Solid-Phase Synthesis of Iterative RAFT Single Unit Monomer Insertion Adducts

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ABSTRACT: In this communication, we disclose the use of a solid-phase methodology to synthesize iterative RAFT single unit monomer insertion (SUMI) adducts. This methodology features a reversible thiocarbonylthio protecting group and radical chain growth of vinyl monomers, with minimal purification required during the synthesis. To achieve this, a RAFT chain transfer agent was immobilized on a common peptide synthesis resin *via* the "R-group" in the first instance. Using an oxygen-tolerant PET-RAFT methodology, we then extended the iterative synthesis of sequence-defined indene-maleimide alternating co-oligomers to 18 units with minimal dispersity, completely unprecedented in SUMI chemistry. Furthermore, as we demonstrate, this solid-phase methodology can be generalized to other maleimide derivatives and other solid-phase resins.

Synthesis of abiological sequence-defined macromolecules and understanding their chemistry are key unresolved challenges in polymer science.[1] Pursuing these challenges can furnish materials with unique properties such as molecular recognition, information encoding, self-assembly, microbicide and fungicide.[2] However, replicating the complexity of biological macromolecules, which have increasingly divergent backbone structures, is difficult with current synthetic methodologies. Such pursuit demands new synthetic methodologies to realize.

Assembling progressively larger macromolecules in a stepwise fashion becomes increasingly untenable. This is because multiple purification steps are needed, which result in diminishing yield and turnover. Immobilizing the relevant material through solid-phase synthesis greatly alleviates these issues, with automated platforms emerging in recent years.[3] For this reason, solid-phase synthesis is a mainstay in the toolkit for synthesizing biological sequence-defined macromolecules such as peptides, nucleotides and glycans.[4]

This general strategy has also been used to synthesize abiological macromolecules with backbones such as those consisting of phosphodiesters/phosphates, esters, amides (non-peptidic), carbamates, triazines and other cycloaddition adducts.[5] There have even been developments in using the benefits of both solution and solid phase synthesis through precipitating anchors.[6] These methodologies generally produce molecules with heteroatom-containing backbones that often made through processes analogous to step-growth polymerization (Scheme 1).

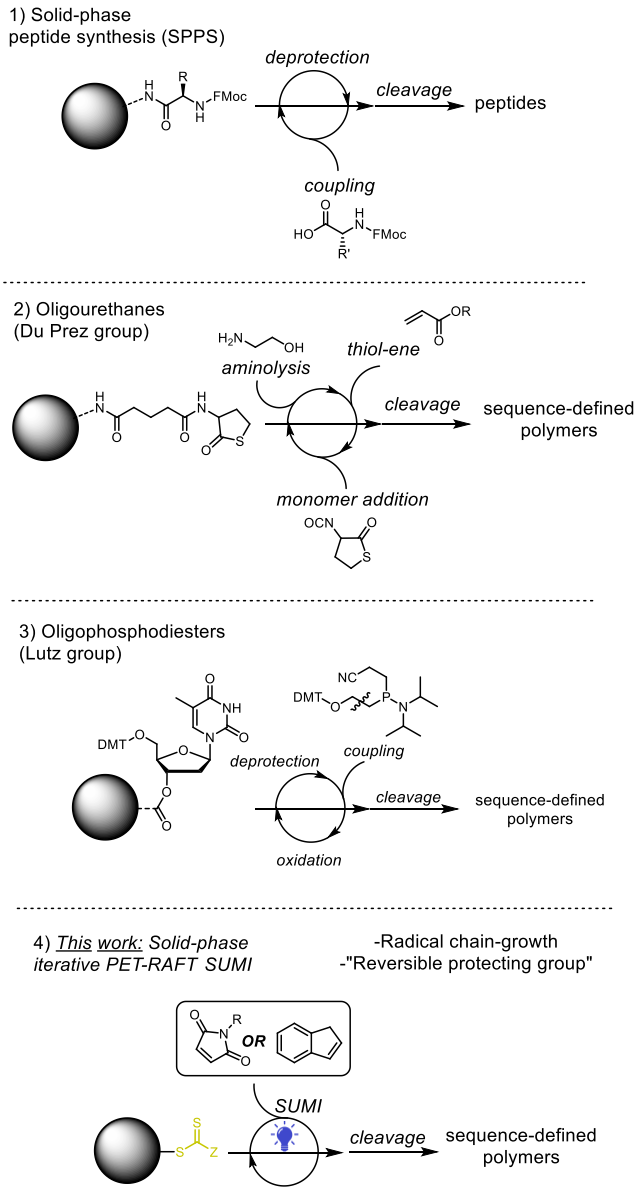
Despite these achievements, there has been almost no developments in using solid-phase synthesis to create sequence-defined macromolecules with all-carbon backbones, such as those found in vinyl-derived polymers.[7] Yet, vinyl-derived macromolecules are arguably among the most commonly studied and manufactured class of synthetic macromolecules.

