Branched Polyphosphazenes with Controlled Dimensions

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Abstract

Using living cationic polymerization, a series of polyphosphazenes is prepared with precisely controlled molecular weights and narrow polydispersities. As well as varying chain length through the use of a living polymerization, amine-capped polyalkylene oxide (Jeffamine) side chains with varied lengths are grafted to the polymer backbone to give a series of polymers with varied dimensions. Dynamic light scattering and size exclusion chromatography are used to confirm the preparation of polymers with a variety of controlled dimensions and thus hydrodynamic volumes. Furthermore, it is demonstrated how the number of arms per repeat unit, and thus the density of branching, can also be further increased from two to four through using a one-pot thiolactone conversion of the Jeffamines, followed by thiol-yne addition to the polyphosphazene backbone. These densely branched, molecular brush-type polymers on a biodegradable polyphosphazene backbone all show excellent aqueous solubility and have potential in drug-delivery applications.

Keywords

branched polymers; biodegradable polymers; drug delivery; living cationic polymerization; polymer therapeutics; polyphosphazenes

INTRODUCTION

Poly(organophosphazenes) are inorganic–organic hybrid polymers with an alternating phosphorus and nitrogen backbone. The hydrolytically instable precursor, poly(dichlorophosphazene), can be readily substituted with a variety of nucleophilic substituents to give poly(organophosphazenes) with a wide range of properties.1 If suitable organic substituents are chosen, the polymers can be biodegradable,2 degrading to nontoxic products. Traditionally prepared by ring-opening polymerization, the poly(dichlorophosphazene) precursor can also be prepared via the room-temperature living polymerization route.3 This living cationic chain growth polycondensation involves the initiation of trichlorophosphoranimine (Cl3PNSiMe3) with two equivalents of PCl5 to give the chain initiating cationic species [Cl3P=N-PCl3]+. The precise mechanism is still a matter of investigation,4 but repeated experimental evidence has shown that this species undergoes living chain growth upon addition of further amounts of Cl3PNSiMe3, accompanied by the condensation of Me3SiCl. This living polymerization route has enabled the synthesis of polyphosphazenes with controlled molecular weights and narrow polydispersities, as well as access to block copolymers5-8 and a variety of star9,10 and brush-type11,12 architectures.
Macromolecular architecture and hydrodynamic volume clearly have a critical impact on many applications and developments in polymer chemistry in recent years, in particular living polymerization techniques and the boom in controlled free-radical polymerizations has led to the availability of a wide range of structures and architectures. With polymers having hydrodynamic volumes in the same order of magnitude as many biological transport systems, it is clear, that size and shape can have a significant impact on the transport of polymers in biological systems, including excretion rates from the kidneys, tissue uptake, and cell interaction. Also the shape of polymeric carriers and even the number of arms have been suggested to play a critical role in determining the biodistribution of macromolecules.

The controlled polymerization, in combination with the inherent biodegradability, make polyphosphazenes good candidates for a number of applications, including drug delivery and indeed a number of bioerodible polyphosphazenes are currently under investigation in this area. In this article, we present the preparation and characterization of a series of water-soluble polyphosphazenes and show how the size and shape can be easily tuned via the length of the backbone, as well as the length and density of the side branches.

EXPERIMENTAL

Materials and Characterization

All solvents were dried using standard laboratory methods. The glassware was dried in an oven at 120 °C before use. All synthetic procedures were carried out under inert atmosphere either under argon in a glovebox (MBRAUN) or under nitrogen using standard Schlenk line techniques. PCl₃ was sublimed under vacuum and stored in the glovebox under argon. Et₃N was dried over molecular sieves and distilled prior to use. The mono-boc protection of 2,2′-(ethylenedioxy)-bis-ethylamine was carried out according to a literature procedure. Jeffamine M-1000 and M-2070 are amino capped statistical poly(ethylene oxide-co-propylene oxides), PEO-PPO-NH₂, and were donated by Huntsman Performance Products (Netherlands). Jeffamine M-1000 has a nominal molecular weight of 1000 g mol⁻¹ and an ethylene oxide/propylene oxide ratio of 19/3. Jeffamine M-2070 has a nominal molecular weight of 2000 g mol⁻¹ and an ethylene oxide/propylene oxide ratio of 31/10. All other chemicals were purchased from Sigma Aldrich and used as received.

