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Synthesis and Assembly of Novel Poly(organophosphazene) Structures Based on Noncovalent "Host–Guest" Inclusion Complexation

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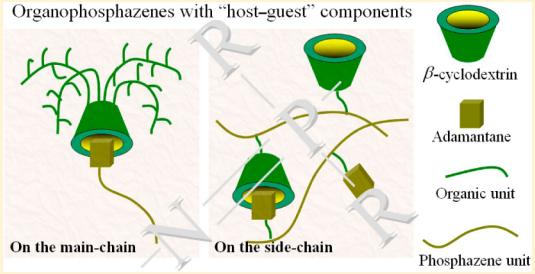
Supporting Information

ABSTRACT: The design and assembly of new organophosphazene polymeric materials based on supramolecular "host–guest" interactions was accomplished by linkage of supramolecular coupling units to either the main-chain terminus or the side-chains of the parent phosphazene polymer. Noncovalent interactions at the main chain terminus were used to produce amphiphilic palm-tree like pseudoblock copolymers via host–guest interactions between an adamantane end-functionalized polyphosphazene and a 4-armed β-cyclodextrin (β-CD) initiated poly[poly(ethylene glycol) methyl ether methacylate] branched-star type polymer. Moreover, noncovalent interactions involving polymer side-chains were achieved between polyphosphazenes with β-CD pendant units and other polyphosphazene molecules with adamantyl moieties on the side-chains. These new organo–phosphazene structures based on noncovalent "host–guest" interactions generate new opportunities for the macromolecular modification of polyphosphazenes. The resultant materials demonstrated useful properties including self-aggregation, supramolecular gelation, and stimulus-responsive behavior.



INTRODUCTION

The assembly of new polymeric structures by noncovalent connections such as hydrogen bonding, ligand–metal coordination, or "host–guest" inclusion complexation has attracted considerable recent interest.[1−4] Such connections at polymer chain-ends or through units on the side chains may respond to various stimuli including changes in temperature, pH, or irradiation and allow the separation and recombination of each connection.[5,6] β-Cyclodextrin (β-CD), a macrocycle with seven glucose units, has long been recognized as a natural host for various small molecules.[7] Chemical attachment of β-CD to polymers has generated considerable interest due to the unique properties of these macromolecules in supramolecular chemistry, analytical studies, separation technology, and pharmaceutical applications.[8,9] Adamantane is one of the most important guests for β-CD due to its effective inclusion entrapment and high binding affinity.[10,11] Several possibilities have been reported using the above "host–guest" inclusion complexation to construct noncovalent polymeric structures. For example, host–guest interactions have been used as a bridge to construct amphiphilic pseudoblock copolymers.[3] Main-chain supramolecular polymers have been obtained by alternating host and guest moieties along the backbone.[12] Self-healing materials have been prepared by mixing β-CD modified polymers with guest molecule modified polymers.[13] However, polymers that contain β-CD present many synthetic challenges including the chemical complexity associated with the seven glucose units, the substantial size of the cyclic molecule, and the potential insolubility of the resultant polymers.[14]

Polyphosphazenes possess a backbone of alternating phosphorus and nitrogen atoms with two (usually organic) side groups attached to each phosphorus. Several hundred poly(organophosphazenes) with different side groups and architectures have been reported in the past several decades.[15] Most of the syntheses of these polymers utilize the replacement of the chlorine atoms in poly(dichlorophosphazene) by alkoxides,[16] aryloxides,[17] or amines.[18] As a unique class of organic–inorganic hybrid polymers, polyphosphazenes possess numerous properties including facile and tunable side group substitution, biocompatibility, and in some cases controllable biodegradability.[15] Construction of β-CD containing polyphosphazenes could expand the category of useful polymers, enable the study of structure–property relationships of novel species and, most important, endow the polymer with new properties which would be of benefit in challenging applications.

In this work, palm tree-like pseudoblock organophosphazene copolymers were prepared by "host–guest" inclusion complexation between a phosphazene polymer chain with a terminal adamantyl group and a tetra-branched β-CD functionalized organic polymeric block. The micellization of the prepared amphiphiles was also studied. In a related system, poly(organophosphazenes) with 10% of the side groups in the form of β-CD pendent units and 10% of adamantane guest units on the side-chains of a second polyphosphazene were synthesized.

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The capability of this configuration to participate in supramolecular gelation of the mixed polymer solutions was investigated (Figure 1).

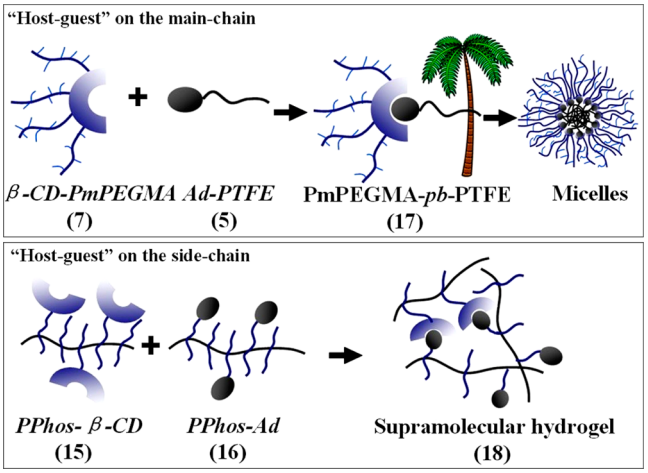

Figure 1. Construction of new organophosphazene structures by host–guest interactions using polymers 5 and 7 or using polymers 15 and 16. The solid circles represent adamantyl units, and the cap-shaped motifs are cyclodextrin hosts.

EXPERIMENTAL SECTION

Materials and Equipment. See Supporting Information.

