Supramolecular Polymerization of a Ureidopyrimidinone-Based [2]Catenane Prepared via Ring-Closing Metathesis

This manuscript is dedicated to the 75th birthday of Professor Bob Grubbs for his life-long extraordinary achievement in research and education.

Abraham J. P. Teunissen,1,2* José Augusto Berrocal,1,2* Christiaan H. W. A. Corbet,2 E. W. Meijer 1,2

1Institute for Complex Molecular Systems, Eindhoven University of Technology, 5600 MB Eindhoven, P.O. Box 513, Eindhoven, The Netherlands
2Laboratory of Macromolecular and Organic Chemistry, Eindhoven University of Technology, 5600 MB Eindhoven, P.O. Box 513, Eindhoven, The Netherlands

Correspondence to: E. W. Meijer (E-mail: e.w.meijer@tue.nl)

Received 23 April 2017; accepted 6 June 2017; published online 3 July 2017
DOI: 10.1002/pola.28694

KEYWORDS: polycatenane; supramolecular polymer; ureidopyrimidinone; ring-closing-metathesis; mechanical bond.

INTRODUCTION Since its first report in 1993,1 Ru-catalyzed ring-closing metathesis (RCM) has established itself as one of the most reliable and efficient reactions to synthesize (macro)cyclic molecules. Many of the catalysts prepared in the Grubbs laboratory are commercially available and show high tolerance to a number of functional groups, thereby making the reaction widely applicable.2 It is even more remarkable that after many years of improvement in catalyst design and efficiency, the “simple” first generation Grubbs catalyst (G1, Fig. 1) is still a benchmark Ru-complex for RCM and olefin metathesis in general. The immense versatility of G1 in RCM was further highlighted when the first 1,10-phenanthroline-based (Phen, Fig. 1) catenanes3a and knots3b were prepared upon merging the ingenious chemistries of Bob Grubbs and Jean-Pierre Sauvage. Although kinetically controlled RCM (ethylene evolution) is the most frequently applied strategy to prepare these interlocked architectures, selected studies have also exploited the reversible character of the process4 by using internal olefins5a and metal templates.5b

Mechanically interlocked molecules are prime components of molecular machines and have found applications in molecular switches,6 coatings,7 and electronics.8 The RCM-assisted introduction of mechanical bonds in defined molecular systems has expanded the field toward interlocked polymeric systems, such as polycatenanes9 and polyrotaxanes.10 The flexibility of the mechanical bonds in these polymers is expected to give rise to unusual rheological and mechanical properties. Many covalent strategies have been developed to synthesize such interlocked polymers,9,11 including the ring-opening metathesis polymerization (ROMP) of monomeric [2]catenanes featuring one or two double bonds in each ring.12 Polymers consisting of covalent linkages alternated with [2]catenanes,13 and covalent polymers functionalized with [2]catenane side-groups, have been made with average degree of polymerization (DPn) up to approximately 25 repeating units.9,11 However, the challenges associated with creating polymers purely consisting of interlocked rings has limited their length to 5 units for linear structures14 and 7 units for interlocked networks.15 It follows that obtaining high DPn polymers solely composed of interlocked rings remains an exciting synthetic challenge.

We envisaged that a strategy based on a [2]catenane monomer which polymerizes via hydrogen bonding represents an alternative to arrive at polymeric systems featuring mechanical bonds. Recently, the self-complementary quadruple hydrogen bonding ureidopyrimidinone (UPy, Fig. 1) motif has been used to obtain “dynamic” [2]catenanes16a and pH-
actuated [2] daisy chain rotaxanes,\textsuperscript{16b} showing its compatibility with mechanically interlocked architectures. Inspired by these examples, we present the synthesis of a symmetrical Sauvage-type [2]catenane featuring a UPy motif in each ring (Fig. 1). Intermolecular dimerization of the UPy motifs induces the hydrogen-bond-driven supramolecular polymerization of the [2]catenane monomer, thereby creating a linear polymer consisting of both hydrogen bonding and mechanical bonds. Our supramolecular approach eliminates the need for a covalent polymerization of the catenane monomers, which potentially reduces the synthetic efforts. As the rings in the UPy catenane are asymmetric, two stereoisomers can be formed upon catenation, that is, with the phenanthroline moieties oriented \(+90^\circ\) or \(-90^\circ\) with respect to each other.\textsuperscript{15,17a} In the absence of a driving force that favors the formation of either isomer, we expect both to be formed in equal amounts. For clarity, only one of the two stereoisomers is depicted throughout this article.

