Synthesis of Novel Fluoroalkylated Oligomers Containing Phosphinico Segments: A New Approach to Functional Materials Possessing Anti-HIV 1 Activity

Hideo Sawada,*,†,‡ Daisuke Tamada,‡ Tokuzo Kawase,§ Yoshio Hayakawa,|| and Masanori Baba⊥

Department of Chemistry, Nara National College of Technology, Yata, Yamatokoriyama, Nara 639-11, Japan, Department of Chemistry, Faculty of Advanced Engineering, Nara National College of Technology, Yamatokoriyama, Nara 639-11, Japan, Faculty of Science of Living, Osaka City University, Sugimoto, Sumiyoshi-ku, Osaka 558, Japan, National Industrial Research Institute of Nagoya, Kita-ku, Nagoya 462, Japan, and Division of Human Retroviruses, Center for Chronic Viral Diseases, Faculty of Medicine, Kagoshima University, Sakuragaoka, Kagoshima 890, Japan

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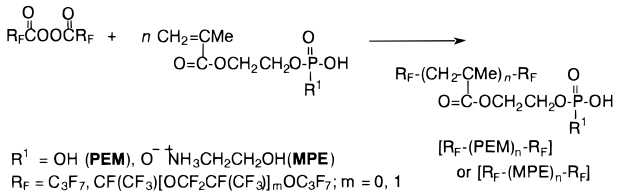
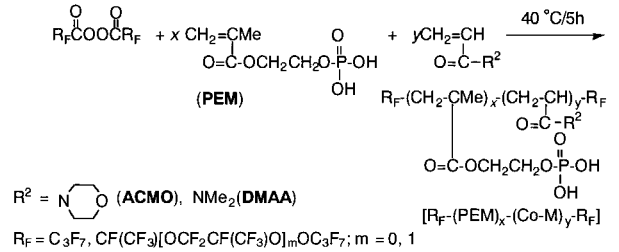
Considerable interest has been devoted in recent years to organofluorine compounds containing phosphorus atoms due to their synthetic utilities and unique properties.[1] In particular, much effort has been focused on the synthesis of new fluorinated phosphonic materials possessing excellent properties imparted by both fluorine and phosphorus. For example, Burton et al. and Boutevin et al. individually reported on the synthesis of various monofluorinated[2] and fluoroalkylated[3] phosphonic derivatives, respectively. In the synthesis of fluoroalkylated organophosphonic compounds, there are some difficulties for the direct introduction of fluoroalkyl groups into phosphonic derivatives, since the usual alkylations cannot be applied to fluoroalkylation due to the high electronegativity of fluorine. Thus, in most fluoroalkylated phosphonic compounds, fluoroalkyl groups are introduced through a C−O−P bond, and these fluoroalkylated phosphonic materials are in general unstable and hydrolyzable. From such points of view, it has been very desirable to explore fluoroalkylated phosphonic compounds with carbon−carbon bond formation. We have been actively studying the development of fluoroalkylated compounds by the use of fluoroalkanoyl peroxides as the key intermediates.[4] Very recently, we have succeeded in preparing various oligomers containing two fluoroalkylated end groups such as fluoroalkylated acrylic acid−trimethylvinylsilane cooligomers, and these oligomers were shown to be applicable to novel fluorinated oligo-surfactants.[5] Now, we have found that new fluoroalkylated phosphonic acid oligomers with carbon−carbon bond formation can be prepared by the reactions of fluoroalkanoyl peroxides with 2-(methacryloxy)ethylphosphonic acid (PEM) or 2-methacryloxy-substituted phosphoric acid monoethanolamine (MPE), and more interestingly, these fluoroalkylated oligomers containing phosphinico segments are applicable to new functional fluorinated materials possessing anti-HIV-1 (human immunodeficiency virus type 1) activity.

* To whom all correspondence should be addressed.
† Department of Chemistry, Nara National College of Technology.
‡ Faculty of Advanced Engineering, Nara National College of Technology.
§ Osaka City University.
|| National Industrial Research Institute of Nagoya.
⊥ Kagoshima University.

