT)_n$-R_F

R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel or R_F-$(NAT)_n$-R_F homopolymer gel (20 mg) (the same gels as those of Fig. 2) was swelled with DMSO (300 μL) in a 10-mL vial. After the addition of hydrophilic compound (0.1 mmol/dm^3) methanol solution (6 mL) into the vial, the vial was allowed to stand for 1 day at room temperature. The hydrophilic compound concentration of supernatant liquid after the incubation was spectrophotometrically (λ_{max}: see Table I) measured, and the uptake ratio of this compound was determined by the above-mentioned method. The hydrophilic compound was released from this compound binding to the fluorinated gel into water (6 mL) for 160 min at room temperature, and then the release ratio ([concentration of the supernatant liquid]/[concentration of the hydrophilic compound − loaded fluorinated gel before incubation]) was spectrophotometrically (λ_{max}: see Table I) determined.

MTX binding or releasing by R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel

R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel (20 mg) (the same gel as that of Fig. 2) was swelled with DMSO (300 μL) in a 10-mL vial. After the addition of MTX (0.1 mmol/dm^3) methanol solution (6 mL) into the vial, the vial was allowed to stand for 1 day at room temperature. MTX concentration of supernatant liquid after the incubation was spectrophotometrically (λ_{max}: 376 nm) measured, and the uptake ratio of MTX determined by the above-mentioned method was 35%. Additionally, MTX was released from MTX-loaded fluorinated gel into water [pH 6.1 (6 mL)] for 30 min at room temperature, and then the release ratio of MTX determined by the above-mentioned method was 26%. Similarly, MTX was released from MTX-loaded fluorinated gel into acetate buffer [pH 4.3 (6 mL)] or Tris buffer [pH 9.1 (6 mL)], and each release ratio of MTX was determined, respectively. These results are shown in Figure 3.

RESULTS AND DISCUSSION

First, we were interested in preparing fluoroalkyl end-capped triol copolymers containing isocyanate-blocked segments which could possess a gelling ability in view of the development of novel gelling fluoroalkyl end-capped copolymer-bound antitumor agents. Because these fluorinated polymers are ex-

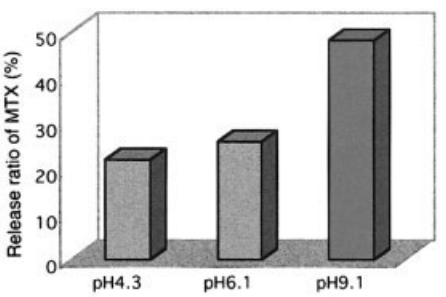
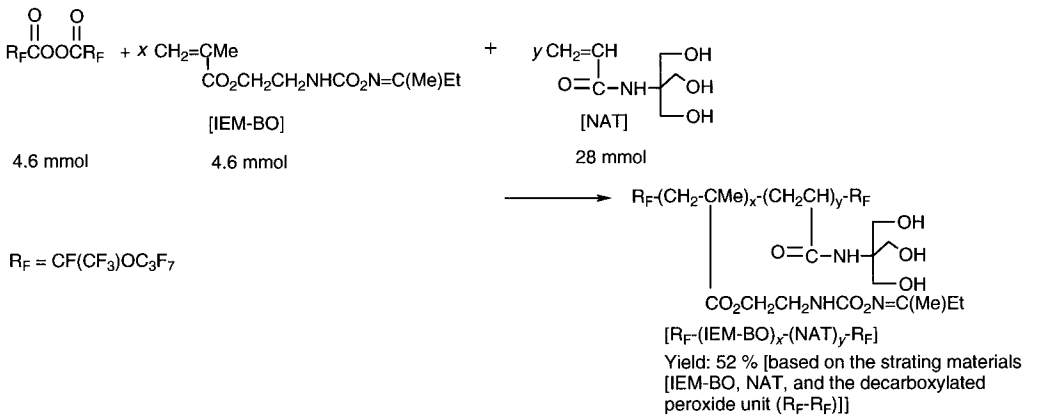


Figure 3 Release ratios of MTX from MTX-loaded RF-$(DOBAA)_x$-$(NAT)_y$-R_F gel into buffer solutions.