¹H NMR spectroscopy was recorded on a Bruker 300 MHz spectrometer and referenced to the signal of internal CDCl₃. ³¹P NMR (121 MHz) spectroscopy was carried out using 85 % phosphoric acid as an external standard. Size exclusion chromatography (SEC) was measured with a Viscothek GPCmax instrument equipped with a PFG column from PSS, (Mainz, Germany) 300 × 8 mm², 5-μm particle size. The samples were eluted with DMF containing 5 mM LiBr at a flow rate of 0.75 mL min⁻¹ at 60 °C. The molecular weights were estimated using a conventional calibration of the refractive index detector versus linear polystyrene standards. ATR-FTIR spectra were measured on a Perkin Elmer Spectrum 100 FTIR spectrometer. A Malvern ZetaSizer Nano-ZS analyser (Malvern Instruments, UK) was used for dynamic light scattering (DLS) measurements. The 4 mW HeNe laser was set at λ = 633 nm with the detector angle at 173° for backscattering measurements. The samples were dissolved in deionized H₂O to give a 1 mg mL⁻¹ concentration, filtered through a 0.2-μm nylon filter and measured in a disposable polystyrene cuvette at 25 °C.

Synthesis of Cl₃PNSiMe₃

The monomer Cl₃PNSiMe₃ was synthesized according to literature procedures with slight modifications. Under argon LiN(SiMe₃)₂ (18.30 g, 0.11 mol) was dissolved in anhydrous diethylether and cooled to 0 °C. PCl₃ (15.02 g, 0.11 mmol) was added dropwise and stirred.
for 1 h at 0 °C. Then SO$_2$Cl$_2$ (14.76 g, 0.11 mmol) was added dropwise and stirred for another hour at 0 °C. Afterward, the solution was filtered, and the solvent was removed under vacuum. Vacuum distillation at 1–5 mbar and 40–45 °C gave Cl$_3$PNSiMe$_3$ as a colorless liquid.

Yield: 13.6 g (55 %); $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): $\delta$ = 0.18 (d, 9H) ppm; $^{31}$P NMR (121 MHz, CDCl$_3$, $\delta$): −54.45 ppm.

Synthesis of Poly(dichlorophosphazene)

The synthesis of the poly(dichlorophosphazene) precursor was carried out in the glove box at room temperature. In a typical procedure, the initiator PCl$_5$ (0.11 g, 0.53 mmol) was allowed to dissolve in anhydrous CH$_2$Cl$_2$. The monomer Cl$_3$PNSiMe$_3$ (1.50 g, 6.68 mmol), also dissolved in dry CH$_2$Cl$_2$, was then added. The solution was stirred for 12 h, and the solvent was removed under vacuum. Yield: quantitative. $^{31}$P NMR (121 MHz, CDCl$_3$, $\delta$): −18.09 ppm.

Synthesis of Polymers 1–8

All polymers were synthesized in the same manner. The following details are given for polymer 1. Polydichlorophosphazene (0.25 g, 1.11 mmol) was dissolved in THF and tertbutyl-2-(2-(2-aminoethoxy)ethoxy)ethylcarbamate (0.03 g, 0.11 mmol) in THF and Et$_3$N (1 eq., 0.02 g) were added. This solution was stirred for 24 h. An excess of Jeffamine M-1000 (5.35 g, 5.35 mmol) in THF and Et$_3$N (1 equiv, 0.54 g) were added to the partially substituted precursor in THF. The solution was stirred in the glove box at room temperature for 24 h. The solvent was removed under vacuum and the polymers were purified by dialysis (12 kDa cut-off) in H$_2$O for 24 h followed by 72 h in EtOH. The solvent was removed under vacuum. Polymers 1-4, with Jeffamine M-1000 side groups formed waxy solids, 5-8 (M-2070) were obtained as highly viscous liquids. The polymers were prepared in yields of 62–76 %.

For polymer 1: $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 1.13 (br, 104H), 1.44 (s, 9H), 3.38 (s, 58H), 3.65 (m, 1171H) ppm; $^{31}$P NMR (121 MHz, CDCl$_3$, $\delta$): 5 0.76 ppm. See Supporting Information for further characterization.

Synthesis of Polymer 9

A suspension of sodium hydride (60% in mineral oil) (0.26 g, 6.42 mmol, 2.4 eq) in THF was cooled to 0 °C with an ice bath. A large excess of propargyl alcohol (2 mL, 1.93 g, 34.36 mmol) was slowly added to improve the solubility of the formed alkoxide and stirred for 1 h at room temperature. The poly(dichlorophosphazene) (0.60 g, 2.67 mmol, 1 equiv) dissolved in THF was added and the reaction was stirred overnight. The reaction mixture was filtered and the solvent was removed under vacuum. The residue was redissolved in CHCl$_3$ and washed repeatedly with water and then brine. The organic phase was dried over MgSO$_4$ and removed under vacuum to yield polymer 9. Yield 0.23 g (55 %). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 2.54 (br, 1H), 4.69 (br, 2H) ppm; $^{31}$P NMR (121 MHz, CDCl$_3$, $\delta$): −7.46 ppm; FTIR (solid): $\nu_{\max}$ = 3290 (C≡C—H), 2129 (C≡C), 1031 (P=N) cm$^{-1}$; SEC: $M_n$ = 10,391 g mol$^{-1}$, $M_w$ = 11,120 g mol$^{-1}$, $M_w/M_n$ = 1.07.

