Preparation and Properties of a Hydrolytically Stable Cyclooctyne-Containing Polymer

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Kelvin Li Stuart A. McNelles Alex Adronov^{*}

Department of Chemistry, McMaster University, 1280 Main Street West, Hamilton, Ontario, L&S 4M1, Canada adronov@mcmaster.ca

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Abstract A poly[(phenylene vinylene)-co-dibenzocyclooctyne] polymer prepared by Wittig polymerization chemistry between dibenzocyclooctyne bisaldehyde [DIBO-(CHO)₂] and bis(triethyleneglycol)phenyl-bis(tributylphosphonium) dibromide is reported. The resulting polymer exhibits moderate molecular weight (M_n : 10.5 kDa, M_w : 21.3 kDa, Đ: 2.02) and is fluorescent. It could be readily functionalized by strain-promoted alkyne-azide cycloadditon with different azides, and fluorescence of the polymer was preserved after functionalization. Grafting azide-terminated 5 kDa poly(ethylene glycol) monomethyl ether chains drastically affected the solubility of the polymer. Cross-linking the polymer with poly(ethylene glycol) that was terminated at both ends with azide groups gave access to a fluorescent organogel that could be dried and reswollen with water to form a hydrogel.

Key words Wittig reaction, cycloaddition, cyclooctyne, conjugated polymer, polymer functionalization, cross-linking

The structural diversity of conjugated polymers enables the preparation of materials with interesting and useful optoelectronic properties. Since the conductivity of polyacetylene was discovered,^{1,2} many different conjugated polymer backbones have been prepared and investigated. These include polyarylenevinylene,³ polyfluorene,^{4,5} polythiophene,^{6,7} polycarbazole,⁸ and a number of others.⁹ It is well documented that variation of the monomer structure allows modification of the polymer properties, such as solubility and processability,10,11 conductivity,12 HOMO-LUMO levels,13 band gaps,13,14 quantum yields,15 as well as absorption and emission maxima.^{16,17} This has led to numerous applications of conjugated polymers, which include lightemitting diodes,¹⁸⁻²² field effect transistors,^{23,24} photovoltaics,^{25,26} printed electronics,²⁷ batteries,^{28,29} supercapacitors,³⁰ and sensors.³¹ Although modification of monomers prior to polymerization is an effective strategy to tune polymer properties, this approach can be problematic if the modified monomer differs in its reactivity toward polymerization. In cases where length of the polymer is critical to the application, de novo polymerization of structurally different monomers can cause difficulties in attaining constant molecular weight. In these cases, post-polymerization modification of the polymer is an ideal alternative.³² Such modification allows for the systematic preparation of distinct polymer structures with a uniform degree of polymerization (DP). However, efficient chemistry must be used if quantitative conversion of each repeat unit is required. Although this approach has been demonstrated for side-chain modification of conjugated polymers,³³ the ability to quantitatively modify the backbone is much less common.³⁴

Recently, we reported the preparation of a dibenzocyclooctyne- (DIBO) containing conjugated Schiff-base polymer [poly(DIBO), Scheme 1],³⁵ which undergoes rapid and efficient strain-promoted azide-alkyne cycloaddition (SPAAC). We have shown that this polymer can be used to easily prepare large graft copolymers, self-healing organogels,³⁶ and libraries of different polymer structures that are useful for the investigation of polymer interactions with single-walled carbon nanotubes (SWNTs).³⁷ The strained cyclooctyne repeat units along the polymer backbone were found to quantitatively react with a variety of azides under mild conditions, resulting in a series of structurally different polymers, but all having identical DP. Unfortunately, imine linkages are hydrolytically unstable, which limits the potential applications for this polymer scaffold. To circumvent this limitation, we sought alternative linkage chemistry, which required modification of the polymerization method. It should be noted that, although the cyclooctynecontaining polymer exhibits alternating single and double (or triple) bonds along its backbone, the strained alkynes prevent optimal overlap of the p orbitals between the cyclooctyne unit and the rest of the π system. Thus, these polymers do not exhibit the extended π conjugation of more traditional conjugated polymers.

Conjugated polymers are typically prepared by stepgrowth polymerization utilizing transition-metal- (i.e. Pd, Ni, Cu) catalyzed cross-coupling reactions.³⁸⁻⁴⁰ However. transition-metal catalysts form metallocyclopropenes with strained cyclooctynes,³⁵ instead of catalyzing the desired coupling reactions to form productive bonds. Alternative metal-free polymerization methods include Wittig chemistry, Horner-Wadsworth-Emmons chemistry, and Knoevenagel condensation.^{9,41-43} Recent developments in Wittig chemistry allow for mild conditions to be used,⁴⁴⁻⁴⁶ making it a powerful carbon-carbon bond forming reaction. In contrast to canonical reaction conditions involving triphenvlphosphoranylides, use of trialkylphosphoranylides has been shown to result in higher yields, stereocontrol, and ease of purification because of the solubility of short trialkylphosphine oxide by-products in polar solvents such as water and alcohols.^{44–46} The efficacy afforded by trialkylphosphoranylides has been utilized to prepare high molecular weight conjugated polymers in the past.^{47,48} Here, we show that these modern Wittig reaction conditions can be used to produce high molecular weight conjugated polymers that contain the DIBO repeat unit.



