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Thermosensitive Cyclotriphosphazenes

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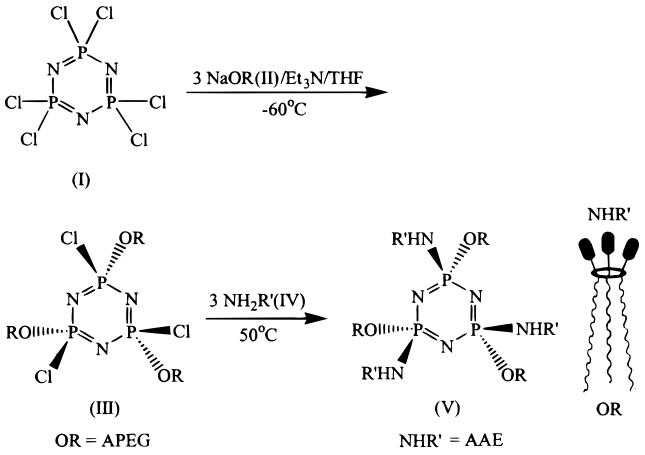
A new class of thermosensitive cyclotriphosphazenes has been first synthesized by stepwise substitution of hexachlorocyclotriphosphazene, $(NPCl_2)_3$, with alkoxy poly(ethylene glycol) (APEG) and amino acid esters (AAE). The initial substitution of the chlorotrimer with 3 mol of sodium salt of APEG at −60 °C was found to follow a cis-nongeminal pathway. Successive substitution with hydrophobic amino acid esters gave rise to trimeric derivatives with a unique molecular structure of octopus shape, in which the three hydrophilic APEG groups were oriented in one direction opposite to the other three hydrophobic AAE groups with respect to the trimer ring plane.

During the past decade, there has been explosive growth in studies of thermosensitive polymers, a new class of stimuli-sensitive materials that have great potential for applications to drug delivery systems (DDS), membranes, separation, enzyme activity control, and cell culture.[1−5] Especially, the polymers with a lower critical solution temperature (LCST) near or below body temperature are of great interest for biomedical applications such as local drug delivery and body temperature sensitive drug release.[6] The LCST is the critical temperature at which polymers or hydrogels in water undergo phase transition from a soluble to an insoluble state as the temperature is raised; it is also called a cloud point. The phenomenon of LCST has been observed mainly in some water-soluble homo- or copolymers of poly(ethylene glycol) and poly(propylene glycol), poly(vinyl alcohol) derivatives, and poly(N-substituted acrylamides).[7,8] However, when these polymers are considered as materials for biomedical applications, they have shortcomings such as nondegradability and toxicity. Furthermore, molecular design to control the hydrophilic/hydrophobic balance for a desired LCST is difficult for these conventional polymers. Recently, we have reported poly(organophosphazenes) with a wide range of LCST,[9,10] but there is no report on oligomeric cyclophosphazenes with thermosensitive properties. We have found that even a small cyclic structural molecule with proper orientation of substituents can exhibit thermosensitivity, and the LCST can be controlled precisely by changing the composition and kinds of the hydrophilic and hydrophobic substituents. Here we report synthesis, structure, and properties of these cyclotriphosphazenes.

The substitution reaction of hexachlorocyclotriphosphazene was extensively studied with primary interest in the regio- and streochemical pathways.[11−19] In particular, partial substitution of hexachlorocyclotriphosphazene usually results in not only stoichiometrically different products but also various geometrical and positional isomers that are not easy to separate from the isomeric mixture. However, in the present study, it was possible to separate the isomers purely using their LCST properties.

Scheme 1



The substitution reaction was performed according to Scheme 1. Hexachlorocyclotriphosphazene (**I**) was reacted initially with the sodium salt of APEG (**II**) to yield the intermediate (**III**), which was successively reacted with amino acid esters (**IV**) to obtain the final trimeric derivatives (**V**) in 70−80% yield.[20] In general, when hexachlorocyclotriphosphazene is substituted by 3 mol of a substituent, three isomers (geminal 2,2,4; nongeminal *cis*-2,4,6; nongeminal *trans*-2,4,6) may be formed.[21] However, in the present study, our choice of low reaction temperature, substituents of selective reactivity, and composition of the substituents seem to afford exclusively a nongeminal *cis*-2,4,6 trimeric isomer with a peculiar molecular structure of octopus shape, which gave rise to thermosensitive properties. The reverse order of the substitution reactions resulted in undesirable byproducts due to hydrolysis of the amino acid esters initially substituted. Many different trimeric derivatives were obtained by variation of the kinds of poly(ethylene glycol) and amino acid esters. These are listed in Table 1. All the title compounds were fully characterized by means of elemental analysis and NMR spectroscopy. The stepwise substitution reactions were monitored by ^{31}P NMR spectroscopy, and the ^{31}P NMR spectral change during the synthetic process for a typical trimer **8** is shown in Figure 1. When hexachlorocyclotriphosphazene was reacted with the sodium salt of MPEG (**II**), the intermediate (**III**) showed one major peak at 42 ppm with some small side peaks at 39 and 43 ppm due to the derivatives