Scheme 1



Scheme 2



A typical experiment for the synthesis of fluoroalkylated oligomers containing phosphinico segments is as follows (Scheme 1); perfluorobutyryl peroxide (4 mmol) in 1:1 mixed solvents (AK-225) of 1,1-dichloro-2,2,3,3,3-pentafluoropropane−1,3-dichloro-1,2,2,3,3-pentafluoropropane (68 g) was added to the aqueous solution (10%, w/w) of 2-phosphonoethyl methacrylate (8 mmol, PEM). The heterogeneous solution was stirred vigorously at 40 °C for 5 h under nitrogen. Methanol was added to the reaction mixture and the solvent evaporated under reduced pressure. The crude product obtained was reprecipitated from methanol−ethyl acetate to give bis(perfluoropropylated) 2-phosphonoethyl methacrylate oligomers (0.70 g). This oligomer showed the following spectral data: IR ν/cm^{-1} 3472 (OH), 1718 (C═O), 1330 (CF_3), 1230 (CF_2), 983 (P−O); ^{1}H NMR (D_2O) δ 0.72−1.48 (CH_3), 1.77−2.14 (CH_2), 4.01−4.25 (CH_2); ^{19}F NMR (D_2O, ext. CF_3CO_2H) δ −5.09 (6F), −43.20 (4F), −52.26 (4F).

As listed in Table 1, a series of fluoroalkylated phosphonic acid and phosphonic acid monoethanolamine oligomers were obtained in 10−23% isolated yields under very mild conditions. Furthermore, the cooligomerizations with comonomers such as acryloylmorpholine (ACMO) and dimethylacrylamide (DMAA) were found to proceed under similar conditions to afford the corresponding fluoroalkylated phosphonic acid cooligomers, as shown in Scheme 2, and the results are shown in Table 1.

The cooligomerization ratio of cooligomers was determined by ^{1}H NMR analyses. In addition, we have tried to measure the molecular weight of each oligomer in Table 1 by GPC (gel permeation chromatography) analyses, and the molecular weights of some oligomers could be measured by using 50 mM $H_2NC(CH_2OH)_3$ and 1 M NaCl solution as the eluent, as shown in Table 1. Considering the fact that water-soluble fluoroalkylated end-capped oligomers easily form molecular aggregates owing to the strong aggregations of fluoroalkyl segments in aqueous solutions,[6] it is suggested that the obtained values by GPC indicate the apparent molecular weights. However, we could not measure the molecular weights of other oligomers by GPC analyses under various conditions. This result strongly suggests that not only the strong aggregations of fluoroalkyl segments but also the hydrogen-bonding interaction between phosphono (or phosphinico) segments could interact synergistically to form the highly viscoelastic fluids (gellike fluids). In

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Table 1. Synthesis of Fluoroalkylated Oligomers Containing Phosphinico Segments by the Use of Fluoroalkanoyl Peroxides

run	R_F in peroxide (amt, mmol)	PEM (or MPE) (amt, mmol)	Co−M (amt, mmol)	product; yield, %;[a] $\bar{M}_n$ ($\bar{M}_w/\bar{M}_n$) [x:y][b]
1	C_3F_7 (4)	PEM (8)		$R_F(PEM)_nR_F$; 22
2	$CF(CF_3)OC_3F_7$ (3)	PEM (6)		$R_F(PEM)_nR_F$; 14; 31 000 (1.11)
3	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (3)	PEM (6)		$R_F(PEM)_nR_F$ 10
4	C_3F_7 (4)	MPE (8)		$R_F(MPE)_nR_F$; 22; 28 000 (1.10)
5	$CF(CF_3)OC_3F_7$ (3)	MPE (6)		$R_F(MPE)_nR_F$; 23
6	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (3)	MPE (6)		$R_F(MPE)_nR_F$ 18
7	C_3F_7 (4)	PEM (12)	ACMO (20)	$R_F(PEM)_x(ACMO)_yR_F$; 5; 72 000 (1.38) [61:39]
8	$CF(CF_3)OC_3F_7$ (3)	PEM (9)	ACMO (15)	$R_F(PEM)_x(ACMO)_yR_F$ 7; 63 000 (1.21) [40:60]
9	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (3)	PEM (9)	ACMO (15)	$R_F(PEM)_x(ACMO)_yR_F$; 11; 84 000 (1.02) [35:65]
10	$CF(CF_3)OC_3F_7$ (3)	MPE (9)	DMAA (9)	$R_F(MPE)_x(DMAAA)_yR_F$; 23; [75:25]
11	$CF(CF_3)OCF_2CF(CF_3)OC_3F_7$ (3)	MPE (9)	DMAA (9)	$R_F(MPE)_x(DMAAA)_yR_F$ 30; [60:40]

