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Clickable Nucleic Acids: Sequence-Controlled Periodic Copolymer/Oligomer Synthesis by Orthogonal Thiol-X Reactions

*Weixian Xi, Sankha Pattanayak, Chen Wang, Benjamin Fairbanks, Tao Gong, Justine Wagner, Christopher J. Kloxin, and Christopher N. Bowman**

Abstract: *Synthetic polymer approaches generally lack the ability to control the primary sequence, with sequence control referred to as the holy grail. Two click chemistry reactions were now combined to form nucleobase-containing sequence-controlled polymers in simple polymerization reactions. Two distinct approaches are used to form these click nucleic acid (CNA) polymers. These approaches employ thiol–ene and thiol-Michael reactions to form homopolymers of a single nucleobase (e.g., poly(A)$_n$) or homopolymers of specific repeating nucleobase sequences (e.g., poly(ATC)$_n$). Furthermore, the incorporation of monofunctional thiol-terminated polymers into the polymerization system enables the preparation of multiblock copolymers in a single reaction vessel; the length of the diblock copolymer can be tuned by the stoichiometric ratio and/or the monomer functionality. These polymers are also used for organogel formation where complementary CNA-based polymers form reversible cross-links.*

DNA is the most capable and powerful biomolecular structure, functional as genetic material and aptamers, hybridizing to complementary strands, and active in transcription and translation. Foremost, DNA conveys genetic information from one generation to the next in living organisms; however, in the materials science realm, its ability for sequence-specific hybridization is often used to facilitate the synthesis of various nanoscale structures and assemblies.[1] For example, particles functionalized with complementary oligonucleotide strands assemble into hierarchical structures simply through hybridization. DNA folding and double-strand formation lead to DNA nanostructures of controlled shape and also to the formation of nanoactuators, nanotweezers, and other nanoscale devices.[2]

All of these enabling functions and applications of DNA are based on the primary nucleobase sequence and its ability to hydrogen-bond and ultimately hybridize in a sequence-specific manner. Similarly, many other polymers formed in nature (e.g., peptides, proteins, polysaccharides) possess the shared characteristic of having specific control of and behavioral dependence on their primary monomer sequence. DNA mimics, such as peptide nucleic acids (PNAs),[3] possess similar functionality, although they are also generally impractical for use as functional materials or in other large-scale applications owing to the difficulties associated with large-scale solid-phase synthesis. In all cases, the sequence specificity in each of these "polymers" results in the storage of information, such as genetic material in DNA, but the primary sequence also dictates the folding of the macromolecules, for example, in polypeptides, into secondary and tertiary structures—all of which makes the material's behavior strongly dependent on the primary sequence of the polymer.

In contrast, for most synthetic polymers, we have essentially no sequence control over their primary structures beyond simple statistical control. Although there have been many exciting efforts focused on achieving sequence control in polymer synthesis,[4] synthetic polymers not produced by solid-phase synthesis generally do not exhibit primary-sequence control, particularly in a manner that would lead to sequence-dependent behavior as observed in nature.[5] In fact, the goal of achieving sequence control in synthetic polymers has been referred to as the holy grail of synthetic polymer science[6] with significant progress made using living polymerization approaches that consider monomer reactivity to gain both dispersity control and good sequence selectivity.[7] These approaches have been successfully employed in making polymers with sequence-ordered blocks or controlling the sequence distribution in the polymer chain. Whereas the development of these synthetic approaches is promising, many still lack both the sequence specificity and functional similarity observed in nature that leads to the unique functions of natural polymers.

Click chemistry has been employed and demonstrated to be a powerful method in both polymer synthesis and materials science.[8] The high conversion and other desirable attributes of click reactions have enabled their widespread implementation in polymer synthesis and modification. Herein, we propose various strategies that utilize thiol-X click chemistry[9] to enable the facile and robust formation of sequence-controlled polymers (Scheme 1), including those functionalized by nucleobases to form mimics of natural oligonucleotides. One particularly versatile thiol-X strategy is the sequential use of a base/nucleophile-catalyzed thiol-Michael addition and a radical-mediated thiol–ene reaction to build up oligomeric sequences.[10] Herein, we developed a robust

