Synthesis of Functional Polymers *via* Click Polymerisation and Multicomponent Reactions

by

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Abbreviations

ACN	Acetonitrile
ATRP	Atom transfer radical polymerisation
BBSF	4-(Bromomethyl) benzyl sulfonyl fluoride
$CDCl_3$	Deuterated chloroform
CROP	Cationic ring opening polymerisation
CuAAC	Copper -catalysed azide alkyne cycloaddition
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DLS	Dynamic Light Scattering
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Đ	Molecular dispersity
EtOx	2-Ethyl-2-oxazoline
ESI-MS	Electrospray ionisation mass spectrometry
ESF	Ethenesulfonyl fluoride
GPC	Gel permeation chromatography
k_{app}	Apparent rate constant
LCST	Low critical solution temperature
$[M]_0$	Concentration of monomer at t = 0
$[M]_t$	Concentration of monomer at t = t
MALDI	Matrix assisted laser desorption ionisation
MeOH	Methanol
MeOx	2-Methyl-2-oxazoline
NMP	Nitroxide mediated polymerisation
NMR	Nuclear magnetic resonance
TEA	Triethylamine
TEM	Transmission electron microscopy
TBD	Triazabicyclodecene
THF	Tetrahydrofuran
UV-Vis	Ultra violet-visible

Acknowledgements

As I finally got a chance to write this, my sincere thanks to Dr Remzi Becer, my supervisor. Thanks for all the opportunity and freedom he provided which allows me to develop my own style and grow as a very, very early-stage researcher. I learnt a lot from him, and all these knowledge would help me advance further and further.

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I would like to thank my family for their support throughout my life.

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I would also like to thank myself for getting through all of these, an interruption, a surgery, a transfer of institution and a pandemic. Almost too many twists in a PhD. Glad I made it. Time to find some new challenges!

Declaration

Experimental work contained in this thesis is original research carried out by the author, unless otherwise stated, in the Department of Chemistry at the University of Warwick, and the School of Engineering and Materials Science at Queen Mary, University of London, from September 2016 to June 2021. No material contained herein has been submitted for any other degree, or at any other institution.

Results from other authors are referenced in the usual manner throughout the text.

Date:

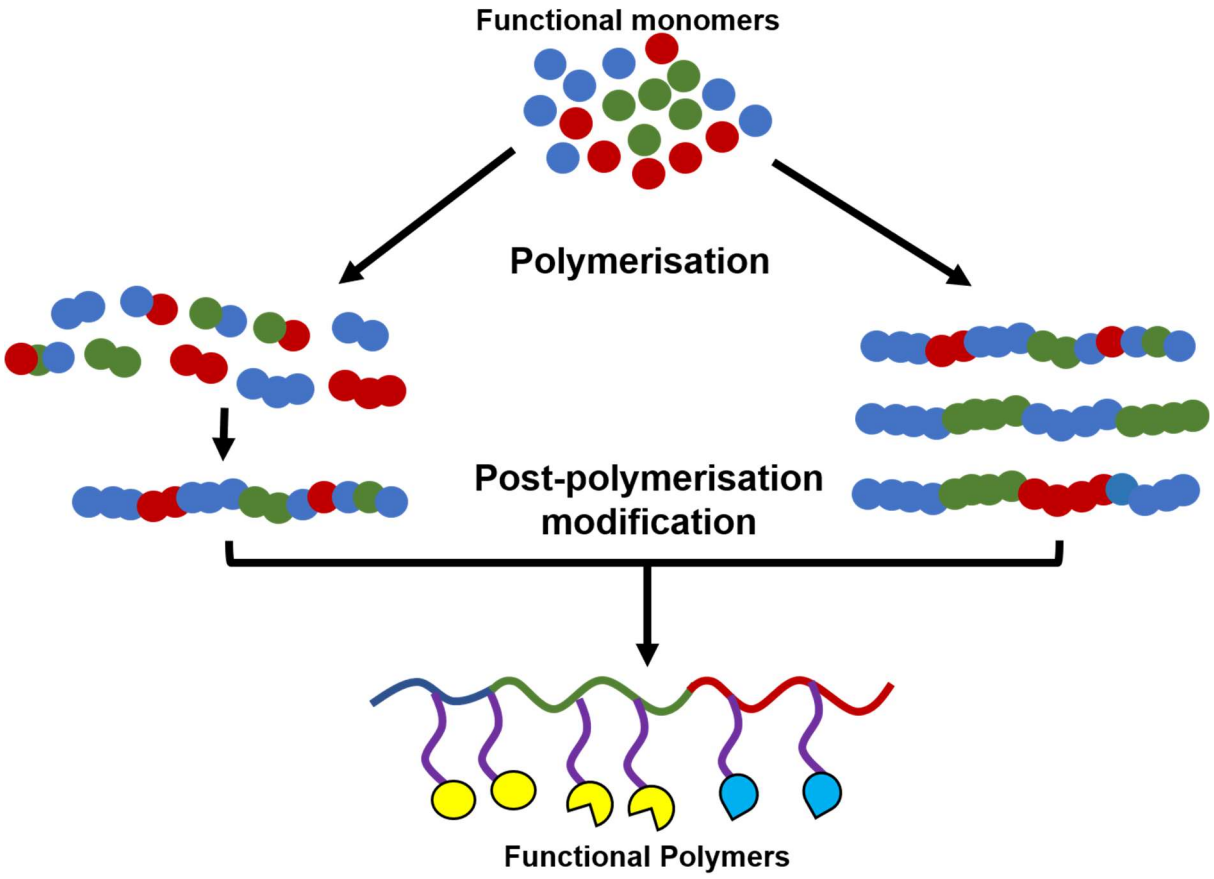
Tieshuai Zhao

Abstract

This work presented herein is aiming to investigate the preparation and post-polymerisation modification of functional polymers with click reactions and multicomponent reactions. Three click reactions, the para-fluoro thiol click reaction (PFTR), the thiol-bromo click reaction and the Sulphur (VI) fluoride exchange (SuFEx) click reaction have been studied in the preparation of step-growth polymers. As a result, novel fluorinated poly (aryl thioether)s via simultaneous PFTR and thiol-bromo click reaction, telechelic polyoxazolines and amphiphilic multiblock polyoxazoline have been synthesized and reported for the first time, whilst corresponding thermal properties, hydrophobicity, and the ability of self-assembly have been characterised. The study on step-growth polymerisation via SuFEx click reaction did not lead to the successful preparation of novel polymers, while the limitation has been investigated. However, SuFEx clickable polyoxazolines has been synthesized for the first time utilizing a sulfonyl fluoride group-containing initiator, which opens an avenue for future investigation.

The Ugi-4-component reaction was employed as an example of multicomponent reaction, and corresponding step-growth polymerisation of sustainable monomers, as well as solid-phase supported synthesis of sequence defined peptoid structures have been investigated. Novel polypeptoids with up to 83.9% bio-sourced mass were prepared via Ugi-4-component polymerisation of bio-sourced diamines and dicarboxylic acids, while the thermal properties could be tuned to produce room temperature elastomers or crystallised polymers, and multi-gram scale synthesis was shown practicable. Sequence defined multifunctional peptoid oligomers were also synthesized and characterised with MALDI-ToF, while these peptoids could be interesting for studies on self-assembly and the effect of side-chain position on polymer properties.

Chapter 1. Introduction: Preparation and post-polymerisation modification of functional polymers



1.1 Synthetic functional polymers

Synthetic polymers are macromolecules constituted by numerous covalently bonded small molecules, while the reactions that links these molecules together, named polymerisation, are artificially done. Properties of synthetic polymers often differ from the small molecules building the polymer, also termed as monomers, due to the high molecular weight of polymers and diverse architecture from linking of monomers. The concept of polymers consist of covalently linked small molecules was coined by Staudinger in the 1920s,[1,2] who was awarded the Nobel prize in chemistry in 1953. Since then, 100 years have passed and significant research advances have been made in the field of synthetic polymer chemistry, with synthetic polymers becoming ubiquitous in people's daily lives.

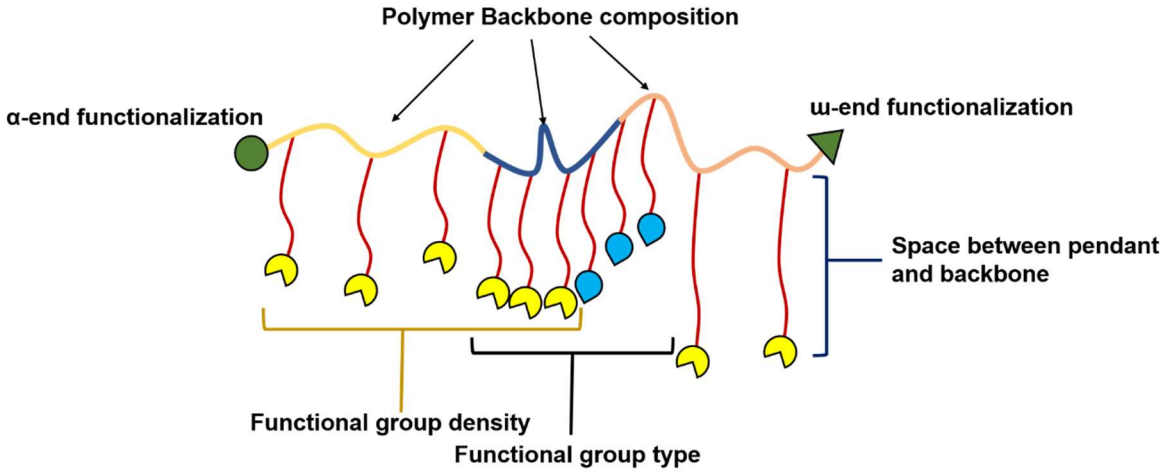
The first synthetic polymer can date back to 1907, where a phenyl formaldehyde called Bakelite was invented by Leo Baekeland.[3] This thermosetting polymer was found to be highly resistant to thermal and chemical stress as well as being electrically insulating. It was then used widely for applications like insulators, iron handles and washing-machine impellers, thanks to its superior functionalities. Since then, functional polymeric materials have constituted an intense research field and an enormous variety of polymers with different functionalities that meet different needs, from water-proof painting[4,5] to drug encapsulating nano vehicles, [6–9] have been manufactured and generalized. Nowadays, it is well accepted that functional polymers are polymers with unique properties or uses. Investigating certain factors that impact functionalities to allow the design and preparation of desired functional polymers is hence important in polymer chemistry.

1.2 Impact of polymer functionality on properties

The properties of functional polymers are determined by their backbone structure and functional groups attached to the backbone jointly while other factors like polymer chain

length, density of side chain functional groups, spacing between side chain functional groups and backbone and polymer architecture also play important roles (**Scheme 1)**. The most

conspicuous and presumably the most important factor in a functional polymer is the kind of functional group introduced to the polymer. Different functional groups provide correspondingly unique functionality. For example, carbohydrates are known to play an important role in cell recognition due to the sugar-lectin binding interaction,[10–14] benefitting from the multivalency effect of enhanced sugar-lectin interactions, and glycopolymers with different carbohydrate pendant groups were hence developed to investigate their biomedical applications such as targeted drug delivery and direct therapeutics.[15–20] By using different sugar pendants, glycopolymeric drugs,[21] HIV inhibition glycopolymers[9,22–24] and glycopolymeric drug delivery systems[25,26] have already been developed. Another good example is light responsive azobenzene groups that undergoes a reversible *trans-cis* isomerization with light irradiation that was firstly reported in 1937.[27] Azobenzene-containing photo-responsive polymers were then studied by polymer scientists and several applications like photo-actuators[28–30] and photo-induced orientation[29,31,32] have been reported based on side chain azobenzene-functionalized polymers. A lot of other functional groups such as positively charged tertiary amines for antimicrobial uses,[33–36] GFP core chromophores for fluorescent imaging applications,[37,38] anti-cancer drug molecules like withaferin A[39] for polymer-prodrug developments and amidine groups for carbon dioxide fixation[40,41] have also been reported to prepare different functional polymers, while polymer scientists continue to investigate novel functional polymers incorporating the numerous functional groups available.



Scheme 1. Examples of factors affecting properties of functional polymers.

The other important factor affecting polymers' properties is the composition and functionality of the polymer backbone. Thermal properties and mechanical properties can differ significantly between polymers with flexible backbones and rigid backbones. For example, polymers like polyphenylene sulfone (PPS),[42–44] polysulfone[45,46] and fluorinated poly (aryl ether)[47–49] are reported to possess excellent thermal properties thanks to their high aromatic content and stable linkages, while polycaprolactone and polylactic acid (PLA) are known to be thermally unstable and mechanically weak with their flexible hydrocarbon backbone and linkages prone to cleavage reactions. However, these polymers are reported to have other applications like serving as bioresorbable scaffolds[50,51] and biodegradable sustainable plastics[6,52] owing to their backbone structure while lacking pendant functional groups. Backbone composition can also affect the architecture of polymers and thus change polymers' functionality; one common example of this is drug-delivery systems based on amphiphilic polymers where the self-assembly architecture of amphiphilic polymers can be adjusted by changing the ratio of hydrophobic and hydrophilic content in polymer backbone, thus affecting the drug encapsulation properties.[53–56] By employing different monomers to obtain diverse linkages and preparing copolymers with varying hydrophilic content, novel functional polymer backbone could be prepared with tailored functionality.

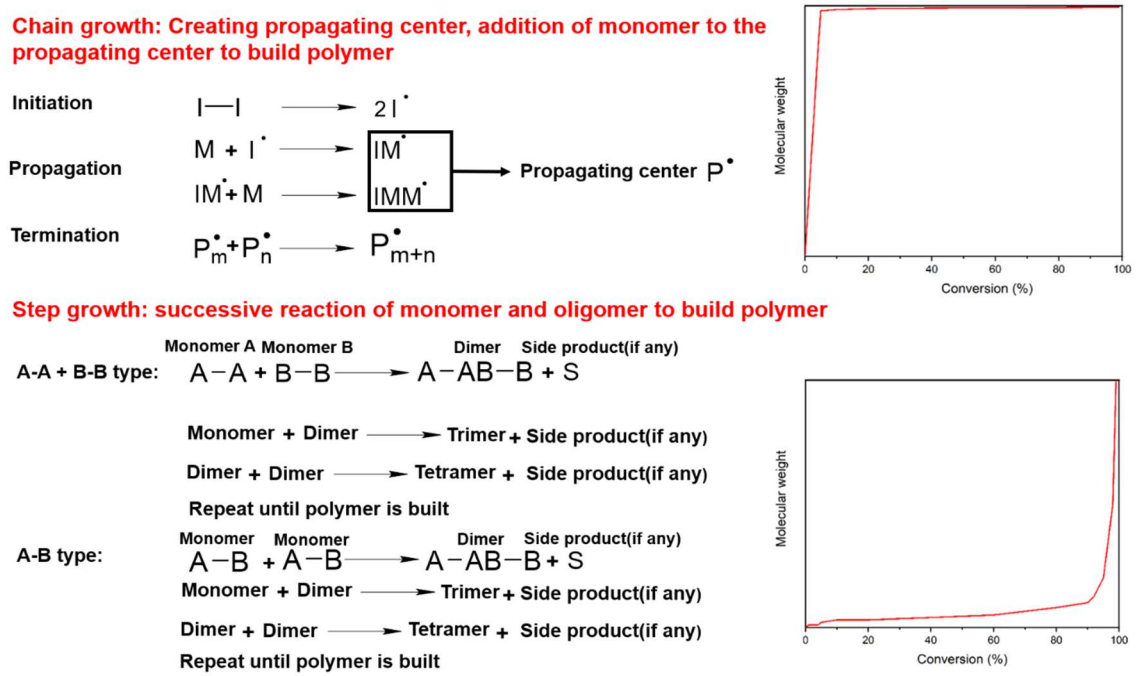
Apart from backbone composition and side chain functionality, precise control of position of side chain functional groups also plays an important role in tuning polymer functionality. Sequence defined polymers mimicking natural sequence defined polymer-like proteins and DNAs have been prepared as biomaterials for several applications like biomimetic scaffolds[57,58] and therapeutic foldamers,[59–61] while the defined position of functional groups has been reported to affect the polymer architecture and bulk properties such as melting temperature.[62–64] Sequence defined polymers also provide access to novel functionality like chemical data storage,[65,66] where the designed position of certain functional groups or monomers allows the storage of data and reading of data can be done *via* tandem mass spectrometry.

Knowing the factors that affect polymer functionality, preparation of novel functional polymers with designed functionality can be achieved by using different polymerisation and post-polymerisation modification techniques to synthesize desired polymer backbone structures and

introduce certain functional groups at controlled positions for designated purposes. The development and employment of proper polymerisation and post-polymerisation modification methods are hence of importance and will be introduced in the following sections.

1.3 Polymerisation techniques

Polymerisation methods can be categorized into chain-growth and step-growth polymerisations based on their different mechanisms (**Scheme 2**). In chain growth polymerisation, a reactive species, either radical or ionic, is generated by an initiator following external energy input like thermal or light irradiation, and monomers successively react only



Scheme 2. Basic mechanisms of chain growth and step growth polymerisation. The different mechanisms result in the different kinetic behaviours.

with the reactive species, regenerating a reactive centre while elongating the polymer chain to eventually generate a high molecular weight polymer chain. The chain extension process is rapid, polymers growing to high molecular weight before termination reactions happen. Then, the reactive centre is terminated, and the chain growth stops. Thus, no intermediate length chains are obtained in chain growth polymerisations even if the monomer conversion is very low, such that chain-growth polymerisation systems only contain monomers, reactive species, growing chains, and high molecular weight polymers; increasing the monomer conversion only increases the amount of high molecular weight polymer chains in the polymerisation system.

A distribution of obtained polymer chains with different molecular weight are be observed due to statistical variations present in the polymerisation processes, and the end group fidelity of obtained polymers is affected by the termination of propagating reactive centres. Termination can happen in several ways, including bimolecular termination of polymer chain with another chain, the initiator species, impurities or inhibitors and disproportionation of radical, not to mention chain transfer reactions.

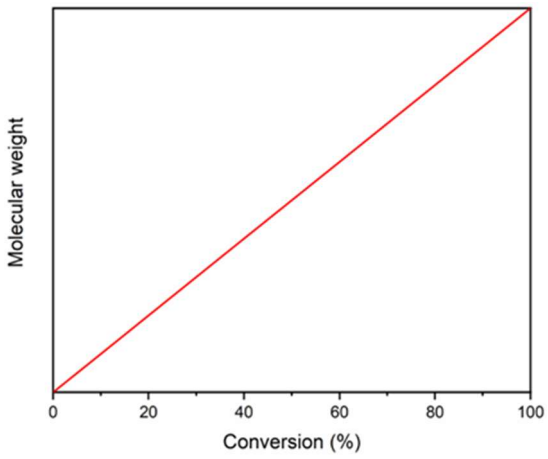
1.3.1 Chain growth polymerisation: radical polymerisation and ring opening polymerisation

Free-radical polymerisation is a classic example of chain growth polymerisation where a radical reactive centre is generated by an initiator, and the selected monomer, typically a vinyl monomer, is then rapidly added to the reactive centre, producing high-molecular weight polymers after multiple additions. This polymerisation has been well industrialized and produced billion-pounds-scale products in America.[67] However, the broad dispersity and undefined chain end fidelity of free radical polymerisation are two major drawbacks of this polymerisation technique, as the physical properties of polymers are significantly impacted by broad distributions, while bad chain end fidelity limits the preparation of copolymers for further demands. As other techniques for the preparation of well-defined polymers like stepwise polymerisation, anionic polymerisation, and transition-metal catalysed polymerisations, suffer from several disadvantages such as tedious approaches, unreasonably long reaction times for high molecular weight polymers or redundant purification processes, polymerisation systems that were designed to have control over molecular weight, polymer distribution, end group fidelity and enabled the synthesis of block copolymer structures were hence invented and named controlled radical polymerisation or reversible deactivation radical polymerisation.[68–70]

In this kind of polymerisation process, the chain termination process is minimized by introducing reversible termination or reversible transfer processes and creating stable radicals in the chain propagation process and forming an equilibrium between free radicals and stable radicals.[70,71] As the stable radicals are significantly favoured in the equilibrium, their concentration is much higher than that of the propagating radicals and the reversible reaction in which stable radical convert propagating radicals into stable species suppresses the bimolecular termination, known as the *persistent radical effect*. Thus, an elongated radical

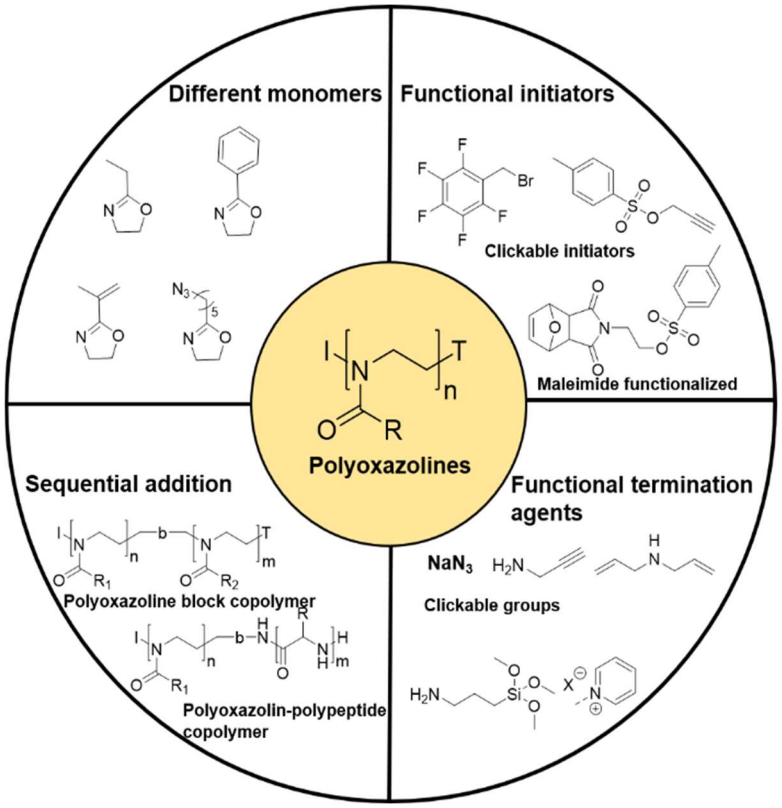
lifetime is retained, from seconds in free radical polymerisation to hours in reversible deactivation radical polymerisation. Impurities in the reaction system are also minimized by selecting certain reaction conditions such as an inert atmosphere. With these control measures in place, subsequent addition of a second monomer for copolymer synthesis is possible, and the molecular weight distribution remains narrow. Several reversible deactivation radical polymerisation processes have been developed, such as atom transfer radical polymerisation (ATRP),[72] reversible addition-fragmentation chain-transfer (RAFT) polymerisation,[73] Cu (0)-mediated reversible deactivation radical polymerisation (Cu(0)-RDRP),[74] and nitroxide-mediated radical polymerisation (NMP).[75] A plethora of functional polymers have been synthesized *via* these methods and several decent reviews have summarized this topic well.[70,76–78]

Ring-opening polymerisation exhibits kinetic behaviour slightly different to that of free radical polymerisation. In ring-opening polymerisation, the conversion versus molecular weight relationship is often a linear dependence with a certain slope (**Scheme 3**). For example, the ring-opening polymerisation of ε-caprolactam was reported to have a linear increase of molecular weight with conversion. Polymerisations that possess this kinetic feature have a fast initiation step and termination reactions are absent. Thus, the propagating centre activity is always present while the molecular weight of obtained polymer can be controlled. This polymerisation technique has been utilized to synthesize several useful functional polymers, especially in the biomedical field, such as polycaprolactones,[19] polypeptides,[79] polypeptoids[80] and polyoxazolines.[81]



Scheme 3. Conversion versus molecular weight relationship in ring-opening polymerisation.

Among these polymers, polyoxazoline has been frequently used for biomedical applications as a substitute for polyethylene glycol (PEG), the golden standard polymer in the biomedical field. By simply changing the oxazoline monomers, sequentially adding monomers for different block synthesis and selecting different initiator and terminating agents (**Scheme 4**), polyoxazolines with different backbones, side chains, end groups and block structures can be easily synthesized and polymers with tailored functionality like antimicrobial polymers, lubricant additives, thermoresponsive drug carriers and polymeric therapeutics can be prepared.



Scheme 4. A few examples on different approaches of polyoxazoline functionalization.

1.3.2 Step-growth polymerisation: backbone diversity and end fidelity

Differing from chain growth polymerisation, step-growth polymerisation is the stepwise process of monomers forming dimers, trimers, tetramers and slowly build up to long polymer chains by successive reactions.[79] Unlike in chain growth where monomers only react with the active reactive centre, in step-growth polymerisation monomers and oligomers react with each

other, dimers react with monomers to form trimer, trimers react with trimers to form hexamers, etc. The formation of large polymer molecules only happens after a series of reactions between small molecules, and thus very high monomer conversion is required for large polymer molecules to appear. Various reactions can be employed for step-growth polymerisation to create unique linkages, and the kinetics and conversion of the reactions employed significantly affect the molecular weight and reaction rate of the step-growth polymerisation. To form linear polymers, two kinds of monomers can be used in step-growth polymerisation. The first one uses two bifunctional monomers that can react with each other, commonly called A-A and B-B monomers. The second one uses a bifunctional monomer that has two functional groups that can react with each other, normally under certain reaction conditions to avoid premature self-polymerisation. This kind of monomer is called an A-B monomer. These bifunctional monomers can either be small molecules or polymers, the latter of which are often referred to as 'macromonomers'. While using A-A monomer and B-B monomers to synthesize step-growth polymers, the stoichiometry between A-A and B-B monomers is very important, as if one functional group is excess, the other one will be completely consumed firstly and end the chain growth with moderate molecular weight. The number average degree of polymerisation of step-growth polymerisation, usually represented by $\underline{X}_n$, can be calculated with a well-known equation established by Carothers in 1936, named the *Carothers equation*:

$$\underline{X}_n = \frac{1}{(1-p)} \qquad (1.1)$$

Where p is the extent of reaction that is affected by the stoichiometry and the reaction conversion. From the Carothers equation, it is very important to select highly efficient reactions to achieve high conversions, as if the extent of reaction p is 0.95, the number average degree of polymerisation $\underline{X}_n$ calculated from Carothers equation is only 20. Stoichiometric imbalance results in reduced extent of reaction. For example, if the mole ratio of monomer A-A to monomer B-B is 1.1 to 1, the extent of reaction p is $p = \frac{1}{1.1} = 0.909$, resulting in a number average degree of polymerisation $\underline{X}_n = \frac{1}{1-0.909} = 10.98$. One common way to overcome stoichiometry imbalance, especially for small scale reactions, is to use stock solutions of reactants to minimize the stoichiometry difference in measurement. However, this feature of step-growth polymerisation can also be utilized to control the end group functionality of step-growth polymers by intentionally adding excess of one monomer. In this case the other monomer would be fully consumed in advance, resulting in the obtained polymer end-functionalized with the excess functional group. Step-growth polymerisation could also be

done with multifunctional monomers; while in this case hyperbranched structure can form, the principle stays the same.