Synthesis of 1-Aminoadamantane-Functionalized Fluoroethoxyphosphoranimine (2) (AdamantaneNH($CF_3CH_2O)_2P$=$NSiMe_3$). To a tetrahydrofuran (THF) solution of 1-aminoadamantane (0.06 g, 0.38 mmol) and triethylamine (TEA) (0.04 g, 0.38 mmol) was added bromophosphoranimine **1** (Br-($CF_3CH_2O)_2P$=$NSiMe_3$) (0.10 g, 0.25 mmol). The reaction mixture was then stirred at room temperature overnight. The white precipitate was filtered off, and all volatiles were removed under reduced pressure to yield a colorless liquid (**2**). ^{31}P NMR ($CDCl_3$): δ (ppm) −4.43. ^{19}F NMR ($CDCl_3$): δ (ppm) −75.67 (s, −OCH_2CF_3).

Synthesis of Adamantyl End-Functionalized Poly[bis-(trifluoroethoxy)phosphazene] (5) (Ad-PTFE). Phosphorus pentachloride (0.10 g, 0.50 mmol) was dissolved in 20 mL of DCM, and trifluoroethoxyphosphoranimine **3** (($CF_3CH_2O)_3P$=$NSiMe_3$) (0.10 g, 0.25 mmol) was added to the solution. The initiation reaction mixture was stirred at room temperature for 1 h, and the chlorophosphoranimine (Cl_3P=$NSiMe_3$) (2.24 g, 10.00 mol) was added rapidly to the reaction medium. This mixture was stirred at room temperature for 4 h to give living poly(dichlorophosphazene). The 1-aminoadamantane functionalized fluoroethoxyphosphoranimine **2** (0.25 mmol) was redissolved in 10 mL of dichloromethane (DCM) in a separate vial, and was added rapidly to the living polymer solution. The reaction mixture was then stirred at room temperature overnight. Solvent was removed under reduced pressure to yield **4** as a colorless viscous liquid. The freshly prepared polymer **4** was then redissolved in 30 mL of anhydrous THF. The solution was treated with an excess of $NaOCH_2CF_3$, prepared by the reaction of $HOCH_2CF_3$ (2.20 g, 22.00 mmol) with NaH (0.88 g, 22.00 mmol) in 50 mL of THF, and the reaction mixture was stirred at room temperature for 12 h to complete the chlorine replacement reaction (monitored by ^{31}P NMR spectroscopy). The medium was concentrated to about 20 mL, and the solid product was precipitated from THF into water (3 × 500 mL), then from THF into hexanes (1 × 500 mL). This product was isolated by centrifugation as a white powder. The product was further purified by redissolving in 50 mL acetone, and dialyzing the solution versus acetone/methanol 80/20 for 3 d (Spectra/Por dialysis membrane; MWCO = 1000). The solvent was removed and the resultant white powder was dried under vacuum (yield: 59%). ^{1}H NMR (acetone-d_6): δ (ppm) 4.36–4.81 (br, 120H, −OCH_2CF_3), 1.97–1.68 (br, 15H, adamantane). ^{31}P NMR (acetone-d_6): δ (ppm) −2.71 (s, 1P), −3.75 (s, 1P), −7.01 to −8.12 (br, 25P). ^{19}F NMR (acetone-d_6): δ (ppm) −75.22 (s, −OCH_2CF_3).

Synthesis of β-CD End-Functionalized Poly[poly(ethylene glycol) methyl ether methacylate] by ATRP (7) (β-CD-PmPEGMA). 4-Bromo-β-cyclodextrin (0.20 g, 0.12 mmol) was dissolved in 20 mL of anhydrous DMF, followed by addition of mPEGMA (33.6 g, 96 mmol) and PMDETA (80 mg, 0.46 mmol). Argon gas was bubbled through the solution for 20 min to remove any dissolved oxygen. Meanwhile, CuBr (34 mg, 0.24 mmol) was weighed in a small vial and air in the vial was removed by three 10 min purge/backfill cycles of vacuum and argon. The degassed CuBr was added to the solution, and the mixture was stirred for 2, 4, or 6 h under argon at room temperature to give polymers with various molecular weights. To terminate the polymerization, air was bubbled into the reaction medium for 10 min, and the copper catalyst was removed by passing the sample through a flash alumina column. Products in the collected clear solution were then precipitated into diethyl ether (200 mL). The precipitates were isolated by centrifugation as colorless adhesives. Each sample was then redissolved in 50 mL of methanol, and the solution was dialyzed versus methanol for 3 d (Spectra/Por dialysis membrane, MWCO: 6,000–8,000). Solvent was removed under reduced pressure to give colorless adhesive polymers (convn % = 6.5%, 12%, and 17%). ^{1}H NMR ($CDCl_3$): δ (ppm) 6.06 (s, β-CD), 5.51 (s, β-CD), 4.24 (s, β-CD), 4.02 (s, PmPEGMA), 3.78 (s, β-CD), 3.74–3.48 (br, PmPEGMA and β-CD), 3.31 (s, PmPEGMA and β-CD), 1.89 (s, β-CD), 1.74 (s, PmPEGMA), 0.96 (br, PmPEGMA).

Synthesis of 2-[2-(Tetrahydropyranyloxy)ethoxy]ethanol (8). 3,4-Dihydro-2*H*-pyran (21.27 g, 0.25 mol) was added over a period of 30 min to a mixture of *p*-toluenesulfonic acid (0.05 g, 0.267 mmol) in diethylene glycol (201.24 g, 1.89 mol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. It was then allowed to warm to room temperature, and was stirred for 1 d. After that, the mixture was poured into 500 mL of 1 M NaOH(aq) and was extracted with DCM (5 × 200 mL). The collected organic layers were dried over $MgSO_4$ overnight. The solvent was removed and the crude product was distilled at 40–50 °C under reduced pressure (4–5 × 10^{-1} mbar) to collect the colorless liquid product, **8** (yield: 69%). ^{1}H NMR ($CDCl_3$): δ 4.55 (t, 1H), 3.80–3.43 (m, 10H), 1.72–1.44 (m, 6H).