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[*] W. Xi, Dr. S. Pattanayak, C. Wang, Dr. B. Fairbanks, Dr. T. Gong, J. Wagner, Prof. Dr. C. N. Bowman
Department of Chemical & Biological Engineering
University of Colorado Boulder
596 UCB, Boulder, Colorado 80309-0596 (USA)
E-mail: Christopher.Bowman@Colorado.edu
Prof. Dr. C. J. Kloxin
Department of Materials Science & Engineering and
Department of Chemical & Biomolecular Engineering
University of Delaware
150 Academy Street, Newark, Delaware 19716 (USA)

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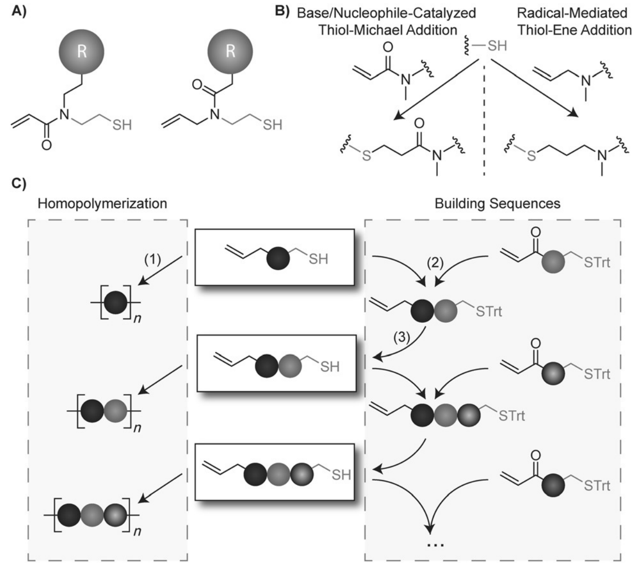


Scheme 1. Thiol-click reaction strategy for sequence-controlled periodic functional oligomers and polymers. A) General monomer structure that enables thiol-based click polymerization, R is a functional group that can be, but not necessarily is limited to a nucleobase (adenine, thymine, uracil, cytosine, or guanine). B) The type of thiol click reaction that takes place—a base/nucleophile-catalyzed thiol-Michael addition or a radical-mediated thiol–ene reaction—is dictated by the chemical nature of the vinyl group (i.e., electron-poor or electron-rich, respectively). C) A functionalized thiol-protected acrylamide monomer is readily coupled to a functionalized thiol–allylamine monomer (1) in a thiol-Michael addition, followed by deprotection of the thiol (2) to restore the thiol and allylamine end groups. In this report, the functional groups, represented by different colors, are nucleobases. At any stage during the sequential thiol-Michael addition reactions, the thiol and allylamine functional groups readily polymerize by radical initiation of the thiol–ene reaction (3). Trt = trityl.

collection of thiol-X approaches for sequence-controlled polymers that are DNA-like oligonucleotides; however, this method is readily extendable to other functional polymer motifs.

These click nucleic acid (CNA) polymers synergistically combine all of the benefits of sequence-specific nucleobases with the robust simplicity of click chemistry to enable their implementation in sequence-specific applications. The two functional groups on the monomer are independently selected to enable the desired reaction from within the thiol-X family of reactions. Specifically, the polymerizable groups employed here include thiols and protected thiols, acrylamides, and allylamines. The unprotected thiols react either with the allylamine in the radical-mediated thiol–ene reaction or with the acrylamide in the base- or nucleophile-catalyzed thiol-Michael reaction.[11] As will be shown later, thoughtful design of the monomer structures enables several simple divergent approaches to yield complex, sequence-specific copolymers in a very small number of reaction steps. In particular, as the allylamine group is unreactive under the reaction conditions of the thiol-Michael addition, the combination of monomers that can undergo thiol–ene and thiol-Michael reactions enables the sequential, self-limiting synthesis of polymerizable oligomers. Furthermore, using the thiol-Michael/thiol–ene combination with just a single thiol deprotection step for the synthesis of the functionalized oligomers enables a wide range of sequence-controlled polymers to be fabricated in a single, robust step from a library of these functionalized oligomers. Thus, from a single polymerization step, the outcome of this approach is such that it is possible to produce sequence-controlled polymers with repeating periodic sequences of nucleobases. Examples of simple methods for the synthesis of repeating sequences of nucleobases are given in Scheme 1.