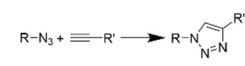
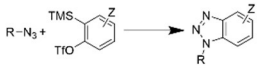
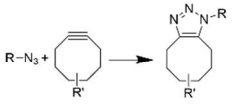
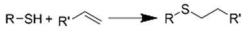
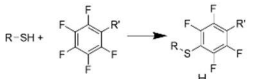
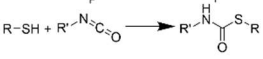
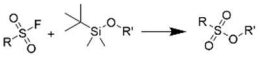
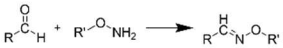
Various reactions can be used for step-growth polymerisation; the diversity of polymer backbones and linkages is huge, and the properties of polymer obtained are heavily dependent on the structure of the polymer backbone. For example, polyurethane, a commercially marketed polymer used for adhesives, foams, and insulators, is a classic example that is typically synthesized *via* step growth polymerisation of a diol compound and a diisocyanate compound in the presence of catalysts.[82–85] By using different monomers, like aliphatic or aromatic diols and diisocyanates, either polyurethane elastomers or rigid polyurethanes can be consequently obtained.[83,84] Another example is polyamide, which can be synthesized from the step growth amidation-polymerisation of a diamine and a dicarboxylic acid monomer. The polyamide synthesized from hexamethylenediamine and adipic acid, which is known as Nylon 66, is a very common synthetic polyamide used for industrial plastic and textile applications. By adjusting the number of carbons in the backbone of the monomers, other polyamide with different properties could be made such as polyamide 12 made from the polycondensation of 12-aminododecanoic acid which has lower water uptake and higher impact strength compared to polyamide 66.[86,87]

As the degree of polymerisation in step-growth polymerisation is associated with the extent of reaction, pushing the reaction equilibrium to achieve full conversion and selecting highly efficient reactions is thus of importance to obtain high molecular weight polymers in a step-growth polymerisation process. For example, in synthesis of high molecular weight polyesters via the polycondensation of diols with diacids or diesters, high temperature and reduced pressure are often required to induce the condensation and remove the small molecule byproducts like water or methanol to push the reaction balance towards polymer formation. Highly efficient reactions that have no or minimal byproducts and proceed under gentle reaction conditions are useful for step-growth polymerisation, and reactions that fit these requirements have been coined by Sharpless in 2001 as ‘click reactions’.[88] These reactions have been widely used in step-growth polymerisation nowadays, and a detailed review on this topic is be presented in the following section.

1.3.3 Click step-growth polymerisation: highly efficient methods for preparing functional polymers

Click reactions are versatile and efficient reactions that fit certain criteria coined by Sharpless *et al.* in 2001; a reaction needs to be '*modular, wide in scope, give very high yields, generate only inoffensive byproducts, exhibit easy purification of product, stereospecific'* and '*use simple reaction conditions, readily available starting materials and reagents, no solvent or benign solvent*' to be called as a 'click reaction'.[88] Since then, several click reactions have been developed and widely used in synthetic chemistry. A few click reactions that are the most studied and reported are shown as examples in **Table 1**.[47,89–106] As in the step-growth polymerisation process, quantitative conversion of functional groups, minimized byproducts and side reactions are desirable, and thus, click reactions are useful in the study of step-growth polymerisations. Among these click reactions, the copper mediated azide-alkyne click reaction (CuAAc) is arguably the most reported click reaction since the introduction of Cu (I) catalysis to Huisgen 1,3-dipolar azide-alkyne cycloaddition in 2001.[88] This CuAAc click reaction creates unique triazoline linkages with great stability and intermediate polarity and the reaction has been reported to be functional-group tolerating and orthogonal to other click and non-click reactions.[107–109] Thus, multifunctional monomers can be synthesized via this click reaction to create a stable and functional linear backbone for subsequent modifications or applications.

Table 1. Examples of the most studied and reported click reactions

Functional group A	Functional group B	Representative Scheme	Mechanism	Conditions, e.g
Azide	Alkyne		Cu-catalysed [3+2] azide-alkyne cycloaddition	RT-80℃, 60s-2h, water/alcohol
	Activated alkyne		Huisgen 1,3-dipolar cycloaddition	50℃, 4h, dry toluene
	Electron-deficient alkyne		Huisgen 1,3-dipolar cycloaddition	RT, 12h, water
	Aryne		[3+2] cycloaddition	RT, 4h/24h, MeCN/THF
	Cyclooctyne		Strain promoted [3+2] azide-alkyne cycloaddition	RT, 1-2h MeCN/MeOH/[MeCN/H2O]
Thiol	Alkene/alkyne		Radical addition	RT, radical initiator/UV irradiation, minutes to hours water/DMF.
	Micheal double bond		Michael addition	RT, minutes to hours, MeCN, acetone, DMSO, water
	Bromo		Nucleophilic substitution	RT, very fast, DMF
	Para-fluoro		Nucleophilic aromatic substitution	RT to 70℃, minutes to hours, DMF/THF/Water
Isocyanate	Thiol/amine		Nucleophilic addition	RT, overnight, THF
Sulfonyl fluoride	Silyl Ether		Nucleophilic substitution	80℃, 3h, DMF
Ketone/Aldehyde	Hydroxyl-amine		Nucleophilic attack and subsequently proton transfer	RT, minutes to hours, aqueous solution
Conjugated diene	Substituted alkyne		[4+2]cycloaddition	RT/-78℃/160℃,catalyst DCM/toluene/water, 0.5-36hours

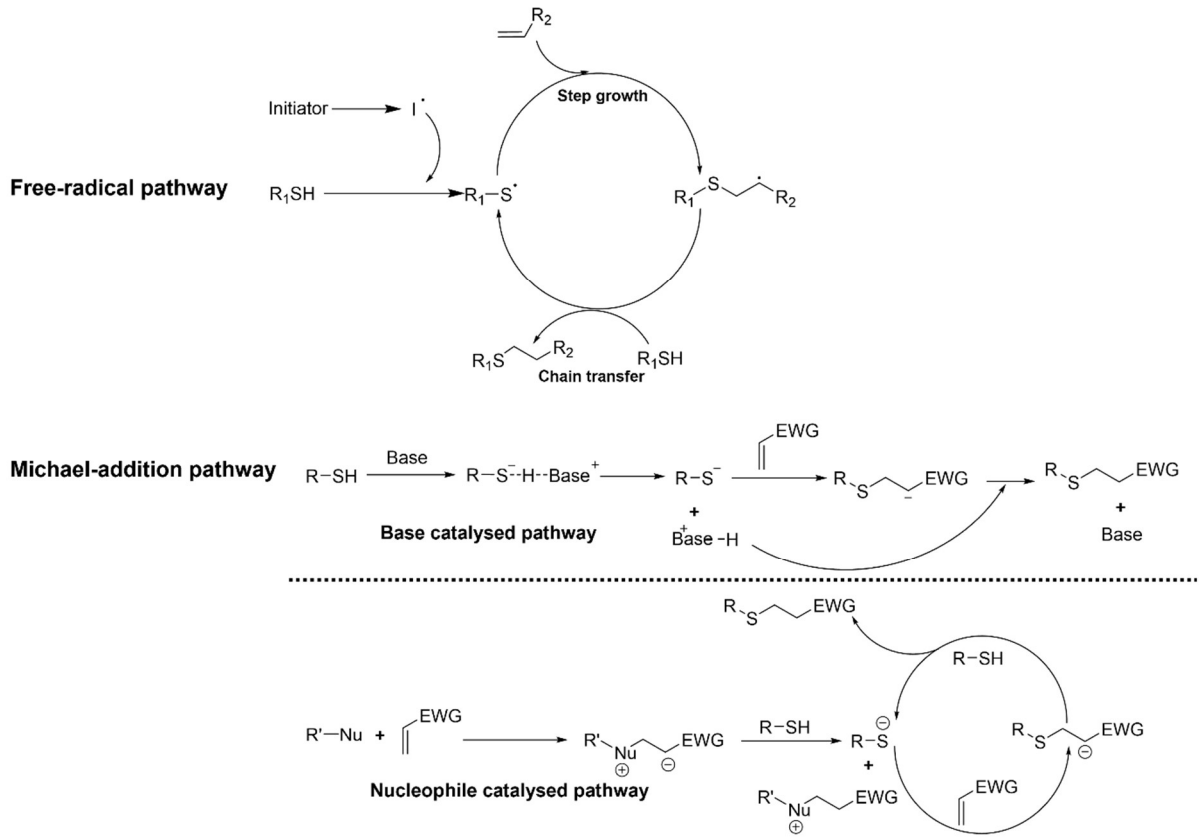
1.3.3.1 CuAAc click step growth polymerisation

CuAAc click reaction has been used in step-growth polymerisation since 2004, when Peng *et al.* investigated preparation of various functional dendrimers via CuAAc click reaction[110] and established that quantitative yield was achieved and in certain cases only simple purification like precipitation is required. Obtained dendrimers were end-functionalized with functional groups like amines and carboxylic acids thanks to the orthogonality of CuAAc click reaction. Nicolay *et al.* reported CuAAc click step-growth polymerisation of short polystyrene telechelic polymers prepared *via* ATRP in 2005.[111,112] α-Alkyne-ɯ-azido functionalized macromonomers with number average molecular weight ($M_{n,SEC}$) ranging from 1500 to 2600 were prepared *via* ATRP and a one-pot click step-growth polymerisation process was executed, resulting in large polymers with $M_{n,SEC}$ from 13700 to 21500. They further investigated the catalyst and ligand effects and provided critical insight on optimizing of reaction conditions of CuAAc click step-growth polymerisation.[113] Aside from copper catalysed ones, other azide-alkyne click reactions like strain promoted and thermo driven ones have also been used to synthesize step-growth polymers.[114,115] Several functional polymers have already been synthesized via CuAAc click step-growth polymerisation, including shape memory polymer networks,[116–118] self-healing polymeric materials,[119–121] biosourced thermally stable polymers,[122,123]glyconanocapsules,[124] thermoplastic semi-crystalline or amorphous polymer materials,[125,126] poly (ionic liquids),[127] luminogenic polymers,[128] bioimaging probes[129,130] and so on. Different structures such as linear, cyclic, hyperbranch, crosslinking and star polymers have been made in these reports. This ubiquitous implementation has demonstrated the success of CuAAc click step-growth polymerisation, thanks to its efficiency, simplicity and orthogonality.

1.3.3.2 Thiol based click step growth polymerisation

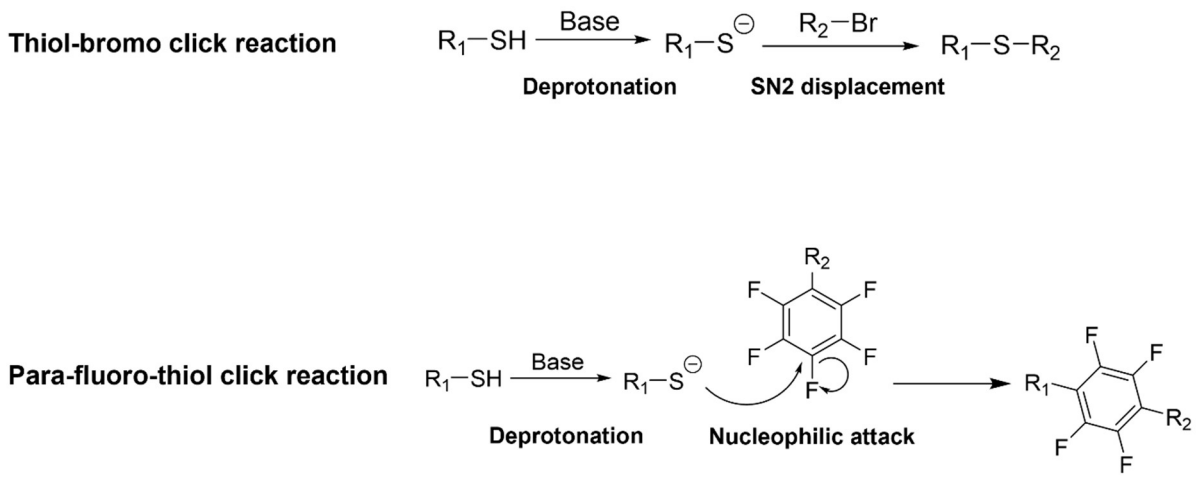
Thiol-based click reactions are another intensively studied family of click reactions. The relatively weak sulphur-hydrogen bonds of thiol allow numerous chemical reactions to happen with high conversions.[131] The reaction between thiols and reactive carbon-carbon double bonds, namely ‘enes’, was reported in the 1900s,[132] and thiol-ene reactions of two mechanisms: radical thiol-ene reaction and thiol-ene Michael addition,(**Scheme 5**) are both highly efficient

reactions that fulfil the requirements for being termed as click reactions, and they are routinely referred to as thiol-ene click reactions in literature nowadays.



Scheme 5. Two mechanisms of thiol-ene click reaction: free-radical pathway and Michael addition pathway. EWG: electron withdrawing group.

The reaction of thiols with alkynes, or 'yne's, were also termed as a 'click reaction'. First investigated in 1940s-1960s,[133,134] literature has shown the extremely efficient nature of the radical mediated thiol-yne chemistry, and as each yne can react with two thiol groups this opens up possibilities for the easy preparation of highly branched structures and high-sulphur content materials.[135] Thiol-halogen click reactions like thiol-bromo[136] and para-fluoro-thiol[137] click reactions are also developed based on the nucleophilic attack of an activated thiolate ion to the polarized halogen-carbon bond, while non-nucleophilic base is required to mediate the reaction. (**Scheme 6**) Although these reactions often either generate halogen acid, sometimes even toxic HF, or use an excess strong base to activate the reaction and act as the scavenger, and hence do not fully fit the criteria of being a 'click reaction' as by-product generation happens in these click reactions and the scope of para-fluoro-thiol click reaction is restricted to pentafluoro aromatic compounds. Nevertheless, they are still highly efficient and create carbon-sulphur heteroatom linkages and thus are recognized as click reactions.



Scheme 6. Brief mechanism of thiol bromo click reaction and para-fluoro-thiol click reaction. Non-nucleophilic base should be used in these two reactions and often in excess to act as the acid scavenger, while the bromo or fluorine salt of the base used is obtained as a by-product.

Step-growth polymerisation using thiol click reactions can result in polymers with high sulphur contents that are useful for optical applications[138,139] or with carbon-sulphur linkage that can be further oxidized or degraded, [98] while the reaction is metal-free and cyto-compatible, thus, this method is playing a pivotal role in synthesis of functional polymers. For example, Lin *et al.* reported the preparation of PEG hydrogels via a thiol-ene click step-growth polymerisation approach in 2011,[140] where the crosslinked polymeric hydrogels were shown to have excellent cytocompatibility and gelation efficiency as well as high cell viability comparing to hydrogels prepared *via* chain-growth polymerisation approach. Vandenbergh *et al.* reported the preparation of biodegradable poly(thioether)s *via* thiol-ene click polymerisation of dithiols and diacrylates in 2012;[141] the prepared polymer had good thermal stability up to 200℃ but remained degradable in phosphate buffers due to the thio-ether and ester linkages. Thiol-yne click chemistry was employed by Liu *et al.* in 2014 to synthesize monolithic polymers;[142] the polymerisation took place in UV-transparent fused silica capillaries and polymer columns were directly obtained with homogeneous porous structure, while the separation of small molecules was shown to be excellent comparing to those prepared with radical polymerisation. Recently high refractive index polymer networks have also been synthesized using thiol-yne click reaction, obtained polymer networks have a refractive index value exceeding 1.68 at 20°C, which is significantly higher than polymer networks obtained via thiol-ene systems.[143] The high sulphur content introduced by thiol-yne click reaction brings the improvement of optical

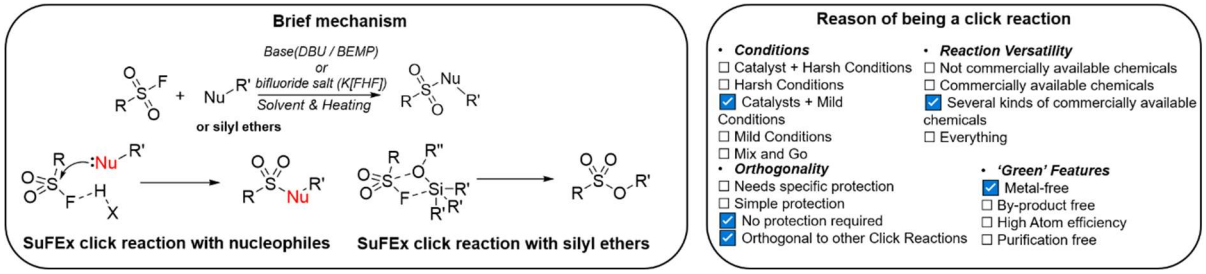
properties to polymers. The para-fluoro-thiol click reaction (PFTR) has also been used in preparation of step-growth polymers, although there were fewer reports and the properties studied remain limited. Baysak *et al.* reported the preparation of linear and branched polymer *via* para-fluoro-thiol click reaction of a bifunctional pentafluoro aromatic monomer with dithiol and tetrathiols.[144] Resultant linear polymers had number average molar mass ranging from 2800 to 7000 g mol^{-1} while the hyperbranched polymers had similar number average molar mass range, from 3100 to 7800 g mol^{1}. The distribution of polymers could be very broad; the maximum molecular dispersity *Đ* for linear polymers was 7.28 while for hyperbranched polymers the maximum *Đ* has reached 14.2, indicating very uneven properties of the resulting polymers. The polymers exhibited glass transition temperature ranging from 0℃ to -31℃. As one monomer in para-fluoro-thiol click reaction would possess fluorinated aromatic rings, potentially interesting thermal or electrical properties could be obtained through preparation of step-growth polymer using this click reaction.

Thiol-bromo click reaction has also been utilized in preparation of step-growth polymers. Zhang *et al.* reported the preparation of multifunctional polymers *via* thiol-bromo click reaction of commercially available and prepared dibromo small molecules in 2015.[136] Obtained polymer showed high refractive indices, owing to the high sulphur content, and high optical transparency, while the tetraphenylethene units introduced during the preparation of dibromo monomer provides extra aggregation-induced emission properties that could be further utilized in the detection of explosive chemicals such as picric acid. Another example of step-growth polymers prepared *via* thiol-bromo click reaction has been reported in 2019,[98] where multiblock copolymers were synthesized with corresponding dibromo macromonomers prepared *via* copper mediated reversible-deactivation radical polymerisation (Cu-RDRP). Obtained amphiphilic multiblock copolymers were shown to be degradable under certain conditions like oxidative and high temperature environment. However, compared to thiol-ene and thiol-yne click reactions which are frequently employed in preparation of step-growth linear polymer and polymer networks, the thiol-halogen click reactions are less studied in the field of step-growth polymerisation. Rational design and synthesis of step-growth polymers *via* thiol-halogen click reactions followed by investigation of polymer functionalities would be an attracting research field to dig into, and studies on utilizing thiol-halogen click reactions will be described in chapters 2 and 3 of this thesis.

1.3.3.3 SuFEx click step growth polymerisation

The Sulphur (VI) Fluoride Exchange reaction, namely SuFEx click reaction, is a recently emerged click reaction coined by Sharpless in 2014 with a comprehensive review article.[101] The click reaction is a basic or acidic catalysed nucleophilic substitution process between a sulfonyl fluoride group and normally a silyl ether group, forming silylated fluorine salt and a heteroatom linkage including sulfonate, sulfate, sulfamide and so on. (**Scheme 7**) This click reaction was investigated with emphasis on step-growth polymerisation due to its efficiency and functional group tolerance; the very first report on this click reaction in 2014 is the preparation of various polysulfates,[102] where the unique diorganosulfate ester linkage obtained with SuFEx click reaction and the high aromatic content backbone provided improved hydrolytic stability and thermal properties for obtained polysulfates when compared to polycarbonate counterparts. Step-growth polymers possessing sulfonate linkage and alkyl backbones were also investigated in 2017 by Sharpless *et al.*,[145,146] where acidic bifluoride salt was employed as the catalyst for the click reaction, differing from the earlier reports where a basic catalytic system was used. Different structures of alkyl polysulfonate were synthesized with molar mass ranging from 16 kDa to 26kDa, and the scalability of the polymerisation was shown by the preparation of 245 grams of polysulfonate. The polysulfonate synthesized was demonstrated to have excellent stability in both acidic and basic environments. By designing the monomer structure, polysulfates and polysulfonates with certain properties can be obtained. One example is polysulfates prepared with designed bifunctional precursors which possess highly conjugated functional groups reported by Fan *et al.* in 2018.[147] Four step-growth polymers were prepared *via* SuFEx click reaction and subsequently used as active layers for memory devices. I-V characterisation demonstrated stable flash-memory behaviour for two polysulfates and write once read many (WORM) behaviours for other two polysulfates. Similar electrical memory performance study of polysulfates *via* SuFEx click reaction was also reported by Xiao et al. in 2018.[148] Recently, linear polymers and polymer networks with fluorescence and cyanide detection properties have been prepared *via* SuFEx click step-growth polymerisation.[149] Designed branching structures showed significant fluorescence emission properties while anion-pi interactions between the backbone naphthylamide groups and cyanide ion provided the detection functionality, although the detection concentration was very low (ten times lower than the standard concentration of cyanide ions in drinking water) and might not be practicable in cyanide detection applications due to oversensitivity. Another

recent report on step-growth polysulfonates has shown unexpected reversible partial degradation under several base-catalysed reaction conditions with SEC evidence.[150] A reaction mechanism of DBU catalysed degradation was suggested in the report; such a degradation could weaken the claims of the stability of polysulfonate structures prepared via SuFEx click step-growth polymerisation, but also open up possible polymer recycling method for polysulfonates. In addition, step-growth unsymmetrical polysulfamide has also been reported in 2020,[151] and hydrolysis reactions showed these polymers could be recycled under base or acid treatment, with the best monomer recovery rate reaching 74%.



Scheme 7. Brief mechanism of SuFEx click reaction with nucleophiles and silyl ethers and possible reasons for SuFEx to be coined as a click reaction.

Numerous step-growth polymers have been synthesized *via* SuFEx click reaction since 2014. However, although the functional group tolerance of this click reaction provides diverse possibilities for polymer backbone functionality, the polymer structure reported was mostly limited to aromatic polysulfates and the synthesis of designed structure and investigation on polymer properties was limited. Thus, exploiting the diversity of polysulfate and polysulfonated backbones to design bifunctional monomers and investigate if the desired functionality is present would be a promising direction to work on in this field. Corresponding studies will be described in chapter 4 of this thesis.

The Oxime click reaction is another click reaction that attracts attention in the polymer chemistry field recently.[103] This carbonyl click reaction between aldehydes or ketones and hydroxylamines was mostly used in bioconjugation due to several advantages like high efficiency, generating water as the by-product and the successful execution of the reaction in aqueous environments. This reaction was rather overlooked in the field of click step-growth polymerisation, mostly due to the accessibility of hydroxylamine structures. Andreana *et al.* reported the preparation of carbohydrate polymers based on oxime click step-growth

polymerisation in 2002,[152] where carbohydrates were modified into b-D-1-O-hydroxylamine sugars and the C-6-CH_2OH were selectively oxidised into an aldehyde for subsequent click polymerisation. Resulting polymers had an average molecular weight ranging from 4.2 kDa to 8.9 kDa, while the polymer yield reported was only moderate, with the highest yield appearing to be only 62%. Ma *et al.* reported another example of oxime click step-growth polymers where a series of glycolipid polymers were synthesized with diketone glycomonomers and multifunctional hydroxylamine monomers,[153] the resulting polymer had unexpectedly good physical properties and was made into stabilized supporting membranes. Collins *et al.* reported the preparation of step-growth polymers up to 35 kDa in minutes with oxime click chemistry in 2016;[154] additionally, several reaction condition optimisations were performed, and the end-functionality of polymers was shown to be controlled with stoichiometry. They also published a detailed review on oxime click chemistry in 2016.[103] Overall, research on step-growth polymerisation using oxime chemistry is still quite limited, only a few polymers have been reported, and their functionality was not thoroughly investigated. However, limited access to hydroxylamine structure, and the possible bad tolerance towards other functional groups could be the reason for limited study.

To summarize, click step-growth polymerisation has been studied with several reported click reactions, and a plethora of functional polymers were designed and prepared, mostly under benign conditions. The high efficiency and minimized byproducts of click reactions allowed access to high molecular weight step-growth polymers in short time periods, while the heteroatom linkage and orthogonality often provided additional benefit to stability and subsequent polymer modification. Exploring novel click reactions for step-growth polymerisation and rationally designing clickable monomers with certain functional structures would be the key factor for subsequent studies in this field.

1.4 Post-polymerisation modification (PPM)

Apart from constructing diverse polymer backbones with different polymerisation techniques, post-polymerisation modification of polymers is also important as not all functional groups can be tolerated with selected polymerisation technique. Thus, preparing polymerizable precursors and attaching desired functional groups onto the polymer backbone after polymerisation is

another feasible way to access designed functional polymers. This approach is known as post-polymerisation modification (PPM), which could arguably date back to the 1840s when natural polymers were modified without fully understanding that process.[155,156] With the development of understanding on polymer chemistry since Staudinger's definition to polymers, the post-polymerisation modification technique was also advanced greatly from the 19th century to now. Limited by the polymerisation technique and modification reaction efficiency, quantitative polymer modification was barely achievable, and the variety of modification functional groups was limited in the early days of polymer chemistry. The tolerance of functional groups in early polymerisation techniques like free radical, cationic and anionic polymerisations was poor. For example, in cationic polymerisation no nucleophilic groups could be present and protecting and deprotecting techniques needed to be applied if any modification would be required. In that case, if the protecting/deprotecting chemistry was not efficient enough, the quantitativity of modification would be further afflicted. Thus, the development of functional-group tolerable polymerisation techniques and discovery of highly efficient reactions using inert precursors for modification is of importance. Reversible deactivation radical polymerisation such as ATRP,[157] RAFT,[158] NMP[159] and Cu(0)-RDRP[160,161] have provided channels towards polymeric precursors with a wide variety of functional groups owing to improved functional group tolerance of these techniques, and the development of highly-efficient reactions, such as click reactions, allows the quantitative modification of polymeric precursors while several functional groups that can be tolerated in polymerisations like alkynes or pentafluoro benzyl groups are employed for these reactions. These two techniques together facilitate the growth of the post-polymerisation modification field, and the development of post-polymerisation modification methods has been comprehensively reviewed in several decent publications.[156,162,163]

Post-polymerisation modification includes sidechain and end-group modification of polymers.[156] For the side-chain modification, functional monomers are required as the precursor to build up a polymeric precursor. For the end-group modification, in chain growth polymerisation a functional initiator is required for the α-end modification of the polymer, while depending on the polymerisation technique used the end-group would be different. For example, in Cu(0)-RDRP the end group is a bromide group which can be further utilized in reactions like thiol-bromo click reaction. In step-growth polymerisation, the end-group

functionality is determined by the stoichiometry of monomers and the excess functional group would become the end-group and can be further modified.