Synthesis of Poly[bis[2-[2-(tetrahydropyranyloxy)ethoxy]-ethoxy]phosphazene] (12). To a THF solution of poly(dichlorophosphazene) (3 g, 25.89 mmol) was added the sodium salt of **10** prepared by the reaction of (tetrahydropyranyloxy)ethoxy]-ethanol (12.3 g, 64.7 mmol) with NaH (2.90 g, 72.5 mmol, 60% in mineral oil). The mixture was stirred under reflux for 2 d. After that, the reaction medium was concentrated, and dialyzed against methanol for 2 d, and then against methanol/acetone/hexanes 50/20/30 for 2 d (Spectra/Por dialysis membrane; MWCO = 12 000–14 000). Solvent was removed by rotary evaporation at 40 °C, and a pale yellow adhesive product was obtained after drying under vacuum (yield: 71%). ^{31}P NMR ($CDCl_3$): δ −8.12 (s). ^{1}H NMR ($CDCl_3$): δ 4.59 (s, 1H), 4.07 (s, 2H), 3.90–3.24 (bm, 8H), 1.92–1.47 (bm, 6H).

Synthesis of Poly[bis[2-(2-hydroxyethoxy)ethoxy]-phosphazene] (13). Compound **12** (2 g, 5.96 mmol) was dissolved in 40 mL of trifluoroacetic acid in 40 mL of water. The solution was stirred at room temperature for 3 h, followed by neutralization of the solution with 5 M aqueous NaOH. The solution was then dialyzed against water for 2 d, then against methanol for 2 d (Spectra/Por dialysis membrane; MWCO = 12 000–14 000). The solution was dried, and a brownish adhesive product was obtained (yield: 62%). ^{31}P NMR (D_2O): δ −8.03 (s). ^{1}H NMR (D_2O): δ 4.11 (s, 2H), 3.72–3.48 (bm, 6H).

Synthesis of Partially Alkyne-Functionalized Poly(organophosphazene) (14). Compound **13** (0.50 g, 1.96 mmol) was dissolved in 20 mL of anhydrous DMF. A suspension of NaH (0.118g, 2.94 mmol, 60% in mineral oil) in 10 mL of anhydrous DMF was added to the polymer solution. The mixture was stirred for 30 min at room temperature. Then, propargyl bromide (0.17 g, 0.78 mmol, 80% in toluene) in 10 mL of anhydrous DMF was added dropwise to

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the reaction mixture. The mixture was stirred at 80 °C for 1 d, and was then dialyzed against methanol/acetone/hexanes 50/20/30 for 2 d (Spectra/Por dialysis membrane; MWCO = 12 000−14 000). The solvent was removed to give pale brown adhesive product (yield: 74%). ^{31}P NMR (D_2O): δ −5.92 (s). ^{1}H NMR (D_2O): δ 4.23 (s, 2H), 4.16 (s, 2H), 3.74−4.58 (br, 6H), 2.86 (s, 1H).

Synthesis of β-CD Containing Poly(organophosphazene) (15) (PPhos-β-CD). Polymer **14** (0.36 g, 1.33 mmol) was dissolved in 10 mL of DMF. To this solution was added β-CD-N_3 (0.47 g, 0.40 mmol) in a mixture of 10 mL of DMF and 4 mL of DMSO, sodium ascorbate (8 mg, 0.04 mmol), and copper sulfate pentahydrate (10 mg, 0.04 mmol). The mixture was stirred at 100 °C under an argon atmosphere for 3 d. The copper catalyst was removed by means of a short neutral alumina column. The collected solution was precipitated into acetone (500 mL), and the suspension was stirred overnight. The pale brown precipitate was isolated by centrifugation, redissolved in 50 mL water, and dialyzed versus H_2O for 3 d (Spectra/Por dialysis membrane; MWCO = 12 000−14 000). Solvent was removed under reduced pressure at 50 °C, and the remaining pale brown solid was freeze-dried (yield: 40%). ^{31}P NMR (DMSO-d_6): δ −8.01 (s). ^{1}H NMR (DMSO-d_6): δ 8.26 (s, 1H, triazole), 5.92−5.68 (s, 14H, β-CD), 4.89−4.76 (s, 7H, β-CD), 4.48−4.36 (s, 6H, β-CD), 4.23 (s, 2H, diethylene glycol), 4.18 (s, 2H, diethylene glycol), 3.89−3.17 (br, 42H, β-CD; 6H, diethylene glycol).

Synthesis of Partially Adamantane Functionalized Poly(organophosphazene) (16) (PPhos-Ad). To an anhydrous DMF solution (30 mL) of polymer **13** (0.40 g, 1.57 mmol) was added an anhydrous DMF solution (5 mL) of 1-adamantyl isocyanate (0.06 g, 0.31 mmol). Then a trace amount of TEA (0.04 mL, 0.31 mmol) was added. The mixture was stirred at 90 °C for 2 d. The polymer solution was then purified by dialysis versus methanol/acetone (40/60) for 3 d (Spectra/Por dialysis membrane; MWCO = 12 000−14 000). The solution was concentrated to 1/3 of its original volume, and precipitated into diethyl ether (200 mL). The pale brown adhesive precipitate was isolated and dried under vacuum to give polymer **16** (yield: 67%). ^{31}P NMR (D_2O): δ −7.21 (s). ^{1}H NMR (D_2O): 4.14 (s, 2H, diethylene glycol), 3.89−3.47 (bm, 6H, diethylene glycol), 2.08−1.53 (bm, 15H, adamantane).