To demonstrate the capacity of the thiol click reaction for the preparation of DNA-mimicking oligonucleotides, nucleobase-functionalized monomers containing a thiol and an allylamine functional group and monomers containing a thiol and an acrylamide functional group were synthesized from readily available starting materials (Figure 1).

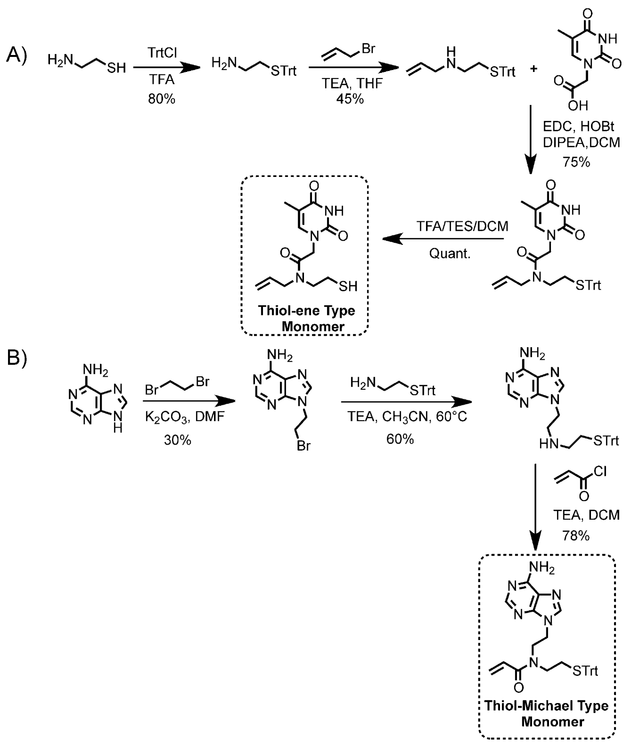


Figure 1. A) Synthetic route for thymine-containing thiol–allylamine monomers. B) Synthetic route for adenine-containing thiol–acrylamide monomers. DIPEA = diisopropylethylamine, EDC = 3-(3-dimethylamino-propyl)-1-ethylcarbodiimide, HOBt = hydroxybenzotriazole, TEA = triethylamine, TES = triethylsilane, TFA = trifluoroacetic acid.

The results of the synthesis of polythymine (polyT) from the thiol–ene radical homopolymerization of the thymine monomer are presented in Figure 2 A. MALDI-TOF analysis reveals that the polyT product has a M_n of 3148 Da, which is equivalent to a degree of polymerization (DP) of 11. The gap between two molecular peaks in the MALDI-TOF spectrum is 283 Da, which is the exact molecular weight of the thymine-functionalized thiol–ene monomer. Furthermore, we monitored the molecular-weight evolution by size-exclusive chromatography (SEC) for irradiation times of 20–480 s. The SEC