However, there are well-developed solution-phase methodologies for the synthesis of sequence-defined oligomers derived from vinyl monomers.[8] These methodologies mostly center around analogues of chain-growth polymerization methodologies, particularly reversible deactivation radical polymerization (RDRP), but with single unit monomer insertions (SUMI).[9] SUMI processes were first conceived of a Giese-type additions using either xanthates or alkyl bromides as radical sources.[10] Since these initial studies, similar single-additions have been performed with the more versatile trithiocarbonates.[11] Using chemical transformations that are analogous to RDRP is particularly attractive for single unit insertions, because the end group can then serve as a reversible protecting group on the main chain. This allows facile access to a broad array of functionalized materials with controlled structures and architectures. However, translating these SUMI reactions to iterative processes limits monomer scope to pairs that typically undergo alternating copolymerizations.[12]

Combining SUMI methodology with solid-phase synthesis could enable access to increasingly large and complex macromolecules. Despite significant achievements in surface-initiated RDRP methodologies, there are relatively few studies that have performed these processes on-resin.[13] Moreover, using radical chemistry for iterative polymer assembly, while fully harnessing the advantages of solid-phase synthesis, is unprecedented. To that end, we detail herein a solid-phase iterative photoinduced electron/energy transfer (PET)-RAFT SUMI methodology (Scheme 1). This synthetic methodology can be used to

straightforwardly access existing sequence-defined indene-maleimide macromolecules with fewer purification steps and minimal solvent use (avoiding liquid-phase extraction and chromatography at every iterative step). It also avoids the hypothetical synthetic dead-end of being unable to separate monomer from product, and is easily monitored (*i.e.,* by NMR spectroscopy, see Supplementary Methods). As this process uses photochemistry under ambient conditions, it minimizes end group decomposition, offers the potential for oxygen tolerance, and by-passes the formation of initiator-derived chains in solution.

Scheme 1. Solid-phase synthesis of sequence-defined biological and abiological macromolecules. (1) Solid-phase peptide synthesis. Two illustrative examples sequence-defined abiological macromolecules from previous works that contain heteroatom backbone, (2) oligourethanes and (3) oligophosphodiesters. (4) Iterative PET-RAFT SUMI on solid-phase synthesis resins



The first step towards performing RAFT chemistry on solid-phase resins was to immobilize a chain transfer agent onto it. In the first instance, we chose the (FMoc-protected) Rink amide variant as a resin and 4-cyano-4-[(dodecylsulphanylthiocarbonylthio]pentanoic acid (CDTPA) as a chain transfer agent. Notably, this chain transfer agent has a terminal carboxylic acid that is necessary for attachment to the resin. We were able to apply an analogous deprotection-amidation-capping sequence used in solid-phase peptide synthesis to CDTPA (see Supplementary Methods in Supporting Information for procedures).