[a] The yields were based on the starting materials [PEM (or MPE), ACMO (or DMAA), and the decarboxylated peroxide unit (R_F-R_F)]. [b] Cooligomerization ratio was determined by ^{1}H NMR.

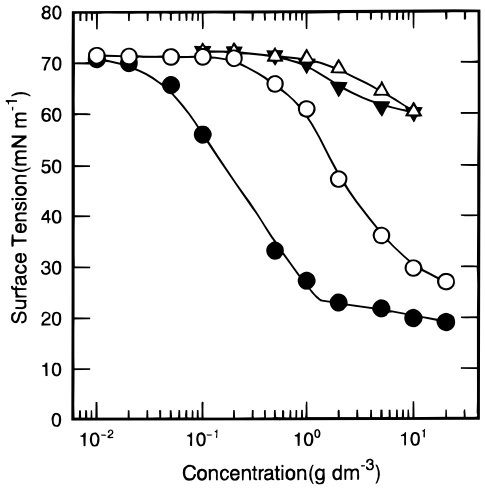

Figure 1. Surface tension of aqueous solutions of phosphonic acid oligomers at 30 °C. $R_F[CH_2C(O{=}COCH_2CH_2OP(O)(R^1)OH)Me]_nR_F$: (●) $R_F = C_3F_7$, R^1 = OH; (○) $R_F = C_3F_7$, $R^1 = O^-{}^+NH_3CH_2CH_2OH$. $-[CH_2C(O{=}COCH_2CH_2OP(O)(R^1)OH)Me]_n-$: (▼) R^1 = OH; (△) $R^1 = O^-{}^+NH_3CH_2CH_2OH$.

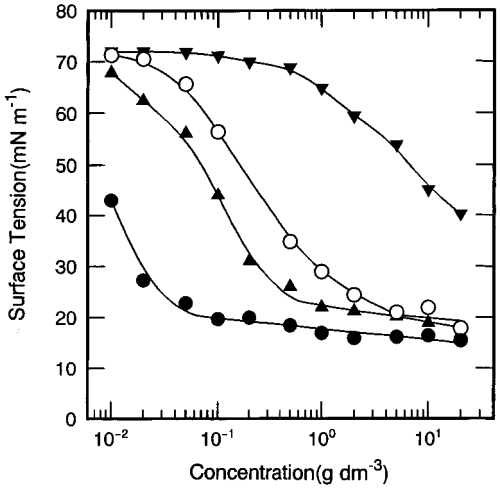

Figure 2. Surface tension of aqueous solutions of $R_F[CH_2C(O{=}COCH_2CH_2OP(O)(OH)OH)Me]_x[CH_2C(O{=}CR^2)H]_yR_F$ at 30 °C. $R^2 = \overline{NCH_2CH_2OCH_2CH_2}$: (▼) $R_F = C_3F_7$; (▲) $R_F = CF(CF_3)OC_3F_7$; (○) $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$; R^2 = NMe_2: (●) $R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$.

fact, it was shown that the oligomers, which cannot be measured at their molecular weights (nos. 1, 3, 5, 6, 10, and 11), are mixed with water to form easily the gellike fluids. In contrast, we were able to measure easily the molecular weights of the corresponding nonfluorinated PEM oligomer [−(PEM)$_n$−: $\bar{M}_n$ = 21 000 ($\bar{M}_w/\bar{M}_n$ = 1.61) and MPE oligomer [−(MPE)$_n$−: $\bar{M}_n$ = 28 000 ($\bar{M}_w/\bar{M}_n$ = 1.30)] by GPC analyses, and these oligomers were completely soluble in water.