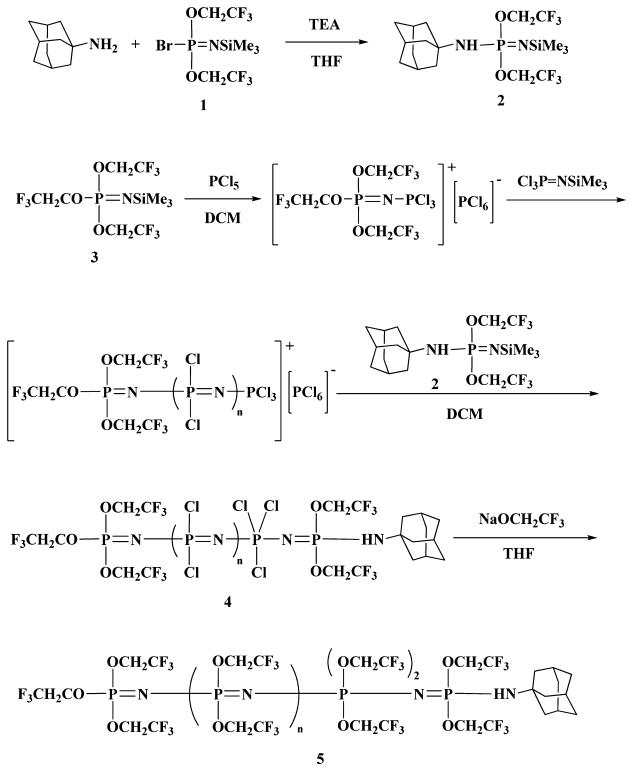
Micelle Preparation. To prepare micelle solutions, nanopure water (80 mL) with a conductivity of 18.2 MΩ/cm was added dropwise to a mildly stirred solution of the 1:1 host (**7**) (0.10 g, 0.005 mmol) and guest (**5**) (0.06 g, 0.005 mmol) polymers in THF (5 mL). Once the host−guest pseudo−block copolymer was formed, all the THF was removed under reduced pressure to give a 2 g/L of micelle aqueous solution. Then, the solution was diluted with water to obtain a micelle concentration in the range of 2 g/L to 1×10^{-5} g/L. For fluorescence measurements, a pyrene solution in THF (1.2×10^{-3} M) was added to nanopure water to give a final pyrene concentration of 12×10^{-7} M. Following dilution, the THF was removed under reduced pressure. The pyrene solution was then mixed with the pseudo-block copolymer solutions to obtain copolymer concentrations ranging from 1 g/L to 5×10^{-6} g/L, while the pyrene concentration of the all samples was maintained at 6×10^{-7} M. The samples were sonicated for 10 min and were allowed to stand for 1 day before fluorescence measurements.

Supramolecular Gelation. PPhos-β-CD (**15**) (200 mg) was dissolved in 2 mL of nanopure water (10% w/v) as a macromolecular host component. Then, PPhos-Ad (**16**) (200 mg) was dissolved in 2 mL of nanopure water (10% w/v) as a macromolecular guest component. The two components were mixed and shaken mechanically at room temperature to allow the formation of the supramolecular gels (**18**). To study the competitive dissociation of the obtained gels, 1 mL of a saturated β-CD aqueous solution was added to the gel and the system was shaken mechanically for 10 min.

RESULTS AND DISCUSSION

Polymer Synthesis and Characterizations. *Synthesis of Adamantane Terminated Linear Phosphazene (Ad-PTFE).* The development of the PCl_5-induced living cationic polymerization of a phosphoranimine for preparing poly(dichlorophosphazene) allows the generation of polymers with controllable molecular weights and narrow polydispersity.[19,20] More important, the modifiable chain-ends provide accessibility to various polyphosphazene-containing polymeric structures including di- or triblock copolymers,[21,22] dendrimers,[23] and graft copolymers.[24] As shown in Scheme 1,

Scheme 1. Synthesis Chart of Ad-PTFE (5)



polymerization was initiated unidirectionally with a target of 30 repeating units. Then, the adamantyl modified phosphoranimine was added to quench the living chain-end. Subsequently, the resultant polymer was treated with an excess of $NaOCH_2CF_3$ to replace the chlorine atoms and yield the hydrophobic phosphazene guest block. The final product was soluble in acetone, DMF and THF, but insoluble in $CHCl_3$, CH_2Cl_2, methanol or water. The chain-end phosphorus signal was detected by ^{31}P NMR, and the adamantyl moiety appeared in the ^{1}H NMR spectrum (Supporting Information, Figure S1). The calculation of the number of the repeating units from the ^{31}P NMR spectra (from integrations of end-phosphorus −2.71 ppm and repeating unit phosphorus −7.74 ppm, 27 repeating units) and from ^{1}H NMR (from integrations of OCH_2CF_3 4.36−4.81 ppm and adamantane 1.97 ppm, 34 repeating units) were close to the target of 30 repeating units. The difference in the number of repeating units calculated by GPC (M_n~12 300 g/mol, repeating units~50, PDI~1.23) is due to the different hydrodynamic radii between Ad-PTFE and polystyrene standards (for the GPC calibration curve).

Synthesis of Branched-Star Shaped Organic Polymers Containing β-CD at the Chain-end (β-CD-PmPEGMA). Atom transfer radical polymerization (ATRP) is one of the most robust controlled/living radical polymerization techniques as it functions with a diversity of monomers, molecular weight control, and narrow polydispersity.[25] Since its development,

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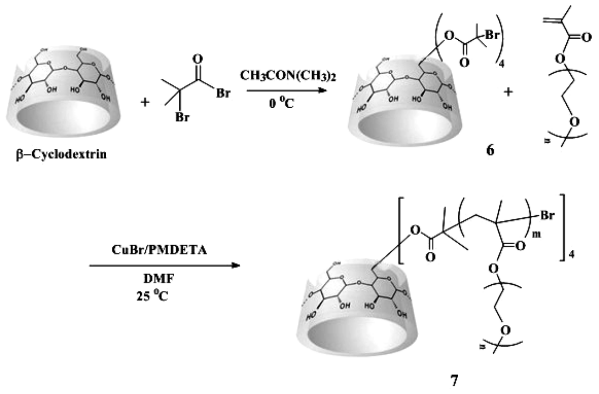
this technique has stimulated research and exploration of the synthetic boundaries of new polymeric structures, especially for synthesizing block copolymers.[26,27] In this work, a β-CD based macroinitiator with four bromo-initiation sites on the primary face of β-CD (primary hydroxyl groups) was obtained following a well established method.[4] With an increasing degree of substitution of 2-bromoisobutyryl bromide units, the solubility of the modified β-CD decreased dramatically in water, but increased distinctly in acetone. Tetra-substituted β-CD is at the boundary of solubility which makes it slightly soluble in both water and acetone. Hence, if treated with four equivalents of the bromo-substituent, the esterification reaction products can be purified by repeatedly washing the crude product with water and acetone. ATRP was carried out using the CuBr/PMDETA complex as a catalyst, with poly(ethylene glycol) methyl ether grafted methyl methacylate as a monomer (Scheme 2). A small