Before arriving at the successful synthesis of the catenane-based supramolecular polymer, we investigated a number of synthetic routes that for a variety of reasons did not lead to the target structure. We discuss them here in some detail to show some remarkable synthetic findings, including a high selectivity in the RCM. The aim of this article is to present the synthetic strategy and furnish a proof of concept, while future work will focus on a more detailed study of the material properties.

Based on the phenanthroline-Cu(I) and RCM approach, we first devised a synthetic procedure for the synthesis of the UPy-based catenane (Scheme 1). Here, phenanthroline was first functionalized with phenol moieties in a two-step strategy and furnish a proof of concept, while future work will focus on a more detailed study of the material properties.

![UPy functionalized polycatenane](image)

**FIGURE 1** Molecular structure of the first generation Grubbs catalyst G1, a phenanthroline (Phen)-based [2]catenane, a dimer of the self-complementary ureidopyrimidinone UPy, and the envisioned UPy-functionalized catenane. At high concentrations, the UPys are expected to dimerize intermolecularly, resulting in a supramolecular polycatenane. This compound can exist as two stereoisomers, which are expected to be formed in equal amounts. For clarity, only one of the two stereoisomers is depicted throughout this article.

biphenol 3 was then alkylated in a statistical manner with a mixture of 4-bromobut-1-ene and t-Boc-protected bromide 4, resulting in t-Boc-protected compound 5. Subsequently, 5 was deprotected using HCl, and amine 9 was coupled to CDI activated isocytosine 8 to afford the UPy-functionalized phenanthroline 10. Cu(I) complex 11 was then prepared in quantitative yields by stirring 10 and commercially available Cu(CH$_3$CN)$_2$PF$_6$ in 2:1 molar ratio. As last part of the synthesis, we planned to perform the G1-catalyzed RCM of 11 and subsequently remove Cu(I) to yield the desired UPy catenane 1.

To avoid the formation of intermolecular bonds, this reaction was performed at a relatively low concentration of 10 mM. Unfortunately, all our attempts to close the rings of 11 using G1 resulted in insoluble precipitates, very likely cross-linked networks deriving from intermolecular reactions. Similar results were obtained using the second generation Grubbs catalyst, or first or second generation Hoveyda–Grubbs catalysts.

The RCM of 11 was then attempted at a lower concentration (1 mM) to prevent the formation of intermolecular contacts. Interestingly, ring-closure of just one of the phenanthroline-based ligands of 11 was consistently obtained in all cases (both E and Z isomers were formed). As Ru-catalyzed metathesis reactions have been successfully performed on similar catenanes\textsuperscript{15b,12} and UPy motifs,\textsuperscript{20} it is unlikely that deactivation of the catalyt took place. Instead, we hypothesized that the first ring-closure event induced the formation of an unusually stable intramolecular UPy–UPy contact, which preorganizes the unreacted terminal double bonds in an unfavorable manner (see Supporting Information for more information).

All our attempts to disrupt the hypothesized intramolecular UPy–UPy contact by performing the RCM in the presence of methanol, a well-known hydrogen bond disrupting agent, or a large excess of competing unfunctionalized UPys (10 eq.) consistently afforded the closure of only one ring. It is possible that the first RCM allowed the formation of an intramolecular UPy–UPy contact with a relatively high effective molarity. As a result, no intermolecular competitive strategy\textsuperscript{19} could induce the second RCM event to yield 1, which forced us to develop another synthetic approach.

We hypothesized that covalently protecting the UPy moieties with a benzyl group would destabilize the intramolecular UPy–UPy dimerization\textsuperscript{21} and afford full conversion in the RCM. To verify our hypothesis, we synthesized benzyl protected ligand 12, which afforded catenane precursor 13 after Cu(I) complexation (Scheme 2). Gratifyingly, RCM on 13 resulted in almost quantitative closure of both rings. After Cu(I) removal, benzyl protected UPy catenane 14 was obtained as a mixture of EE, EZ, and ZZ isomers. Unfortunately, all our attempts to remove the benzyl protecting groups \textit{via} a number of hydrogenation procedures were unsuccessful, most likely due to coordination of 14 to the catalysts used (see Supporting Information for details on the procedures attempted).