One example showing the importance of post-polymerisation modification in polymer chemistry is the preparation of functional polyoxazolines. Polyoxazolines are prepared *via* the cationic ring opening polymerisation (CROP) of oxazoline monomers, where any nucleophilic functional groups would terminate the chain growth and result in undesired molecular weight and end fidelities. Thus, the post-polymerisation modification of polyoxazolines is vital for obtaining polyoxazolines with certain functionalities. For example, primary amine and secondary amine groups are not tolerable in the CROP process, however, by using protection chemistry or hydrolysis of polyoxazoline side chains, these two functional groups can be easily introduced to the polyoxazoline backbone for applications such as nanoparticles formation[164,165] and DNA complexation.[166–168] By using a functionalized initiator or using terminating agents, polyoxazoline could also be end-functionalized and further couple with other polymers such as poly(acrylate)s, poly(lysine)s and glycopeptides to prepare functional polymers for applications like microbial adhesion and micelle formation.[169–171] These multiple reactive sites provide a channel to prepare multifunctional polyoxazolines for different applications, which is a major advantage when comparing polyoxazolines to polyethylene glycol (PEG), the 'golden standard' polymer in biomedical applications.

To access more facile and efficient functionalization, click reactions have been widely applied in the preparation of functionalized polyoxazolines. Due to the tolerance of CROP process to alkene, alkyne and azide groups, oxazoline monomers, initiators and terminating agents functionalized with these functional groups have been firstly investigated while corresponding thiol-ene, Diels-Alder, thiol-yne and azide-alkyne cycloaddition click reactions were employed for the functionalization. For example, thermoresponsive polyoxazolines synthesized *via* thiol-ene click reaction was reported in 2009,[172] where a set of polyoxazolines with different thermo-responsive properties were prepared from a clickable poly[2-(isopropyl/3-butenyl)-2-oxazoline] scaffold. By using thiols with different functional groups such as alkyl chains, carboxylic acids and carbohydrate moieties in thiol-ene click reaction, resulting polyoxazolines were quantitatively functionalized and showed different lowest critical solution temperature (LCST) that varies with the nature of functional groups from the thiol. Kempe *et al.* reported

the preparation of a multi-clickable polyoxazoline in 2011,[173] where the polyoxazoline backbone was functionalized with Diels-Alder clickable initiator, alkene-containing side chain from a functionalized oxazoline monomer, and end capped with sodium azide to introduce the SPAAC clickable azide group. The multifunctional polyoxazoline were then reacted with a thiol-containing sugar, maleimide and cyclooctyne in one-pot, showing the orthogonality of thiol-ene, Diels-Alder and SPAAC click reactions. The polyoxazoline was then prepared into a nanoparticle, while the cyclooctyne hydroxyl group was labelled by a biomarker to give a nanoparticle with potential lectin-binding and detection applications. Apart from these click reactions, other click reactions like para-fluoro-thiol click reactions, thiol-bromo click reactions and SuFEx click reactions have not been investigated in the polyoxazoline functionalization field yet, while in this thesis studies on these click reactions with polyoxazolines will be presented.

Click reactions for post-polymerisation modification is also popular in other polymerisation systems, while being more versatile when the functional group tolerance is better. CuAAc click reaction is presumably the most reported click reaction used for post-polymerisation modification due to not only the efficiency of the reaction but also the compatibility of alkynes to polymerisation systems. Thiol-ene and thiol-yne reactions were also frequently reported thanks to the large family of commercially available thiols and the availability of alkene and alkyne groups. There have been numerous publications that reviewed the post-polymerisation modification using CuAAc,[174,175] thiol-ene[131,174,176] and thiol-yne[174,176] click reactions, and thus these click reactions would not be emphasized here. Due to the accessibility of pentafluorobenzyl groups, post-polymerisation modification with the para-fluoro-thiol click reaction is mostly restricted to the modification of poly(2,3,4,5,6-pentafluorostyrene) and its copolymers. For instance, this click reaction has been used in a NMP polymerisation system in 2009 where poly(2,3,4,5,6-pentafluorostyrene) and copolymers of pentafluorostyrene and oligo(ethyleneglycol) methacrylate were prepared at different composition and then modified with thiophenol to tune their thermo-responsive properties.[177] The newly emerged SuFEx click reaction was used orthogonally with CuAAC click reaction to modify functionalized polystyrenes,[178] different dyes were attached to the polystyrene backbone and a triply functionalized polystyrene was prepared with two orthogonal SuFEx reactions and one CuAAc click reaction. However, reports on SuFEx click reaction were mostly about preparation of step-growth polymers, thus great potential exists for exploring post-polymerisation

modification with SuFEx click reaction. The thiol-bromo click reaction was mostly used for polymer-polymer coupling or preparation of star and step-growth polymers as polymerisation techniques like Cu(0)-RDRP provides chain end bromo groups,[47,98,136] while the side chain modification of polymers with thiol-bromo click reaction remains absent, possibly due to the high reactivity of both groups causing incompatibility with polymerisation techniques, while other functional groups like alkenes and alkynes can also click with thiols, and thus the bromo pathway was not the most popular method.

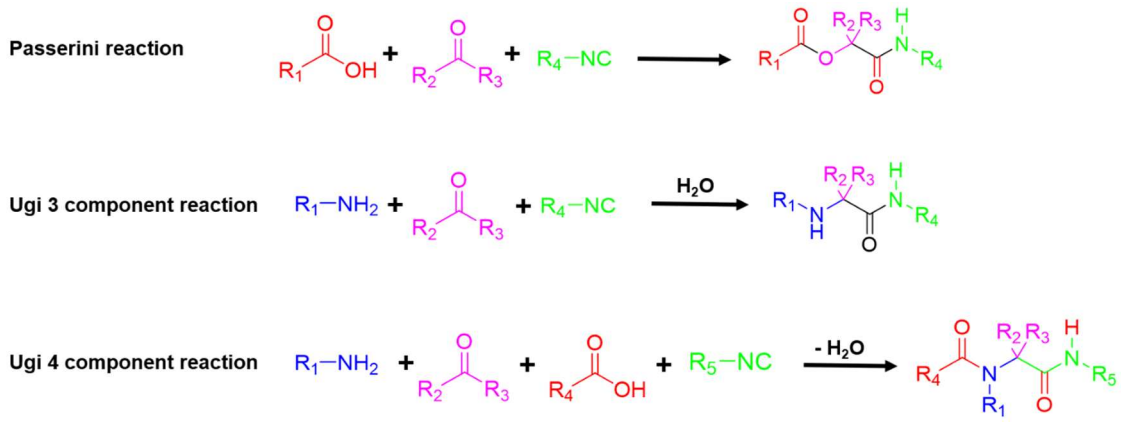
By choosing appropriate polymerisation methods and functional monomers as well as designing the synthesis pathway accordingly, one can prepare functional polymers with pre-determined chain length, structure, and corresponding functionality, while click reactions, due to their convenient and efficient nature, are playing an increasing vital role in this field of polymer chemistry. In the preparation of high molecular weight step-growth polymers and quantitative functionalization of polymeric precursors, click reactions play an indispensable role now.

Apart from click reactions, another kind of reaction is popular in the field of step-growth polymerisation, post-polymerisation modification, and precise polymers synthesis: multicomponent reactions. These reactions have more than two starting materials and produce complex heteroatom linkages, which could provide interesting properties. The use of multicomponent reactions in step growth polymerisation and post-polymerisation modification will be introduced in the following section.

1.5. Multicomponent reactions towards step growth polymers, post-polymerisation modification, and sequence-defined polymers.

Multicomponent reactions are efficient, convergent, and high atom-efficiency one-pot reactions that happen among three or more components to typically form one final product. These reactions were initially discovered to overcome the tedium of multistep synthesis in organic chemistry but soon found their place in polymer chemistry due to their efficiency and

the interesting linkages created *via* these reactions.[179–182] Several multicomponent reactions have been reported such as Biginelli,[183] Hantzsch,[184] van Leusen,[185] Passerini,[186] Strecker[187] and Ugi multicomponent reactions.[188–191] Among these reactions, Ugi multicomponent reaction is arguably the most popular one in polymer chemistry due to the availability of starting materials and the unique peptidomimetic structure formed in this multicomponent reaction. Ugi multicomponent reactions include 3 component and 4 component reactions, while the Passerini reaction is often mentioned as they have similar starting materials. The reaction schemes of Ugi 3, 4 component reaction and Passerini reaction are shown in **Scheme 8**. To induce polymerisation with these reactions, at least two of the starting materials should be at least bifunctional, while to produce linear polymers exactly two starting materials should be bifunctional. By using combinations of different bifunctional monomers, for the Ugi 3 component reaction and the Passerini reaction there are three types of polymers that could be obtained from the multicomponent polymerisation process, while for the Ugi 4 component reaction there are six types of polymer that could be produced. This large diversity of obtained product provides wide scope for the preparation of different polymer structures with multiple side chain functionalities *via* the Ugi 4 component reaction, and thus scientists started to investigate this topic.



Scheme 8. Reaction schemes of Ugi 3, 4 component reaction and Passerini reactions.

1.5.1 Ugi 4 component Polymerisation into step-growth polymers

Using Ugi 4 component reaction to prepare substituted polyamides was firstly studied in 2014, where Sehlinger *et al.* firstly reported the investigation on all six types of Ugi 4 component polymerisation,[192] the effects of monomer type, solvent, and temperature were investigated

while some optimised reaction conditions for certain bifunctional combinations have been found, such as using THF/MeOH (2:1) solvent mixture for Ugi polymerisation with diamine and dicarboxylic acid. Gangloff *et al.* reported the Ugi polymerisation with aromatic monomers in particular in 2015,[193] where similar parameters like solvent composition and temperature were investigated. This report did show some different results compared to the one mentioned before, like the effect of water and the efficiency of aromatic monomers. The high atom efficiency and green reaction conditions, like room temperature and use of 'green' solvents like methanol, have made Ugi reaction potentially useful in the field of green chemistry, as shown by a report published in 2016 where polyamides were prepared from the direct Ugi 4 component polymerisation of levulinic acid with excellent yield and short reaction time.[194] As amino acids naturally possess amine and carboxylic acid functional groups, they are thus easily incorporated in Ugi reaction as bifunctional monomers to produce polypeptoids. Wang and coworkers investigated this polymerisation with three different amino acids where the structure of amino acids minimized the chance of cyclisation which would prevent generation of high molecular weight polymers.[191] Al Samad *et al.* reported a unique peptide-peptoid alternating structure prepared *via* Ugi 4 component reaction of dipeptides with aldehydes and isocyanides in 2017,[195] revealing the possibility of utilizing peptide oligomers to create polymers with novel structures. The preparation of peptoid structures via Ugi reaction was reported in 2018 and 2019 where alternating charged polypeptoids and sequence defined polypeptoids were prepared, respectively.[196,197]

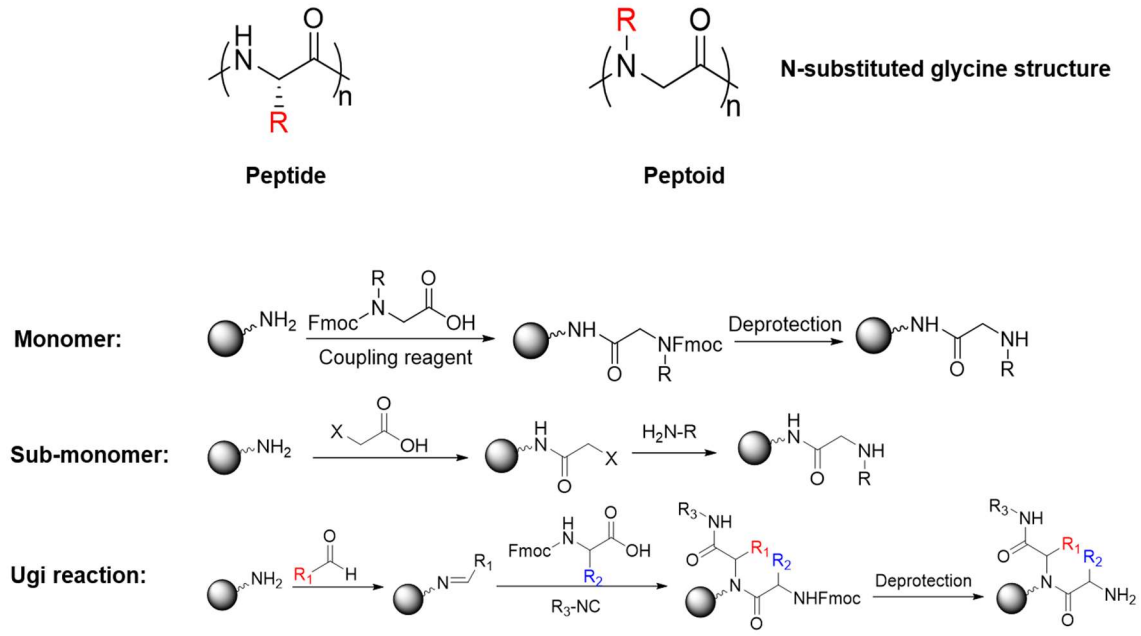
Polymers prepared from Ugi-4-component reactions possess a N-substituted polyamide structure, namely polypeptoid structure. These polymers have less ability to form intermolecular hydrogen bonding, thus possess lower melting temperature and more flexible backbones, which makes them potentially useful elastomers. As Ugi reactions can be treated as a 'green' way to synthesize polymers, the use of more bio-sourced 'green' monomers would be useful for the preparation of sustainable polymers. Another benefit of Ugi 4 component polymerisation is the functional rich nature of the polymer obtained, as there are multiple side chains on each repeating unit, which could be further functionalized for desired purposes. Thus, using Ugi 4 component reaction should be considered as a method with wide scope and investigations on preparing different structures with 'green' monomers, tuning the properties of polymers with different side chain compositions and producing elastomers for desired applications should possibly be considered as low-hanging fruits.

1.5.2 Peptoids via solid-phase Ugi-4-component reactions

Polymer chemists were always chasing one ultimate goal, which is known as 'the holy grail' of polymer chemistry. The goal is to have complete control over monomer sequences and dispersity and obtain sequence-defined monodisperse polymers that have uniform, pre-designed functionality, just like how nature manufactures polypeptides and proteins. Natural polymers like proteins and nucleic acids can fold into complex architecture and perform crucial biological functions, and the precise positioning of building blocks is of importance in the folding process of natural polymers. While nature assembled numerous polymers with defined sequence structure with limited kinds of building blocks like amino acids, a great diversity of novel functional polymers could be prepared with the huge library of synthetic monomers available if facile and precise synthesis of sequence defined polymers could be achieved. Thus, the research on developing efficient methods to synthesize novel sequence defined functional polymers has been an intensively focused field.

Solid-phase supported synthesis (SPSS) has been the most reported method of preparation of sequence defined polymers.[198] This technique employs a functionalized resin as the solid support which can swell in certain solvents and allow the functional groups to be more accessible. The functional group on the resin is often protected to prevent undesired loss of functionality. Certain synthetic methods were performed by firstly deprotecting the resin to free functional groups, followed by addition of reactants allowing selected chain-growth reactions to happen. Usually another protected chain-end was created after the chain-growth reaction to allow the following additional iterative deprotection and chain-growth processes. Excess reactants could be removed by just simple filtration, and thus large amounts of reactants could be used to push the equilibrium of reaction to reach full conversion. Upon completion of polymerisation, excess reagents were removed by filtration, followed by the cleavage of desired polymer from the solid support. Although this process requires iterative washing, deprotection and chain-growth reactions, the introduction of automated synthesizer allowed the preparation of long sequence defined polymers (>50 building blocks).[199,200] Thus, it is the most common way to synthesis sequence defined polymers now, while solution phase synthesis of sequence defined polymers is still possible.

As peptides and proteins are crucial in biological behaviours, the preparation of similar structures has attracted interest. Synthetic peptides and peptoids are the two most studied peptide-like synthetic polymers, known as peptidomimetics, while peptoids were popular recently due to the structure diversity compared to the limited library of amino acids constructing peptides. Peptoids are polymers or oligomers of N-substituted glycines, which different functional groups installed on the nitrogen can be introduced via a monomer approach where protected N-substituted glycine was coupled to a primary amine followed by deprotection of primary amine for the next repeating unit, or submonomer approach that was developed by Ronald Zuckermann in 1992.[201–204] (**Scheme 9**) A haloacetic acid and a primary amine were used in an alternating step-growth polymerisation approach to construct a peptoid backbone, while thanks to the large library of primary amines available and the automation technique, it is hence possible to obtain various functionalities onto a peptoid backbone, such as charged groups and sugar moieties. Polypeptoids with designed interesting properties have been widely synthesized and reported,[80,205,206] and thermal responsiveness, electrostatic-driven self-assembly, π-π stack driven self-assembly and lectin-binding properties were quite straightforward to introduce. These properties are useful to peptoids as the formation and disassembly of nanostructures and lectin binding to cell recognition properties are crucial in drug delivery or in the drug discovery industry.



Scheme 9. Structure difference between peptides and peptoids and the three solid-phase supported synthesis methods of polypeptoids.

Besides the sub-monomer approach, Ugi 4-component reaction has been discovered as another practicable approach to synthesize peptoid compounds, and due to the function rich product obtained, which possess three side chains with tailorable functionalities, it has attracted more research interest since it was firstly reported on 2008, with several studies since reported.[191,195,197,207] Ugi-4-component reaction is the reaction of a primary amine, a ketone/aldehyde, a carboxylic acid and an isocyanide. The imine formation between the amine and the aldehyde is followed the nucleophilic attack and rearrangement to form a peptoid backbone. The other functionalities on reagents are introduced as three sidechains, which makes the peptoid function rich. Thanks to the large availability of these reagents, tailoring the side chain functionality of the peptoid obtained is thus possible.

The Ugi-4-component reactions enable the synthesis of peptoids with three functional groups on one repeating unit and could serve as a decent platform for designing several properties and integrating them into one backbone, thus obtaining a versatile sequence-defined functional polymer. For biomedical applications, the most interesting properties are responsiveness, self-assembly and cell recognition properties. Responsiveness allows the control of polymer architecture under determined conditions, while self-assembly brings several extra benefits, like the ability of encapsulating drugs and improving the sugar-lectin binding efficiency. The cell recognition properties allow the interaction of synthetic polymers with living organisms, which would either allow us to affect the biological nature of cells and thus achieve goals like treat illness or detect the behaviour of cells to provide more understanding of this nano-scale world.

Based on all these highly-efficient chemistry, like click chemistry and multicomponent chemistry, that has been developed by organic chemists, it is important to exploit these reactions in polymer chemistry for purposes including step-growth polymerisation and post-polymerisation modification, as features like high conversion, good atom efficiency and mild reaction conditions are beneficial to not only obtaining high molecular weight step-growth polymers but also reaching 100% side chain modification ratio. Besides, these highly-efficient reactions also create unique linkages or polymer backbone structures, such as thiol-ether linkage, perfluorobenzene backbone and N-substituted peptoid backbone structure. These advantages on backbone preparation and side chain modification are of great importance to preparing novel functional polymers. Thus, this thesis aims to investigate the application of

less studied highly-efficient reactions, like para-fluoro-thiol click reaction, thiol-bromo click reaction, sulphur(VI) fluoride exchange reaction, and Ugi-4-component reaction in polymer chemistry and prepare functional polymers with these reactions. By investigating these highly-efficient reactions in polymer chemistry and prepare polymers with different properties like thermal resistance and self-assembly properties, this work should open more avenue on designing and synthesis of functional polymers.

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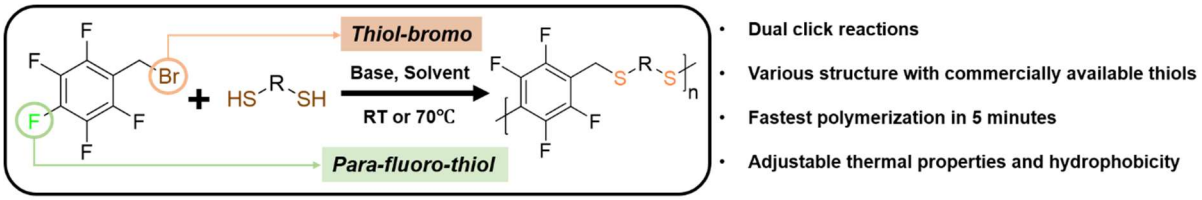
Chapter 2: Fluorinated Polymers via para-Fluoro-Thiol and Thiol-Bromo Click Step Growth Polymerization



Abstract

Click reaction are utilized widely to modify chain ends and side groups of polymers while click polymerizations based on step-growth polymerization of bifunctional monomers have recently attracted increased attention of polymer chemists. Herein, the combination of two highly efficient click reactions, namely para-fluoro-thiol click and thiol-bromo substitution reactions, is demonstrated to form fluorinated polymers with tuned hydrophobicity owing to the nature of the dithiol linker compound. The key compound in this study is 2,3,4,5,6-pentafluoro benzyl bromide that provides the combination of thiol-click reactions. The thiols used here are 4,4-thiobisbenzenthiol, 2,2'-(ethylenedioxy) diethanethiol, and 1,2-ethanedithiol that allow tuning of the properties of obtained polymers. The step-growth click reaction conditions are optimized by screening the effect of reaction temperature, base, solvent, and stoichiometric ratio of the compounds. Thermal properties and hydrophobicity of synthesized polymers are determined via water contact angle, thermogravimetric analysis and differential scanning calorimetry measurements, showing thermal stability up to 300 °C, glass transition temperatures ranging from -25°C to 82 °C and water contact angles ranging from 55 to 90 °C.

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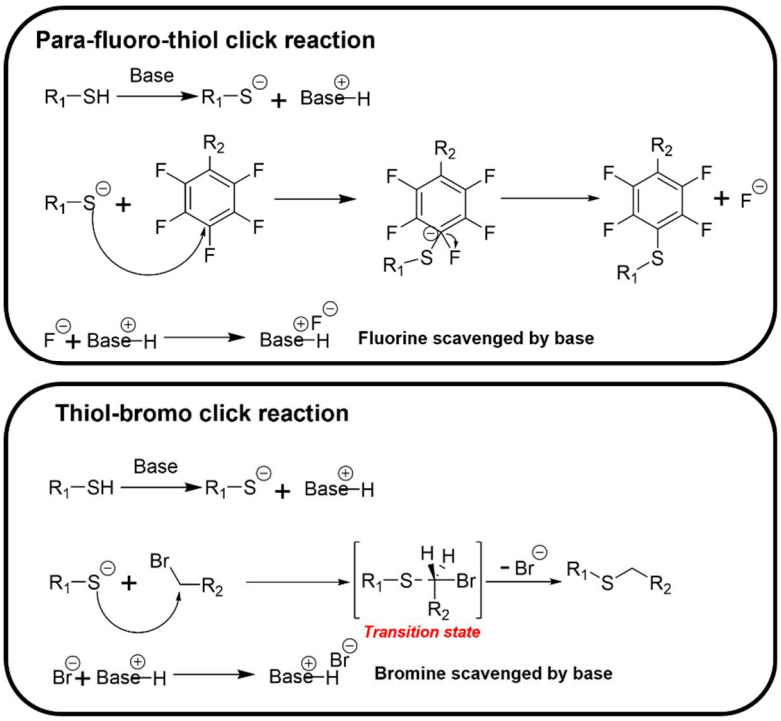
2.1 Introduction

Fluorinated polymers are gaining growing attention in polymer chemistry since the discovery of polytetrafluoroethylene (PTFE) in 1938.[1] The existence of carbon-fluorine bonds and the electronegative nature of fluorine atoms provide several noteworthy properties of fluorinated polymers such as good thermal stability, hydrophobicity and chemical resistance. Besides PTFE, various fluorinated polymers with different backbone and sidechain structures including poly(vinyl fluoride) (PVF), polychlorotrifluoroethylene (PCTFE) and poly (vinylidene fluoride) (PVDF) have been developed and thoroughly investigated for different applications involving gas separation membranes[2,3], artificial muscle actuators[1], photoresists[4] and optical waveguides[5]. Fluorinated polymers are usually synthesized by either fluorination of polymers or direct polymerization of fluorine-containing monomers via chain-growth or step-growth methodologies. The fluorination approach is rarely employed due to the requirement of aggressive fluorination agents and non-quantitative degrees of fluorination of the post-polymerization modification.[6] However, the direct polymerization of fluorinated monomers is widely employed to synthesize numerous commercially available fluorinated polymers.[6,7] More recently, the synthesis of novel fluorinated monomers in combination with various polymerization methods have been the subject of intensive research. [3,8–10]

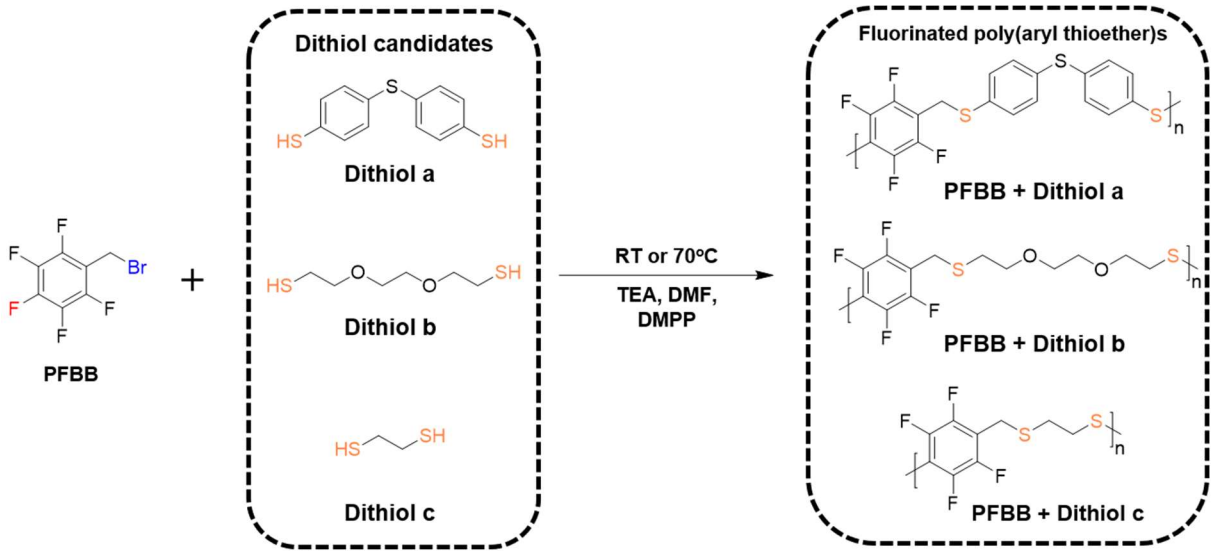
Due to the potential for the synthesis of polymers on industrial scales, step-growth polymerization emerged as a powerful tool for the synthesis of materials with different heteroatoms across the backbone. The inherited high dispersity enables the facilitated processing of the obtained polymers.[11,12] The advent of click chemistry opened avenues for the synthesis of step-growth polymers with novel architectures and properties.[8,13–16] The prerequisites of click reactions[13,17] such as fast reaction kinetics, atom economy, orthogonality and modularity, are promising features for step-growth polymerization, allowing the synthesis of high molecular weight polymers in very short reaction times. Several different click reactions have been reported to produce step-growth polymers. In 2018, Mohapatra and coworkers reported the synthesis of a linear polytriazole and cross-linked polymeric gel via copper-catalysed azide-alkyne cycloaddition (CuAAc) under ultrasound irradiation[18]. Song and coworkers studied the synthesis of linear and hyperbranched polymers of bifunctionalized azide and multifunctional alkynes via CuAAc and investigated the kinetics in 2016.[19] Besides CuAAc, sulfonyl fluoride exchange (SuFEx) click reaction, which was coined by Sharpless in 2014, was applied to synthesize polysulfates and polysulfonates.[20–22] Various bisphenol A (BPA) based disulfonyl compounds were used as monomers and resulting polysulfates have

shown good thermal properties and processability[20,21]. The combination of orthogonal SuFEx and CuAAc click reaction has been reported by Yang and coworkers on the synthesis of sequence-regulated polymers on a solid phase utilizing solvent phase click reaction[23]. Recently, thiol-halogen nucleophilic substitution reactions, including para-fluoro-thiol click reaction (PFTR)[24–26] and thiol-bromo click reaction[27–30] attracted growing attention due to the increasing interest in incorporating sulphur-based compounds into polymeric materials. The mechanisms of these two click reactions are shown in **Scheme 1**. The commercial availability of a multitude of thiol compounds with diverse functionalities enables the synthesis of numerous different polymer compositions *via* PFTR and thiol-bromo click reactions[26]. PFTR and thiol-bromo reactions are both base-activated coupling reactions with triethylamine (TEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) frequently employed to induce the reaction[26,29–31]. These two types of click reactions have been well investigated and reported for post-polymerization modification (PPM)[8,25,26,28,29,31–34], yet only a handful of reports demonstrated the preparation of step-growth polymers.[35–39] The fluorinated poly (aryl thio-ether) structures obtained from PFTR have great potential due to their remarkable physical properties[39] such as high refractive index (RI) values[29], and low optical loss.[10] Thus, in order to take an advantage of efficient PFTR and thiol-bromo click reactions and investigate novel fluorinated polymer structures, a combination of these two click reactions has been utilized to synthesize fluorinated polymers from different monomer precursors.