Owing to the application of our present fluoroalkylated oligomers containing phosphinico segments as new phosphorus-containing fluorinated functional materials, it is interesting to evaluate the surface properties of the aqueous solutions of these oligomers. We have measured the reduction of surface tension by these oligomers with the Wilhelmy plate method at 30 °C. These results are shown in Figures 1 and 2.

As Figure 1 shows, a significant decrease in the surface tension of water, to around 20 mN m^{-1}, was found for perfluoropropylated PEM and MPE homooligomers compared to the corresponding nonfluorinated PEM and MPE oligomers. In addition, as shown in Figure 2, fluoroalkylated PEM cooligomers, especially perfluorooxaalkylated cooligomers, were more effective for reducing the surface tension of water to around 15−20 mN m^{-1} levels than perfluoropropylated ones. Usually, it is well-known that hydrocarbon polysoap solutions exhibit no CMC or a break point resembling a CMC.[7] However, these fluoroalkylated oligomers were clarified to possess a break point resembling a CMC (critical micelle concentration). This finding is unique and is an interesting feature in these fluorinated oligomers and also suggests the formation of molecular aggregates constructed by aggregation of fluoroalkyl units and the hydrogen-bonding interaction between phosphonic (or phosphinic) segments in aqueous solutions.

Additionally, it is interesting to evaluate the adhesive properties of our new fluorinated oligomers to metal, since our present oligomers possess phosphorus atoms. In fact, these new fluorinated oligomers were tested for stainless steel surface activity as a new type of phosphorus-containing fluorinated surface-active substances. Contact angles for dodecane on stainless steel treated with these oligomers are shown in Table 2. Contact angles for dodecane on the treated stainless steel were found to increase significantly compared with those of the corresponding nonfluorinated oligomers and nontreated stainless steel, indicating that the oligomers having longer perfluorooxaalkyl chains possess a higher oil-repellent property. This finding would result from the strong action of fluoroalkyl groups that exhibit an oleophobic property when arranged more regularly above the surface. Thus, it was demonstrated that our present fluoroalkylated oligomers containing phosphinico segments are applicable to new polymeric fluorinated surface-active substances containing phosphorus atoms.

Table 2. Contact Angles of Dodecane on Stainless Steel Treated with Fluoroalkylated Oligomers

oligomer	contact angle (deg)
$R_F(PEM)_nR_F$	
$R_F = C_3F_7$	28
$R_F = CF(CF_3)OC_3F_7$	31
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	32
$R_F(MPE)_nR_F$	
$R_F = C_3F_7$	28
$R_F = CF(CF_3)OC_3F_7$	31
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	32
$-(PEM)_n-$	0
$-(MPE)_n-$	0
nontreated stainless steel	0

Table 3. Inhibitory Effect of Fluoroalkylated Oligomers on the Replication of HIV-1 in MT-4 Cells

oligomer	EC_{50},[a] μg/mL	CC_{50},[b] μg/mL
$R_F(PEM)_nR_F$		
$R_F = C_3F_7$	9.3	>100
$R_F = CF(CF_3)OC_3F_7$	7.7	>100
$R_F = CF(CF_3)OCF_2CF(CF_3)OC_3F_7$	12	>100
$R_F(MPE)_nR_F$		
$R_F = C_3F_7$	4.0	>100
$R_F = CF(CF_3)OC_3F_7$	35	>100
$-(PEM)_n-$	1.6	>43
$-(MPE)_n-$	1.6	>43

[a] Fifty percent effective concentration, based on the inhibition of HIV-1-induced cytopathicity in MT-4 cells. [b] Fifty percent cytotoxic concentration, based on the reduction of viability of mock-infected MT-4 cells.

Hitherto, it is well-known that polyanionic compounds, such as dextran sulfate, heparin, pentosan polysulfate, and their derivatives were shown to be highly potent and selective inhibitors of HIV-1 replication in vitro.[8] However, there have been few reports on the approach of polymeric phosphorus derivatives as polymeric inhibitors of HIV-1, so far. Previously, we reported that fluoroalkylated end-capped acrylic acid oligomers [$R_F(CH_2CHCO_2H)_nR_F$] are potent and selective inhibitors of HIV-1.[9] Thus, our present fluoroalkylated oligomers containing phosphinico segments are expected to become novel polymeric inhibitors of HIV-1 with the surface-active property. Such fluoroalkylated oligomers have been evaluated for activity against HIV-1 replication in MT-4 cells (see Table 3).