Scheme 2. Synthetic Chart of β-CD-PmPEGMA (7)



amount of DMF was added to dissolve the macroinitiator, and the polymerization conditions were optimized for the control of molecular weight and polydispersity. Because the presence of trace quantities of oxygen could oxidize the Cu(I) catalyst and quench the living radical, oxygen was carefully excluded from all reagents and the reactions were carried out under an inert atmosphere. In this work, the molar ratio of monomer to one initiation site (4 initiation sites on each ring) was 200:1. This large excess of monomer was intended to produce a narrower polydispersity by lowering radical concentrations and minimizing chain terminations. A series of guest blocks (**β-CD-PmPEGMA**) with increasing molecular weights were prepared by varying the polymerization time from 2 to 6 h (Figure 2). The proton resonances of both the chain-end β-CD and four armed PmPEGMA units were detected in the ^{1}H NMR spectrum (Supporting Information, Figure S2).

Synthesis of Graft Phosphazenes with Pendent β-CD Units: Macromolecular Hosts (PPhos-β-CD). Generally speaking, the substitution reactions of poly(dichlorophosphazene) become more challenging as the structures of the chlorine-replacement nucleophiles become more complex. Large side groups generate more steric hindrance with a corresponding decrease in reactivity. Meanwhile, the solubilities of the polymers usually decrease after the attachment of large or complex side groups. This tends to hinder their synthesis, characterization and processability. Complex or multifunctional side groups also necessitate multistep protection and deprotection reactions in order to prevent cross-linking or side reactions during the macromolecular substitutions. Thus, linkage of β-CD units to polyphosphazene side-chains is a

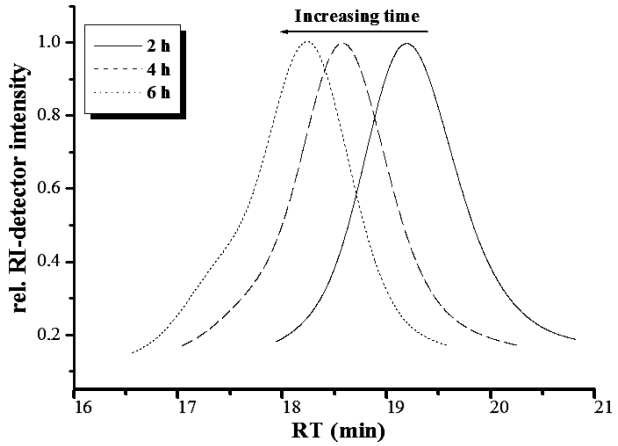


Figure 2. GPC traces of a series of β-CD-PmPEGMA.

challenging prospect because the mutliple hydroxyl functional groups on β-CDs may require serious synthetic efforts to prevent unwanted cross-linking. Moreover, the possibility also exists that the resultant polymers will have poor solubility, or that sterically induced low reactivity will be experienced during the secondary macromolecular modifications.[28,29] In order to solve these problems, two strategies were employed for designing the polymeric structure and the synthesis protocols. First, one of the 21 hydroxyl groups on the β-CD must be converted to a different functional group, leaving the remaining hydroxyl groups unmodified. The new functional group should be able to undergo a distinct reaction while the other hydroxyl groups are inert under the reaction conditions. Second, a long and flexible spacer group must connect the polymer backbone to the β-CD to increase the accessibility of the functional groups in the bulky β-CDs. Meanwhile, the spacer groups should not change the water solubility or increase the potential toxicity of the resultant polymers depending on their applications.

Progress on modification techniques for CDs, especially for monofunctionalization, has greatly accelerated the diversity of compounds based on β-CD containing polymers in recent years.[30] Also, since Sharpless and co-workers introduced the "click" chemistry concept in 2001,[31] this copper-catalyzed azide–alkyne cycloaddition (CuAAC) has proved to be an extremely useful tool for construction of polymer networks due to its mild reaction conditions, high reactivity, solvent and functional group tolerance, and lack of byproducts.[32] Thus, based on earlier work,[33] β-CD was monoazidified (**10**) on the primary face to selectively react with alkyne functional groups introduced as side units on the polyphosphazene backbone. In order to enhance the reactivity of the "click" reaction, diethylene glycol groups were used as spacer units to increase the side chain flexibility and lower steric hindrance. Monoprotection of the hydroxyl groups on diethylene glycol (**8**) was carried out before macromolecular substitution to prevent polymer cross-linking (Scheme 3). Dihydropyran was selected as the protecting group due to the ease of macromolecular deprotection under acidic conditions.