Scheme 1. Mechanism of para-fluoro thiol click reaction(nucleophilic aromatic substitution) and thiol-bromo click reaction(S_N2 displacement).

Herein, three commercially available dithiol building blocks and pentafluoro benzyl bromide were employed in the synthesis of fluorinated polymers with aryl thiol ether segments via simultaneous PFTR and thiol-bromo click reaction. (**Scheme 2**) The effect of base activation has been investigated and it was shown that the base is not acting catalytically in this polymerization. The obtained materials were tested on their thermal stability and hydrophobicity *via* TGA, DSC, and water contact angle, respectively.



Scheme 2. Synthesis of fluorinated poly(aryl thioether)s via thiol-bromo and thiol-para fluoro click reactions.

2.2 Results and Discussion

2.2.1 Kinetics investigation of step-growth polymerization of 2,3,4,5,6-pentafluoro benzyl bromide (PFBB) with dithiol compounds

Initial kinetic investigation of step-growth polymerization of 2,3,4,5,6-pentafluoro benzyl bromide (PFBB) with 4,4-thiobisbenzenethiol (dithiol, a), 2,2'-(ethylenedioxy) diethanethiol (dithiol, b) and 1,2-ethanedithiol (dithiol, c) was performed in DMF at 70°C or ambient temperature (**Figure 1**). Triethylamine (TEA) was selected as the base to initiate both para-fluoro-thiol click reaction and thiol-bromo reaction and act as the acid scavenger. These three dithiols were selected because polymers obtained would have aromatic, aliphatic and heteroatom backbones which could be representative, while the nucleophilicity difference of these three dithiols could assist the investigation on reaction rate to monomer nucleophilicity. To prevent disulfide bridge formation, which affects stoichiometry, dimethylphenylphosphine (DMPP) was added to the mixture of PFBB and dithiol DMF solution before the slow addition

of TEA to the mixture. T_0 samples were taken before the addition of base to prevent inaccurate t_0 trace because of rapid reaction. A swift exothermic was observed in room temperature reactions. Gel permeation chromatography (GPC) in THF showed the formation of polymers and molar mass values were calculated relative to PS standards, ranging from 2300 g/mol for 1,2-ethanedithiol (dithiol c) to 4700 g/mol for 4,4-thiobisbenzenthiol (dithiol a). These values indicate a calculated extent of reaction of 12-15 for these polymers. For dithiol a and dithiol c the polymer chain growth stops in less than 20 minutes, while due to relatively weak nucleophilicity of 2,2'-(ethylenedioxy) diethanethiol (dithiol, b), the polymerization continues over 10 hours, which is anticipated as the nucleophilic substitution mechanism of both click reactions employed. (**Figure 1**) The reactivity of the corresponding thiolate ion of dithiol b might be hampered by the strong electronegativity of two backbone oxygen atoms while dithiol a benefit from the aromatic ring resonance and dithiol c has a very low steric hindrance. Comparing the kinetics graph under 70℃ and 25℃, at higher temperature shorter time was required to reach the completion of polymerization and molar masses of polymers produced were slightly higher. This could be the consequence of elevated temperature accelerate the deprotonation of thiol groups into thiolate ions and the nucleophilic attack that leads to polymer growth.

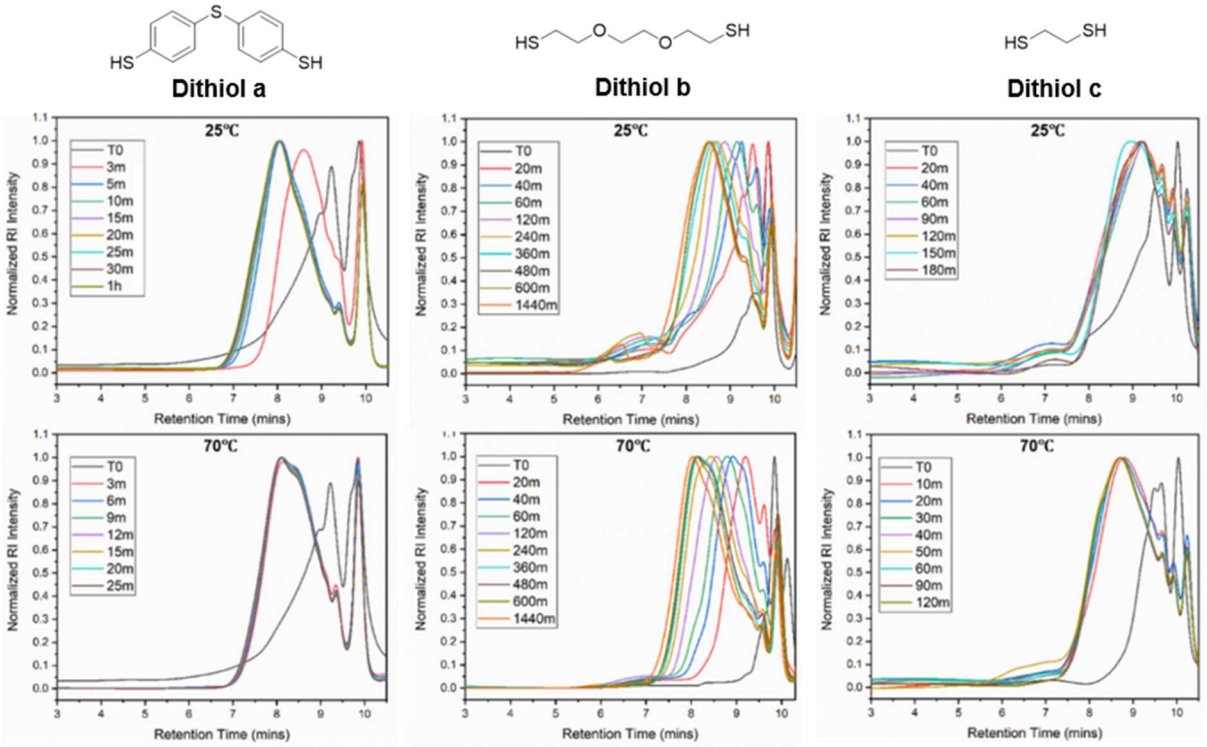


Figure 1 GPC traces of step-growth polymerization of PFBB and dithiol a, dithiol b and dithiol c at various time intervals at 25℃ and 70℃, respectively.

When analyzing the reaction kinetics of PFBB with dithiol b under 25℃ by ^{1}H and ^{19}F NMR, full monomer conversion for thiol-bromo reaction was observed within minutes (**section 2.4.4**, **Figure 10**), shown by the shift of hydrogens of PFBB from 4.50 to 3.89 which indicates the removal of electron drawing bromine, while ^{19}F NMR showed the para-fluoro-thiol click reaction proceeds and allows the formation of polymer chains (**Figure 11, 12**). These results suggests the possibility of a fast thiol-bromo reaction leads to the formation of an AB type precursor followed by the PFTR dominated chain growth process as a consequence of weak nucleophilicity of dithiol b, while also suggesting higher reactivity of the C-Br bond in the nucleophilic substitution. The conversion versus time and $M_{n,GPC}$ versus conversion plots (**Figure 2, a, b**) were drawn based on the quantitative ^{19}F NMR kinetics of polymerisation of PFBB with dithiol b, where the conversion was determined by the change of integration value of para-fluoro peak in ^{19}F NMR, examples were shown in section 2.4.4, **Figure 13** (a) and (b). The overall trend fits the prediction of Carothers equation despite at high conversion the experimental $M_{n,GPC}$ was lower than the theoretical $M_{n,GPC}$, which might be the consequence of cyclic polymer production and stoichiometry distortion which would be discussed later with NMR and MALDI-ToF evidence. ^{1}H NMR, ^{19}F NMR and MALDI-ToF analysis of the purified polymer revealed the existence of desired polymer structure.

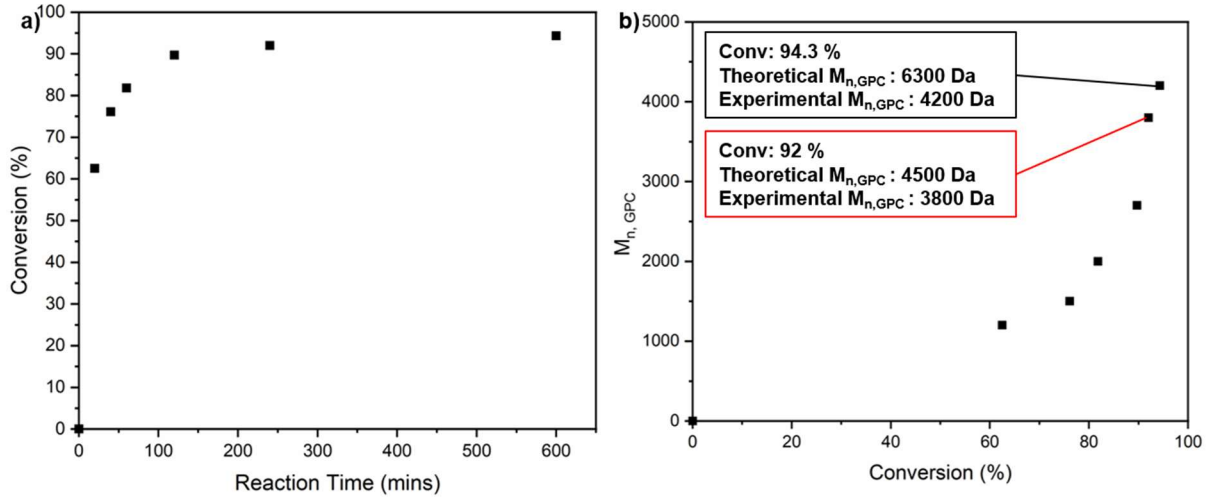


Figure 2. Conversion versus time (a) and number average molecular weight versus conversion(b) plots. The conversion of monomer was calculated using quantitative ^{19}F NMR.

As shown in **Figure 3,** using PFBB-dithiol a polymer as an example, formation of desired polymer backbone structure was confirmed by MALDI-ToF, the experimental mass number matches the calculated mass with desired repeating unit structure with penta-fluoro and

tetrafluoro benzyl bromide as end groups, the stoichiometry ratio of meta and ortho fluorine and the mass of the repeating unit shown in MALDI indicates the formation of a linear polymer backbone with no meta- or ortho- fluorine substitution occurred during polymerization. Polymers of PFBB with other two thiols (b and c) were also purified and characterized to show the desired structures have been obtained (Section 2.4.4, **Figure 14**), although polymer of (PFBB-dithiol c) does not show a clean MALDI-ToF signal, which might be due to the high content of fluorinated aromatic ring.

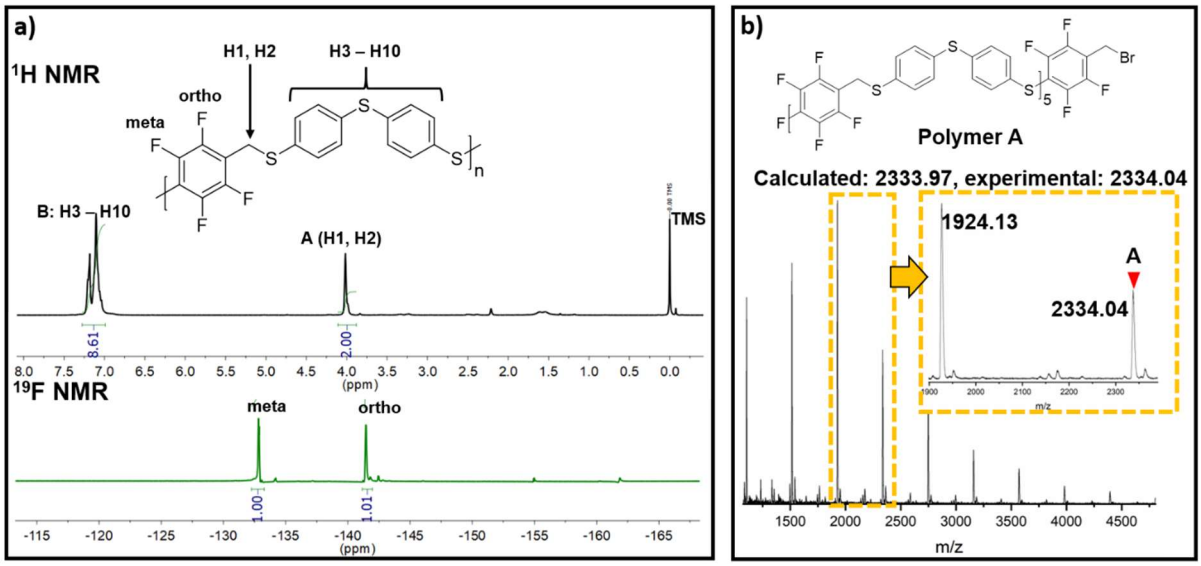


Figure 3. ^{1}H NMR, ^{19}F NMR (a) and MALDI-ToF MS (b) analysis of polymer of PFBB and dithiol a.

The calculated moderate extent of reaction values indicates achieving full conversion might be hampered. Possible reasons include cyclisation, imbalanced stoichiometry, and side reactions. MALDI-ToF analysis effectively shows the mass that corresponds to the repeat unit as well as by performing end group analysis the existence of cyclized polymer chains was easily determined. The possibility of cyclisation is evidenced further with MALDI-ToF data in section 2.4.4, **Figure 15, 16**. ^{1}H NMR of mixed PFBB stock solution and dithiol a stock solution (**Figure 4**) has shown that without the addition of base even with the most nucleophilic dithiol a, no click reaction would happen and allows the monitoring of stoichiometry by ^{1}H NMR. The molar ratio of both reactants can be calculated via integration, where the ratio of PFBB to dithiol a is 0.98:1 and the theoretical extent of reaction should be 50 if the reaction reaches full conversion. The difference between the theoretical extent of reaction based on stoichiometry calculated from ^{1}H NMR and the molar mass gained from the GPC indicates the existence of other hindrances. To investigate possible side reactions dithiol a was selected as

the model compound for step-growth polymerization with PFBB in DMF with TEA assistance and different reaction procedures were executed. It was revealed that no significant difference

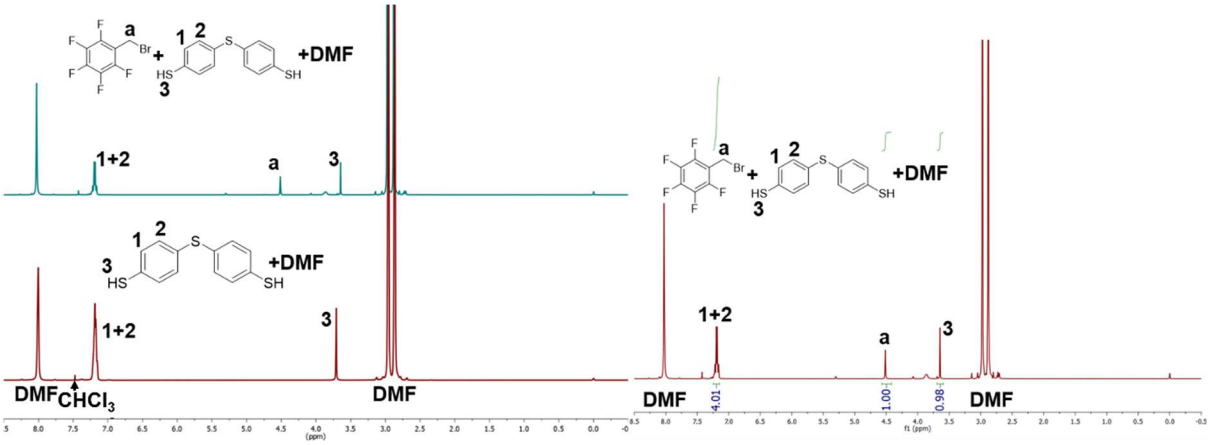


Figure 4. ^{1}H NMR comparison of PFBB-disthiol a stock solution mixture to dithiol a stock solution (left) and the integration of ^{1}H NMR of PFBB-dithiol a stock solution mixture(right).

of resulting polymer molar mass observed while adding PFBB to a mixture of dithiol and TEA, comparing to the original approach where PFBB and dithiol were mixed first. However, when mixing PFBB with TEA and subsequently adding dithiol a, significantly restricted polymer growth was observed (**Figure 5a**). To investigate the reason of this limited chain growth, 1 equivalent of PFBB and 2.05 equivalents of TEA were mixed in DMF for 30 minutes. ^{19}F NMR characterisation demonstrated the formation of secondary distribution for ortho-, meta- and para-fluoro pattern, which corresponds with the shift of TEA and PFBB peaks in ^{1}H NMR spectrum (**Figure 5b**) where the -CH_2- hydrogens from PFBB shifted from 4.50 to 4.94, indicates the presence of a stronger electron withdrawing group comparing to bromine, the methyl hydrogens of TEA shifted from 1.03-1.07 to 1.51-1.55 and the methylene hydrogens of TEA shifted from 2.53-2.59 to 3.59-3.64. These shifts suggesting the possible formation of quaternary salt of PFBB and TEA, which might be the side reaction that diverts the stoichiometry. As tertiary amines have been reported as an efficient end-capping reagent for poly(2-oxazoline)s[40,41], the limited chain growth obtained was most likely a consequence of quaternary salt of monomers and oligomers and thus stop the chain growth and affects the stoichiometry, which is also responsible for the sharp tailing peak at 10 minutes region, as the THF GPC solvent includes TEA that could react with oligomers and form the quaternary salt structure. It was also noticeable that if dithiol and TEA were mixed first and PFBB was then added slowly, gelation of the reaction system was observed in seconds, suggesting that potential side reactions on meta-fluorine is possible if the base amount is substantial.

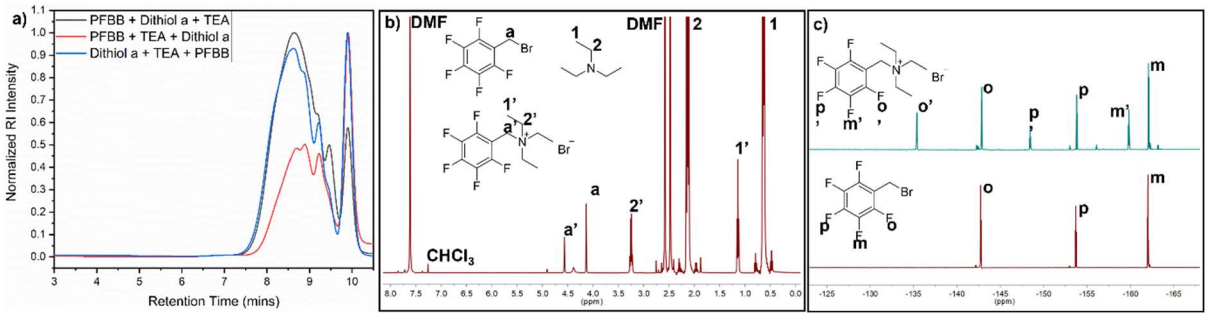


Figure 5. a). GPC (THF eluent) traces of polymer of PFBB-dithiol a via different addition order **b**). ^{1}H NMR of PFBB and TEA mixture in DMF. **c**) ^{19}F NMR comparison of PFBB and TEA mixture in DMF with PFBB in DMF, where a secondary pentafluoro pattern was observed.

2.2.2 Screening of different stoichiometry, bases, and solvent systems

To diminish possible side reactions caused by the base, increase the extent of reaction, and obtain longer polymer chains, the effect of different bases and their stoichiometry were investigated. As ring structures of TBD and DBU were bulkier than TEA and it has been reported that both TBD and DBU can be utilized as organocatalysts for para-fluoro-thiol click reaction[16,39], TEA, DBU and TBD were selected to initiate the step-growth polymerization of PFBB and dithiol a. These bases were not only differing in their pKa but also different in terms of nucleophilicity, where DBU and TBD were known as non-nucleophilic bases. By screening 2.05, 1.05, and 0.05 equivalent of the base, the contribution of the base to the reaction and its impact on the degree of polymerization were investigated. The obtained results are presented in **Table 1** and GPC traces are shown in **Figure 6**. Based on the M_n given by the GPC and the molar mass of polymer repeating unit, the theoretical extent of reaction ξ was calculated following Carothers equation and shown in Table 1.

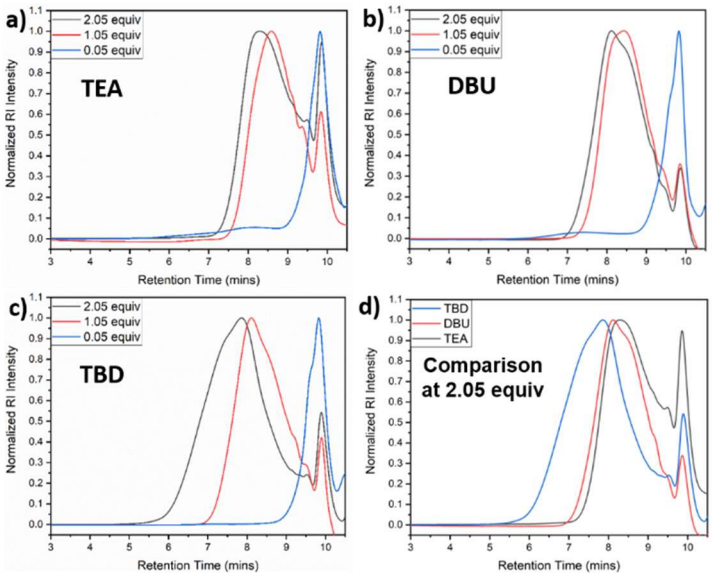


Figure 6. GPC traces of step-growth polymerization of PFBB and dithiol a with different amounts of (a) TEA (b) DBU, (c) TBD and (d) comparison of TEA, DBU and TBD using 2.05 equiv. of the respective base.

The polymerization reactions, which were carried out with 0.05 equiv. of the respective base (**P3**, **P6**, **P9**) show, that only very low molecular weight polymers are formed, regardless of the base strength. These results underpin the non-catalytic nature of the base in this reaction. It is assumed, that the base is removed from the reaction mixture by scavenging the formed HF and HBr, reducing its concentration in the reaction solution. Therefore, the stoichiometric ratio of the base was increased, yielding the highest molecular weights, when 2.05 equiv. were used. The obtained results for **P1**, **P4** and **P7** demonstrate further the effect of base strength on molecular weight. When using the stronger base TBD (**P7**), the highest number average molecular weight was obtained (9.7 kg/mol). The increased average molecular weight is thought to result from the ease of thiol groups deprotonate into thiolate anions with a stronger base while the increased dispersity is presumably due to kinetic quenching from polymer precipitation as reported in the previous literature.[39] It should be noted that fast reactions may also decrease the possibility of producing cyclic polymers, which is indicated as the low molecular weight tail that lowers down the number average molar mass in the GPC trace. It is also possible that as already shown in Figure 1, both click reactions are quite efficient, thus after a short period of time the polymer concentration is high which allows more long-chain coupling that distorting the molar mass distribution to higher molecular weights, while for

stronger base not only the click reaction but also the chain-chain coupling is more efficient.

The effect of solvent was investigated with DMF, THF and $CHCl_3$, as PFTR click reactions require aprotic polar solvent environment, while the dithiol compounds show poor solubility under such conditions. Furthermore, the formation of a dimer precursor by utilizing PFTR-unfavored solvent[26] like $CHCl_3$ and a subsequent solvent system change were explored to drive the polymerization. The obtained results are summarized in **Table 1** and the corresponding GPC traces are displayed in **Figure 7**. When $CHCl_3$ was employed in the polymerization (**P12**), the absence of higher molecular weight species was observed in the GPC traces. However, conducting the reaction in DMF (**P10**) and THF (**P11**) resulted in the formation of polymers with moderate molecular weights of 7.0 and 2.3 kg/mol, respectively. The low molecular weight, which was observed for the reaction in THF was thought to result from the low solvent polarity and the observed precipitation of a yellow gel during the reaction. The gelation indicated the possibility of side reactions with meta- or ortho-fluorine atoms and hence crosslinking. The step-growth polymerization was shown to proceed in solvent mixtures of $CHCl_3$ /DMF and THF/ DMF at a concentration of 0.66 *M* concentration (**P13, P14**). However, the obtained molecular weights were lower, when compared to the polymerization reactions at the same concentration, which were conducted in solely DMF (**P10**).

Table 1. Investigations on the type of base, stoichiometry and solvent effect on step growth polymerization of PFBB and dithiol a.