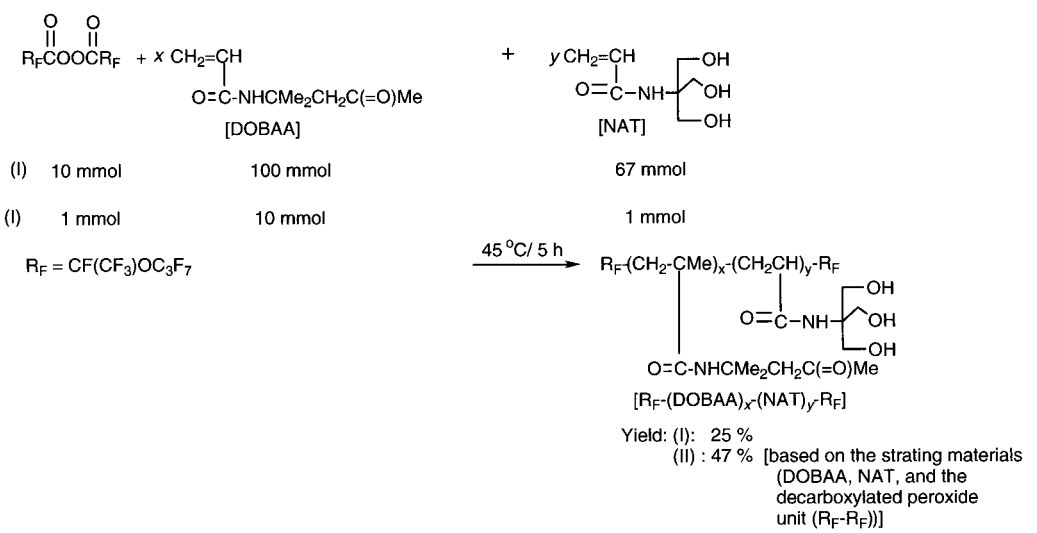


Scheme 1

pected to become useful pre-copolymers for the synthesis of fluorinated copolymers containing antitumor agents and to cause gelation, the aggregations of end-capped fluoroalkyl segments and the hydrogen-bonding interactions between triol segments are involved in establishing a physical gel network in water and polar organic solvents under noncrosslinked conditions.[5] Thus, we attempted the reaction of fluoroalkanoyl peroxide with IEM-BO and NAT, as shown in Scheme 1.

As shown in Scheme 1, the reaction of fluoroalkanoyl peroxide with IEM-BO and NAT was found to react smoothly to afford fluoroalkyl end-capped IEM-BO–NAT copolymer under very mild conditions. However, the obtained fluorinated copolymer was shown no solubility in water and various organic solvents, and this fluorinated copolymer could not cause gelation in water and polar organic solvents such as DMSO and *N*,*N*-dimethylformamide (DMF). This finding would be dependent upon the presence of highly oleophilic IEM-BO units in fluorinated copolymer.

Previously, we reported that self-assembled molecular aggregates of fluoroalkyl end-capped *N*-(1,1-dimethyl-3-oxobutyl)acrylamide oligomers [R_F-(DOBAA)$_n$-R_F] can selectively recognize hydrophilic amino and *N*,*N*-dimethylamino compounds as guest molecules.[6] We also reported that fluoroalkyl end-capped NAT homopolymers [R_F-(NAT)$_n$-R_F] can cause a gelation not only in water, but also in organic media, the behavior of which is governed by the synergistic interaction of strong aggregations of end-capped fluoroalkyl segments in polymers and intermolecular hydrogen bonding between triol segments under noncrosslinked conditions.[5] Therefore, it is very interesting to prepare fluoroalkyl end-capped DOBAA–NAT copolymers and to study their gelling ability due to the application of encapsulation of a



Scheme 2

variety of guest molecules. In fact, we tried to react fluoroalkanoyl peroxide with DOBAA and NAT; the results are shown in Scheme 2.