To demonstrate that CDTPA was successfully immobilized and to quantify its extent, the cleavage of CDTPA from the loaded resin (in 50% v/v trifluoroacetic acid in dichloromethane) was analyzed through UV-visible spectroscopy of the π,π* transition (300 nm, see Figure 1A). The CDTPA concentration was calibrated against absorbance of the free molecule in solution. A control consisting of an *N*-acetamide functional Rink amide resin yielded no significant change in absorbance at the relevant wavelengths (Figure 1B). NMR analysis (Figure 1C) of the cleavage product also confirmed that CDTPA was covalently linked to the Rink amide resin and largely intact.

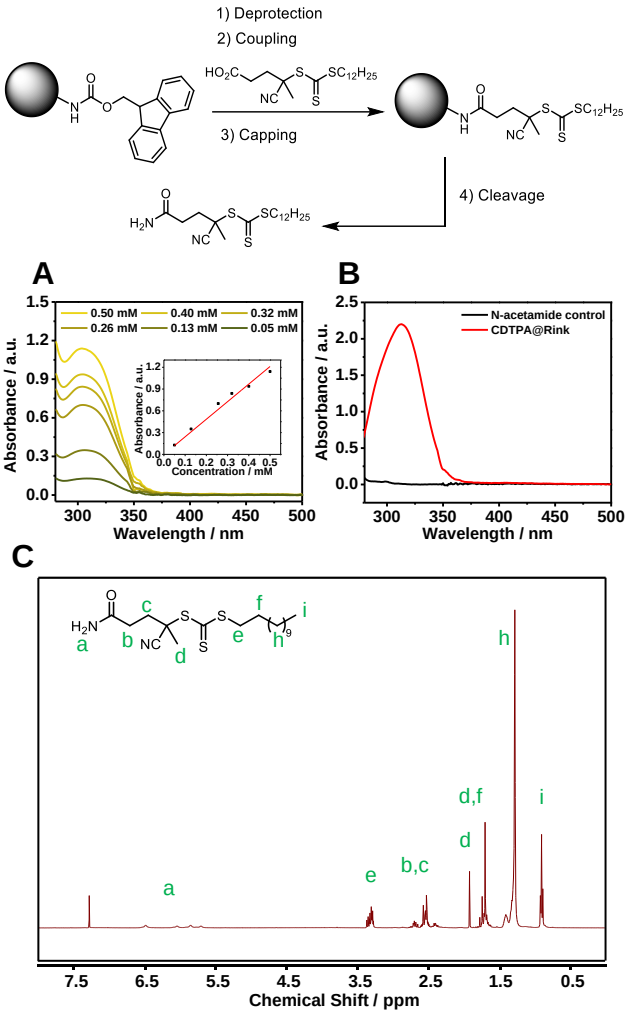


Figure 1. Immobilization of CDTPA on Rink amide resin by methods detailed in Supplementary Materials and Methods of SI. UV-visible spectra (TFA in DCM, 50% v/v) of CDTPA and calibration of concentration to absorbance at 300 nm (y= ax, a= 2.42 ± 0.08, R^2 = 0.99) (A), UV-visible spectra (TFA in DCM, 50% v/v) of the cleavage products from the CDTPA@Rink resin (0.4 mg mL^{-1}) (red) and acetyl Rink amide resin as a

control (black) (B), ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the cleavage product of CDTPA from Rink amide resin (C). *N.B.,* "capping" here refers to the procedure of blocking unreacted amine residues with an acetate group.