Name	Base type	Base eq.	Solvent	Conc. [M]	$M_{n,\,GPC}$ (kg/mol)	$M_{w,\,GPC}$ (kg/mol)	*Đ*	*Conv. (%)*
P1	TEA	2.05	DMF	1.00	4.2	8.0	1.93	90
P2	TEA	1.05	DMF	1.00	3.0	5.6	1.92	86
P3	TEA	0.05	DMF	1.00	n. d	n. d	n. d	n. d
P4	DBU	2.05	DMF	1.00	4.5	10.4	2.33	91
P5	DBU	1.05	DMF	1.00	3.6	7.6	2.08	88
P6	DBU	0.05	DMF	1.00	n. d	n. d	n. d	n. d
P7	TBD	2.05	DMF	1.00	9.7	40.1	4.31	95
P8	TBD	1.05	DMF	1.00	4.7	10.1	2.15	91
P9	TBD	0.05	DMF	1.00	n. d	n. d	n. d	n. d
P10	TBD	2.05	DMF	0.66	7.0	18.8	2.70	94
P11	TBD	2.05	THF	1.00	2.3	5.2	2.24	82
P12	TBD	2.05	$CHCl_3$	1.00	n. d	n. d	n. d	n. d
P13	TBD	2.05	THF/DMF	0.66	4.7	14.6	3.10	91
P14	TBD	2.05	$CHCl_3$/DMF	0.66	4.4	17.0	3.81	90

TEA: triethyl amine, **DBU**: 1,8-diazabicyclo [5.4.0]undec-7-ene, **TBD**: 1,5,7-Triazabicyclo-[4.4.0]dec-5-ene, **n.d.**: not determined as very low oligomeric products formed. Conversion

was based on change of integration of para-fluoro peak in ^{19}F NMR which representing the consumption of para-fluorine.

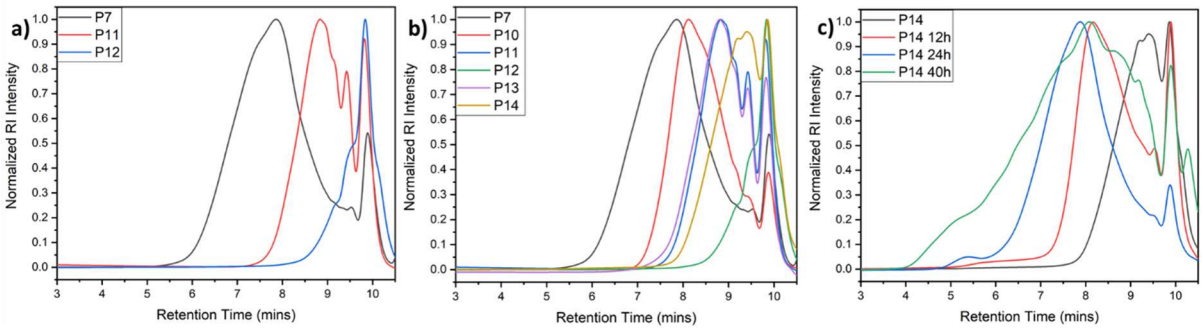


Figure 7. GPC traces for the investigation of solvent effects for step-growth polymerization of PFBB and dithiol a. a) Step-growth polymerization of PFBB and dithiol a in DMF (P7), THF (P11) and $CHCl_3$ (P12) respectively. b) Step-growth polymerization of PFBB and dithiol a in DMF (P7), THF (P11), $CHCl_3$ (P12), DMF with a concentration of 0.66 M (P10), addition of DMF to THF (P13, c(DMF) = 0.66 M), and addition of DMF to $CHCl_3$ (P14, c(DMF) = 0.66 M). c). GPC traces of P14 at 12h, 24h, and 40h.

It was also shown that in $CHCl_3$/DMF mixtures, the polymerization rate is decreased dramatically, yielding high molecular weight species in 24-48 h, while also forming an insoluble gel. The increase in molecular weight at later stages of the polymerization was thought to result from the different reaction kinetics of thiol-bromo and PFTR reaction in $CHCl_3$. Therefore, thiol-bromo reactions occur rapidly, which leaves para-fluorine group to react with thiol after the addition of DMF and the suggested base end-capping reaction cannot interfere with the growth of polymer chain, thus plentiful of long-chain coupling was allowed in elongated time which yield broadly dispersed polymer with high molecular weight species.

Based on the conducted screening results, 2.05 equiv. of TBD mediated the step-growth polymerization in a DMF solvent system at room temperature at 1.0 *M* concentration was employed as model conditions to prepare the largest polymer in this study. TBD catalyzation results in slow chain growth that gives a polymer with a molecular weight of lower than 3000 after 48 hours, while DBU has performed best to produce a polymer with moderate molecular weight. Thus, step-growth polymers of PFBB-dithiol a, PFBB-dithiol b and PFBB dithiol c were synthesized using TBD and DBU catalysis under previously mentioned model conditions and the MALDI-ToF analysis have shown the formation of desired polymer structure (Section 2.4.4, **Figure 15, 16**). As fluorinated polymers are mainly termed as polymers possessing good thermal stability and hydrophobicity, thus these two functionalities of three prepared polymers

were characterized and discussed below. Based on the preparation of step-growth polymers with dithiol a b and c, it is possible that other step growth polymers can also be synthesized via this approach based on the large library of commercially available dithiol candidates (Section 2.4.4, **Figure 17**) while some of the backbones can provide interesting properties include hydrophilicity from hydroxy groups, post-polymerization modification from double bonds, rigidity and intermolecular forces from aromatic rings.

2.2.3 Thermogravimetric and hydrophobicity analysis

Thermal properties of obtained polymers were examined by thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) (**Figure 8**). TGA traces of all three polymers have shown thermal resistance up to the temperature range of 310 -350 ℃, although weight loss was different among the three polymers due to differences in aromatic content and elemental composition. The remaining weight of polymers of dithiol a was still high after the facile decomposition at 348℃, the percentage weight loss of the decomposition corresponds to the degradation of thiol-ether function and decomposition of sulphur atoms in the polymer while until heated to 1000℃ the remaining weight is still over 40%, owing to the high carbon content of this polymer. A similar weight loss pattern has been observed in the polymer of dithiol c. In the decomposition of polymer of dithiol b the weight loss is more significant, 81% of weight loss was observed at 327℃ which might associate with the vaporization of the volatile ethylene glycol unit after the decomposition of the thio-ether linkers. The thermal decomposition pattern of these three polymers indicates despite the thermal resistance to heating above 300℃, the potential of obtaining better thermal stability by oxidation of thio-ether functions in these three polymers is possible. Analysis of DSC traces, which was taken from the second heating process of three polymers shows good structure-property correspondence. The polymer of PFBB and dithiol a has the highest aromatic content and theoretically most rigid chain structure among three polymers, while the T_g obtained was 82℃, the highest of three polymers. The polymer of PFBB with dithiol c has a short linear carbon chain in the backbone, the extra flexibility brings the T_g down to 35℃ while the polymer of PFBB with dithiol b has a long flexible polyethylene glycol segment that reduces the T_g to -25℃.

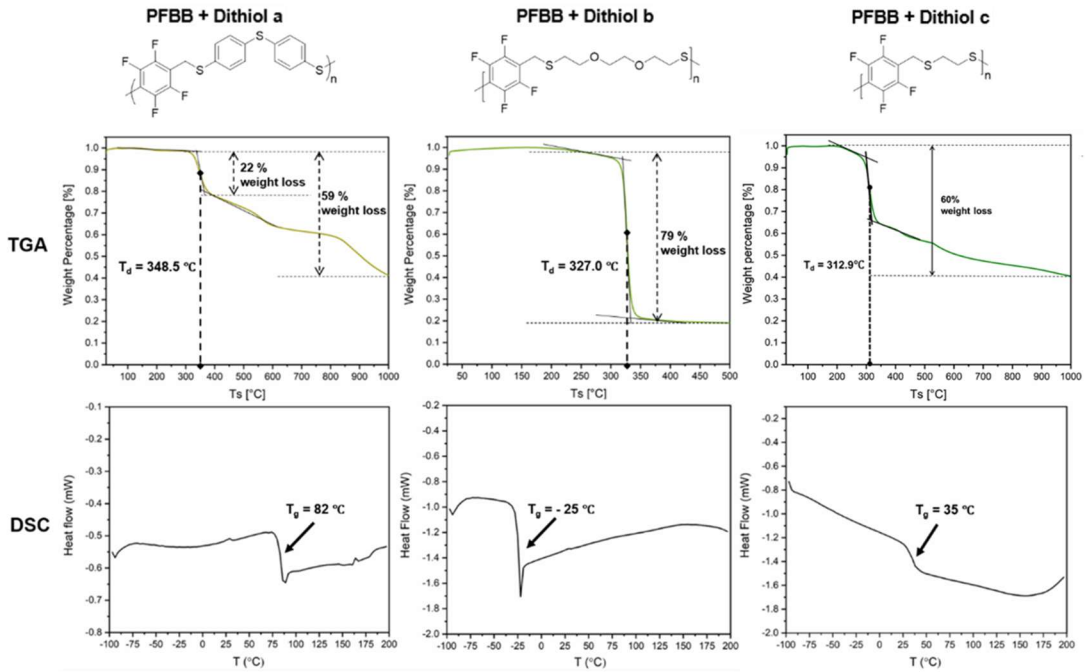


Figure 8. Thermogravimetric analysis (TGA and DSC) of step-growth polymers of PFBB-dithiol a (left), PFBB-dithiol b (middle) and PFBB-dithiol c (right).

Finally, spin-coated polymer films on quartz slides were fabricated to investigate the hydrophobicity of obtained polymers, and contact angle (CA) data was presented in **Figure 9**. Given the high aromatic and fluorinated aromatic content in the polymer chain, the polymer of PFBB and bisthiol a present a CA value of 90.2° which fits the anticipation. The polymer of PFBB and bisthiol c also shown a CA value of 78.8°, indicates moderate hydrophobicity that decreased comparing to the polymer of PFBB and dithiol a due to the absence of aromatic segments. The polymer of PFBB and dithiol b was shown the least hydrophobic one with a CA value of 55.0°, which was expected as the presence of the ethylene glycol segment raises the hydrophilicity, although the polymer is still more hydrophobic than plain glass surface that has a CA value of 30.9°.

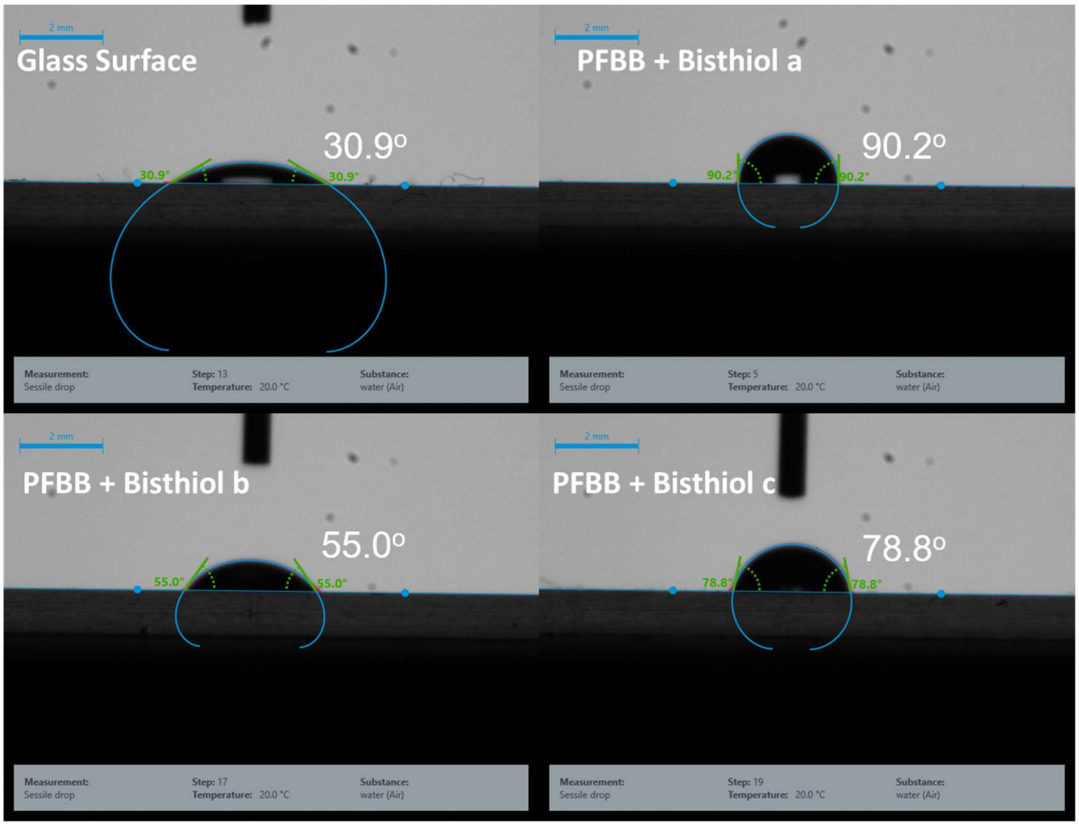


Figure 9. Water contact angle measurement of polymers of PFBB and bisthiol a, bisthiol b and bisthiol c.

2.3 Conclusion

A new method for the synthesis of a series of fluorinated polymers using commercially available dithiol compounds and 2,3,4,5,6-pentafluoro benzyl bromides has been reported. The step-growth polymerization can proceed at room temperature while based on the nucleophilicity of dithiol compounds the completion could be reached in 10 minutes. A stoichiometric amount of base activates the synthesis of a linear polymer and a stronger base allows the formation of longer polymer chains. DMF acts as the optimum solvent for polymerization, although a sequential addition of DMF into a $CHCl_3$ solvent system provides further polymer growth during elongated reaction time. The obtained polymers have a good thermal resistance up to 300℃ and hydrophobic character was measured by water contact angle measurements.

2.4 Experimental

2.4.1 Materials and methods

2,3,4,5,6-Pentafluorobenzyl bromide (PFBB) (Aldrich, 99%), 4,4′-Thiobisbenzenethiol (Aldrich, 98%), 2,2′-(Ethylenedioxy)diethanethiol (Aldrich, 95%), 1,2-ethanedithiol (Aldrich, ≥98.0% (GC)) were selected as monomers. Triethylamine (Aldrich, ≥99.5%), 1,8-Diazabicyclo[5.4.0]undec-7-ene (Aldrich, 98%) and 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (Aldrich, 98%) were used to activate PFTR and thiol-bromo click reactions.

N,N-Dimethylformamide (DMF, Aldrich), chloroform (Aldrich), tetrahydrofuran (THF, Aldrich) and methanol (Aldrich) were used as the solvent for polymerization and precipitation.

Dimethylphenylphosphine (Aldrich 99%) was used to prevent the disulfide bond formation.

2.4.2 Instrumentation

Nuclear Magnetic Resonance (NMR) spectroscopic measurements were performed on 300 or 400 MHz Bruker instruments in 5 mm NMR tubes. Residual solvent signals of $CHCl_3$ (δH = 7.26 ppm, δC =77.2 ppm) were used as reference. ^{19}F NMR chemical shifts are given relative to a $CFCl_3$ standard. Gel permeation chromatography (GPC) measurements were conducted on an Agilent 1260 infinity system operating in THF with 2% TEA and equipped with refractive index detector and variable wavelength detector, 2 PLgel 5 μm mixed-C columns (300 × 7.5 mm), a PLgel 5 mm guard column (50 × 7.5 mm) and an autosampler. The instrument was calibrated with linear narrow PS standards. All samples were filtered through 0.2 μm PTFE filters before analysis. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF MS) was performed on a Bruker Autoflex Speed mass spectrometer using a nitrogen laser delivering 2 ns pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The matrix used was trans-2-[3-(4-tertbutylphenyl)-2-methyl-2-propylidene]malonitrile (DCTB) dissolved in THF. Sodium trifluoroacetate used as a cationic agent (solution in acetonitrile). The compound (diluted in THF) was applied after separate loadings of DCTB and sodium trifluoroacetate. Samples were measured in reflective or linear mode and calibrated against poly(methyl methacrylate) standards. Thermalgravimetric analysis (TGA) and differential scanning calorimetry (DSC) was performed on a Mettler Toledo TGA/DSC with a heating rate of 10°C/min under nitrogen. Water contact angle measurements were performed on a Krüss drop shape analysis system

DSA100 with a tilting table. Measurements were executed under 25℃ and 65% relative humidity; all measurements were repeated five times and the mean value of contact angle was collected and presented.

2.4.3 General Procedures

General procedure of step-growth polymerization of dithiol compounds with 2,3,4,5,6-pentafluoro benzyl bromide (PFBB)

Certain volume (e.g, 5ml) of stock solution of dithiol compounds and PFBB at 2 mol/L concentration was prepared by dissolving reagents in DMF to obtain certain concentration of stock solution. Equal volume of PFBB and dithiol stock solution were mixed and well stirred to prepare a 1.00 mol/L reaction mixture, 0.15 mol% of DMPP was added to the reaction mixture before the calculated equivalent of the base was added to activate the polymerization. The reaction mixture was allowed to stir under a set temperature for a determined time and then ten volume folds of methanol were added to precipitate the polymers out. The precipitation mixture was then centrifuged, and the remaining liquid was decanted, another ten-volume fold of methanol was added to the precipitation, centrifuged, and decanted again. Obtained polymer crudes were then dried under vacuum for following characterisation.

Kinetics study of step-growth polymerizations of dithiol compounds with 2,3,4,5,6-pentafluoro benzyl bromide (PFBB)

2.5 ml stock solution of dithiol compounds and PFBB at 2 mol/L concentration were made and mixed to prepare 5ml reaction mixture with the concentration of 1.00 mol/L following the general procedure. 0.1ml kinetics sample was taken at preset time points and neutralized with formic acid; the pH value of the sample mixture was determined by Hydrion® Insta-Check® 0-13 pH test paper (Aldrich). The sample was then made into GPC, NMR or MALDI ToF MS samples and characterized accordingly.

2.4.4 Additional characterisation

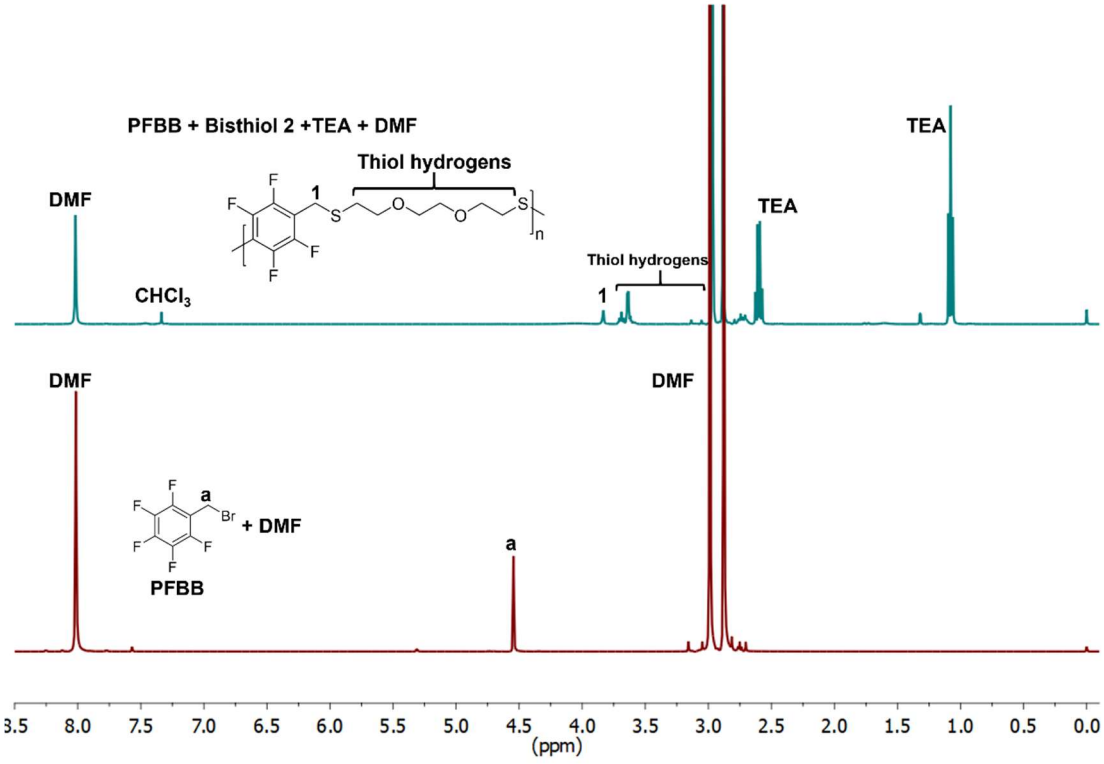


Figure 10. Comparison of PFBB stock solution in DMF and reaction mixture measured at t0. The shift of methylene hydrogens(peak a, bottom),

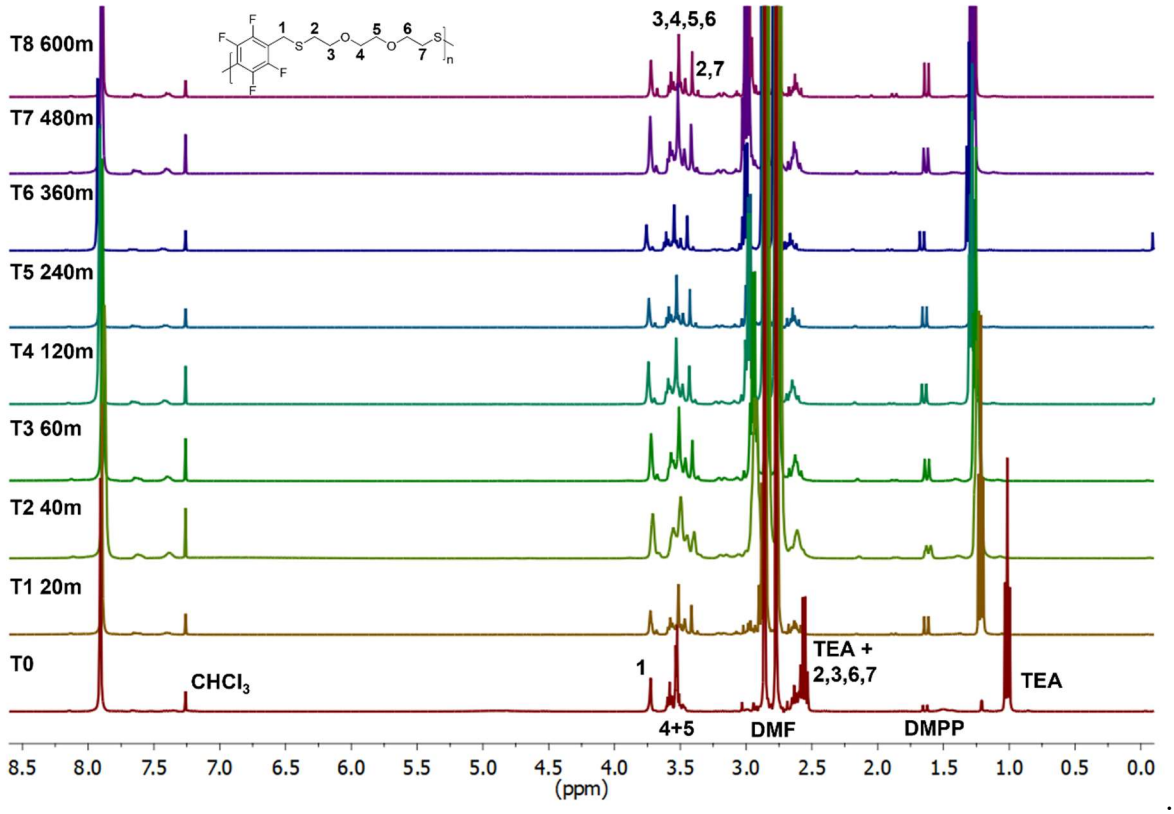


Figure 11. [1]H NMR kinetics from t0 to t8 (10 hours) of PFBB-dithiol b polymerization.

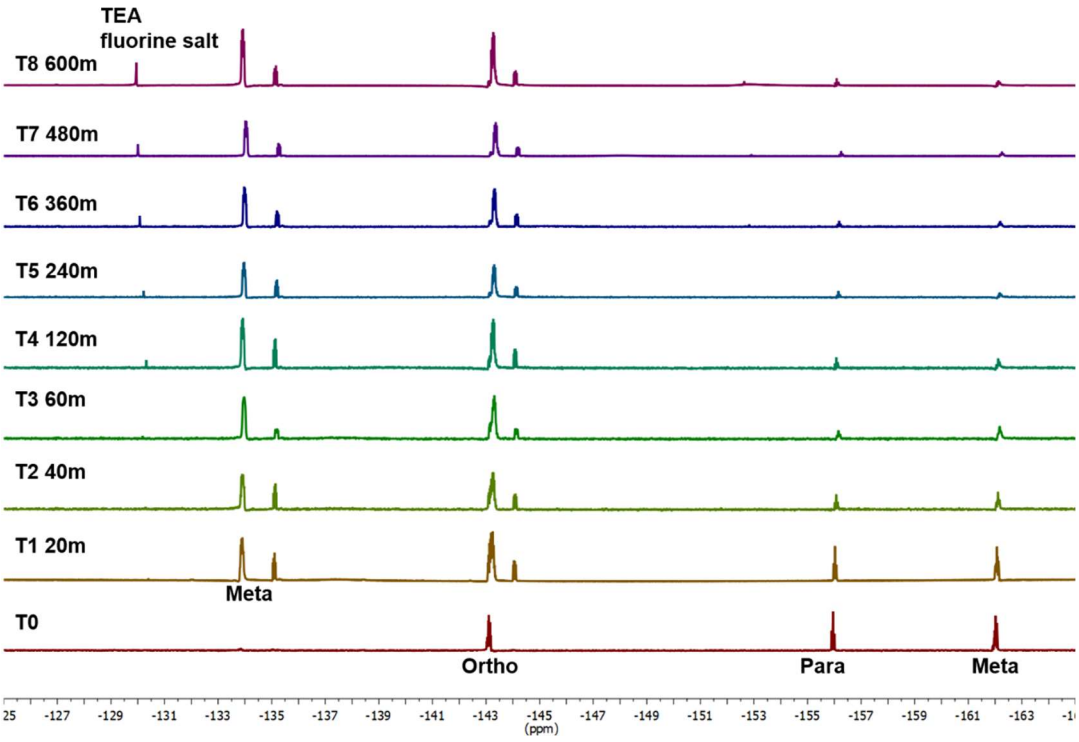


Figure 12. ^{19}F NMR Kinetics of PFBB-dithiol b polymerisation.

