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Alkyne-X modification of polypeptoids

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ABSTRACT

Poly(*N*-propargyl glycine) (PNPG) can be readily prepared by ring-opening polymerization of *N*-propargyl glycine *N*-carboxyanhydride (NCA) and modified using various addition reactions such as copper catalyzed [3+2] cycloaddition of azide, radical (photo-)addition of thiol, nucleophilic addition of ethylene oxide, and thermal induced cross-linking. It is demonstrated that PNPG can serve as a modular platform to produce a bibliography of novel functional polypeptoid or pseudopeptide materials, including polypeptoid ionic liquids and graft copolymers.

1. Introduction

Having access to well-defined functional polymers, newly referred to as precision polymers, is of great importance for many technical applications but also for basic research. Their synthesis often requires tedious development of new monomeric units and sophisticated polymerization strategies aiming to control molar mass, molar mass distribution, microstructure, architecture, and functionality. Nowadays more flexible and modular polymer platforms are desirable, enabling one to introduce specific functionalities or tailored properties for special applications in reasonable short time scales. In this context, post-polymerization modifications or polymer-analogue reactions (a term going back to Staudinger and Scholz from the early 1930s) [1] have raised much attention; especially since the concept of click chemistry was introduced by Sharpless [2]. Click chemistry includes modular and highly efficient reactions, which have been well established for many decades, like for instance the copper catalyzed azide–alkyne [3+2] cycloaddition, (hetero-) Diels–Alder [4+2] cycloadditions, and thiol–ene/–yne additions [3]. These chemistries allow a mild and efficient incorporation of solubility enhancing groups, functional and targeting moieties (e.g. antibodies, sugars, etc.) to synthetic polymer backbones or biopolymers, which are of particular interest for use in biological applications [4]. Biopolymers, or bio-relevant polymers, include polysaccharides, polypeptides, and *pseudo*peptides like polypeptoids, i.e. poly(*N*-substituted glycine)s [5], or polyoxazolines [6]. Polypeptoids are an emerging class of biocompatible materials [7], which are readily available through either solid-phase synthesis [8] or "living" ring-opening polymerization of *N*-substituted glycine *N*-carboxyanhydrides (NCAs) [9]. However, very few examples have been reported describing the "click" modification of polypeptoid materials, for instance the photo-addition of thiol to poly(*N*-allyl glycine) [10] or copper catalyzed addition of azide to poly(*N*-propargyl glycine) copolymers [11].

Here, we explore the diversity of the alkyne functionality in the chemical modification of poly(*N*-propargyl glycine) by cyclo, radical, and nucleophilic addition

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reactions. All polymer products were characterized by nuclear magnetic resonance (NMR), Fourier transform infrared (FT-IR) spectroscopy, and by size exclusion chromatography (SEC).

2. Experimental section

2.1. Chemicals

All chemicals were purchased from commercial sources and used as received (Sigma–Aldrich, ACROS, or Alfa Aesar); methyl 3-bromepropionate (97%), methyl 3-mercaptopropionate (98%), bromoethane (99+%), phosphazene base *t*Bu-P_4 (0.8 M solution in hexane), ethylene oxide (99.8%). Anhydrous dichloromethane (DCM), dimethyl sulfoxide (DMSO), and *N*-methyl-2-pyrrolidone (NMP) were ordered in septum-sealed bottles under dry argon atmosphere over molecular sieves. Acetic anhydride (Ac_2O) and benzylamine ($BnNH_2$) were distilled from calcium hydride and stored under the same conditions. Tetrahydrofuran (THF) was distilled from sodium prior to use.

The *N*-propargyl glycine *N*-carboxyanhydride (NCA) monomer was synthesized as described elsewhere [9c,11a] and isolated in ~70% yield after sublimation (~0.015 mbar, 55 °C, 30 h). ^{1}H NMR (400 MHz, DMSO-d_6): δ/ppm = 4.27 (s, 2H, C(O)CH_2N), 4.17 (d, 2H, NCH_2), 3.44 (t, 1H, CH). GC–MS: R_t = 6.9 min; *m/z* 139.0.