As shown in Table 3, a series of fluoroalkylated oligomers containing phosphinico segments have proved to inhibit HIV-1 replication in cell cultures. The 50% effective concentration (EC_{50}) of these oligomers was 4.0−35 mg mL^{-1} in MT-4 cells, whereas they are not toxic at concentrations up to 100 mg mL^{-1}. On the other hand, nonfluorinated PEM and MPE oligomers were toxic to the host cells.

In this way, our new fluoroalkylated oligomers containing phosphinic segments may be developed into novel functional polymeric material possessing even better anit-HIV-1 activity and surface active property. Further extension to the synthesis and properties of these phosphorus-containing fluorinated oligomers is now being studied.

References and Notes

(1) (a) Stackman, R. W. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 328. (b) Fonong, T.; Burton, D. J.; Pietrzyk, D. J. *Anal. Chem.* **1986**, *55*, 1089. (c) Burton, D. J.; Pietrzyk, D. J.; Ishihara, T.; Fonong, T.; Flynn, R. M. *J. Fluorine Chem.* **1982**, *20*, 617. (d) Chiotis, A.; Clouet, G.; Brossas, J. *Polym. Bull.* **1982**, *7*, 303. (e) Kim, D. Y.; Kong, M. S.; Kim, T. H. *Synth. Commun.* **1996**, *26*, 2487. (f) Classen, R.; Hagele, G. *J. Fluorine Chem.* **1996**, *77*, 71. (g) Maslennikov, I. G.; Mayakova, S. V.; Lavrent'ev, A. N. *Zh. Obshch. Khim.* **1995**, *65*, 1878; *Chem. Abstr.*, **1996**, *125*, 10975k. (h) Kawasaki, T.; Saito, K.; Ohta, H. *Chem. Lett.* **1997**, 351. (i) Yoza, N.; Nakashima, S.; Nakazato, T. *Chem. Lett.* **1997**, 53.

(2) Burton, D. J.; Yang, Z.-Y.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641.

(3) Brondino, C.; Boutevin, B.; Hervaud, Y.; Pelaprat, N.; Manseri, A. *J. Fluorine Chem.* **1996**, *96*, 193.

(4) Sawada, H. *Chem. Rev.* **1996**, *96*, 1779.

(5) (a) Sawada, H.; Tanba, K.; Itoh, N.; Hosoi, C.; Oue, M.; Baba, M.; Kawase, T.; Mitani, M.; Nakajima, H. *J. Fluorine Chem.* **1996**, *77*, 51. (b) Sawada, H.; Itoh, N.; Kawase, T.; Mitani, M.; Nakajima, H.; Nishida, M.; Moriya, Y. *Langmuir* **1994**, *10*, 994.

(6) (a) Sawada, H.; Katayama, S.; Oue, M.; Kawase, T.; Hayakawa, Y.; Baba, M.; Tomita, T.; Mitani, M. *J. Jpn. Oil Chem. Soc.* **1996**, *45*, 161. (b) Sawada, H.; Ohashi, A.; Baba, M.; Kawase, T.; Hayakawa, Y. *J. Fluorine Chem.* **1996**, *79*, 149. (c) Sawada, H.; Katayama, S.; Nakamura, Y.; Kawase, T.; Hayakawa, Y.; Baba, M. *Polymer*, in press.

(7) Anton, P.; Koberle, P.; Laschewsky, A. *Makromol. Chem.* **1993**, *194*, 1.

(8) (a) Mitsuya, H.; Loony, D. J.; Kuno, S.; Ueno, R.; Wong-Staal, F.; Broder, S. *Science* **1988**, *240*, 646. (b) Baba, M.; Pauwles, R.; Balzarini, J.; Arnout, J.; Desmyter, J.; De Clercq, E. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 6132; (c) Mohan, P.; Baba, M. *Drugs Future* **1993**, *18*, 351.

(9) Baba, M.; Kira, T.; Shigeta, S.; Matsumoto, T.; Sawada, H. *J. Acquir. Immun. Defic. Syndr.* **1994**, *7*, 24.

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