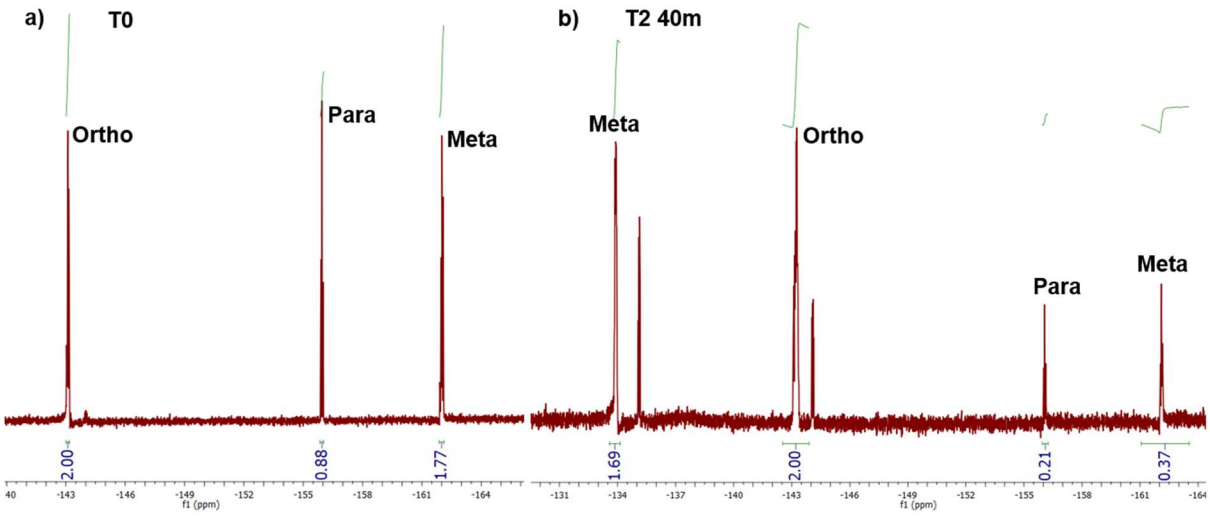


Figure 2. Examples of using quantitative ^{19}F NMR to calculate the conversion of monomer. These two samples were taken from Figure 12 t = 0 and t = 40 min. At t=0 (a) the integration value of ortho- and para- fluorine were taken as the initial amount. While at t = 40m (b) the integration value of ortho-fluorine was used as a reference to calculate the change of the integration value of para-fluorine.

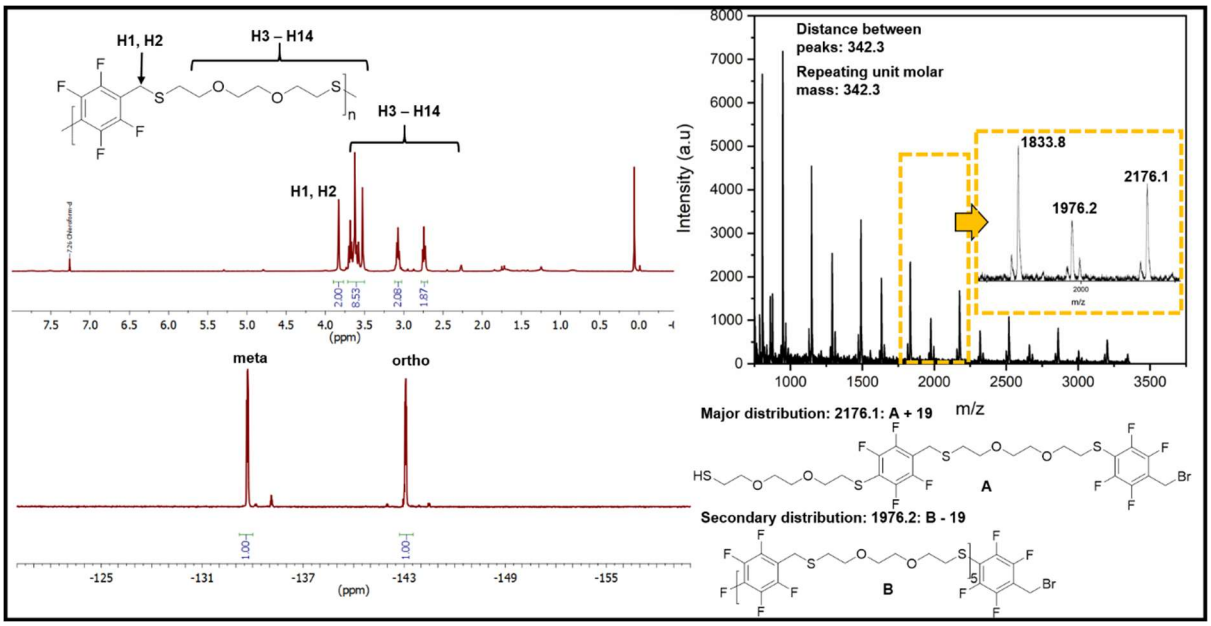


Figure 3. [1]HNMR, [19]F NMR and MALDI-ToF analysis of PFBB-bisthiol b.

[1]H NMR (400MHz, $CDCl_3$): δ 3.83 (s, 2H), 3.70-3.53 (m, J = 6.8 Hz, 6.4 Hz, 12.4 Hz, 4.4 Hz, 8.4 Hz, 10.8 Hz, 20.0 Hz, 8H), 3.10-3.03 (m, J = 5.6 Hz, 6.4 Hz, 6.4 Hz, 10.4 Hz, 2H), 2.74 (t, J = 6.4 Hz, 6.4 Hz, 2H)

[19]F NMR (376MHz, $CDCl_3$): δ -133.69 (dd, J = 23.7 Hz, 12.2 Hz, 2F), -143.04 (ddd, J = 35.9 Hz, 23.6 Hz, 11.9Hz, 2F)

MALDI-ToF analysis gives a major and secondary mass distribution which corresponds to the desired polymer structure.

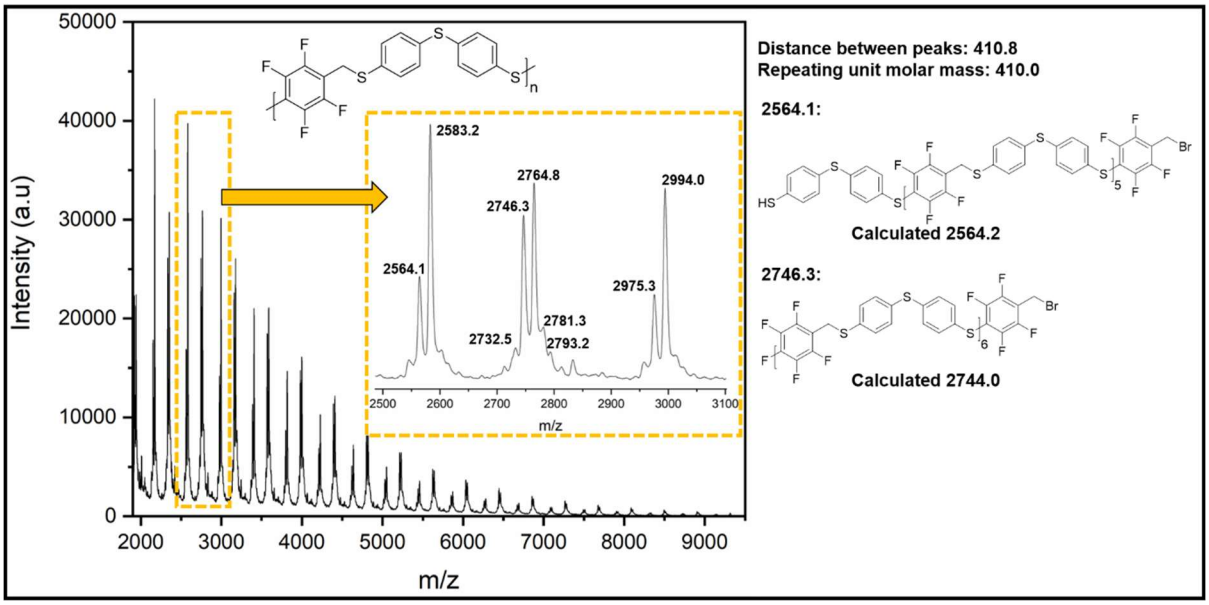


Figure 15. MALDI-ToF analysis of PFBB-Bisthiol a polymer under 2.05 eq TBD mediating the polymerization. MALDI-ToF analysis of PFBB-dithiol a polymer shows two distributions that both corresponds to a possible end group combination.

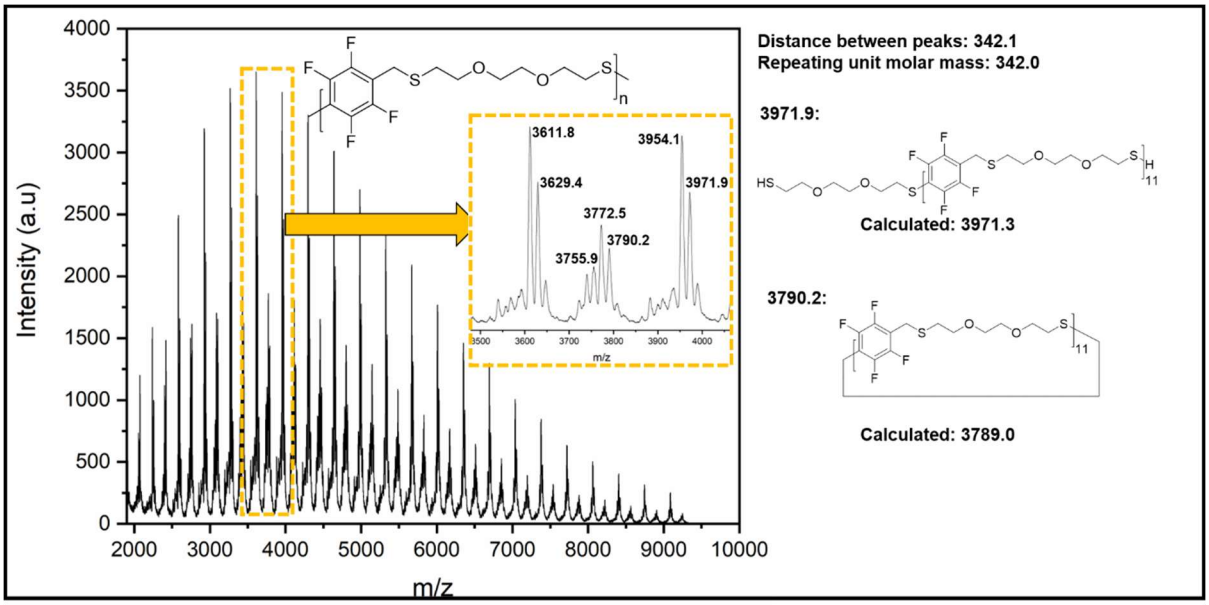


Figure 16. MALDI-ToF analysis of PFBB-dithiol b polymer under 2.05 eq TBD mediating the reaction. MALDI-ToF analysis of PFBB-dithiol b polymer shows two distributions that both corresponds to a possible end group combination

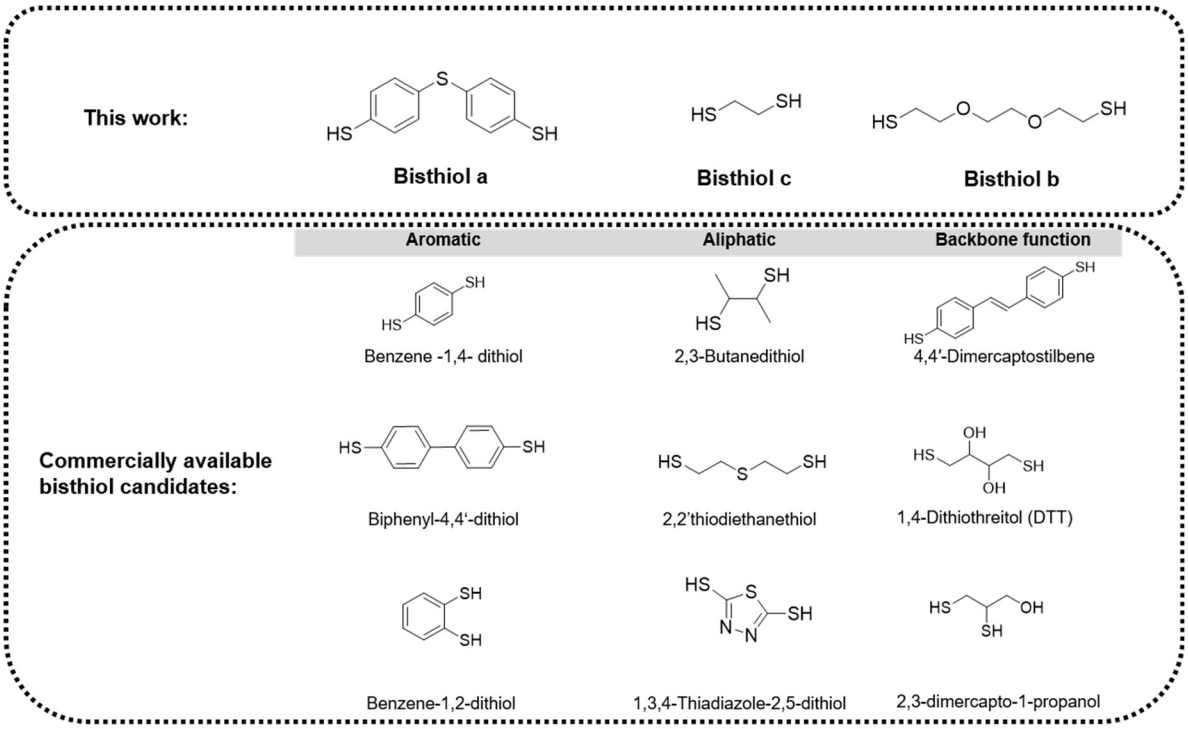


Figure 17. Comparison of commercially available dithiol candidates with aromatic, aliphatic and backbone functions with dithiol candidates utilized in this work.

2.5 References

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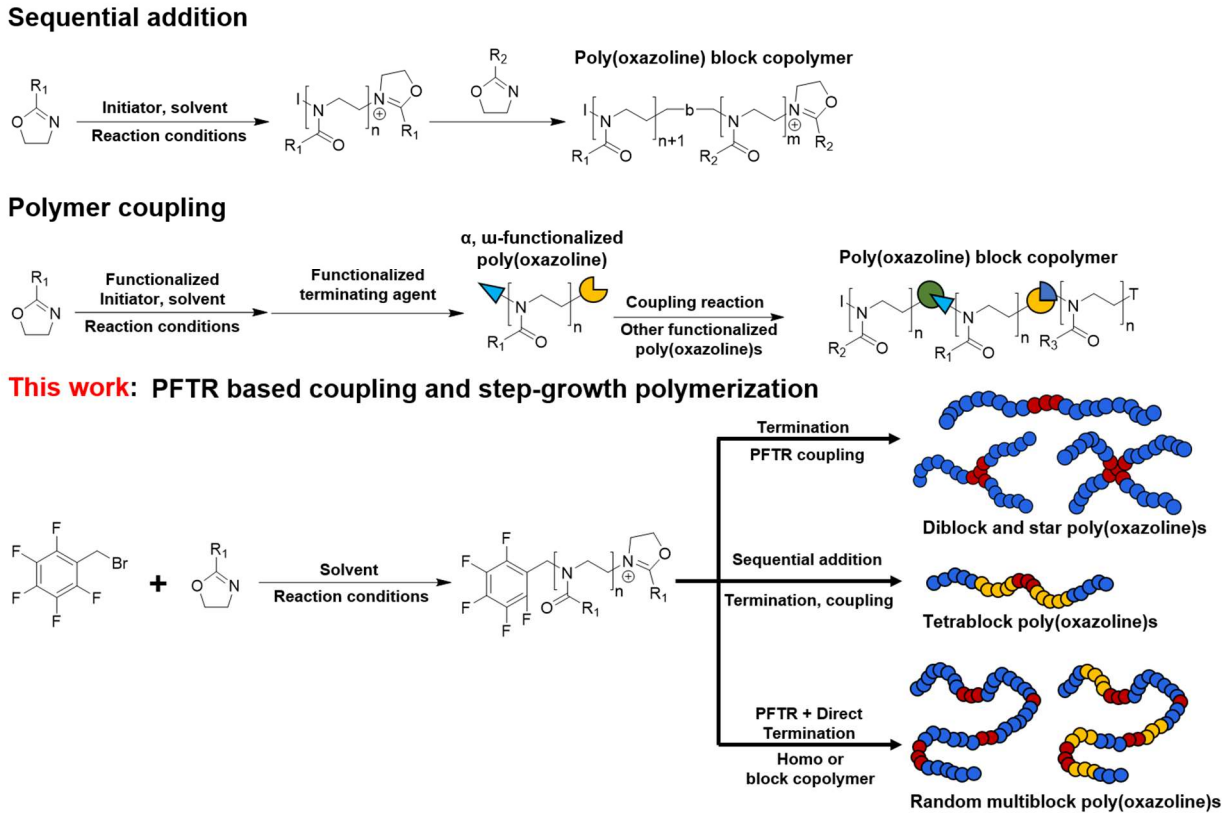
Chapter 3: One-pot synthesis of amphiphilic multiblock poly(2-oxazoline)s via *para*-fluoro-thiol click reactions



Abstract

A clickable initiator pentafluoro benzyl bromide has been investigated for the cationic ring-opening polymerization (CROP) of poly(2-oxazolines). Clickable poly(2-oxazolines) has been synthesized and characterized. Additionally, the clickable end group was then utilized in a para-fluoro-thiol click reaction (PFTR) to synthesis diblock and tetrablock poly(2-oxazolines) using dithiol compounds. Moreover, a one-pot approach of combining the para-fluoro-thiol click reaction and direct termination of the poly(2-oxazoline) living chain with 4,4-thiobisbenzenethiol has been performed to synthesize multiblock polymers of poly(2-ethyl-2-oxazoline) and poly((2-ethyl-2-oxazoline)-b-(2-methyl-2-oxazoline). All obtained polymers were fully characterized with gel permeation chromatography (GPC), ^{1}H nuclear magnetic resonance (NMR) and Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-ToF) mass spectrometry. The self-assembly properties of prepared amphiphilic polymers were studied with DLS and TEM. Nanospheres that has a diameter from 184 nm to 250 nm were observed in TEM of multiblock poly(2-ethyl-2-oxazoline).

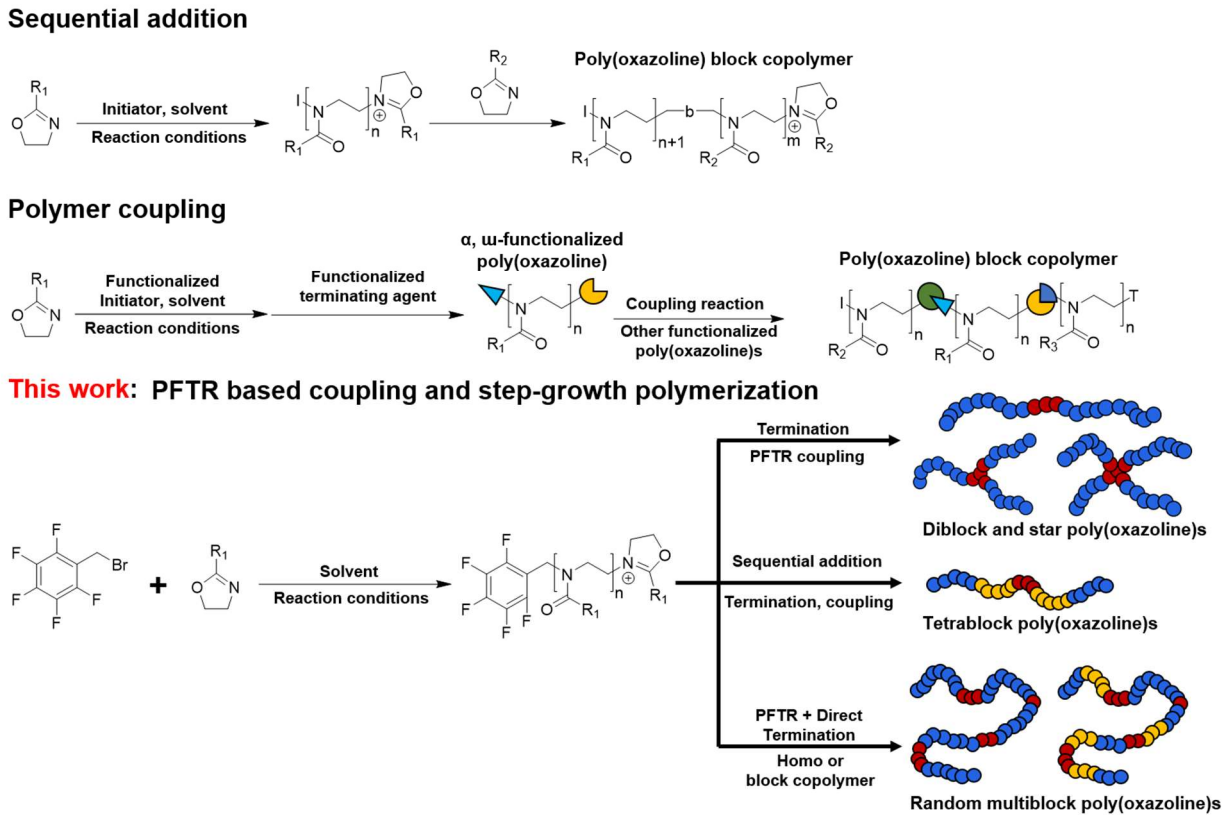
3.1 Introduction

Poly(oxazoline)s have attracted intense research attention as they possess various properties including biocompatibility,[1–3] thermal responsive ability,[4–7] hydrophilicity[3,4] and low cytotoxicity[2] which were useful for biomedical and industrial applications such as adhesives[5] and lubricants.[2] Preparation of poly(oxazoline)s nowadays is mostly performed through a living cationic ring-opening polymerization (CROP) process with several commercially available initiators such as methyl tosylate and benzyl bromide,[8] giving rise to well-defined polymers with narrow molecular weight distributions. Moreover, the living chain end can be further utilized in chain extension reactions to synthesis block copolymers[3,5,9,10] or functionalized to introduce functional groups for post-polymerization modification (PPM).[11–13] Due to the biocompatibility of poly(2-oxazoline)s, synthesis of block copolymers of poly(oxazoline)s with amphiphilic structures to form polymeric micelles or nanoparticles have been a research focus. Many studies have shown the preparation of diblock, triblock and tetrablock poly(oxazoline)s and subsequent manufacturing of micelles and nanoparticles.[3,5,7,9,14–16] Methods of preparing block copolymers of poly(2-oxazoline)s include sequential addition of monomers to the polymerization mixture after complete consumption of the previous monomer, and the coupling of end-functionalized polymers.[6] The former method, or the macroinitiation method, was mostly employed because the one-pot process is convenient to prepare multiblock polymers, although the chain length of block polymers synthesized is limited by the decreased chain end fidelity and the shielding of the living chain end at high molar mass.[8] The backbone diversity of obtained block polymer is also restrained to peptidomimetic backbones such as poly(oxazoline) and polypeptides.[17,18] The coupling method, or the polymer-polymer conjugation method, can introduce more diverse backbone functionality into poly(2-oxazoline) block copolymers. For example, poly(oxazoline)s were synthesized and end-capped with functional groups for subsequent coupling with vinyl polymers.[19] However, the efficiency of coupling method is limited by the efficiency of the coupling reaction employed and the availability of functional groups on the α- and ɯ- terminal of the poly(2-oxazoline).

Click reactions are highly efficient, require mild conditions and give high yields, which makes them good candidates for step-growth polymerization and polymer-polymer conjugation. For example, the well-known copper(I) catalyzed azide-alkyne cycloaddition (CuAAc) click reaction has been utilized in the synthesis of block copolymers and dendrimers of poly(oxazoline)s.[20] The clickable azide or alkyne group is introduced through the use of a

functional initiator[21] or by termination[22] to make functionalized poly(oxazoline) chains and subsequently reacted with other polymers to synthesize diblock,[3,9,23] triblock,[5] and star[21] polymers. However, the interaction between tertiary amines on poly(oxazoline)s backbone and copper catalyst makes the purification difficult, ppm level of metal ions could remain after purification.[24] Utilizing metal-free thiol-ene[25] and strain-promoted azide–alkyne cycloaddition(SPAAC)[26] click reactions to synthesize block copolymers have also been reported. Besides, studies on α- and ɯ- terminal functionalized poly(oxazoline)s always leads to synthesis of diblock polymer or triblock polymer due to low coupling efficiency of polyoxazolines,[8,13] while the coupling reaction utilized in reports was mostly CuAAc click reaction[3,9] and other click reactions were not investigated. Additionally, research on the synthesis of multiblock poly(oxazoline)s using a bi-functionalized poly(oxazoline) precursor via a step growth approach remains absence.

Herein, we introduce the use of pentafluoro benzyl bromide (PFBB) as a clickable initiator for the CROP of poly(2-ethyl-2-oxazoline) (PEtOx) and the preparation of diblock, star and multiblock poly(oxazolines) (**Scheme 1**). Utilizing commercially available dithiol and multi-thiol compounds, diblock and star polymers of PEtOx were synthesized via a para-fluoro-thiol click reaction (PFTR) approach. The block copolymer of 2-ethyl-2-oxazoline and 2-methyl-2-oxazoline was also prepared using PFBB as the initiator, and a tetrablock block copolymer prepared with PEtOx-b-MeOx diblock copolymer with a dithiol compound was synthesized via a PFTR click reaction and characterized. Furthermore, a combination of the PFTR and direct termination of the living chain end of PEtOx or PEtOx-*b*-MeOx with dithiol as the nucleophile gives rise to a multiblock poly(2-oxazoline) within 10 minutes in one-pot. The synthesized diblock and multiblock poly(2-oxazoline)s have amphiphilic structures and therefore the self-assembly properties of these polymers were investigated with transmission electron microscopy (TEM), while nanostructures include sphere and vesicle-like nanoparticles that has diameters ranging from 184 nm to 250 nm were observed.



Scheme 10. Methods of synthesis towards poly(oxazoline) block copolymers and the method utilized in this work.

3.2 Results and discussion

3.2.1 Kinetics investigation of PFBB initiated CROP of 2-ethyl-2-oxazoline

Kinetics investigation of the CROP of 2-ethyl-2-oxazoline (EtOx) using PFBB as the initiator was firstly performed to study the feasibility of using PFBB as a clickable initiator and to understand the corresponding polymerization kinetical nature. Initial reaction conditions were a [monomer] to [initiator] ratio of 60:1, giving a theoretical degree of polymerization (DP) of 60, microwave-assisted heating at 140 °C, monomer concentration of 4.0 M and using dry acetonitrile (MeCN) as the solvent. These conditions were employed in other kinetic investigations for the CROP of oxazolines with other commercially available initiators such as methyl tosylate[27] and benzyl bromide,[28] this allows the results including rate constant of polymerization to be compared with reported commercially available initiators. A 4.0M monomer stock solution of 2-ethyl-2-oxazoline and PFBB in dry MeCN was made and equal amounts of stock solution were distributed into different microwave vials under inert and anhydrous conditions. These samples were then transferred to the microwave reactor, heated to 140°C and quenched with a sodium hydroxide/methanol solution at six predetermined time

points. ^{1}H NMR and GPC were utilized to determine the monomer conversion and the molecular weights of obtained polymers at different time points as well as the polymerization rate constant. Results obtained are shown in **Figure 1**. Monomer conversion was calculated based on integration of ^{1}H NMR of 2-ethyl-2-oxazoline peaks (**section 3.4.4, Figure 7**) while also represented by $\ln([M]_0/[M]_t)$, where $[M]_0$ is the initial concentration of monomer and $[M]_t$ is the concentration of monomer at time t. The ^{1}H NMR spectrum at each kinetic time point collected is shown in **Figure 7, section 3.4.4**, where the NMR results also show the shift and split of the peak for the methylene group of PFBB and the consumption of monomers.