To circumvent the need of using a catalyst, we opted for the UV-labile o-nitrobenzyl protecting group\textsuperscript{21b,22} in the UPys.
Compound 17 was synthesized with a similar route to 14 (Scheme 2). This molecule was irradiated with UV light and purified by column chromatography and preparative GPC. The obtained UPy catenane 1 was characterized with $^1$H-NMR and mass spectrometry. The characteristic low field resonances (10–13 ppm range) observed in the $^1$H-NMR spectrum are indicative of UPy–UPy dimerization, thereby suggesting the formation of a supramolecular polymer (Fig. 2). Consistently, all $^1$H-NMR signals observed for deprotected UPy catenane 1 were broadened compared to the protected UPy catenane 17 (Fig. 2). In addition, the observed changes upon Cu(I) complexation are in good agreement with structurally similar catenanes reported in literature. More specifically, the signal at 6 ppm observed in the presence of Cu(I) results from the Ar–H protons adjacent to the ether bonds when catenated. Further characterization of the solution-phase behavior of metalated and demetalated 17 and 1 was attempted by two-dimensional diffusion-ordered
spectroscopy (2D-DOSY) NMR, but the broadness and signal overlap in the NMR spectrum of (de)metalated 1 did not offer reliable results.

As an alternative, the supramolecular polymerization of 1 was investigated with dynamic light scattering (DLS). Solutions of metalated and demetalated 1 were prepared in CHCl₃ at 1 mM and compared to similar solutions of metalated and demetalated o-nitrobenzyl protected 17. Featureless correlation functions were measured for protected catenane 17, both in the absence and presence of Cu(I), which suggests that these compounds do not self-assemble. This is consistent with the sharp

SCHEME 2 Successful synthesis of UPy catenane 1. UPy-functionalized phenanthroline 10 was protected with benzyl and o-nitrobenzyl ethers.

FIGURE 2 ¹H-NMR spectra of o-nitrobenzyl protected UPy catenane 17 in CDCl₃ and deprotected UPy catenane 1 in CD₂Cl₂. The insets shows the changes in the aromatic region upon the insertion of Cu(I). The signals at 6 ppm observed upon Cu(I) coordination are indicative of catenation and result from the Ar—H protons directly adjacent to the ether bonds connecting the aromatic rings and aliphatic spacers. [Color figure can be viewed at wileyonlinelibrary.com]
In conclusions, we have reported on the synthesis of a Sauvage-type [2]catenane featuring a quadruple hydrogen bonding UPy motif in each ring and have shown that this motif allows supramolecular polymerization of the catenane via UPy–UPy dimerization. The paramount reaction in our approach was the Grubbs catalyzed RCM, which proved excellently suited to create the necessary interlocked structure of the catenane monomer. Our results also show that protection of the UPy motifs is necessary for this reaction to reach completion. Analysis of the unprotected UPy catenane by $^1$H NMR revealed the formation of UPy–UPy dimers and significant broadening of the signals, both in presence and absence of Cu(I). Such broadening is in line with DLS measurements performed on the unprotected metalated UPy catenane, which showed the presence of aggregates with sizes in the 100 nm to 1 μm range in solution. The absence of such aggregates observed for the deprotected demetalated UPy catenane is believed to result from the formation of intramolecular UPy contacts. Such contacts will severely limit the polymerization to very short oligomers, which might therefore not be detected by DLS. Our approach represents an alternative method to form polymers containing mechanically interlocked junctions, and aids the development of functionalized catenanes in general. Future work will focus on the characterization of the supramolecular polymer and its material properties.

ACKNOWLEDGMENTS

The authors would like to thank Ralf Bovee and Dr Xianwen Lou for their help with the mass analysis, Mr Gijs M. ter Huurne is acknowledged for DLS measurements. This work is financed by the Dutch Organization for Scientific Research (Graduation School and TOPPUNT Program) and the Dutch Ministry of Education, Culture and Science (Gravity program 024.001.035).

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