Scheme 1 The chemical structure of polyimine poly(DIBO) and its triazole derivative upon click coupling by strain-promoted azide-alkyne cycloaddition (SPAAC)

Our synthetic approach toward a suitable DIBO monomer substitute started with the diiodo intermediate **1** (Scheme 2, a), prepared according to literature procedures from the commercially available dibenzosuberone.³⁵ In situ formation of the enol triflate from **1**, and subsequent elimination afforded **2**. A modified Bouveault aldehyde synthesis converted **2** into the dialdehyde monomer **3**, which allows access to any of the metal-free polymerization reactions mentioned above. Since we chose to investigate Wittig chemistry, we next prepared the phosphonium salt comonomer **5** by quaternization of tributylphosphine with dibenzyl bromide **4**⁴⁹ at 75 °C (Scheme 2, b).

Monomers 3 and 5 were polymerized by first deprotonating **5** with $LiOH \cdot H_2O$ to form the trialkylphosphoranylide, followed by addition of dialdehyde **3** and heating at reflux overnight to afford the product polymer **P0** (Scheme 3).⁵⁰ The polymer was initially characterized using ¹H NMR and FT-IR spectroscopy, as well as gel permeation chromatography (GPC). The ¹H NMR spectrum for this polymer exhibits the expected aromatic signals from the backbone, aliphatic signals from the oligo(ethylene glycol) side chains, and a set of vinvl proton signals characteristic of the alkenvl linkages between repeat units (Figure 1). On the basis of the NMR and FT-IR data, it can be concluded that the stereochemistry of the double bonds is a combination of *cis* (proton signals appearing at 6.6-6.8 ppm) and trans (proton signals at ~7.2 ppm, overlapping with aromatic protons). Although the trans linkages cannot be easily distinguished in the NMR spectrum, the FT-IR spectrum clearly shows a signal at 955 cm⁻¹, which is consistent with an out-of-plane bending mode for the trans stereochemistry (Figure S2). In addition, the protons corresponding to the ethylene bridge of the cyclooctyne repeat unit were observed at 2.42 and 3.3 ppm, though the latter could not be resolved as it overlaps with the protons of the oligo(ethylene glycol) side chains. Endgroup analysis of the aldehyde (proton signal at 9.99 ppm), and the methyl group of the tributylphopshonium (proton signal at 0.94 ppm) affords a number-average polymer molecular weight of 22.8 kDa (end-group NMR signals are magnified in the Supporting Information, Figure S13). However, GPC indicated a lower molecular weight (M_n: 10.5 kDa, M_w: 21.3 kDa, Đ: 2.02) for the conjugated polymer. The



Scheme 2 Synthesis of the 2,7-dialdehydedibenzocyclooctyne [DIBO-(CHO)₂] monomer 3 (a), and the bis(tributylphosphonium salt)benzene dibromide co-monomer 5 (b)

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Scheme 3 Synthesis of the strained cyclooctyne-containing polymer P0 from 3 and 5, and its click functionalization to produce P1 and P2

disparity between the observed molecular weights may be attributed to the mixture of *cis* and *trans* linkages within the backbone, which results in a significantly kinked, compact structure whose molecular weight is underestimated by GPC. Further characterization was carried out by absorption and fluorescence spectroscopy. The absorption spectrum for **P0** is shown in Figure 2, a and exhibits an absorption maximum at 392 nm ($\varepsilon = 14,045 \text{ M}^{-1} \text{ cm}^{-1}$). Interestingly, this polymer is fluorescence spectrum is shown

in Figure 2, b (λ_{ex} = 392 nm; λ_{em} = 447, 474 nm). Quantum yield of fluorescence measurements were performed relative to a quinine sulfate standard, and furnished a value of 14%.

Having prepared **P0**, we set out to investigate its postpolymerization functionalization chemistry. Two different azides were investigated as reaction partners for **P0**, including octyl azide and a 5 kDa poly(ethylene glycol) mono methyl ether that had been end-functionalized with an azide (N_3 -mPEG_{5k}) by mesylation and subsequent substitu-



Figure 1 ¹H NMR in CD₂Cl₂ of **P0** and **P1**. The complete disappearance of the chemical environments for the ethylene bridge protons of **P0** indicates quantitative functionalization of the strained alkyne. The inset highlights the ethylene bridge proton signals of interest.