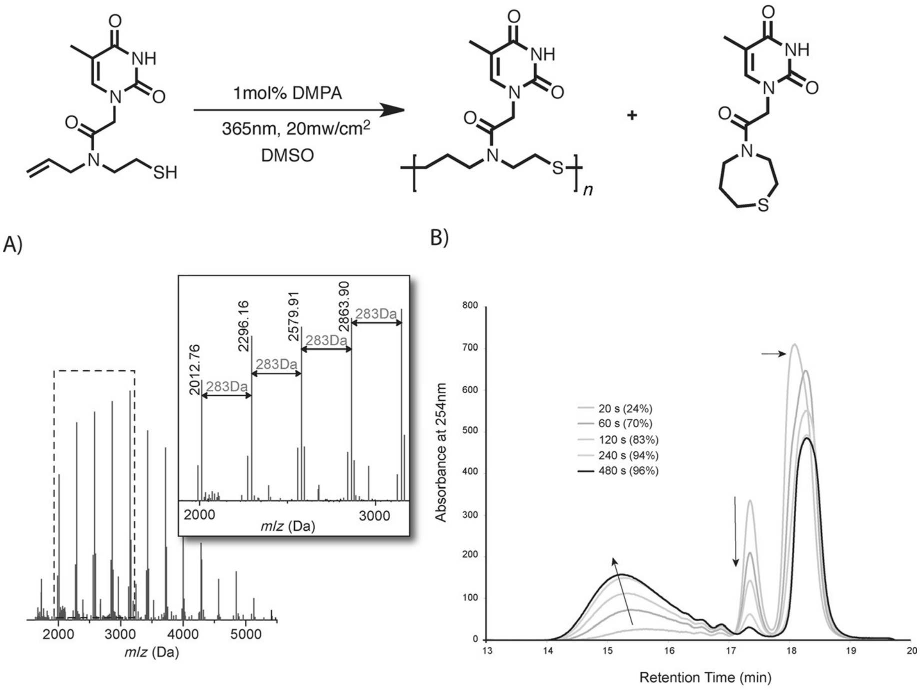


Figure 2. The thymine thiol–allylamine monomer (0.1 mmol) is photopolymerized by irradiation with 365 nm light (20 mW cm^{-2}) for 10 min in the presence of 1 mol% DMPA. A) The MALDI-TOF spectrum reveals $M_n = 3148$ Da; the spacing between the peaks corresponds exactly to the monomer molecular weight. B) Overlaid SEC traces (DMSO at 50 °C) of the thymine thiol–ene polymerization mixture with various irradiation times. The exposure times in seconds as well as the conversion of the allyl group as determined by ^{1}H NMR spectroscopy are given.

traces indicate that higher-molecular-weight polymers were generated with increasing polymerization time. However, the peak in the low M_w region was still present after the polymerization with almost full conversion of the functional groups (Supporting Information, Figure S1). We propose that this unusual peak whose retention time is almost the same as that of the starting monomer arises from the thiol–ene cyclization product of a single monomer. The cyclized product was removed by washing the crude product with methanol and isolated in 58% yield; its structure was confirmed by ^{1}H NMR spectroscopy and ESI mass spectrometry (Table 1, Figures S2 and S3). After removal of the cyclized monomer, ^{1}H NMR spectral analysis of the polyT product indicated that this polymer still has an allyl group at the end, indicative of a linear polymer structure. We also performed thermal analysis of the polyT polymer, which was found to have a glass transition temperature (T_g) of 127 ± 4 °C as determined by DSC (Figure S3).

Table 1: Molecular-weight distributions and product yields for nucleobase-functionalized homopolymers and copolymers/oligomers.

Entry	Polymer	M_n [Da]	M_w [Da]	PDI	Yield[b] [%]
1	polyT	9700	14000	1.42	42
2	poly(T-*alt*-A)	3200	4000	1.20	83
3	poly(TAA)	2100	2400	1.14	85
4	PEG–polyT[a]	10000	14000	1.36	87

[a] Polymerization conditions: PEG-SH/monomer = 1:10. M_n, M_w, and PDI values were determined by SEC using poly(methyl methacrylate) standards (DMF at 50 °C). [b] Polymerization/oligomerization yield. The polymerization yield is reduced primarily by the formation of low-molecular-weight cyclic structures.

Both the cyclic monomer and the intermediate-molecular-weight polymer formed at relatively low conversions are unexpected for a canonical step-growth polymerization. Thus, it is apparent that the presence of both a thiol and a vinyl group in a single monomer with a short distance between them is capable of inducing relatively facile intramolecular chain-transfer and propagation reactions. The intramolecular chain-transfer reaction would tend to extend the chain beyond that expected for a classical step-growth polymerization whereas the intramolecular propagation reaction would be expected to lead to cyclic structures.

After the successful preparation of thymine-containing homopolymers, we developed the strategy further to synthesize functionalized CNAs by incorporation of a thiol-functionalized monomer into the polymerization mixture to generate diblock copolymers. We employed poly(ethylene glycol) (PEG) monothiol ($M_n \approx 2000$) as a model monofunctional thiol, then added the thymine thiol–ene monomer in a stoichiometric ratio of 1:4 or 1:10 (PEG monothiol/thiol–ene monomer; Table 1). Under typical thiol–ene photopolymerization conditions, the diblock polymer PEG–polyT was prepared. SEC trace analysis indicated that changing the stoichiometric ratio of the starting materials influenced the length of the diblock copolymer (Figure 3). With the incorporation of a hydrophilic PEG tail into the hydrophobic polyT, the solubility of the CNA(polyT) in aqueous solution increased (Figure S4). We have thus demonstrated that a simple thiol–ene copolymerization provides a relatively facile method and general approach to functionalize our CNAs with different thiols.