Thus, as shown in Scheme 4, poly(dichlorophosphazene), prepared by the thermal ring-opening polymerization of hexachlorocyclotriphosphazene, was treated with the sodium salt of monoprotected diethlyene glycol to give polymer **12** with a molecular weight (g/mol) of 520 000 (~2720 repeat units). The side group deprotection reaction was carried out in

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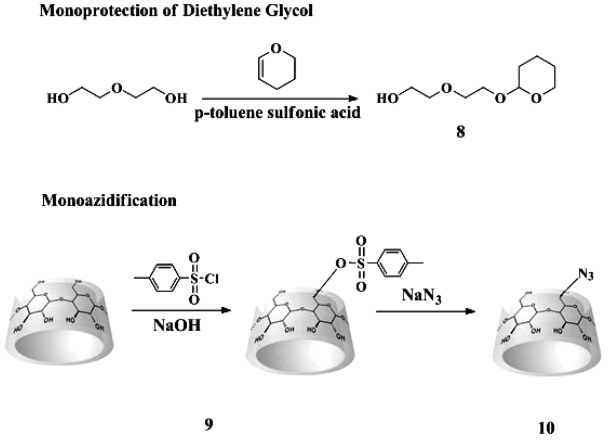
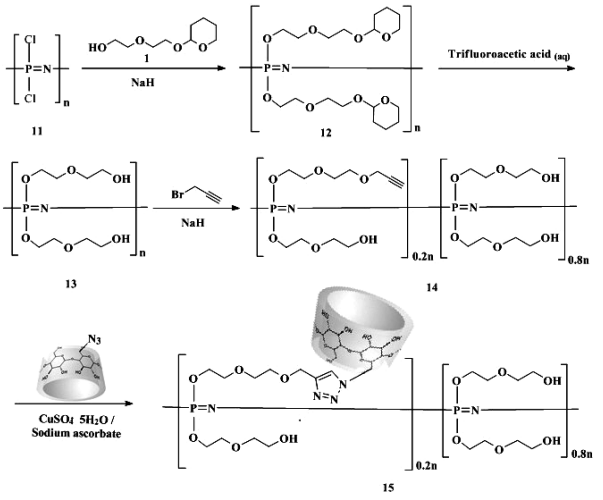
Scheme 3. Synthesis Chart of Small Molecules for Macromolecular Reactions



Scheme 4. Synthetic Scheme Leading to PPhos-β-CD (15)



aqueous trifluoroacetic acid to release the free hydroxyl groups for further reaction (**13**). The success of the deprotection reaction was easily verified by the disappearance of the peaks at 1.92−1.47 ppm (dihydropyran) in the ^{1}H NMR spectrum (Figure 3). Thus 10% of the hydroxyl groups were activated to alkyne group **14** to further react with β-CD-N_3. A new peak at 2.8 ppm from ^{1}H NMR indicated the success of the alkyne activation at the terminus of the polymer side-chains. A maximum of 10% of β-CD could be "clicked" to the side chains even though the alkyne-activation in the prior step was more than 10%. Because the size of β-CD is significantly larger than the repeating units of the polyphosphazene backbone, a substantial increase in steric hindrance occurred after the β-CD units were introduced. This sheltered the remaining functional groups on the polymer from access to additional β-CD. Meanwhile, the azide functional group on the bulky β-CD can only interact effectively with alkyne functional groups on the polymer from one direction (at the primary face), which further decreases the overall reactivity. New peaks assigned to β-CD from the ^{1}H NMR spectra indicated the presence of the β-CD in the polymer. The peak of one end-proton of the alkyne at 2.8 ppm shifted to around 8.3 ppm and represented the formation of a triazole bridge. The new polymer, PPhos-β-CD, shows no obvious shift in the ^{31}P NMR spectra (−7 ppm) because the modifications were too distant from the backbone

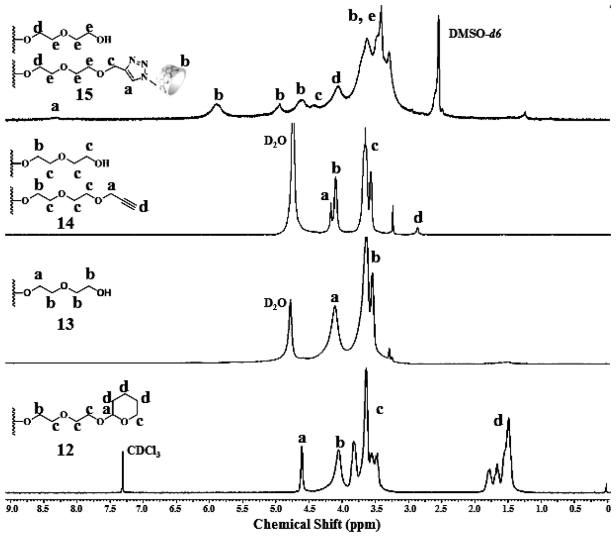


Figure 3. ^{1}H NMR of polymers **12**−**15**.

phosphorus atoms (Supporting Information, Figure S3). Meanwhile, ^{31}P NMR spectra of **12**−**15** showed similar signal peaks without significant broadening. This implies that degradation of the polymer was minimal during the multistep macromolecular side-chain modifications. PPhos-β-CD (**15**) showed no evidence of cross-linking since it was soluble in DMF, DMSO (room temperature), and water (heated), but insoluble in less polar organic solvents.

DSC measurements provide additional evidence of the successful linkage of β-CD to the polyphosphazene backbone (Supporting Information, Figure S4). Polymer **14** with flexible diethylene glycol side chains had a low glass transition temperature (T_g) at around −47 °C. After clicking 10% of β-CD onto the polymer side-chains, the T_g of PPhos-β-CD (**15**) increased substantially to about 50 °C. This major increase in T_g is attributed to an increase in side chain steric hindrance which prevents network movement, together with assisting the formation of additional hydrogen bonding from the multiple hydroxyl groups on the β-CD. The significant change in T_g could also be detected directly by the different textures of **14** (adhesive gum) and **15** (glassy powder) at room temperature. No melting behavior was detected for **15** up to 220 °C. Above that temperature, intense signal fluctuation was detected from the DSC experiments due to the thermal decomposition.

Synthesis of Graft Phosphazene Containing Adamantane Units at the Termini of the Side-Chains: Macromolecular Guests (PPhos-Ad). For the macromolecular guests, around 10% of the adamantyl moieties were linked to the polyphosphazene side-chain. The diethylene glycol spacer groups were required to utilize more flexible side-chains in order to better interact with the host component during "host−guest" complexations. Initial attempts following the same method for synthesizing polymer **14**, by reacting polymer **13** with NaH and 1-bromoadamantane, were not successful, probably due to the low reactivity of bulky 1-bromoadamantane. Later, 1-adamantyl isocyanate was used for the formation of a carbamate linkage (Scheme 5). New peaks appeared at 2.08−1.53 ppm indicating the successful introduction of the adamantyl group by this method (Supporting Information, Figure S5). The resultant adhesive polymer **16** was soluble in water and DMSO.