As shown in Scheme 2, the copolymerizations of fluoroalkanoyl peroxide with DOBAA and NAT were found to proceed under very mild conditions to afford fluoroalkyl end-capped DOBAA–NAT copolymers in 25 and 45% isolated yields. Interestingly, fluoroalkyl end-capped DOBAA–NAT copolymers thus obtained were found to cause gelation in water, DMSO, and DMF. In contrast, the corresponding nonfluorinated DOBAA–NAT copolymer had no gelation in these solvents and was not able to exhibit solubility in these solvents at all. This finding suggests that this gelling behavior for our present R_F-$(DOBAA)_x$-$(NAT)_y$-R_F is not governed by only the intermolecular hydrogen bonding between triol segments, but by the strong aggregations between end-capped fluoroalkyl segments in copolymers. We tried to measure the copolymerization ratios and the molecular weights of these fluorinated copolymers by using NMR and GPC analyses under various conditions. However, we could not measure the ratios and the molecular weights owing to the gel formation.

The gelation ability of fluoroalkyl end-capped DOBAA–NAT copolymers [R_F = $CF(CF_3)OC_3F_7$] was studied by measuring the minimum concentration (C_{min}) of these fluorinated copolymers necessary for gelation in water and DMSO at 30°C according to the method reported by Hanabusa et al.[7] We also demonstrated the C_{min} of R_F-$(NAT)_n$-R_F [R_F = $CF(CF_3)OC_3F_7$], which was prepared by the method (molar ratio of NAT/peroxide is 5.0) described in Ref. [5], for comparison. These results are as follows:

	C_{min} (g/dm^3)	
	· H_2O	DMSO
R_F-$(DOBAA)_x$-$(NAT)_y$-R_F[a]	46	39
R_F-$(NAT)_n$-RF[b]	18	24

[a] (I) in Scheme 2.
[b] See Ref 5.

where *a* is (I) in Scheme 2, and *b* refers to ref.[5]

The gelling ability of R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer is not superior to that of R_F-$(NAT)_n$-R_F. This would result from the finding that R_F-$(DOBAA)_x$-$(NAT)_y$-R_F could not have a stronger association through intermolecular hydrogen bonding than that of R_F-$(NAT)_n$-R_F because of the presence of DOBAA units.

From the view of the development of our present fluorinated polymer gels to drug carrier, it is very interesting to study the adsorptive properties against some popular hydrophilic compounds such as methylene blue on the swelling equilibrium of R_F-$(DOBAA)_x$-$(NAT)_y$-R_F. For example, it was reported that guest molecules such as Rose Bengal can be physically entrapped into the internal cavity of high-generation poly(propylene imine) dendrimers, and several attempts have been made to design dendrimers as drug carriers.[8] Thus, we attempted to perform quantitative measurements of the uptake of methylene blue by R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel [(I) in Scheme 2]. The methylene blue concentration of supernatant liquid after incubation (at room temperature for 24 h) was spectrophotometrically determined from a calibration curve showing the relationship between the methylene blue concentration and absorbance at 653 nm. The results are shown in Figure 1.

As shown in Figure 1, there was an remarkable decrease (a) → (b) in the absorbance of methylene blue at 653 nm after the addition of R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel. This indicates that methylene blue can bind strongly to R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel. In addition, R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel was found to increase linearly the uptake of methylene blue with an increase in the initial concentration of methylene blue as in Figure 2. However, R_F-$(NAT)_n$-R_F polymer gel was found to have a stronger methylene blue binding power compared to that of R_F-$(DOBAA)_x$-$(NAT)_y$-R_F. This result suggests that R_F-$(NAT)_n$-R_F polymer gel could provide a highly hydrophilic gel network to interact with methylene blue.

Furthermore, we studied the uptake and release of a variety of hydrophilic compounds including methylene blue under similar conditions, and the results are listed in Table I.