Synthesis of Polymers 10–11

In the glove box Jeffamine M-1000 (3.88 g, 3.88 mmol, 12 equiv), N-acetylhomocysteine thiolactone (1.24 g, 7.74 mmol, 24 equiv) and 4-dimethylaminopyridine (DMAP) (0.04 g,
0.38 mmol, 1.2 equiv) were dissolved in 10 mL of degassed CH$_2$Cl$_2$ and stirred over night at room temperature. The solvent was then removed under vacuum. Polymer 9 (0.05 g, 0.32 mmol, 1 equiv) and 2,2-dimethoxy-2-phenylacetophenone (DMPA) (0.02 g, 0.10 mmol, 0.3 equiv) were dissolved in 9 mL of degassed CHCl$_3$ and transferred into the reaction tube of an immersion well photoreactor filled with argon. UV irradiation was carried out with a 125-W UV lamp with emission peak at 360 nm for 1 h with cooling. The solvent was removed under vacuum. The polymer was purified by dialysis (12 kDa cut-off) in H$_2$O for 24 h followed by 72 h in EtOH and dried under high vacuum to obtain polymer 10 as a viscous product.

Yield 0.44 g (28 %). $^1$H NMR (300 MHz, CDCl$_3$, $\delta$): 1.13 (m, 8H), 3.38 (s, 3H), 3.65 (s, 64H) ppm; $^{31}$P NMR (121 MHz, CDCl$_3$, $\delta$): −7.61 ppm; SEC: $M_n = 23,218$ g mol$^{-1}$, $M_w = 27,360$ g mol$^{-1}$, $M_w/M_n = 1.18$. Polymer 11 was prepared in the same manner, with Jeffamine M-2070.

RESULTS AND DISCUSSION

Polymer Synthesis

The macromolecular precursor, polydichlorophosphazene, was prepared via the cationic living polymerization of trichlorophosphoranimine Cl$_3$PNSiMe$_3$. Using this method, a series of polymers could be prepared with chain lengths ranging from $n = 25$ to $n = 100$. Complete conversion of the monomer could be confirmed by $^{31}$P NMR spectroscopy [Fig. 1(a,b)]. The chlorine atoms then undergo facile nucleophilic substitution to give poly(organophosphazenes). In this work (Scheme 1), the polymers were first substituted with small amounts (5%) of the mono-boc protection of 2,2′-(ethylenedioxy)-bis-ethylamine, in order to have some (protected) functionality for subsequent fluorescent labeling of the polymers (not shown here). The remaining majority (95%) of the chlorine atoms were then substituted with hydrophilic, monofunctional Jeffamine (PEO-PPO-NH$_2$) oligomers.

$^{31}$P NMR spectroscopy was used to confirm the absence of P-Cl units, (up to $^{31}$P NMR detection limits) and thus complete substitution of the polyphosphazene backbone [Fig. 1(c)]. The combination of the flexibility of the polyphosphazenes backbone, as well as of the Jeffamine oligomers, means that it is possible to produce molecular brush-type polymers with an extremely high density of side groups, effectively 100% grafting of two side chains per backbone repeat unit, with an effective repeat unit molecular weight of up to 4000 g mol$^{-1}$. Complete substitution is also critical as residual chlorine atoms are known to cause instability of the polyphosphazenes backbone. This highly branched structure, alongside the hydrophilic nature of the Jeffamine groups means that these polymers have extremely high aqueous solubilities, (they are miscible with water in all proportions) and low viscosities.

Molecular Weight Investigations

As expected, size exclusion chromatography (SEC) investigations confirmed the increase in molecular weight with increasing monomer to initiator ratio (Table 1). However, this could only be reliably repeated for chain lengths up to $n = 75$. Above and around this chain length it was found that, despite numerous attempts, precise control of the molecular weight could not be attained reproducibly. An upper limit to this polymerization has also been reported by other researchers. Our SEC studies showed the appearance of a shoulder at $n = 75$ and 100 (Fig. 2). This would be consistent with a second, competitive initiation process occurring at low levels of PCl$_5$, or a macrocondensation. Further increases in chain length proved impossible. As would be expected, this observation is also reflected in the molecular weight.