We then moved to performing iterative RAFT SUMI reactions. To that end, we opted to use a PET-RAFT SUMI methodology which has been extensively investigated by our group and others, with thermal analogues having been investigated previously too.[8c, 11, 14] In order to translate PET-RAFT processes to solid-phase synthesis, we required the reaction to be run in solvents other than DMSO, due to its inability to swell polystyrene resins.[15] To this end, we applied recent work in which an additional radical scavenger allowed us to perform PET-RAFT SUMI under ZnTPP catalysis, in DMF solvent.[16]

We opted to investigate on-resin sequential PET-RAFT SUMI reactions of indene and *N*-phenylmaleimide (PhMal) monomers on the CDTPA-functionalized Rink amide resin. Previous work in our group has determined the two monomers to be a reasonable pair for iterative PET-RAFT SUMI.[17] This is because losses of yield in iterative SUMI processes, mainly due to neighboring unit effects, seems minimal. However, homopolymerization must be carefully considered, particularly for the SUMI of maleimide derivatives.[18] Furthermore, incomplete addition can be an issue when using indene for SUMI.[17b] Thus, we acknowledge that some impurities and side-reactions could lead to difficulties in isolating a perfectly discrete product. However, an ideal system of monomers, which perfectly combines both activity and selectivity, has yet to be discovered in PET-RAFT SUMI processes.

In any case, we proceeded with the single addition of indene onto our CDTPA-functionalized Rink amide resin with little variation in basic reaction conditions to the analogous solution-phase procedure (see Supplementary Methods solution-phase procedure). NMR analysis of the reaction solution after 14 h of irradiation (identical to the solution-phase methodology) indicated a 36% loss of indene (Table 1 Entry #1), which corresponds to the conversion of monomer at full conversion of the RAFT agent (for procedures, see Supplementary Methods). The NMR spectra of the crude material cleaved from the resin is almost indistinguishable from that of the purified indene-RAFT single adduct synthesized by the analogous solution-phase methodology (see Supplementary Data Figure S2-1). Both approaches also resulted in comparable yields of this adduct.

With this data, we were confident that a PET-RAFT SUMI process could be successfully carried out on-resin. We then analyzed the second and third SUMI steps, first by ^{1}H NMR spectroscopy of the reaction mixture (Figures 2A and 2C) as evidence of monomer conversion (and of consistent RAFT agent stoichiometry), (Table 1 Entry #2-3) and then by nESI-MS of the cleaved product to analyze reaction outcomes. (Figure 2B and 2D, and Supplementary Data Figures S5-1 and S5-2 for isotope distribution) As well as the intended product, observed as both the proton and sodium adduct, there were signs of two side-reactions. *N*-Phenylmaleimide multi-additions were observed by a +173.17 *m/z* deviation from the expected mass peak (Figure 2B). Incomplete indene additions were observed by a -116.16 *m/z* deviation from the expected mass peak. (Figure 2D)

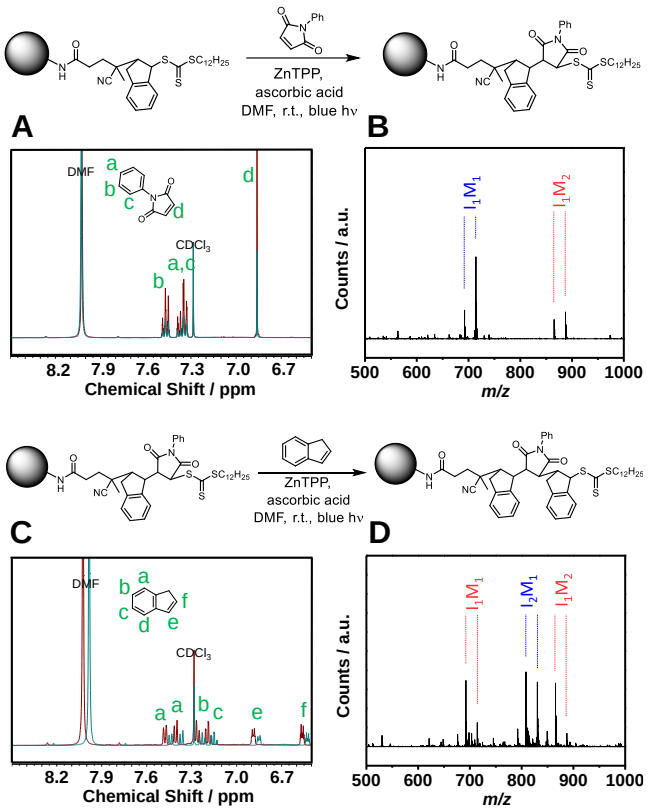
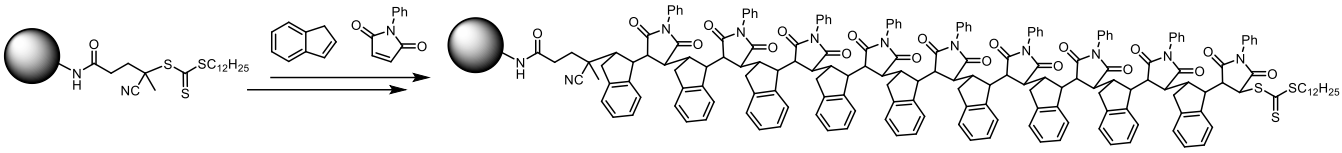