As shown in Table I, R_F-$(NAT)_n$-R_F polymer gel was found to have higher uptake and release ratios toward each hydrophilic compound in Table I than R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel. In acriflavine hydrochloride, R_F-$(DOBAA)_x$-$(NAT)_y$-R_F polymer gel could not have an uptake power, although R_F-$(NAT)_n$-R_F polymer gel was shown to exhibit good uptake ratio (60%) and release ratio (22%) toward this compound. Of particular interest, we can find a selectivity in the release of hydrophilic compounds by R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel, and this gel exhibited no releasing power toward methylene blue, acridine hydrochloride, lucigenin, and fluorescein. This interesting result cannot be explained in detail at the present time; however, one thought is that R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel would enable these hydrophilic compounds to interact more strongly with the DOBAA segments in the fluorinated copolymer gel networks. In contrast, each hydrophilic compound in Table I should release easily from R_F-$(NAT)_n$-R_F polymer gel networks into methanol solution, because the interaction of hydrophilic compounds with R_F-$(NAT)_n$-R_F polymer gel becomes weak among the gel networks because of the absence of DOBAA segments.

TABLE I
Uptake and Release Ratios of a Variety of Hydrophilic Compounds by R_F-$(NAT)_n$-R_F Gel and R_F-$(DOBAA)_x$- $(NAT)_y$-R_F Gel[a]

Hydrophilic compound (λ_{max})	R_F-$(NAT)_n$-R_F		R_F-$(DOBAA)_x$-$(NAT)_y$-R_F	
	Uptake ratio (%)	Release ratio (%)	Uptake ratio (%)	Release ratio (%)
Methylene blue (653)	66	17	12	0
Methyl orange (422)	56	56	21	16
4-Hydroxyazobenzene-4′-sulfonic acid sodium salt (355)	49	97	16	62
2,4-Dihydroxyazobenzene-4′-sulfonic acid sodium salt (380)	53	24	20	14
Acriflavine hydrochloride (460)	66	22	0	0
Acridine hydrochloride (355)	72	13	50	0
Lucigenin (369)	31	8	5	0
Fluorescein (480)	56	76	74	0

[a] Uptake and release ratio: see Experimental.

Hitherto, there has been a great interest in the application of dendrimers to drug delivery systems, and their interior has been shown to be capable of encapsulating anticancer drugs such as MTX and adriamycin.[3a,3b] Our present R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel was clarified to exhibit a unique behavior for the uptake and release of hydrophilic compounds. Therefore, it is interesting to develop this fluorinated polymer gel [(I) in Scheme 2] to the drug carrier. In fact, MTX-loaded R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel was prepared by the uptake of MTX (the uptake ratio: 35%) to this fluorinated gel after incubation at room temperature for 24 h. The drug release characteristics of R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel was then investigated *in vitro*. After the addition of the drug-loaded R_F-$(DOBAA)_x$-$(NAT)_y$-R_F copolymer gel into water (pH 6.1), the aqueous solutions containing the fluorinated gel were allowed to stand for 30 min at room temperature, and the drug concentration of supernatant liquid (the release ratio) after the incubation was 26%. More interestingly, we were able to observe the controlled release of MTX; the pH values become higher (from 4.3 to 9.1), and the release ratios become higher as shown in Figure 3.

The higher release ratio of MTX in pH 9.1 would depend on whether the hydrophilicity of MTX becomes higher because of the presence of carboxy segments in MTX.

In conclusion, it was demonstrated that fluoroalkyl end-capped DOBAA–NAT copolymers were prepared by using fluoroalkanoyl peroxide as a key intermediate. These obtained fluorinated copolymers were found to cause a gelation in water and DMSO, although the corresponding DOBAA–NAT copolymer could cause no gelation in these solvents. This gelation is derived from the synergistic interaction of the aggregations of end-capped fluoroalkyl segments and the intermolecular hydrogen bonding between triol segments. This fluorinated DOBAA–NAT copolymer gel was applicable to the uptake and release of a variety of hydrophilic compounds such as methylene blue and methyl orange by this fluorinated copolymer gel. Additionally, this fluorinated gel exhibited the controlled release of anticancer drug such as methotrexate, and the release ratios of MTX became higher with increasing pH values. Therefore, these findings are of great importance for designing new fluorinated biomaterials.

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