Supramolecular gels are soft materials based on noncovalent interactions, such as hydrogen bonding, host–guest, or electrostatic interactions.[12] They have emerged as a broad class of smart materials as their multiresponsive properties have been widely used in materials science.[7d,13] DNA-based gels, in particular, have been used in drug delivery and cell-free protein production, for example.[14] Nucleobase interactions are often used as a sequence-specific physical crosslink within a polymer gel; this type of gel is responsive to the presence of other sequences, temperature, and various other molecular stimuli.

To demonstrate the capacity of CNA polymers to serve as reversible physical crosslinks, we synthesized a gel structure that utilizes self-complementary pairs of nucleobases [poly(T-

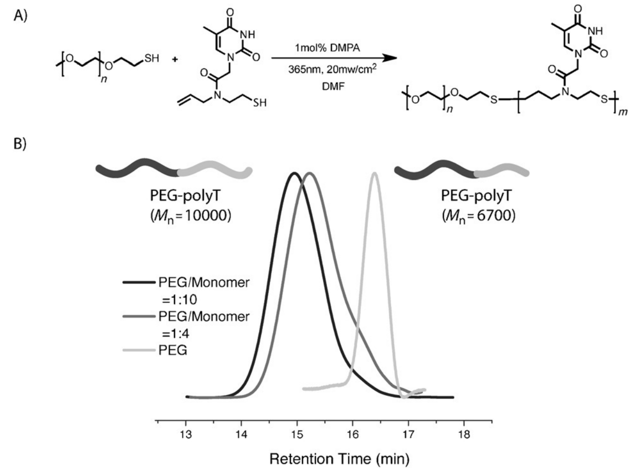


Figure 3. A) Synthesis of the diblock polymer PEG–polyT in a one-pot copolymerization of PEG-SH and the thymine thiol–allyl monomer. B) Overlaid SEC traces (DMSO at 50 °C) of PEG–polyT with different polyT molecular weights and PEG-SH (M_n = 2000). PolyT homopolymers were removed by precipitation in MeOH prior to dialysis.

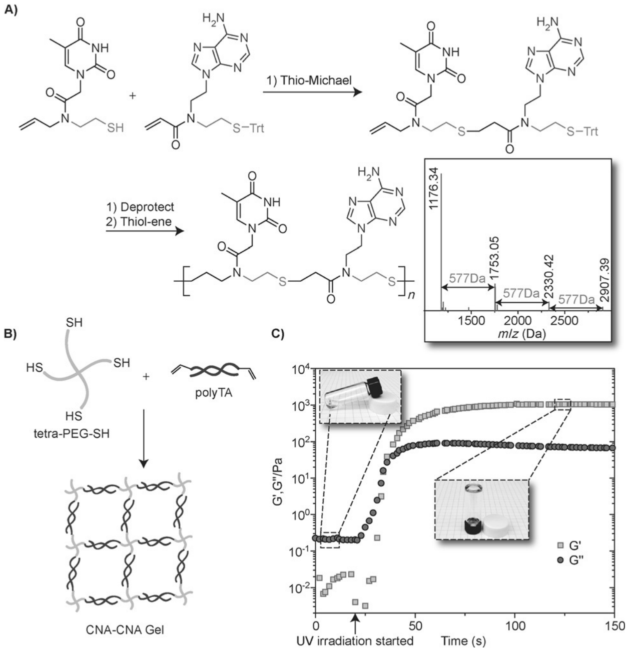
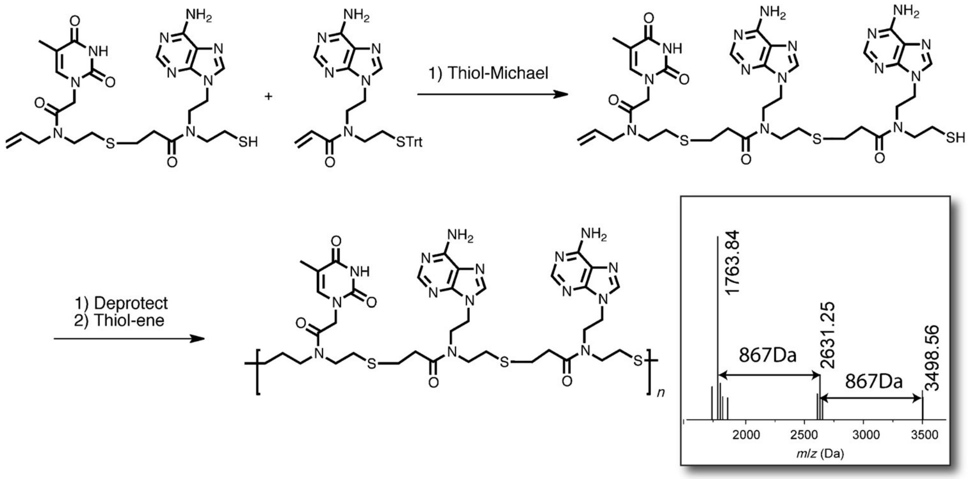