Methyl 3-azidopropionate was synthesized according to a procedure described elsewhere [12]. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 3.67 (s, 3H, OCH_3), 3.52 (t, 2H, CH_2C(O)), 2.53 (t, 2H, N_3CH_2). GC–MS: R_t = 4.8 min; *m/z* 129.0. Yield: ~42%, slightly yellow viscous liquid.

2.2. Polymer synthesis

Poly(*N*-propargyl glycine), PNPG [9c]. Freshly prepared NCA (4.69 g, 33.73 mmol) was transferred into the reactor flask under dry conditions and dissolved in ~47 ml of dry DMSO (to give a ~10 wt% monomer solution). Then, 0.48 ml of a 1 M solution of benzylamine in NMP was injected (0.48 mmol, $[NCA]_0/[BnNH_2]_0$ = 70) and the reaction was kept under positive argon pressure for 40 min. The mixture was stirred for 13 d at room temperature, during which frequent degassing was applied to release the evolved carbon dioxide. The polymerization was terminated with acetic anhydride (3 ml, 27.2 mmol). After removal of volatiles under reduced pressure, the crude product was re-dissolved in THF and dialyzed (MWCO 3500 Da, regenerated cellulose) against THF. Solution from the bags were collected and concentrated down to a yellowish powder (gravimetric yield: 3.36 g, 71%). ^{1}H NMR (400 MHz, CD_3CN,): δ/ppm = 7.40–7.24 (m, 5H, benzyl), 4.73–3.90 (br, ~292H, C(O)CH_2N, NCH_2), 2.85–2.38 (br, ~60H, CH), 2.15–2.10 (s, ~2H, acetyl). ^{13}C NMR (100 MHz, TFA-*d*): δ/ppm = 172.3 (C(O)N), 130.3 (benzyl), 76.6, 75.9 (C≡C), 50.3 (C(O)CH_2N), 40.4, 38.9 (CH_2). FT-IR: $\tilde{\nu}/cm^{-1}$ = 3260 (CH, CH_2), 2128 (C≡C), 1647 (C=O, Amide I). $\overline{M}_n^{NMR} = 292/4 \times 95\ g\ mol^{-1} + M_{benzyl} + M_{acetyl} = 7090\ g\ mol^{-1}$ (number-average degree of polymerization, *n* = 73). SEC (NMP, PMMA calibration): $\overline{M}_n^{app} = 3900\ g\ mol^{-1}$, $\overline{M}_w^{app} = 5120\ g\ mol^{-1}$, $(\overline{M}_w/\overline{M}_n)^{app} = 1.3$.

2.3. Polymer modifications

1a. To a solution of $PNPG_{73}$ (99.5 mg, 1.02 mmol C≡C) and methyl 3-azidopropionate (271 mg, 2.1 mmol) in 25 ml of THF was added an aqueous solution (deionized water, 6.758 g) of copper sulfate (12.6 mg, 0.078 mmol) and sodium ascorbate (46.1 mg, 0.23 mmol) (strong orange discoloration). The reaction mixture was stirred at 66 °C for 12 h (to give a clear yellow solution and an orange precipitate) and then evaporated to dryness. The precipitate was re-dispersed in THF, filtered and washed with acetone to yield a greyish powder. ^{1}H-NMR (400 MHz, TFA-*d*): δ/ppm = 8.64–8.24 (br, ~72H, CH triazole), 7.29–7.03 (m, 5H, benzyl), 5.25–4.33 (br, ~468H, triazole-CH_2N, C(O)CH_2N, C(O)CH_2CH_2), 3.84–3.54 (br, ~250H, OCH_3), 3.26–3.00 (br, ~154H, C(O)CH_2). ^{13}C NMR (100 MHz, TFA-*d*): δ/ppm = 174.9 (C(O)O, C(O)N), 130.6, 123.4 (triazole), 68.0 (NCH_2-triazole), 54.2 (C(O)CH_2N), 50.8 (OCH_3), 44.1, 34.2 (C(O)CH_2CH_2). FT-IR: $\tilde{\nu}/cm^{-1}$ = 3123, 3075, 3006, 2958, 1726, 1655, 1637, 1173, 1052, 1134, 1048, 943, 786.