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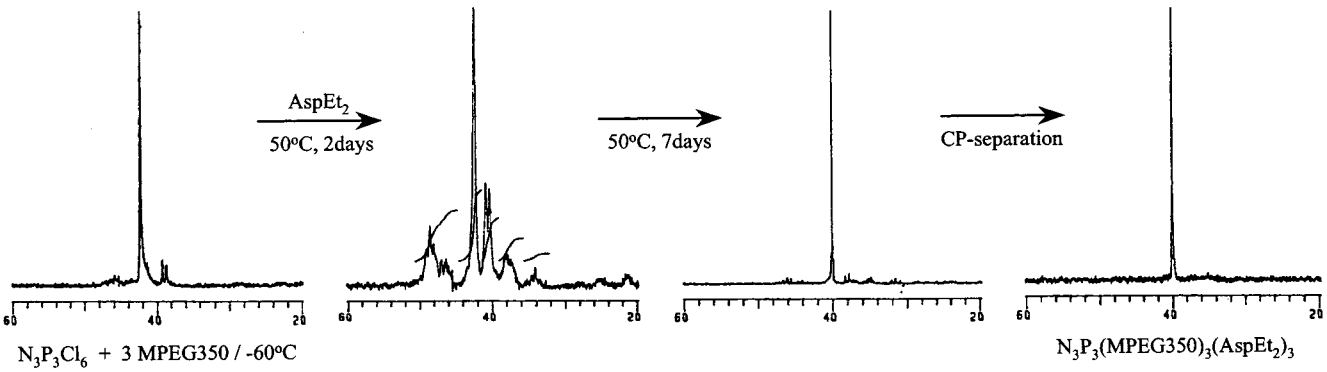

Figure 1. ^{31}P NMR spectral change monitored during the substitution reaction to yield the trimer **8**.

Table 1. Characteristics of Cyclotriphosphazenes

trimer	formula[a]	LCST (°C)	ΔLCST ($T_{0.5M} - T_{0M}$) NaCl	ΔLCST ($T_{0.5M} - T_{0M}$) TPAB[b]	T_g (°C)
1	$N_3P_3(MEE)_3(GlyEt)_3$	>100			−56
2	$N_3P_3(MEE)_3(GlyBz)_3$	10.5	−4.0	2.0	−45
3	$N_3P_3(MEE)_3(AspEt_2)_3$	47.5	−16.0	18.5	−29
4	$N_3P_3(MEE)_3(GluEt_2)_3$	30.0	−10.5	12.0	−27
5	$N_3P_3(EEE)_3(AspEt_2)_3$	21.5	−6.5	5.0	−40
6	$N_3P_3(MPEG350)_3(GlyBz)_3$	65.5	−10.0	26.5	−53
7	$N_3P_3(MPEG350)_3(MalEt_2)_3$	95.0	−18.5	+	−61
8	$N_3P_3(MPEG350)_3(AspEt_2)_3$	83.0	−26.5	16.0	−55
9	$N_3P_3(MPEG350)_3(AspBz_2)_3$	42.5	−13.0	3.0	−49
10	$N_3P_3(MPEG350)_3(GluEt_2)_3$	73.0	−18.5	+	−47
11	$N_3P_3(MPEG550)_3(AspBz_2)_3$	69.0	−11.0	9.5	−45
12	$N_3P_3(MPEG750)_3(AspBz_2)_3$	78.5	−12.5	15.0	−33

[a] MEE: 2-(2-methoxyethoxy)ethoxy. EEE: 2-(2-ethoxyethoxy)ethoxy. MPEG350: methoxy poly(ethylene glycol) with molecular weight of 350. [b] Plus indicates that the LCST of polymer increased to over 100 °C by addition of TPAB.