Figure 4. A) Thiol-Michael coupling of thymine and adenine monomers (5 mol% DBU in DCM, 1 h), yielding a thymine–adenine dimer that is photopolymerized using 20 mW cm^{-2} of 365 nm light for 10 min in the presence of 1 mol% DMPA. B) Thiol–ene photocoupling of hybridized poly(T-*alt*-A) with tetrathiol-PEG (20 kDa) leads to the formation of a supramolecular organogel (20 wt% in DMSO). C) Rheological monitoring of the polymerization before irradiation and after irradiation (365 nm, 20 mW cm^{-2}) reveals the formation of an organogel with a modulus of 1 kPa and a crossover point of 20 s of irradiation. All rheological tests were performed at fixed frequency (10 Hz) and strain (500%) at 25 °C.

alt-A); Table 1]. This self-complementary polymer is formed in a single homopolymerization step using a thymine-and adenine-functionalized thiol/allylamine-terminated dimer, which was prepared from the thiol-Michael coupling reaction between the thiol of the thymine and the acrylamide of the adenine monomers, (Figure 4 A). The ^{1}H NMR spectrum of the thymine–adenine dimer, which is soluble in chloroform, indicated hydrogen bonding between the thymine and the adenine (Figure S6). After thiol–allyl polymerization, the cyclized product was also observed, but in a lower relative yield (ca. 17%) owing to the increase in the minimum cycle size compared to polyT. MALDI-TOF analysis indicates a 577 Da spacing, which corresponds to the molecular weight of the TA dimer (Figure 4 A). Although MALDI-TOF accurately determines repeat-unit molecular weights, the molecular-weight averages and distributions determined by this method do not accurately reflect the degree of polymerization because of insufficient ionization in the spectrometer. Furthermore, the T_g of the poly(T-*alt*-A) polymer was found to be 133 ± 6 °C by DSC. Upon mixing of hybridized CNA-(poly(T-*alt*-A)) with tetra-PEG-thiol (20 kD) and photoinitiator in DMSO, the specimen remained in a liquid state. After irradiation, which induced the coupling of CNA(poly-(T-*alt*-A)) to the four-armed PEG core, a CNA-hybridized crosslinked gel was formed as evident from the significant change in viscosity and, ultimately, solidification (Figure 4 B). The organogel formation was monitored using photorheometry (Figure 4 C). From the rheological trace, we determined that gelation occurred after 20 s of UV light irradiation. We also performed a control experiment in which a polyT polymer that is not capable of self-complementary binding was coupled to a PEG core with four tetrathiol arms. Whereas there was a change in the mechanical properties upon irradiation, likely owing to hydrophobic interactions after conjugation, the material did not gel ($G' < G''$), and the elastic modulus was much less than for the CNA(poly(T-*alt*-A)) crosslinked material (Table S1). The organogel was also found to be thermoreversible as heating and cooling cycles resulted in obvious viscosity changes (Figure S5). A strain sweep of the organogel revealed a sharp decrease in the modulus at high strains associated with disruption of the CNA(poly(T-*alt*-A)) crosslinks, elimination of the large strain leads to recovery of the higher modulus associated with reforming of the CNA(poly(T-*alt*-A)) physical crosslinks. (Figure S7). Both reversibility tests and control experiments indicated a non-covalent and sequence-specific interaction that was necessary for organogel formation. For comparison, we also covalently crosslinked an organogel using tetra-PEG-SH and tetra-PEG-maleimide, which exhibited a slightly larger elastic modulus than our CNA(poly(T-*alt*-A)) organogel (ca. 6000 Pa vs. 1000 Pa), likely owing to the reversible nature of the hybridization in the CNA(poly(T-*alt*-A)) gel as compared with the permanent, covalent crosslinks formed in this type of control gel.