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distributions ($M_w/M_n$), whereby very narrow distributions (1.1–1.3) could only be reproducibly attained for chain lengths of $n = 25$ and 50 (Table 1). Above this, the $M_w/M_n$ tended to be slightly increased, lying generally in the range of 1.3–1.5.

The molecular weight values reported in Table 1 are measured in DMF against conventional polystyrene standards and confirm the relative increase in molecular weight with increased monomer to initiator ratios. However, as would be expected for such highly branched polymers, the apparent absolute molecular weights are grossly underestimated. Multi-detector SEC experiments were also carried out (Supporting Information Table S1), which, although giving values in the correct molecular weight region, only had poor reliability due to the extremely low $dn/dc$ values observed for these polymers.

**Hydrodynamic Volume**

The biodegradability, aqueous solubility, multifunctionality, and tunable size make these polymers excellent candidates for use as polymer therapeutics. With this in mind we sought to investigate the hydrodynamic volume of the polymers in aqueous solutions as this is the property, as oppose to the absolute molecular weight, which is expected to primarily determine the biodistribution of the polymers. Through addition of different sized side-chains the breadth of the polymers could easily be varied (Fig. 3). Such reactions are facilitated by the extremely labile nature of the polyphosphazene precursor. As expected the hydrodynamic volume of the polymers increased significantly upon going from M-1000 to M-2070. The slightly more hydrophobic nature of M-2070 (1:3 PPO/PEO compared to 1:6 for M-1000) could explain slightly lower (83–92%) than expected increase in hydrodynamic volume in aqueous solutions. In comparison, the hydrodynamic volumes measured in DMF showed increases of ~100% upon exchanging M-1000 with M-2070 (see Supporting Information Table S1). A selection of the polymers were also tested in a pH 7.4 phosphate buffer and at various temperatures (up to 37 °C), but this was observed not to make a significant difference to the measured hydrodynamic volumes. Variations in concentration (0.5–2 mg mL$^{-1}$) did also not result in any discernible differences.

**Thiolactone-thiol-yne Addition**

To further tailor the dimensions of the polymers, we looked to increase the brush density from two side-chains per repeat unit to four, through a thiol-yne addition reaction in which two thiol groups can be readily coupled onto a single alkyne group. In order to achieve this, the polydichlorophosphazene precursor was first fully substituted with propargyl alcohol to give the alkyne-functionalized polymer 9 (Scheme 2) with a narrow $M_w/M_n$ according to SEC analysis and a single peak in its $^31$P NMR spectrum (Supporting Information Fig. S4). A recently developed one-pot thiol-ene addition of ring-opened thiolactones was then adapted in an attempt to increase the number of arms per repeat unit from two to four (Scheme 2). In this reaction, thiol groups are generated in situ through the ring-opening addition of a thiolactone with the amine groups of the Jeffamines. Addition of a photoinitiator, is followed by irradiation with UV-light upon which the thiolated Jeffamines couple to the alkyne units on the polymer backbone.

In accordance with literature reports, it was observed that no alkene derivates were formed (within $^1$H NMR detection limits) with the reaction going straight through to the di-substituted product. Thus, the density of Jeffamine side groups per phosphazene repeat unit can be doubled. As with polymers 1–8, the size of the polymers could also be tuned through the addition of Jeffamines with different chain lengths (1000 and 2070). Figure 4 depicts the increase in molecular weight after the thiol-yne addition.
No remaining alkyne groups could be observed in $^1$H NMR and in FTIR analysis (see Supporting Information Figs. S1 and S2, respectively), thus suggesting a complete (up to detection limits) substitution of the alkyne groups on the polyphosphazenes backbone. SEC analysis of polymers 10 and 11 show similar hydrodynamic volumes to those of the graft polyphosphazenes 2 and 6 ($n = 50$, M-1000 and M-2070, respectively), thus the density of the branching appears to have been doubled with only a minimal change in the hydrodynamic volume of the resulting polymers.