substituted more or less than the stoichiometric amount. The singlet ^{31}P-resonance indicates that the intermediate trimer, $N_3P_3(MPEG350)_3(Cl)_3$ (**III**), is the cis-nongeminal isomer.[12] The major singlet peak became complex when L-aspartic acid ethyl ester was added. However, as the reaction progressed, the side peaks disappeared, finally resulting in a singlet peak after 7 days. The sharp singlet ^{31}P-resonance provides decisive evidence that the final product is clearly a cis-nongeminal isomer.[12] The final product, $N_3P_3(MPEG350)_3(AspEt_2)_3$ (**8**), was purified by cloud point separation and subjected to HPLC to confirm its isomeric purity (>99.0%). The purity and exact molecular weight (1057.1) of another trimer **3** were confirmed by MALDI MS.

The regioselectivity for bulky alkoxy or aryloxy substituents in hexachlorocyclotriphosphazene is strongly nongeminal due to the steric demands of the reagent[13] and as such nongeminal products are usually obtained. Although sodium methoxide,[22] sodium 2,2,2-trifluoroethoxide,[12] and lithium enolate[14] are small alkoxy or vinyloxy groups, they preferentially give nongeminal derivatives for an electronic reason: these substituents are electron donors toward the phosphorus atoms in the trimer ring, which makes the remaining P−Cl bond stronger and less susceptible to further substitution.[12] Similarly, the present APEG group seems to reduce electrophilicity of the substituted phosphorus center, thus yielding a nongeminal isomer.

Among the models for the stereoselectivity inducing cis isomers,[14] substituent stabilization of the highly polar methoxide salt seems to be operative, yielding the present cis isomer from substitution reaction of hexachlorocyclotriphosphazene with APEG. Since sodium salt of APEG is a highly polar alkoxide salt, the α-oxygen of APEG seems to be stabilized by a sodium ion in the cis position. In addition, the APEG molecule contains many oxygen atoms in the chain that are known to be stabilized by ion−dipole interaction with sodium,[23] which induces the gathering of APEG molecules to cis alignment against the trimer ring. All the trimers showed glass transition temperatures (T_g) lower than room temperature, as shown in Table 1.

Most of the present trimers showed their LCST in the range of 10.5 to 95.0 °C, depending on the kind of side groups as shown in Table 1. Higher LCSTs were observed for the trimers with a longer APEG: trimer **8** (83.0 °C) showed a higher LCST than trimer **3** (47.5 °C). Increased alkyl chain length of the terminal alkoxy group decreased the LCST: trimers **3** (methoxy) and **5** (ethoxy) showed their LCST at 47.5 and 21.5 °C, respectively. The more hydrophobic amino acid ester afforded the lower LCST: the LCST of trimers **1** and **2** was >100 and 10.5 °C, respectively. Such a wide LCST distribution of the present thermosensitive trimers makes them suitable for a variety of applications such as sensor, switch, and recording materials. Furthermore, these thermosensitive trimers could be synthesized reproducibly with the same high degree of purity and exactly the same LCST.

The changes in LCST, $\Delta LCST(T_{0.5M} - T_{0M})$, associated with the change in the ionic strength of these salts from 0 to 0.5 M, are also listed in Table 1. It is seen from the table that more prominent salting-out effects by NaCl were observed for the trimers with more hydrophilic groups (cf. polymers **2** vs **6** and polymers **3** vs **8**). However, $\Delta LCST(T_{0.5M} - T_{0M})$ for the trimers with aspartic benzyl ester was independent of the chain length of MPEG (cf. polymers **9**, **11**, and **12**). The salting-in effect by TPAB showed different trends, but interestingly, the LCSTs of polymers **2** and **9** were observed to be independent of the ionic strength of TPAB, which has not been observed in the conventional thermosensitive polymers.

In summary, a new class of thermosensitive cyclotriphosphazenes were prepared by stepwise substitutions of $N_3P_3Cl_6$ with hydrophilic APEG and hydrophobic AAE, which yielded a nongeminal isomer of a unique octopus-like molecular shape. These trimeric derivatives exhibited remarkably different LCST properties than the conventional thermosensitive polymers.

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Supporting Information Available: A typical synthetic procedure and characterization data for new compounds **1**−**12**, salting-out effect by NaCl, salting-in effect by tetrapropylammonium bromide, and MALDI-TOF mass spectrum for **3** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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