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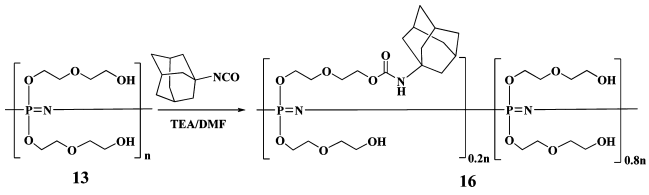
Scheme 5. Synthetic Scheme for PPhos-Ad (16)



Assembly of Organo–Phosphazene Structures by Host–Guest Interactions. *Host–Guest Interactions at the terminus of the Main-chain.* Palm tree-like pseudoblock copolymer structures (PmPEGMA-*pb*-PTFE, **17**) were obtained by exploiting the supramolecular interaction between adamantane guest **5** and *β*-CD host **7** in water. Previous studies have showed that the association constant for adamantane and *β*-CD is high in the presence of water (10^4–10^5 M^{-1}).[34] Meanwhile, the host–guest interaction between *β*-CD and oligo(ethylene glycol) is minimal due to the inappropriate size.[35] The 2D ^{1}H NOESY spectrum was obtained after mixing equimolar quantities of the host block and the guest block in DMSO-d_6 with a few drops of D_2O (Supporting Information, Figure S6). The cross-peaks at around 3.5 and 1.9 ppm are assigned to the inner protons of *β*-CD and the protons of the adamantyl moiety, respectively. This indicates the close proximity of these protons, which is direct evidence in favor of the host–guest interactions.

Micelles were prepared by dissolving host and guest blocks in THF. Then a large amount of water was added dropwise to reach a target block copolymer concentration of 2 g/L, followed by the removal of THF at reduced pressure. This stock micelle solution was further diluted to various lower concentrations. The formation of micelles was demonstrated by four methods, fluorescence, dynamic light scattering, TEM, and AFM. The critical micelle concentrations (cmc) of **PmPEGMA-*pb*-PTFE** (**17**) were studied by a standard fluorescence technique using pyrene as a fluorescence probe.[34,36,37] Although pyrene is a guest molecule for *β*-CD as well, the partition of pyrene in the *β*-CD cavity is negligible due to the presence of the adamantyl moiety since adamantane is a better guest with a much higher association constant.[4,38] In the excitation fluorescence spectra of pyrene, the peak initially at 333 nm at low polymer concentrations red-shifted to 336 nm when the polymer concentrations increased to a certain point. At the same time, the intensity of the pyrene fluorescence increased substantially. This turning point of the pyrene's fluorescence behavior is due to the inclusion of pyrene from aqueous solution into the hydrophobic core of the micelles, which indicates the lowest concentration of the pseudoblock copolymer required for the formation of micelles (cmc). The cmc value can then be calculated by plotting the ratios of the peak intensities at 336 to 333 nm (I_{336}/I_{333}) versus the logarithm of the polymer concentrations (Supporting Information, Figure S7). The threshold concentration at the turning point of I_{336}/I_{333} reflected the shift of pyrene from an aqueous environment into the hydrophobic environment in the micelle core. The cmc values summarized in Table 1 showed that higher cmc values were obtained with an increase in the molecular weight of the hydrophilic block.

Dynamic light scattering (DLS) suggested an absence of self-aggregation for any of the three host blocks in water. However, when **Ad-PTFE** was introduced as a guest block (**PmPEGMA-*pb*-PTFE**), self-aggregations were detected for all of variations

Table 1. Summary of PmPEGMA-*pb*-PTFE Micelles

entry	M_n (g/mol) (Ad-PTFE)	M_n (g/mol) (*β*-CD-PmPEGMA)	cmc (mg/L)	r (nm)
PmPEGMA-*pb*-PTFE-1	12 300	19 450	4.6	32
PmPEGMA-*pb*-PTFE-2	12 300	34 660	8.1	44
PmPEGMA-*pb*-PTFE-3	12 300	49 310	28.2	60

(1 g/L) due to the formation of amphiphilic pseudoblock copolymers (Figure 4). Meanwhile, the hydrodynamic radius of

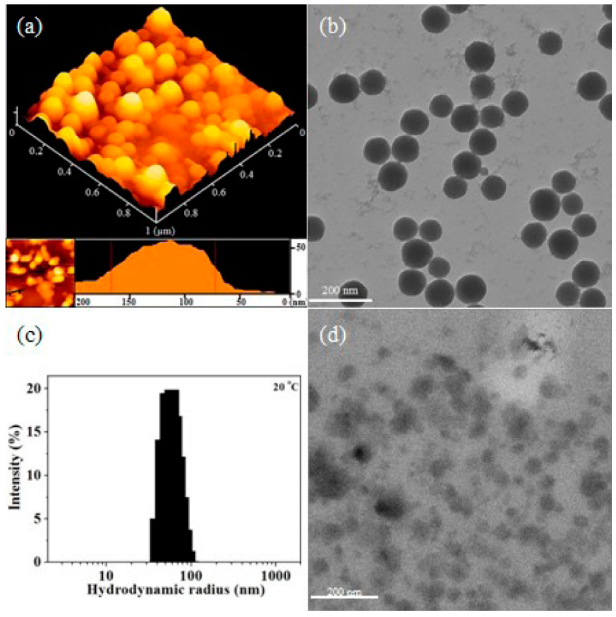


Figure 4. AFM (a), TEM (b), and DLS (c) of micelles formed by **PmPEGMA-*pb*-PTFE-3**; TEM (d) after the addition of pure *β*-CD guests.