As demonstrated by the CNA(poly(T-*alt*-A)) synthesis, our approach to forming periodically repeating sequences is based on using sequential thiol-Michael addition reactions to form monomers of a desired sequence and subsequently employing the thiol–ene reaction in a single polymerization step to form polymers of controlled, periodic sequences. The DNA analogues of these repeating sequences are also ubiquitous in nature. In fact, completion of the human genome project revealed that nearly half of the genome



Scheme 2. Thiol-Michael coupling of the thymine–adenine dimer and adenine monomers (5 mol% DBU in CH$_2$Cl$_2$, 1 h), yielding a thymine–adenine–adenine trimer that is photopolymerized by irradiation with 365 nm light (20 mW cm^{-2}) for 10 min in the presence of 1 mol% DMPA (DMPA = 2,2-dimethoxy-2-phenylacetophenone). Inset: MALDI spectrum of this polymer, showing the 867 Da spacing associated with the TAA trimer.

consists of repetitive sequences, and in many cases, their roles are not yet fully understood.[15] Whereas many of these repeating structures are non-functional, studies have shown that repetitive DNA is essential for genome function, and many of these sequences have critical roles in aging and disease.[16] For example, at least 16 human-inherited neurological diseases are caused by simple trinucleotide repeat expansions (e.g., CAG, CUG) that are known as trinucleotide repeat disorders and affect hundreds of thousands of individuals worldwide.[17] This class of diseases includes Huntington disease (caused by a CAG repeat), myotonic dystrophy type 1 (caused by a CUG repeat), the fragile X syndrome (caused by a CGG repeat), and several types of ataxia. Thus, the robust formation of polymers based on nucleotide-repeating sequences has significant potential in genetic diagnostics and even controlling disease expression as well as in sequence-directed self-assembly. Herein, a CNA monomer consisting of the trimer TAA was synthesized by reacting the TA allylamine–thiol dimer with the adenine-functionalized protected thiol–acrylamide monomer. Following deprotection to yield a TAA trimer with allylamine/thiol function groups, CNA polymer strands with a TAA repeating sequence [CNA(polyTAA)] were formed in a single-step polymerization in similar yield (ca. 17%) as the cyclized side product by the same general strategy used to form CNA(poly(T-*alt*-A)) (see Scheme 2 and Table 1).

In summary, the utilization of click chemistry provides a route to sequence-controlled periodic copolymer/oligomer synthesis that, when combined with functional side groups in general and nucleobases in particular, enables the creation of novel, highly functional materials in a robust, simple, and scalable manner. CNA polymers possessing nucleobase side groups mimic the functional aspects of DNA and can be used for the formation of organogels in a sequence-specific manner. This approach is the first demonstration of nucleobase-functionalized sequence-controlled periodic copolymers/oligomers and polymers synthesized without the use of a solid support. As the nucleobase represents a very small subset of the possible functional side groups, the extension of the click conjugation strategy for a wide range of functional backbones (e.g., amino acid side chains or sugars) can be readily envisioned. Moreover, hybrid materials present a new canvas of molecular design where nature-inspired structures are readily combined with the hope of synergistic properties. Indeed, the simple materials and concepts outlined herein provide a powerful framework from which the click chemistry approach can be used to create new classes of synthetic polymeric materials.

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