Figure 2. Second and third PET-RAFT SUMI reactions on-resin (in both reactions, *n*(monomer): *n*(CDTPA@Rink) = 2:1) with ^{1}H NMR spectra (400 MHz, $CDCl_3$, δ 8.3-6.6 ppm) (A, C) of the reaction mixtures (red: t = 0 h, cyan: t = 14 h – 61% conversion for (A) and t = 14 h – 49% conversion for (C)), and nESI mass spectra (MeCN) of the products cleaved from resin (B, D). Peaks corresponding to both the H^+ and Na^+ charge states are grouped as the same species. *N.B.,* I – indene, M – PhMal, *e.g.,* 'I_2M_1' means the oligomer with the sequence of indene-indene-PhMal.

We then carried out iterative alternating indene and *N*-phenylmaleimide insertions, analyzing the ^{1}H NMR spectra of the reaction mixture of each step to confirm reaction of the alkene (for procedure, see Supplementary Methods). Separately, we also investigated the kinetics of the first five monomer additions, while understanding the difficulties of accurately capturing the kinetics of the system. Such difficulty is because removing reaction aliquots actively changes the reaction stoichiometry and opens the reaction headspace (See Supplementary Data S3 for more details).

With confidence of the synthetic outcomes of early SUMI steps, we continued with further subsequent additions until the apparent 18-mer. This represents a completely unprecedented chain length achieved in iterative RDRP-SUMI. We analyzed the apparent molecular weight distribution, of multi-adducts made (Table 1, Figure 2).

Table 1. Conversion, molecular weight and yield data from the synthesis of sequence-defined indene-PhMal oligomers on-resin.



Entry	Oligomer	Monomer	[M]:[CDTPA@Rink]	Reaction time (h)	Conv. (%)[a]	$M_{n,\,GPC}$ (g mol^{-1})[b]	Đ	Total yield (%)[c]
#1	1-mer	Ind	3:1	14	36	-	-	91
#2	2-mer	PhMal	2:1	14	61	-	-	-
#3	3-mer	Ind	2:1	24	49	6900 ± 700	1.01	-
#4	4-mer	PhMal	2:1	14	55	-	-	-
#5	5-mer	Ind	2:1	24	54	7100 ± 700	1.01	-
#6	6-mer	PhMal	2:1	14	47	-	-	-
#7	7-mer	Ind	2:1	64	50	7200 ± 700	1.01	-
#8	8-mer	PhMal	2:1	14	67	-	-	-
#9	9-mer	Ind	2:1	64	52	-	-	-
#10	10-mer	PhMal	2:1	14	48	8400 ± 800	1.01	12
#11	11-mer	Ind	2:1	64	47	-	-	-
#12	12-mer	PhMal	2:1	14	61	-	-	-
#13	13-mer	Ind	2:1	64	51	8700 ± 900	1.01	-
#14	14-mer	PhMal	2:1	14	57	-	-	-
#15	15-mer	Ind	2:1	64	47	9000 ± 1600	1.03	-
#16	16-mer	PhMal	2:1	14	61	-	-	-
#17	17-mer	Ind	2:1	64	57	-	-	-
#18	18-mer	PhMal	2:1	14	63	9200 ± 1600	1.03	2
#19	Copolymer	Ind + PhMal	6:6:1[d]	20	>95	8000 ± 4500	1.32	-

[a] Measured by ^{1}H NMR spectroscopy of the reaction mixture.