1b. A dispersion of **1a** (38 mg, 0.17 mmol triazole) in dried acetonitrile (~1.7 ml) and equal volumetric amounts of bromoethane (1.7 ml, 23.35 mmol) was refluxed under argon for 7 d, following a modified procedure from Liebscher et al. [13]. After evaporation of volatiles, the final product was isolated as a brown waxy material. ^{1}H NMR (400 MHz, TFA-*d*): δ/ppm = 9.14–8.28 (br, ~40H, CH triazolium), 7.27–7.06 (br, 0.1H, benzyl), 5.58–4.03 (br, ~512H triazolium-CH_2N), 4.55 (br, ~502H, NC(O)CH_2N, C(O)CH_2 CH_2), 4.00–3.47 (br, ~250H, OCH_3), 3.46–2.91 (br, ~131H, C(O)CH_2), 1.94–1.02 (br, ~173H, NCH_2CH_3). ^{13}C NMR (100 MHz, TFA-*d*): δ/ppm = 175.0 (C(O)O, C(O)N), 141.6, 131.7 (triazolium), 54.7 (CH_2N), 51.3 (OCH_3), 49.4 (CH_2CH_3), 34.4 (C(O)CH_2), 13.9 (CH_2CH_3).

2. A solution of PNPG (95 mg, 0.97 mmol C≡C), methyl 3-mercaptopropionate (0.21 ml, 1.90 mmol) and benzophenone (15.1 mg, 0.082 mmol) in 20 ml of THF was purged with argon for 25 min and subsequently irradiated with UV light (mercury medium pressure lamp, Heraeus TQ150) for 18 h. The crude product was precipitated in water and dialyzed against acetone to yield a yellow, viscous material. ^{1}H-NMR (400 MHz, DMSO-d_6): δ/ppm = 7.38–7.18 (br, ~5H, benzyl), 5.32 (br, very weak, =CH), 4.77–3.89 (br, ~177H, C(O)CH_2N), 3.63–3.55 (br, ~507H, CH_3), 3.19–2.97 (br, ~112H, CH_2CHS, NCH_2), 2.91–2.52 (br, ~916H NCH_2, CH_2S). ^{13}C NMR (100 MHz, DMSO-d_6,): δ/ppm = 171.9 (C(O)O, C(O)N), 66.4 (C(O)NCH_2, NCH_2), 51.4 (OCH_3), 34.2 (SCH_2, C(O)CH_2), 27.3 (C(O)CH_2 CH_2). FT-IR: $\tilde{\nu}/cm^{-1}$ = 2952, 1728, 1665, 1169, 1014, 977, 822. SEC (NMP, PMMA calibration): $\overline{M}_n^{app} = 8130\ g\ mol^{-1}$, $\overline{M}_w^{app} = 10,430\ g\ mol^{-1}$, $(\overline{M}_w/\overline{M}_n)^{app} = 1.3$.

3. To a solution of PNPG (301.01 mg, 3.10 mmol C≡C) in ~47 ml of THF was added 1.01 ml of a 8.3 mM solution of *t*Bu-P_4 in hexane/THF. After stirring for 30 min, ethylene oxide (EO) was added by cryo-condensation, and the mixture was stirred at ambient temperature for 24 h. Residual EO and THF were evaporated, the crude product was re-dissolved in methanol and treated with ion exchange resin

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