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tion with sodium azide.⁵¹ To carry out the SPAAC functionalization with the octyl chain, the polymer was added to a 50 mM solution of octyl azide in THF (1.5 equiv per alkyne) and the mixture was stirred for 30 minutes at room temperature (Scheme 3). The solvent was then evaporated, and the residue was triturated in ether to purify **P1**,⁵² which was isolated as a yellow-brown solid. To confirm that guantitative SPAAC functionalization occurs at each cyclooctyne of the polymer, we followed the distinct ¹H NMR signals of the ethylene bridging protons, which undergo a shift from 2.46 ppm to 2.92 and 3.13 ppm (Figure 1, inset). Similarly, P0 was allowed to react overnight at room temperature with N₃-mPEG_{5k}. The longer reaction time was required to quantitatively functionalize P0 with the macromolecular side chain. Again, ¹H NMR spectroscopy provided evidence of complete conversion in the form of a clean shift of the ethylene bridge protons (Figure S15). As expected, the graft copolymer product, P2,53 exhibits significantly increased hydrophilicity, becoming highly soluble in both polar or-

ganic solvents, such as methanol and ethanol, as well as in aqueous solution. This contrasts with the solubility of **PO** and **P1**, both of which dissolve in relatively nonpolar solvents such as tetrahydrofuran, chloroform, toluene, and *N*,*N*-dimethylformamide, and are insoluble in polar/aqueous solvents. Figure 3, a depicts two vials containing a biphasic mixture of 1:1 hexanes/toluene, and water, along with a small amount of either the **PO** starting material (left), or the **P2** click product (right). It can clearly be seen that the reaction with N₃-mPEG_{5k} resulted in a dramatic change in the polymer's solubility, from organic to aqueous solvents. Fluorescence from the polymer before and after the click reaction could be observed upon irradiation with a handheld UV lamp at 365 nm, as depicted in Figure 3, b.



Figure 3 Photos of biphasic mixtures of 1:1 hexanes/toluene and water containing **P0** (left) and **P2** (right) dissolved in the organic and aqueous layers, respectively. The vials were photographed under ambient light (a) and upon irradiation with a handheld UV lamp at 365 nm to show polymer fluorescence (b).

The stability of the alkene bridging polymer was investigated by adding a drop of 6 M HCl to a solution of **PO** in THF. No physical change in the polymer solution was observed upon addition of acid. GPC showed no significant change in the molecular weight of the polymer upon addition of the acid, even after allowing the mixture to stand overnight (Figure S3). In comparison, the corresponding polyimine hydrolyzes within only a few minutes, as observed in our previous studies.³⁷ The optical properties of **P0** after click coupling in THF were also studied. Upon introduction of the octyl chain in **P1**, the UV-vis absorption spectrum exhibits no significant changes, indicating that the SPAAC coupling did not lead to any electronic modification to the polymer backbone (Figure S5). Likewise, the fluorescence spectrum before and after click coupling does not exhibit any appreciable changes (Figure S6), and the quantum yield of fluorescence for P1 in THF was measured to be 13%, which is almost identical to what was measured for PO. However, dissolving P2 (Figure 3, b) in water results in a bathochromic shift, with the emission spectrum exhibiting a maximum at 486 nm (Figure S7).

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As a final set of experiments, we chose to crosslink PO by the SPAAC reaction with a bifunctional PEG-based crosslinker. The crosslinked gels of PO are also of interest, as gels composed of fluorescent π -conjugated building blocks have attracted recent attention.^{54,55} Previously, we prepared an organogel from the corresponding polyimine [poly(DIBO), Scheme 1], but the addition of a poly(ethylene glycol) crosslinker, and the accompanying water retained by this hydrophilic cross-linker resulted in the gradual loss of rigidity of the gel over the course of several hours due to hydrolysis.³⁶ Here, we cross-linked **PO** with a 10 kDa poly(ethylene glycol) terminated at both ends with azide groups $[PEG_{10k}]$ $(N_3)_2$], allowing it to gel in an organic solvent. Cross-linking was performed by mixing **PO** and PEG_{10k} -(N₃)₂ in a 1:1 molar ratio of the alkyne repeat unit relative to the azide end group of PEG_{10k} -(N₃)₂ in THF at a concentration of 0.05 M with respect to the functional groups (Scheme 4). Gelation was observed upon standing for 15 minutes in a mold (see Supporting Information). The resulting yellow-brown gel held its shape upon removal from the mold, and exhibits fluorescence upon excitation with 365 nm light (Figure 4). By removing the organic solvent under vacuum, and equilibrating the gel in water, the cross-linked network underwent significant swelling, and increased in volume relative to the organogel. The resulting hydrogel retained its fluorescence upon excitation with 365 nm light, showing promise as a scaffold to prepare a variety of fluorescent gels in either organic or aqueous solvent, under mild conditions.