[b] Error in M_n presented as one standard deviation using the formula $Đ = 1 + (\sigma/M_n)^2$.

[c] Measured by mass recovered relative to mass expected from resin loading and alkene conversion with each step.

[d] Since this is a copolymerization, "[M]" refers to two monomer components.

The apparent molecular weight of the immobilized material grew with each iterative PET-RAFT SUMI reaction. Along with this, narrow and symmetric peaks were observed when compared with a control experiment consisting of an alternating copolymerization performed on-resin (Table 1 Entry #19, [Ind]:[PhMal]:[RAFT] = 6:6:1) (see Supplementary Data S4 for procedure and Supplementary Data and Figure S4-1 for the single GPC elugram). However, slight frontal tailing in the GPC elugrams becomes clearer as the oligomer molecular weight grew (Figure 3). nESI-MS data again confirmed this as originating from multiple *N*-phenylmaleimide additions occurring as well as the presence of incompletely reacted oligomers from previous steps (see Supplementary Data S5). nESI-MS data for the 18-mer was not collected due to severely diminished ionization of higher molecular weight species, even with a higher tube lens potential. It is also noted that multi-additions were observed with *N*-phenylmaleimide but almost never with indene.

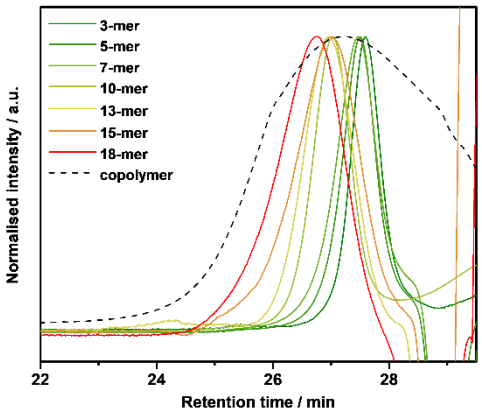


Figure 3. GPC (DMAc, 1 mL min-1, 50 °C) data from the synthesis of sequence-defined indene-phenylmaleimide oligomers on-resin.

From conversion data (Table 1), a few interesting observations can be made. *N*-phenylmaleimide additions occur at a very consistent rate throughout the synthesis but ex-

hibited a higher average conversion (57 ± 7%) than expected for a single addition with a 2:1 stoichiometry. This can be attributed to the occurrence of double-addition, as seen in the mass spectrometry data. Indene additions, on the other hand, slowed significantly after its third addition (5th overall addition) but exhibited an average conversion (51 ± 3%), closer to that expected for a single addition with a 2:1 stoichiometry. We attribute the eventual difference in required reaction time between additions of indene and phenylmaleimide to oxygen-containing inhibiting species (specifically those which operate *via* chain transfer) generally being more effective on electron-rich monomers than those that are electron-deficient.[19]

While these observations suggest that this system may not be optimal for assembling sequence-defined polymers, our methodology still offered acceptable material recovery. We obtained a 12% total yield of the apparent 10-mer after cleavage and a 2% total yield of the apparent 18-mer after cleavage, with an 81% stepwise yield and high chain end fidelity as indicated by consistent monomer conversion with stoichiometry (Table 1). As this approach to assembling sequence-defined polymers is iterative, it would especially benefit from further optimizing synthesis and purification methodology, which is the subject of further research in our laboratory.