**Degradation**

Polymers 1–8 are hydrophilic polyphosphazenes with P-NH-R backbone linkages and thus would be expected to be biodegradable, with hydrolysis followed by ejection of the organic side groups and subsequent degradation of the backbone to phosphates and ammonia. Phosphate determination studies were therefore carried out and indeed after several days in aqueous solutions at 37 °C, phosphates could be detected, suggesting hydrolytic degradation of the polymers (see Supporting Information). Although it is often observed that P-NH-R groups (as in polymers 1–8) degrade faster, a lower hydrolytic stability for polymer 10 with P-O-R linkages was observed. This is possibly due to the adjacent amide groups, which may promote degradation. Indeed, similar observations have been made for amino acid ester, pyrrolidone, and tertiary amine side groups. The increased steric congestion around the repeat units could however also be responsible for this decreased hydrolytic stability.

**CONCLUSIONS**

Living cationic polymerization of trichlorophosphoranimine was used to prepare a series of multiarm polycarbonanophosphazenes with controlled chain lengths, up to $n = 75$, and narrow polydispersities (1.1–1.3). Grafting of hydrophilic Jeffamine side chains onto the polyphosphazene backbone gave a series of densely branched cylindrical molecular brush polymers with up to four arms per repeat unit. By varying the repeat unit molecular weight from 2000 to 8000 (2×1000 to 4×2000 side chains), it was also demonstrated how the breadth and branching density of the polymers could be systematically varied. The controllable and tunable size of these aqueous soluble polymers, alongside their multifunctionality and biodegradability, make these polymers excellent candidates for use as polymer therapeutics. Indeed these polymers are currently undergoing in vitro and in vivo investigations, the results of which will be reported elsewhere in the near future.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.
Polymerization progress followed by $^{31}$P NMR spectroscopy. (a) Monomer Cl$_3$PNMe$_3$; (b) polydichlorophosphazene; (c) polymer 1, substituted with Jeffamine M-1000.
FIGURE 2.
Sample SEC chromatographs of Polymers 2 and 4, with \( n = 50 \) and \( n = 100 \), respectively. Although excellent control of polymerization is achieved at \( n = 50 \) and below, the shoulder seen for Polymer 4 is observed to various extents at \( n = 75 \) and above.
FIGURE 3.
Dynamic light scattering measurements in H$_2$O showing the increase in hydrodynamic diameter for polymers (a) 1-3 (M-1000 side groups, and backbone $n = 25, 50, 75$) and (b) 5-7 (M-2070, $n = 25, 50, 75$).
FIGURE 4.
SEC analysis of polymers 9, 10, and 11 showing the increase of molecular weight after thiol-yne addition of Jeffamine M-1000 and M-2070 ($n = 50$).
SCHEME 1.
Synthetic route to polymers 1–8, with a random, mixed grafting onto the polyphosphazene backbone. Reagents and conditions: (i) and (ii) Et$_3$N, THF, r.t., 16 h.
SCHEME 2.
Synthesis of polymers 9, 10, and 11. Reagents and conditions: (i) NaH, THF, 16 h, (ii) DMAP, CHCl₃, 16 h, and (iii) DMPA, polymer 9, CHCl₃, hν; 1 h.
### TABLE 1

Size Characterization of Polymers 1–8

| Polymer | \( n^a \) | \( R^b \) | \( M_n^{calc} \) (kg mol\(^{-1}\)) | \( M_n^{SEC} \) (kg mol\(^{-1}\)) | \( M_w/M_n \) | \( d^c \) (nm) |
|---------|--------|--------|------------------|------------------|----------------|----------------|
| 1       | 25     | 1,000  | 49.20            | 10.41            | 1.22           | 5.88 (±0.10)   |
| 2       | 50     | 1,000  | 98.39            | 19.08            | 1.17           | 8.30 (±0.17)   |
| 3       | 75     | 1,000  | 147.59           | 36.22            | 1.48           | 11.06 (±0.18)  |
| 4       | 100    | 1,000  | 196.78           | 30.08            | 1.27           | 10.41 (±0.08)  |
| 5       | 25     | 2,000  | 96.70            | 26.76            | 1.14           | 9.77 (±0.01)   |
| 6       | 50     | 2,000  | 193.39           | 41.44            | 1.25           | 14.22 (±0.07)  |
| 7       | 75     | 2,000  | 290.09           | 76.23            | 1.40           | 19.58 (±0.33)  |
| 8       | 100    | 2,000  | 386.79           | 76.82            | 1.35           | 19.17 (±0.37)  |

\( a \) \( n \) = number of repeat units based on the previous observation that two molecules PCl5 are required per propagating chain.\(^4\)

\( b \) \( R \) = nominal molecular weight of Jeffamine substituent.

\( c \) Calculated molecular weights.

\( d \) Apparent molecular weight as measured by SEC in DMF versus linear polystyrene standards.

\( e \) Hydrodynamic diameter measured by dynamic light scattering in H\(_2\)O.