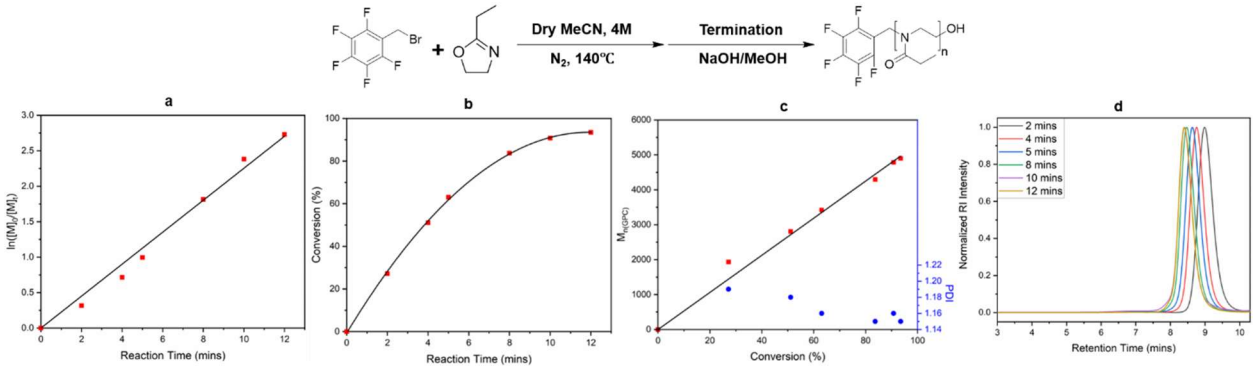


Figure 1. Kinetics investigation of PFBB initiated CROP of 2-ethyl-2-oxazoline. a): $\ln([M]_0/[M]_t)$ versus reaction time plot. b): Monomer conversion versus reaction time plot. c): $M_{n,GPC}$ versus monomer conversion and PDI versus monomer conversion plot. d): THF GPC monitored hydrodynamic volume change through the kinetics investigation.

The plot of $\ln([M]_0/[M]_t)$ versus time shown in **Figure 1a** shows a linear relationship, while the conversion versus reaction time plot shown in **Figure 1b** also indicates that the concentration of active, propagating chains is constant. Therefore, the plot indicates that the CROP of 2-ethyl-2-oxazoline initiated with PFBB, under these conditions is living. That is, with the absence of significant chain termination processes. In addition to this, the $M_{n,GPC}$ vs conversion plot **Figure 1c** shows a linear dependence further confirming a living, controlled chain-growth polymerization absents of termination or coupling reactions, while the Đ values were below 1.20 throughout the kinetics investigation, showing the polymerization proceeded in a controlled fashion. **Figure 1a** and **Figure 1c** shown good agreements between experimental data with the fitting line and adj.R-square values over 0.995 were obtained. This indicates the linear dependence found was reliable. The hydrodynamic volume change in **Figure 1d** together with the $M_{n,GPC}$ value indicated the growing of polymer chain, while the experimental $M_{n,GPC}$ value was smaller than the theoretical value. For example, at t = 12 mins

where the monomer conversion was 93%, the theoretical M_n value was 5700 g/mol, which was calculated from the theoretical molecular weight times conversion and add the molecular weight of initiating pentafluoro benzyl group, while the experimental $M_{n,GPC}$ at t = 12 mins was only 5000. Possible explanations are the $M_{n,GPC}$ of obtained P(EtOx) was calculated with a PMMA standard, the tertiary amine of P(EtOx) might lead to column interaction and affect the accuracy of hydrodynamic volume measurement. Additionally, obtained P(EtOx) has a hydrophobic pentafluoro benzyl groups attached, together with all the ethyl chains the P(EtOx) might have an amphiphilic nature and lead to folding in THF, which would possibly decrease the hydrodynamic volume of the polymer.

The apparent rate constant of polymerization k_{app} was determined via the first-order kinetics following equations shown in the supporting information. While based on the assumption of equal concentration of initiator and living propagating chain end and given concentration of initiator at t_0 ($[I]_0$), the apparent rate constant k_{app} was calculated as 3.38 x 10^{-3}L(mol/s) with the equation shown in section 3.4.4. Further kinetic studies under different temperatures could obtain the frequency factor and activation energy values for PFBB via the Arrhenius equation, however, this will not be discussed further here as it is not the focus of this work. This kinetic study has shown that it is feasible to use PFBB as a clickable initiator for the CROP of 2-ethyl-2-oxazoline, although the reaction rate is rather moderate compared to benzyl bromide.[27] As the counter ion in each initiating system remains the same, a possible reason for moderate polymerization rate could be the pentafluoro benzyl group is more electron-withdrawing and sterically large than a benzyl group, which makes the cationic species generated in initiation and propagation more energetically unfavourable and thus the lower polymerization rate.

Before further exploitation of the clickable pentafluoro benzyl group on poly(2-ethyl-2-oxazoline), an investigation of the end nature of the end group of polymers obtained is necessary. To ease the characterisation with MALDI-ToF and allow accurate integration in ^{1}H NMR to calculate the initiator efficiency, poly(2-ethyl-2-oxazoline) (PEtOx) of DP 10 was synthesized using PFBB as the initiator and the polymerization was terminated with sodium hydroxide methanol solution to provide hydroxyl end groups. The obtained PFB-PEtOx, which has pentafluoro benzyl bromide (PFB) at the α-end of polymer, was purified and characterized with GPC, ^{1}H NMR and MALDI-ToF (**Figure 2**). In the MALDI-ToF spectrum shown in

Figure 2c, a major distribution that fits the theoretical value of PEtOx with pentafluoro benzyl and hydroxyl end groups was observed where, for example, the experimental peak at 1113.9 fits the theoretical calculations of the sodium salt of a 9-mer polyoxazoline chain possessing hydroxyl and pentafluoro benzyl (PFB) end groups, while the peak at 1213.7 fits the theoretical calculations of the sodium salt of a 10-mer polyoxazoline chain with PFB and hydroxyl end groups, the gap between the peaks was 99.8 which is the molecular weight of the EtOx repeating units.

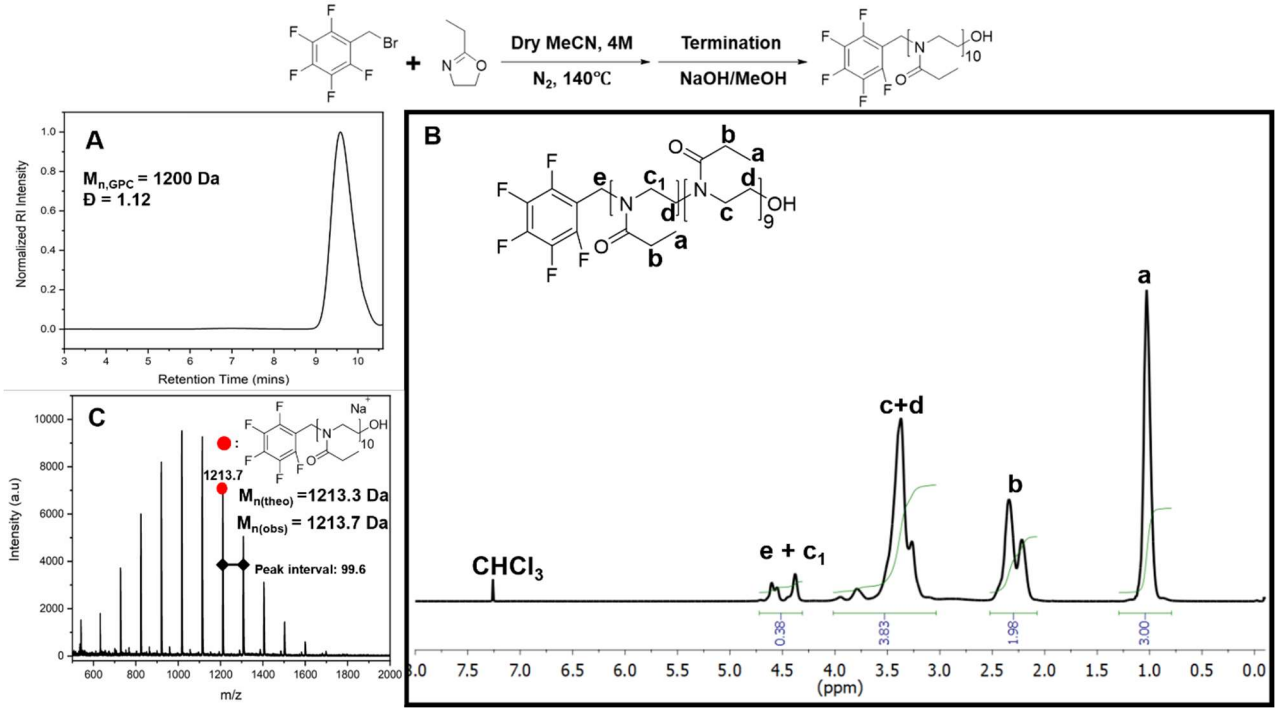


Figure 2. THF GPC(A), ^{1}H NMR(B) and MALDI-ToF(C) analysis of PFB-PEtOx$_{(10)}$. The GPC trace and the distribution shown in MALDI-ToF indicates a DP10 polymer. In the ^{1}H NMR, corresponding peaks were labelled, while part of the backbone hydrogens was shifted to larger chemical shift around 4.5.

One thing to notice is in the ^{1}H NMR, the total integration number of peaks was 9.2, where the polymer side chain ethyl group hydrogens fit nicely to the NMR integration. However, the ratio of integration number of hydrogens of the methylene group from pentafluoro benzyl end, which was around 4.5 ppm, to the side chain methyl group (a, **Figure 2b**) does not fit the theoretical ratio of 1:15. That is because of the two backbone hydrogens closest to the α-end of the polymer has split from the main peak c, **Figure 2b** and move towards a larger chemical shift, give peak c_1 **Figure 2b** that close to the two hydrogens from the pentafluoro benzyl group and affects the ratio calculation. It was also supported by the GPC and MALDI-ToF analysis which shown the

polymer has a majority DP10 distribution with pentafluoro benzyl bromide group on the α-end of polymer.

Preparation of block copolymers of EtOx and MeOx was also performed using PFBB as the initiator. The synthesis of block copolymers was monitored by ^{1}H NMR and GPC. Collected results were shown in **Figure 8, section 3.4.4**. This serves as the proof of concept of block copolymer synthesis of polyoxazoline using PFBB as the initiator and adds potential for easy tetra block copolymer synthesis, which will be investigated and discussed later in this work.

3.2.2 Synthesis of di-block PEtOx and star polymer via PFTR click reaction

As reported in our earlier work, PFTR click reaction can be utilized in the preparation of step-growth polymers with PFBB and dithiol compounds.[29] Thus, it is natural to investigate the possibility of using this highly efficient coupling strategy to synthesize di-block, tetra-block and star polymers of PEtOx and PEtOx-MeOx with different dithiol and multi-thiol compounds via an 'arm first' approach, utilizing the α-end of prepared PEtOx. Homopolymer $P(EtOx)_{10}$ was firstly synthesized as the polymeric precursor **P1** (**Figure 3, (1)**). Three dithiol compounds, one tri-thiol compound and one tetra-thiol compound have been selected as thiols **A**, **B C**, **D** and **E** to synthesis diblock and star polymers of $PEtOx_{10}$ (**Figure 3, (2)**). A DMF solvent system with TEA mediating the reaction was employed, as PFTR click reactions favour aprotic polar solvents and requires a non-nucleophilic base to mediate the nucleophilic attack process.[30] The molar ratio of [dithiol]:[PEtOX]:[Base] was set as 1:2:2, where the mole ratio of PEtOx was calculated from the mole amount of the pentafluoro benzyl group, with the concentration of dithiol A in DMF set at 1.0 M for solubility. 0.5 mol% DMPP was added to prevent the formation of dithiol bridges which reduces the coupling efficiency. The coupling reaction was performed in one-pot with the preparation of corresponding PEtOx or PEtOx-MeOx, which allows precise measurement of initiator mole amount. The one-pot synthesis procedure was summarized in section 3.4.3. All four coupling reaction was performed under room temperature as it has been proved efficient and convenient in our previous work. A mixture of TEA, dithiol candidate and DMPP in DMF was added to the reaction mixture of PEtOx to start the coupling reaction. Samples were taken at different time points and GPC were employed to monitor the hydrodynamic volume change of samples. Obtained results were collected in **Figure 3 a-f** and corresponding average molecular weights and Đ of obtained polymers were collected in **Table 1**. It was shown that for dithiol A and C in 2 hours the hydrodynamic volume of the polymer increased significantly, indicating the formation of diblock polymers where extra chain length

leads to increased hydrodynamic volume.

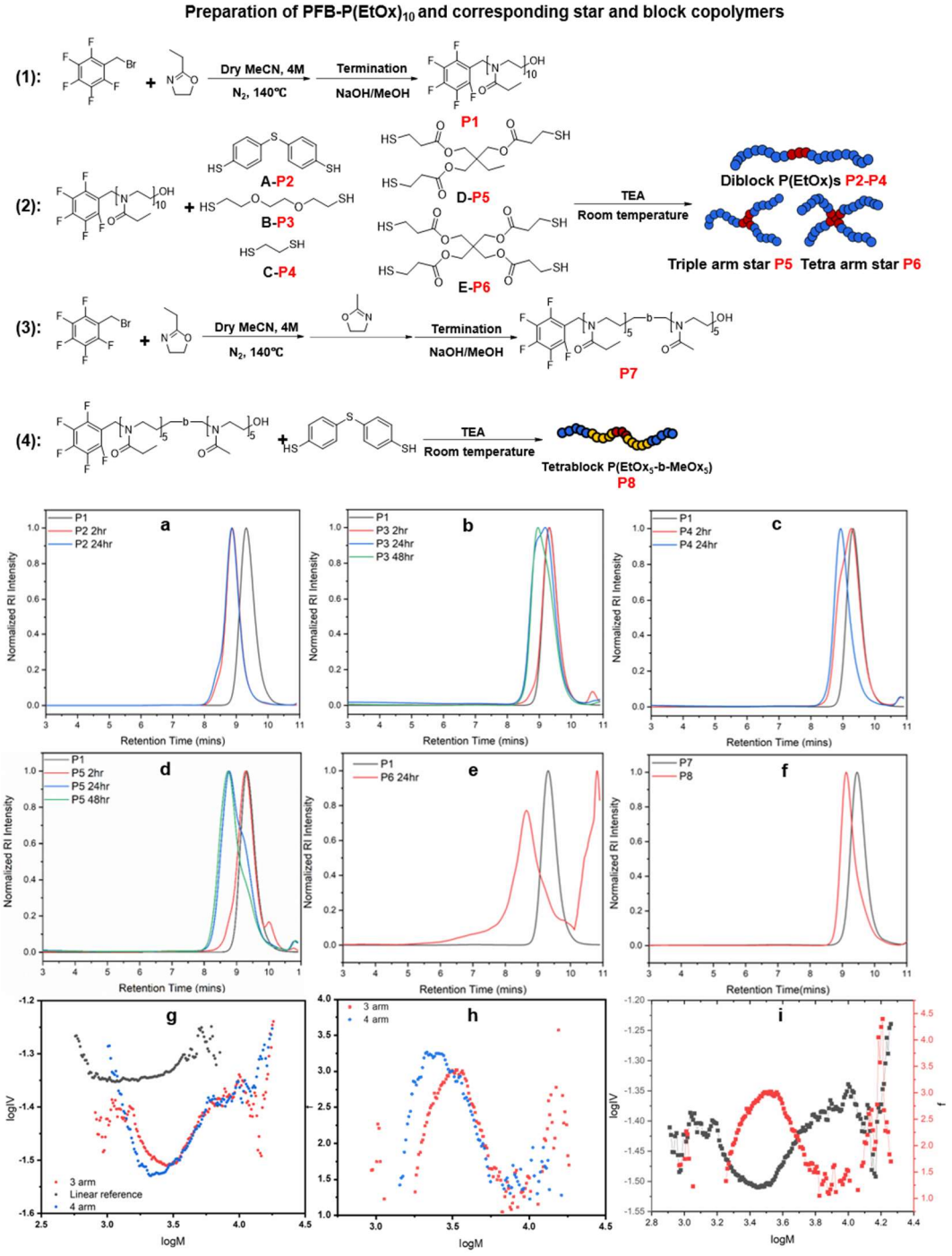


Figure 3. Reaction schemes, GPC traces and advanced GPC analysis of diblock, tetrablock and star poly(2-oxazoline)s. **a-f**: corresponding GPC traces of PFTR coupling reaction of **P1**, **P7** with thiols A-E. **g-i**: viscosity analysis of star polymer **P5** and **P6**, **g**: Mark-Houwink plot for the 3 arm (red) and 4 arm (blue) star polymers formed from the click reaction. A reference PEtOx polymer is also displayed (black).**h**: Functionality plot for the two star polymers showing how the number of arms varies with molecular weight. **i**: overlapped Mark-Houwink

plot and functionality plot of 3 arm polymers showing the correspondence of decreased viscosity and increased number of arms.

Table 1. Homopolymer, copolymer and star polymers of PEtOx prepared via PFBB initiation and PFTCR click reaction

No.	Polymer name	Architecture	$M_{w,GPC}$ (Da)	$M_{n,GPC}$ (Da)	Đ
P1	$PEtOx_{10}$	Homopolymer	1400	1200	1.12
P2	$PEtOx_{10}$-A-$PEtOx_{10}$		2600	2200	1.21
P3	$PEtOx_{10}$-B-$PEtOx_{10}$	Diblock copolymer	1600	1300	1.23
P4	$PEtOx_{10}$-C-$PEtOx_{10}$		2500	2100	1.20
P5	D-$(PEtOx_{10})_3$	Star polymer	4100	2900	1.41
P6	E-$(PEtOx_{10})_4$	Star polymer	5100	3200	1.60
P7	P($EtOx_5$-b-$MeOx_5$)	Block copolymer	1300	1100	1.21
P8	P7-A-P7	Tetrablock polymer	2600	2000	1.24
P9	PFB-PEtOx-A multiblock	Multiblock	22100	8300	2.64
P10	PFB-P(EtOx-MeOx)-a multiblock	Multiblock	5400	4100	1.32

For dithiol B (**Figure 3, b)** only a small increase of hydrodynamic volume was observed at two hours. That might be the consequence of low nucleophilicity of the dithiol B, caused by the electronegative oxygen atom on the backbone, leading to a slow coupling reaction. Additionally, the long, flexible backbone of dithiol b increases the chance of entangling. For dithiol b the increase of hydrodynamic volume was significant after 24 hours with no significant increase seen after 48 hours. This suggests that the reactions proceed albeit at a slower rate than dithiol A. For dithiol c, an increase of hydrodynamic volume was observed

after 2 hours but the overlay of GPC traces with P1 suggests the coupling reaction was not complete (**Figure 3, c**), the shift of GPC traces was significant after 24 hours without any leftover homopolymers present. Star polymer formation with thiol D (**Figure 3**, **d**) shows a small change in hydrodynamic volume after 2 hours, while a significant shift of the polymer peak was observed after 24 hours with a distorted curve shape that has a low molecular weight contribution, indicating there might be polymer chains without a pentafluoro benzyl end group as the leftover, or three reacting sites of the star polymer core did not fully react with pentafluoro benzyl groups and thus generated dimers. For star polymer formation with thiol E (**Figure 3, e**) after 24 hours significant increase of hydrodynamic volume was observed with high molecular weight tailing presenting, which might be the consequence of star-star coupling. ^{1}H NMR and MALDI-ToF characterisation results of the coupling reaction of PFB-PEtOx with dithiol A is displayed in **section 3.4.4 Figure 9**. Analysis of the characterisation results for the coupling reaction of PFB-PEtOx with dithiol A has shown that the coupling reaction has good efficiency as the major distribution in the MALDI-ToF fits the calculated theoretical molecular weight of the diblock polymer. Additionally, specific peaks from the aromatic rings of the aromatic dithiol have been observed in the ^{1}H NMR results and this along with the significant change in hydrodynamic volume in the GPC chromatogram support the generation of a diblock polymer. The existence of other desired diblock polymers was proved by MALDI-ToF characterisation and is shown in **Figure 10 and 11, section 3.4.4.** The tetrablock polymer of P(EtOx$_5$-MeOx$_5$)$_2$-A does not give a clean MALDI-ToF spectrum, thus it was characterized with ^{1}H NMR and the spectrum are shown in **Figure 12, section 3.4.4**

In the MALDI-ToF shown in **Figure 9-11**, peak intensities of these block polymers shown were weak, while the star polymer does not give significant peaks, indicating that the polymer obtained was not easily ionized in the MALDI. Thus, to prove the formation of star polymer, advanced GPC with an RI and viscosity detector was employed to analyze the degree of branching and therefore obtain the number of arms of the obtained star polymer. Collected viscosity analysis data was shown in **Figure 3, g-i**. **Figure 3, g** shows the Mark-Houwink plot for the two-star polymers studied here. Before any calculations as to the number of arms is undertaken it is useful to analyse qualitatively the plots. This is because to obtain numerical values from intrinsic viscosity data an assumptive value for the structural factor, ε, is required. First, consider the star polymer made from a trifunctional core. It is obvious that in this case, the maximum number of arms is 3 and that only a monomer, dimer or trimer is possible.

Therefore, it can be assumed that the minima are 3 arms because a monomer and dimer appear equivalent to a linear reference in a Mark-Houwink plot. However, there are data points between the reference and the minima which is due to co-elution. Here, co-elution is likely because the arms only have a theoretical molecular weight of 1000 Da whereas a 3-arm star has a theoretical molecular weight of only 3000 Da meaning their hydrodynamic sizes are not significantly different. Thus, leftover arms (and/or monosubstituted cores) and dimers will co-elute with the star polymer and will lead to intrinsic viscosity (IV) values that are a weighted average of the species eluting. As will be shown later this leads to species that appear to have arms between 1-3 but this is, in reality, a mixture. In the same way, we can qualitatively interpret the star made from a tetrafunctional thiol core. The minima is slightly lower than that of the 3 arm star although this is not significant enough to suggest the formation of a 4 arm star polymer. However, given that it has a lower IV than that of the 3 arm it is possible to infer that there is some degree of 4 arm species but that the presence of a 3 arm species increases the viscosity as a result of co-elution.

The number of arms, f, can also be estimated using the viscosity data and assuming a structural factor of 0.75.[31] With the assumption of a polydisperse system the arms were calculated and are shown in **Figure 3, h.** In keeping with the assessment previously provided the 3-arm star was found to have an average of 2.2 arms with a maximum of 3 arms. The 4-arm star was found to have an average of 2.3 arms and with a maximum of approximately 3.3 arms. As previously discussed, this implies that some 4 arm species is present to enable an average of 3.3. In **Figure 3, i**, the functionality plot and the Mark-Houwink plot of the 3-arm star was overlapped as an example to show the agreement between the viscosity and the number of arms, where the lowest viscosity point matches the highest number of arms. Overall, neither of the stars have a constant number of arms and the results show significant co-elution. It is worth noting that the results rely heavily on the structural factor being 0.75 which can vary.[32,33] Small deviations of this cause significant changes to the number of arms. In P. Guégan *et al.*, whereby they used a starshaped initiator they used a method whereby the theoretical number of arms was considered in order to estimate a more accurate value for ε.[33] Considering the 3-arm polymer case where it is known that a maximum of 3 arms are possible the assumptive value for ε seems valid given that this is what the calculation and model used gave as an output.

3.2.3 Synthesis of multiblock PEtOx via PFTR and direct termination

The mechanism of PFTR click reaction was discussed in numerous publications, the nucleophilic attack of thiolate ions to the para-fluorine has been reported as an important step in this click reaction. While in the synthesis of polyoxazolines, the termination step involves using a nucleophile to attack the oxazolinium ion to end-cap the propagating chain, stopping the chain growth and installing functional groups on the chain end. Various nucleophiles including amines, alcohols and thiolate salts have been reported to be utilized in the end-functionalization of poly(oxazoline)s.[34] As both termination of polyoxazoline living chain ends and PFTCR are effective reactions that requiring nucleophilic attack, by polymerizing 2-ethyl-2-oxazoline with PFBB as the initiator, the living propagating chain could be treated as a A-B functionalized macromonomer, and using a dithiol as a bi-nucleophile to simultaneously terminate polyoxazoline chains and take part in PFTCR could results in preparation of multiblock oxazoline polymers in one-pot. While by using sequential addition of monomers to synthesis polyoxazoline block polymers, it could be possible that multiblock polymers with different polyoxazoline backbone can be easily synthesized. (**Figure 4**).