These oligomers were then analyzed through UHPLC-MS (high resolution APCI ionization). APCI was used here due to more facile ionization of the analyte albeit at the cost of further diminished ionization of higher molecular weight species. In the first instance, individual oligomeric species could not be separated and eluted as a singular peak. This was expected given the choice of monomer units, the periodic sequencing thereof and the presence of 2^n diastereomers. As with nESI-MS, we observed multi-addition of PhMal and incomplete single-addition of indene in the APCI. The PDA detector in the UHPLC component was also useful to observe trithiocarbonate elimination in the product. Such a side-reaction could be attributed to several things. Firstly, with many iterative PET-RAFT steps, disproportionation at the end group becomes increasingly likely. Furthermore, termination in general is more likely with an immobilized chain transfer agent in an "R-group" approach. Finally, there could be an effect of the cleavage reaction under strong acid. Such elimination upon acid treatment would be, however, unusual as trithiocarbonate-terminal polymers have been subjected to similar TFA deprotection conditions with minimal evidence of decomposition.[20] However, this elimination was found to be partially minimized by adding a cation scavenger as observed by the less prominent side-peak in the UHPLC (triisopropyl silane, TIPS – see Supplementary Data Figure S6-13). We hypothesize that such acidolysis would occur through an intermediate tautomerization step, meaning it would mostly occur on maleimide-terminal oligomers.[21] In any case, the decomposition allowed us to detect higher oligomers in the APCI with better resolution as a side-effect.

To demonstrate that our methodology readily allows sequence variations, other maleimide derivatives were investigated. To that end, after the fifth SUMI step, we performed the sixth iteration with different maleimide derivatives, namely, hydroxyethyl (C_2H_4OH-Mal), 2-pyrenyl (PyMal) and β-alanyl ($C_2H_4CO_2H$-Mal) maleimide and characterized the corresponding products with GPC, NMR and UHPLC-MS (Figures 4A and 4B for GPC and NMR data respectively, and Supplementary Data Figures S6-10, S6-11 and S6-12, and Tables S6-6, S6-7 and S6-8 for UHPLC-MS data). The incorporation of pyrenylmaleimide could be easily confirmed from its unique absorbance in the UV-detector GPC and its unique resonances in the ^{1}H NMR spectrum (Figures 4A and 4B respectively). Furthermore, the UHPLC-MS data showed that most of the species contained the respective derivative monomer in all cases (see Supplementary Data Tables S6-6, S6-7, S6-8).

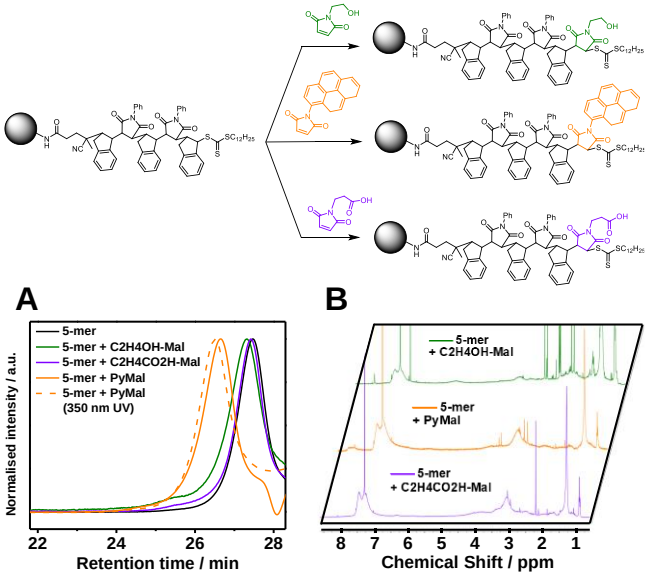


Figure 4. Synthesis of aperiodic maleimide-indene oligomers with GPC elugrams (DMAc, 50 ^{o}C, 1 mL min^{-1} – See Supplementary Methods for calibration data) (A) and ^{1}H-NMR spectra (400 MHz, $CDCl_3$) (B) of the relevant products.