In conclusion, by switching from the hydrolytically unstable imine bonds to more robust vinylene linkages, we prepared a polymer with strained cyclooctyne moieties whose backbone is stable under acidic and aqueous conditions. Using ¹H NMR spectroscopy, we demonstrate that each cyclooctyne repeat unit undergoes functionalization in the presence of an organic azide. Utilizing this reactivity, we functionalized **P0** to yield a water-soluble graft copolymer, and a fluorescent gel that can be interchanged with either organic or aqueous solvent. In addition, we characterized the optical properties of both the alkyne polymer and the functionalized triazole polymer. The parent polymer and all subsequent functionalized polymers and gels are fluorescent, showing promise as a scaffold to prepare a range of fluorescent materials.



Figure 4 Successive photographs of the gel prepared from P0 and PEG_{10k} -(N₃)₂: (a) As-prepared organogel in THF; (b) excitation of the organogel with 365 nm light; (c) vacuum-dried cross-linked polymer; (d) cross-linked polymer swelled in water to form a hydrogel; (e) excitation of the hydrogel with 365 nm light

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610636.

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(50) Synthesis of PO

A 3 mL microwave vial equipped with a stir bar was charged with **5** (0.500 g, 0.503 mmol), lithium hydroxide monohydrate (0.093 g, 2.213 mmol, 4.4 equiv), and dry THF (1.2 mL). The reaction mixture was stirred at r.t. for 15 min, followed by the addition of **3** (0.131 g, 0.503 mmol, 1 equiv). The reaction vessel was crimped with a cap and stirred overnight at 67 °C. Caution!! Pressure can build up in the microwave vial when heated above the boiling point of the solvent. The molecular weight of the polymer was monitored by GPC. Once the desired molecular weight was achieved, the reaction mixture was acidified with 1 M HCl and dissolved with DCM. Once dissolved, the reaction mixture was precipitated into cold 1:9 DCM/EtOH, and filtered. (Note: Prevention of solvent evaporation is crucial to reproducible formation of product. Significant solvent evaporation typi-

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cally leads to formation of insoluble product. Other experimental conditions were explored, including the addition of 10 equiv of base, and the solvent and base combination of DMF and Cs₂CO₃, both of which resulted in similar polymer formation, as long the solvent did not evaporate.) Yield: 75% (0.248 g, 0.378 mmol of the repeat unit) of a yellow-brown solid. ¹H NMR (600 MHz, CD₂Cl₂): δ = 7.55–7.11 (m, 9 H), 6.80–6.59 (m, 1 H), 4.24–4.13 (m, 3 H), 3.92–3.20 (m, 27 H), 2.39 (m, 2 H) ppm. GPC: M_n: 10.5 kDa, M_w: 21.3 kDa, Đ: 2.02.

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(52) Synthesis of P1

A 20 mL glass vial equipped with a stir bar was charged with the octyl azide (2.9 mg, 0.019 mmol, 1.5 equiv), THF (0.380 mL), and **P0** (8.3 mg, 0.013 mmol, 1 equiv), and the mixture was sonicated briefly until the polymer dissolved. After dissolving the polymer, the mixture was stirred at r.t. for 30 min. THF was evaporated under reduced pressure, and the polymer was triturated with Et_2O (3 × 1 mL, to remove excess azide) and then dried under vacuum. Yield: 99% (10.4 mg, 0.012 mmol) of a yellow-brown solid. ¹H NMR spectrum in the Supporting Information. M_n : 10.0 kDa, M_w : 17.8 kDa, \oplus : 1.79 (GPC).

(53) Synthesis of P2

A 20 mL glass vial equipped with a stir bar was charged with N₃-mPEG_{5k} (23.9 mg, 0.0048 mmol, 1.5 equiv) and THF (0.950 mL), and heated briefly until the azide dissolved. **P0** (2.1 mg, 0.0032 mmol, 1 equiv) was added, and the mixture was sonicated briefly until the polymer dissolved. After dissolving the polymer, the mixture was stirred at r.t. over night. The THF was removed under reduced pressure, and the polymer was triturated with Et₂O (3 × 3 mL, to remove excess azide) and then dried under vacuum. Yield: 99% (18.0 mg, 0.0032 mmol) of a yellow solid. ¹H NMR spectrum in the Supporting Information. M_n: 71.4 kDa, M_w: 107.7 kDa, Đ: 1.51 (GPC).

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