the aggregations increased with an increase in molecular weight of ***β*-CD-PmPEGMA**. The sizes and shapes of the micelles were also examined by TEM and AFM as shown in Figure 4. The average micelle diameter measured by TEM and AFM was in agreement with the mean diameter measured by DLS. The existence of larger micelles with diameters in excess of several hundred nanometers resulted from intermicellar aggregations with the resultant formation of multicore micelle structures.[39] Because of the noncovalent connection between the hydrophilic and the hydrophobic blocks, the micelles showed competing guest–responsive self-disassembly behavior. Thus, the addition of pure *β*-CD host to the micelle solutions induced the dissociation of the micelle structure. *β*-CD competed with ***β*-CD-PmPEGMA** to associate with the adamantyl group on the phosphazene block, thus breaking the noncovalent connections. The TEM results in Figure 4 showed the contours of the micelle becoming diffuse, and the spherical shape evident in image b no longer existed after the addition of *β*-CDs. DLS also confirmed the dissociation since the previous narrow size distribution became broad, with a decrease of average radius.

Host–Guest Interaction on the Side-Chain. Pyrene was introduced as a probe guest molecule to study the interaction between the hydrophobic guest and the hydrophobic cavity of *β*-CD on the side-chains. As shown in the excitation spectra (Figure 5), the fluorescence peak of pyrene was red-shifted with an increased intensity in the presence of PPhos-*β*-CD.

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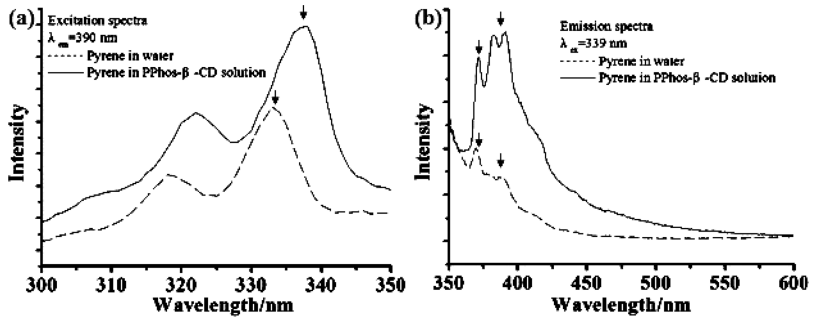

Figure 5. Fluorescence studies of side-chain host–guest interactions: excitation spectra (a), emission spectra (b).

Meanwhile, the intensity ratio of the first and third vibrational bands (I_1/I_3) of pyrene from the emission spectra changed substantially from $I_1 > I_3$ to $I_1 < I_3$, and the overall fluorescence intensity increased after the addition of PPhos-β-CD. This indicated that the pyrene was transferred from the aqueous environment to the hydrophobic β-CD cavities pendent to the polyphosphazene backbone.

A supramolecular gel was obtained by mixing the "guest component" PPhos-Ad and the "host component" PPhos-β-CD. Host–guest interactions between the side chains of the two polyphosphazenes formed noncovalent cross-links. As shown in Figure 6, a gel (**18**) could be obtained within 1 h at

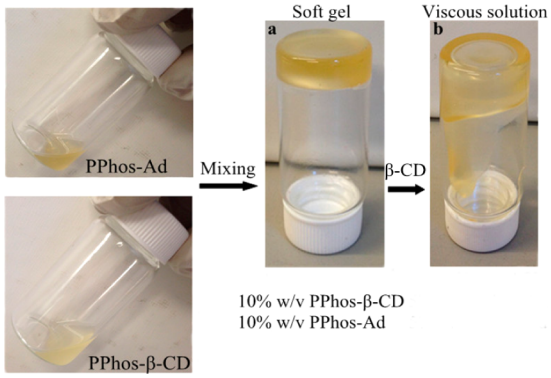

Figure 6. Formation of a supramolecular gel by "host–guest" interactions.

higher host polymer and guest polymer concentrations (a, 10% w/v), while only a viscous solution was generated if the concentrations of the two components were lower. Rheological measurement demonstrated the formation of a soft gel, since the storage modulus (G' = 5.1 kPa) surpassed the loss modulus (G'' = 1.8 kPa). The soft gel (**18**) showed no injectable behavior due to a high association constant between adamantane and β-CD. The soft gel (a) turned into viscous solution (b) if a pure β-CD host aqueous solution was added with mechanical shaking for a certain time. The small-molecule host, β-CD, competes with macromolecular host PPhos-β-CD to interact with PPhos-Ad leading to dissociation of some of the physical cross-links. Moreover, the formation of gel was also inhibited if the macromolecular guest component PPhos-Ad was premixed with pure β-CD before mixing with PPhos-β-CD.

CONCLUSIONS

The assembly of new polyphosphazene structures based on noncovalent "host–guest" interactions (β-CD and adamantane) was achieved both at the termini of the phosphazene main-chain and on the side-chains. Amphiphilic palm-tree like pseudoblock copolymers were obtained through the host–guest coupling of an adamantane end-functionalized polyphosphazene and 4-armed β-CD initiated poly[poly(ethylene glycol) methyl ether methacylate]. The micelle properties of the noncovalent amphiphiles were studied by various techniques. β-CD or adamantane were also introduced onto the side-chains of polyphosphazenes to form macromolecular hosts or macromolecular guests. The β-CD containing polyphosphazene functions as a macromolecular host demonstrated its capability to carry hydrophobic molecules and the ability to form supramolecular gel when mixed with a macromolecular guest. The success of constructing these new poly(organophosphazene) structures not only extends the synthetic boundary of phosphazene related materials but, more important, could endow the new materials aggregative, stimulus-responsive, guest–carrying/releasing, and gelation properties which could extend the areas of application for this system.

ASSOCIATED CONTENT

Supporting Information

Experimental section including NMR spectra, DSC plots, and a plot of I_{336}/I_{333} vs log C. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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