To show the versatility of this methodology for other resins, we also functionalized 2-chlorotrityl chloride (CTC) resins with 2-[(butylsulphanylthiocarbonylthio]-2-methylpropanoic acid (BDMAT) to similar effect but using a different synthesis route. This was namely *via* a nucleophilic displacement, again, analogous to a procedure used in solid phase peptide synthesis (see Supplementary Methods and Materials for the procedure and Supplementary Data Figure S7-1 for the data). Iterative PET-RAFT SUMI reactions with the same original monomer system could be performed with minimal changes in reaction conditions (see Supplementary Data Figure S7-2 and Table S7-1).

Finally, we demonstrated the feasibility of performing post-polymerization reactions on homopolymers all on-resin without purification steps, *e.g.,* dialysis or precipitation. The first RAFT homopolymerization on-resin was performed with xanthates using a "Z-group approach" (to minimize termination reactions), strictly anoxic conditions and with heating.[13b] We believe our approach simplifies this procedure and renders it more versatile, potentially reviving this methodology as a useful approach for multi-step polymer synthesis. To that end, we homopolymerized glycidyl methacrylate (GMA) on-resin with PET-RAFT and then performed a post-polymerization nucleophilic ring opening of the pendant epoxide with sodium azide (see Supplementary Data S4 for procedure and Figure S4-2 for final product characterization).

To conclude, we have developed a solid-phase synthesis methodology to perform iterative PET-RAFT SUMI processes. Through the advantages of a solid-phase process, we were able to assemble minimally dispersed products of unprecedented molecular weight, up to the apparent 18-mer. Furthermore, we were able to synthesize aperiodic derivatives. Analysis of the products revealed double-additions and incomplete single-additions inherent to the process. In spite of these considerations, this work represents a step towards building larger sequence-defined oligomers through our newly developed methodology.

Solid-phase synthesis can dramatically minimize the number of necessary purification steps, but some impurities will inevitably remain. This is not unique to our methodology and is a commonly encountered problem in solid phase synthesis. More generally, in macromolecular assembly, imperfections in reaction outcomes can accumulate in an iterative synthesis.[22] To assemble perfectly discrete sequence-defined polymers, we are undertaking further research to identify monomer pairs which exhibit the ideal combination of activity, selectivity, end group fidelity and chromatographic separability.

While our work has focused on iterative RAFT-SUMI processes, we have also demonstrated that post-polymerization reactions on conventional homopolymers can be performed analogously on-resin. We anticipate that a solid-phase synthesis methodology can be applied to synthesize polymers with other controlled facets such as molecular weight distribution, monomer unit composition and architecture.

ASSOCIATED CONTENT

Supporting Information. Information on methods and additional experiments and characterization of our methodology is available free of charge *via* the internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. CRediT author statement. Karen Hakobyan: conceptualization, methodology, formal analysis, writing – original draft, visualization. Benjamin Noble: writing – review & editing, funding acquisition. Jiangtao Xu: conceptualization, methodology, supervision, writing – review & editing, funding acquisition.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

APCI, atmospheric pressure chemical ionization; CDTPA, 4-cyano-4-[(dodecylsulfanylthiocarbonylthio]pentanoic acid; CTC, chlorotrityl chloride; GMA, glycidyl methacrylate (epoxide); nESI-MS, nanoelectrospray mass spectrometry; PET, photoelectron transfer; PhMal, *N*-phenylmaleimide; PyMal, *N*-pyrenylmaleimide; RAFT, reversible addition-fragmentation chain transfer; RDRP, reversible deactivation radical polymerization; SUMI, single unit monomer insertion; TFA, trifluoroacetic acid; UHPLC, ultra-high performance liquid chromatography; ZnTPP, zinc tetraphenylporphyrin

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