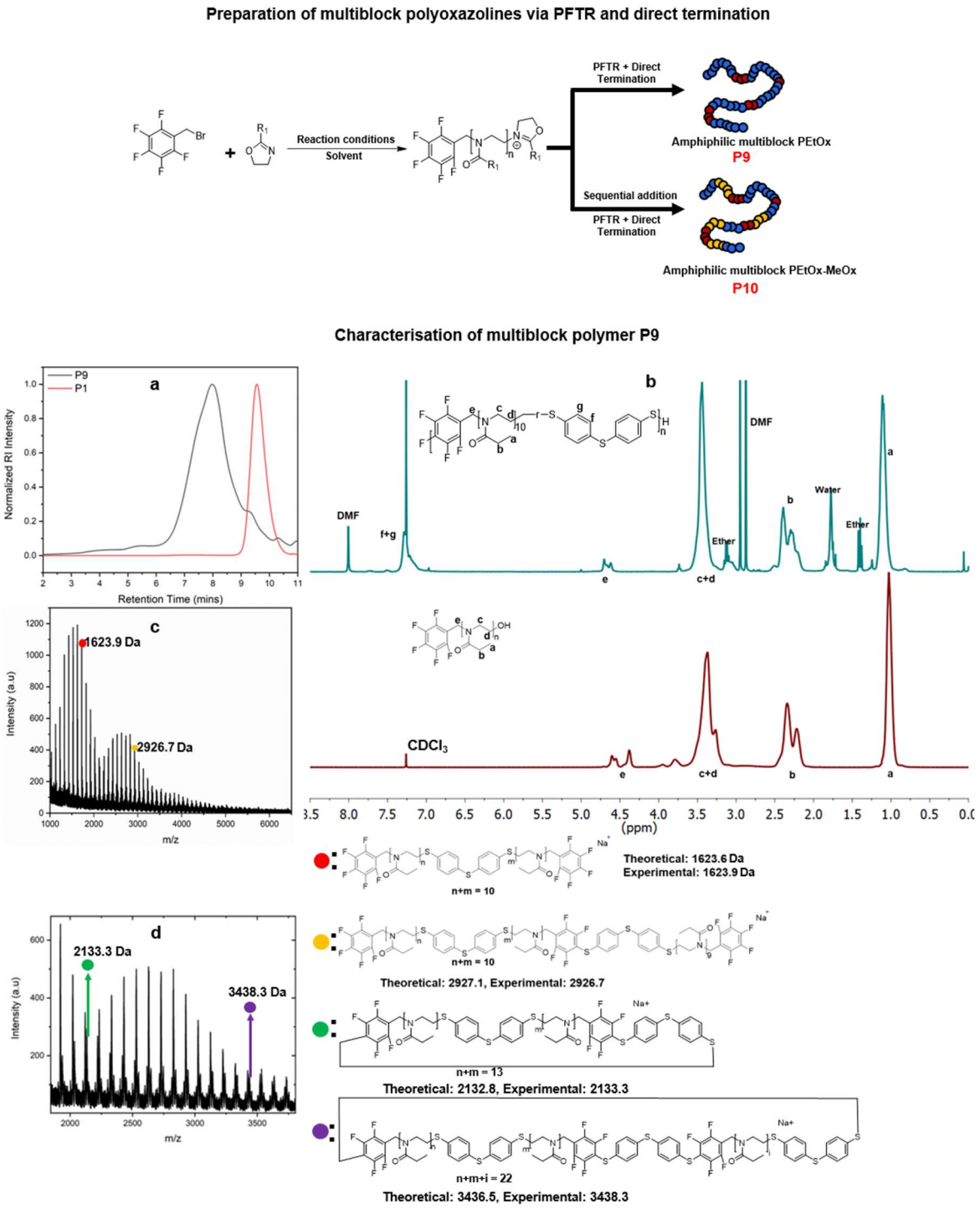


Figure 4. Preparation of multiblock PEtOx and characterisation of Multiblock polymer P9 with GPC(**a**), 1H NMR (**b**) and MALDO-ToF (**c** and **d**) showing the non-regioselective growth of multiblock polymer and potential cyclic structure formation.

Dithiol A was selected as the dithiol candidate due to the superior performance in the previous results described in this paper. PEtOx with [monomer] to [initiator] molar ratio equal to 10 to 1 was first synthesized under microwave heating with PFBB as the initiator, employing the

reaction condition and monomer concentration mentioned in the kinetics investigation section. After 6 minutes reaction the polymerization mixture was cooled to 40℃ with compress air, then removed from the microwave reactor and a vacuum dried and nitrogen degassed solution of dithiol A, dry TEA and DMPP in dry DMF was added into the polymerization reaction. The molar ratio of reactants and base were kept at 100:100:205:1.5 [Dithiol A]: [Initiator]:[TEA]: [DMPP]. The reaction mixture was then transferred into the microwave reactor and heated for another 3 minutes at 70℃. The obtained polymer was then analyzed with ^{1}H NMR, GPC and MALDI-ToF. A significant increase of hydrodynamic volume and average molecular weight distribution were observed (**Figure 4, a**), indicating the formation of a multiblock PEtOx. Longer microwave heating did not lead to an increase in hydrodynamic volume, indicating that this was the full extent of reaction. The polymer was purified by precipitation, filtration and oven drying and ^{1}H NMR analysis were carried out which showed the presence of aromatic peaks indicative of the dithiol in the polymer backbone (**Figure 4**, **b**). The MALDI-TOF spectrum for the multiblock polymer only shows peaks of low molecular weight, this is likely due to multiple aromatic and fluorinated aromatic rings making ionization of the polymer more difficult, and the heavier polymers tend to be difficult to ionize.[35,36] Nevertheless, observed values prove that the direct termination and the PFTR click reaction are both happening and resulting in polymer growth (**Figure 4**, **c** and **d**). For example, as shown in **Figure 4, c** the mass peak observed at 1623.9 fits to the sodium salt of a diblock polymer with two pentafluoro benzyl end groups which are connected via the termination with dithiol A and have ten EtOx repeating units in total. Additionally, the peak observed at 2926.7 fits to the value of the sodium salt of the polymer at 1623.9 have one aromatic dithiol reacted with one pentafluoro benzyl group, and the aromatic dithiol end-caps another PEtOx chain with nine repeating units and a pentafluoro benzyl bromide group, indicates the mixed ways of chain growth presenting in the multiblock PEtOx formation. The zoom-in analysis of secondary distributions (**Figure 4, d**) revealed potential cyclic structures formation as shown with two example peaks at 2133.3 and 3438.3, which is an inevitable side reaction in step-growth polymerization. These results suggesting the one-pot direct termination approach for preparing multiblock PEtOx was successful.

Based on the approach of synthesizing multiblock PEtOx with dithiol A, preparation of multiblock PEtOx-MeOx with dithiol A was performed using the same procedure. However, the polymer obtained does not have a large hydrodynamic volume change to the block copolymer comparing to the block polymer of PFB-P(EtOx-MeOx), despite the high molecular

weight tail shown in the GPC traces. (**Figure 13, section 3.4.4)** A possible reason might be the chain end livingness of the block poly(oxazoline) was hampered by the inevitable tiny amount of air or moisture introduced into the reaction mixture while adding the second block, which changed the stoichiometry of step-growth polymerization and restricts the size of the final polymer. Possible chain transfer during the reaction also interferes with the α-end fidelity and prevents the step-growth from reaching high conversion. Preparing the polymer in a dry environment, for example in a glovebox, might be helpful to increase the size of the polymer obtained.

The results discussed so far indicate that PFBB is a useful clickable initiator for the CROP of EtOx, the synthesis of desired diblock, star and multiblock polymers of PEtOx utilizing α-end and ɯ-end functionality was shown by GPC, ^{1}H NMR and MALDI-ToF characterisation. Using a microwave-assisted preparation strategy, it is possible to obtain multiblock PEtOx in one pot in 10 minutes, which is fast and convenient. Among obtained polymers, diblock polymer **P2,** tetrablock polymer **P8** and multiblock polymer **P9** and **P10** have an amphiphilic backbone structure with aromatic and fluorinated aromatic rings (as shown in **Figure 4**). Thus, the thermal responsive and self-assembly properties of these polymers were investigated. Surprisingly, no evidence for thermal responsiveness was found in THF. Moreover, these polymers were not soluble in water which is likely due to the presence of fluorinated and non-fluorinated aromatic rings within the backbone structure. The self-assembly behaviour of these polymers will be discussed in the following section.

3.2.4 Self-assembly properties analysis of amphiphilic polymer P2, P8, P9 and P10

The self-assembly properties of **P2, P8, P9** and **P10** were investigated via a thin-film deposition approach. 5 mg of the polymer was dissolved in a 2.5ml 8:2 THF/ether mixture to make a 2 mg/ml solution and then allowed to evaporate to prepare the polymer film. Distilled water was then added to the dried polymer film and stirred for 7 days to prepare nanoparticles. The prepared nanoparticle solution was filtered through a hydrophobic 0.2 micron PTFE filter and then characterized with TEM. which revealed that the architecture of polymer nanoparticles was predominantly spheres (**Figure 5**) with diameters ranging from 184 nm to 250 nm. The diameters shown were obtained from the average value with the standard deviation of 15 different particles. The particles formed from these amphiphilic polymers were not monodispersed apart from the particles of **P9**. Particles of **P2** are nanospheres but the size distribution is wide, while the particles of **P8** has a distorted shape, which should be the

consequence of the PEtOx-b-PMeOx backbone. As only one hydrophobic region presents in **P9**, the hydrophilicity difference of PEtOx and PMeOx segment results in the shape distortion. The nanospheres formed from **P9** are the biggest in these four polymers as the chain length of polymer **P9** is the longest among these polymers. Nanoparticles of P9 aggregate in the TEM image, which could be a consequence of hydrophobic interaction. As the aggregation affects the measurement of nanoparticle size, only nanoparticles have a clear boundary like **Nanosphere 1** shown in **Figure 5, P8** was measured to give the average diameter value. Nanoparticles from P9 are monodisperse and spherical, indicating controlling the chain length to reduce the number of aromatic rings might be helpful to prevent aggregation. However, the DLS analysis at different temperature of the nanoparticle solution of P2 shown in **Figure 6** indicating that the dimension of particles before and after heating were too large for secondary force driven self-assembly to happen, as the particle formed were sized around 200 nm while the polymers used for nanoparticle fabrication were short DP20 polymers which should be sized around 10-20 nm per chain. This large difference in size indicating the formation of nanoparticles were driven by hydrophobic effects rather than secondary force. Nanoparticle solutions of **P2**, **P8** and **P10** also presented thermal-induced reversible aggregation behaviour, which is unexpected as corresponding polymers do not show such responsiveness. However, that should be avoided in future modification as nanoparticles aggregated under body temperature would have a negative impact on drug delivery applications.

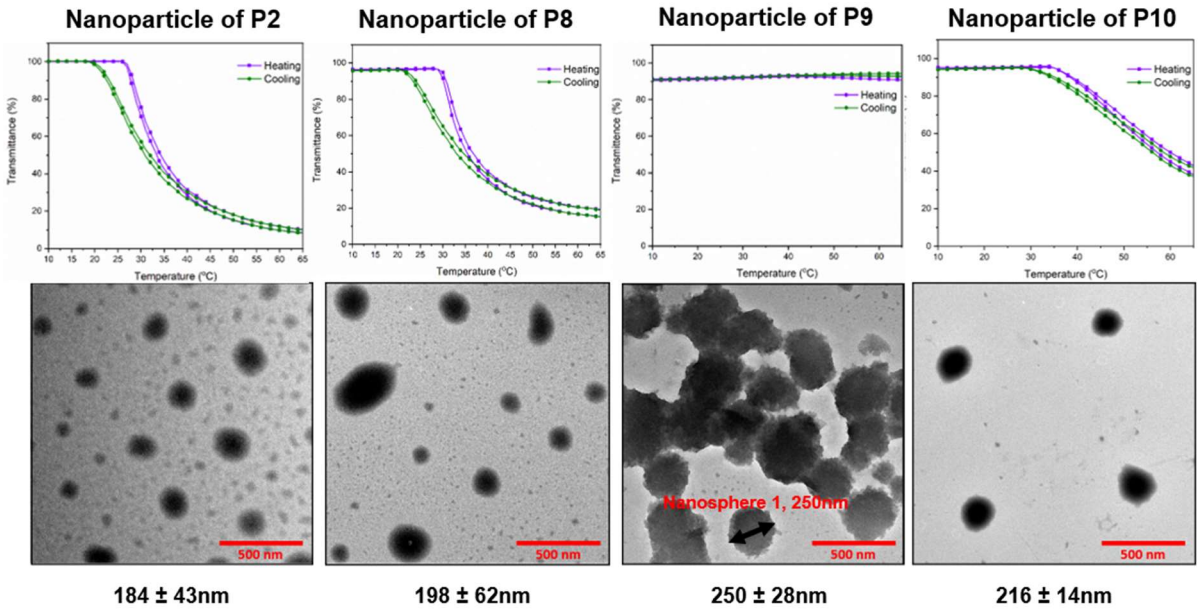


Figure 5. Thermal responsiveness investigation of 2mg/ml nanoparticle water solution of amphiphilic polymer **P2**, **P8**, **P9** and **P10** (top)and TEM (bottom) measurement of 2mg/ml

nanoparticle solution of **P2, P8, P9** and **P10.** The nanoparticle solution of **P2**, **P8** and **P10** shown a reversible aggregation behaviour with elevated temperature ranging from 10-65ºC.

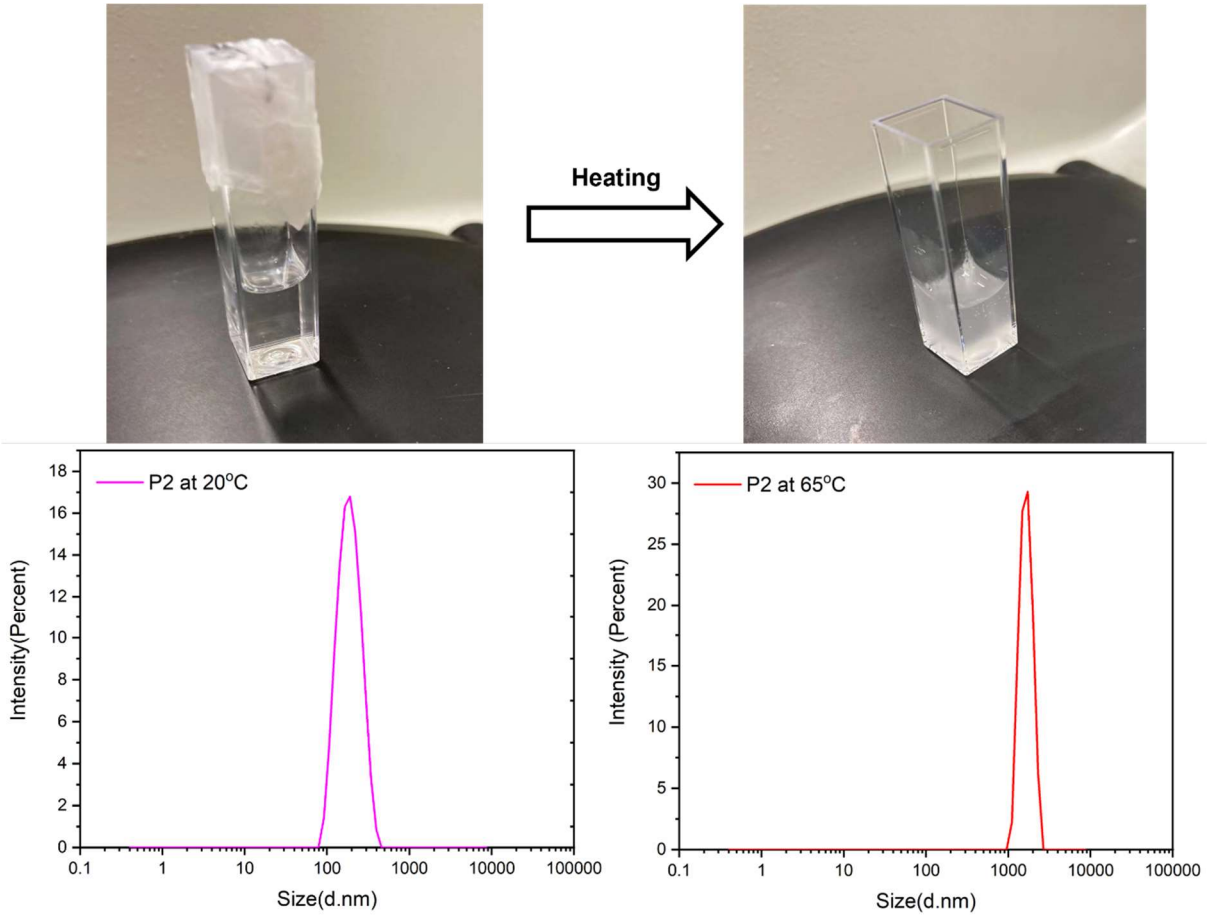


Figure 6. DLS measurements of 2mg/ml nanoparticle water solution of polymer **P2** at 20ºC and 65 ºC. A clear change in particle solution transparency was observed, while the DLS analysis indicating that at 65 ºC macroparticles were presented in the solution due to hydrophobic effect driven aggregation.

3.3 Conclusion

In summary, using 2,3,4,5,6-pentafluoro benzyl bromide as a clickable initiator for the cationic ring-opening polymerization of EtOx and EtOx/MeOx copolymers was investigated and shown to be feasible. The utilization of a clickable pentafluoro benzyl group to synthesize diblock, tetrablock and star polymers have been investigated and the desired polymer structures obtained. Furthermore, we investigated the possibility of using a poly(2-oxazoline) with a pentafluoro benzyl group and utilising the living chain end as a macromonomer for the synthesis of multiblock polymers using a dithiol. Poly(2-oxazoline) multiblock polymers were obtained and the self-assembly properties of amphiphilic polymers prepared were studied.

Polydispersed nanoparticles sized from 184 nm to 250 nm were observed under TEM. This synthesis method provides a convenient and facile one-pot approach to prepare amphiphilic multiblock poly(2-oxazoline)s with different architecture and backbone compositions, while the self-assembly behaviour of these amphiphilic polymers might be worthy to investigate for biomedical applications like drug encapsulation.

3.4 Experimental

3.4.1 Materials and methods

2,3,4,5,6-Pentafluorobenzyl bromide (PFBB) (Aldrich, 99%), 2-ethyl-2-oxazoline (Aldrich, 99%), 2-methyl-2-oxazoline (Aldrich, 99%), 4,4′-thiobisbenzenethiol (Aldrich, 98%), 2,2′-(ethylenedioxy)diethanethiol (Aldrich, 95%), 1,2-ethanedithiol (Aldrich, ≥98.0% (GC), pentaerythritol tetrakis(3-mercaptopropionate) (Aldrich, 95%) and trimethylolpropane tris(3-mercaptopropionate) (Aldrich, 95%) were selected as initiators and starting materials of preparation of clickable polyoxazolines and subsequent click reactions. Triethylamine (Aldrich, ≥99.5%) was used to activate PFTR and thiol-bromo click reactions.

N,N-Dimethylformamide (DMF, Aldrich), chloroform (Aldrich), tetrahydrofuran (THF, Aldrich), diethyl ether (Aldrich) and anhydrous acetonitrile (Aldrich) were used as the solvent for polymerization and precipitation.

Dimethylphenylphosphine (Aldrich 99%) was used to prevent the disulfide bond formation.

3.4.2 Instrumentation

Nuclear Magnetic Resonance (NMR) spectroscopic measurements were performed on 300 or 400 MHz Bruker instruments in 5 mm NMR tubes. Residual solvent signals of $CHCl_3$ (δH = 7.26 ppm, δC =77.2 ppm) was used as reference. ^{19}F NMR chemical shifts are given relative to a $CFCl_3$ standard. Gel permeation chromatography (GPC) measurements were conducted on an Agilent 1260 infinity system operating in THF with 2% TEA and equipped with refractive index detector and variable wavelength detector, 2 PLgel 5 μm mixed-C columns (300 × 7.5 mm), a PLgel 5 mm guard column (50 × 7.5 mm) and an autosampler. The instrument was

calibrated with linear narrow PS standards. All samples were filtered through 0.2 μm PTFE filters before analysis. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF MS) was performed on a Bruker Autoflex Speed mass spectrometer using a nitrogen laser delivering 2 ns pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The matrix used was trans-2-[3-(4-tertbutylphenyl)-2-methyl-2-propylidene]malonitrile (DCTB) dissolved in THF. Sodium trifluoroacetate used as a cationic agent (solution in acetonitrile). The compound (diluted in THF) was applied after separate loadings of DCTB and sodium trifluoroacetate. Samples were measured in reflective or linear mode and calibrated against poly(methyl methacrylate) standards. The morphologies of the self-assembled structures were analysed by Transmission Electron Microscopy (TEM), using a JEOL 2100 instrument operating at an acceleration voltage of 200 kV and equipped with a CCD camera from Gatan. Each TEM sample was prepared by dropping 20 μL of the nanoparticle aqueous solution on a Fresh glow-discharged carbon-coated copper grid for 1 min. The residue of the aqueous solution was blotted away with a strip of filter paper and then the grid was dried under vacuum and stored at room temperature until imaging.

3.4.3 General Procedures

General procedure of cationic ring-opening polymerisation of oxazoline monomer with 2,3,4,5,6 pentafluoro benzyl bromide (PFBB).

An oven-dried clean microwave vial was loaded with a dried magnetic follower, sealed and connected to a vacuum line for 10 minutes before switching to nitrogen flow. PFBB (1 equiv) that distilled and stored over molecular sieves were transferred to the sealed microwave vial under inert conditions with purged syringes. Anhydrous acetonitrile was transferred to the sealed microwave vial under inert conditions with purged syringes, the amount of anhydrous acetonitrile used was calculated to give a 4.0M solution of the selected oxazoline monomer. Distilled and stored over molecular sieves oxazoline monomer (equiv depends on the required degree of polymerization) was then transferred to the sealed microwave vial under inert conditions with purged syringes. The reaction mixture was then transferred to a microwave reactor and heated at a determined temperature for the determined reaction time. The subsequent termination step was done by injecting NaOH/MeOH solution to give a hydroxyl

chain end or a solution of selected dithiol in dry DMF to allow the step-growth polymerization to happen.

3.4.4 Additional characterisation

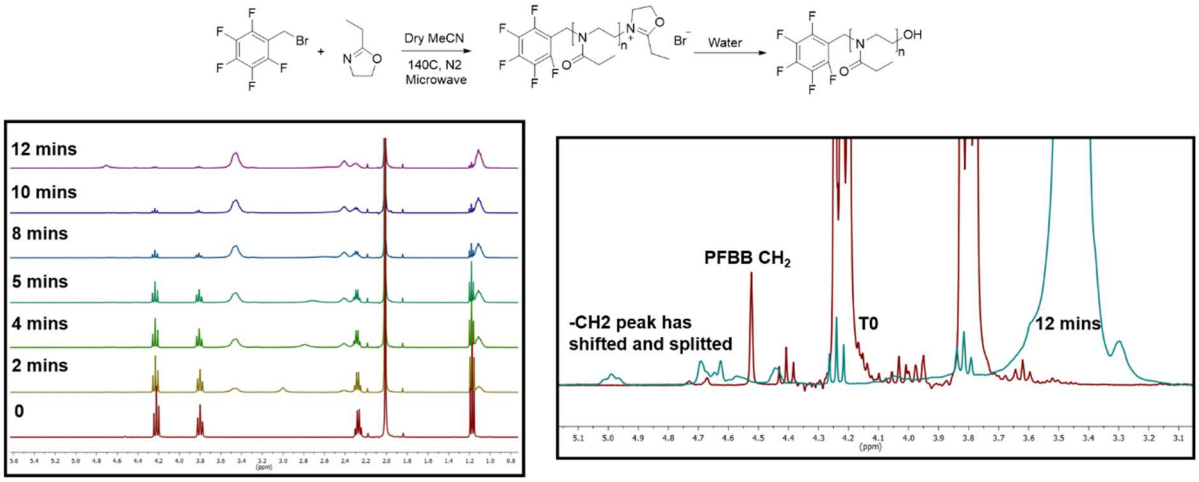


Figure 7. ^{1}H NMR kinetics of PEtOx polymerization with pentafluoro benzyl bromide as the intiator. The ^{1}H NMR kinetic shows the elimination of monomers and the shift and split of methylene group from pentafluoro benzyl bromide.

Calculation of apparent polymerization rate

eq 1, in presence of the assumption that the concentration of active chains [P*] is equal to the concentration of initiator $[I]_0$:

$$-\frac{d[M]}{dt} = k_{app}[P^*][M] \quad (1)$$

Integration of eq 1 with substitution of [P*] with [I] give rise to eq 2

$$ln\frac{[M]_0}{[M]_t} = k_{app}[I]_0 t \quad (2)$$

General procedure of MALDI-ToF sample preparation

20mg/ml *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) solution, 0.5mg/ml polymer solution and 1mg/ml sodium trifluoroacetate solution were

prepared fresh. 0.5µl of each solution were mixed and 0.5µl of mixed solution was taken to prepare one MALDI spot.

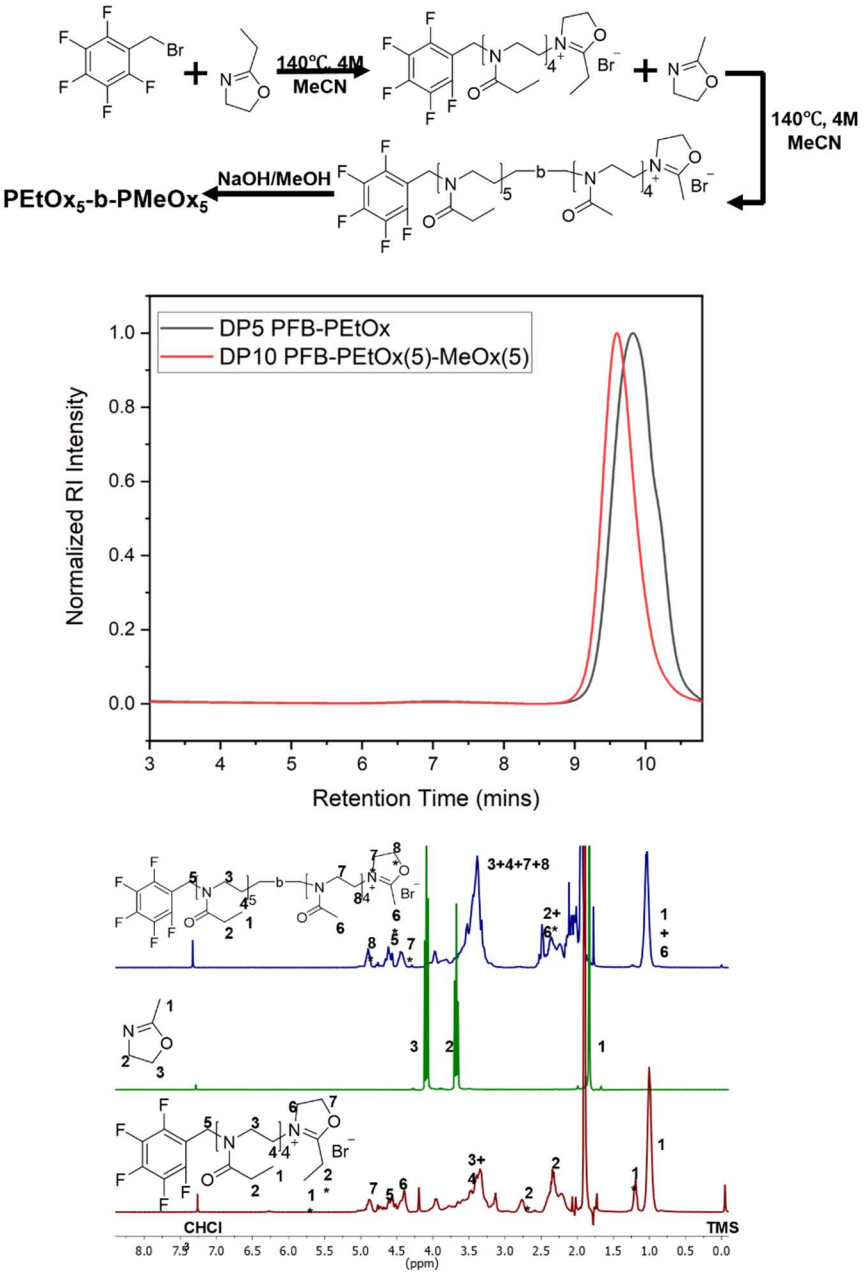


Figure 8. THF GPC and ^{1}H NMR characterisation of P(EtOx)$_5$-b-P(MeOx)$_5$ using PFBB as the initiator. THF GPC traces shown a hydrodynamic volume change while ^{1}H NMR shows the presence of desired polymer, and the consumption of MeOx monomer.

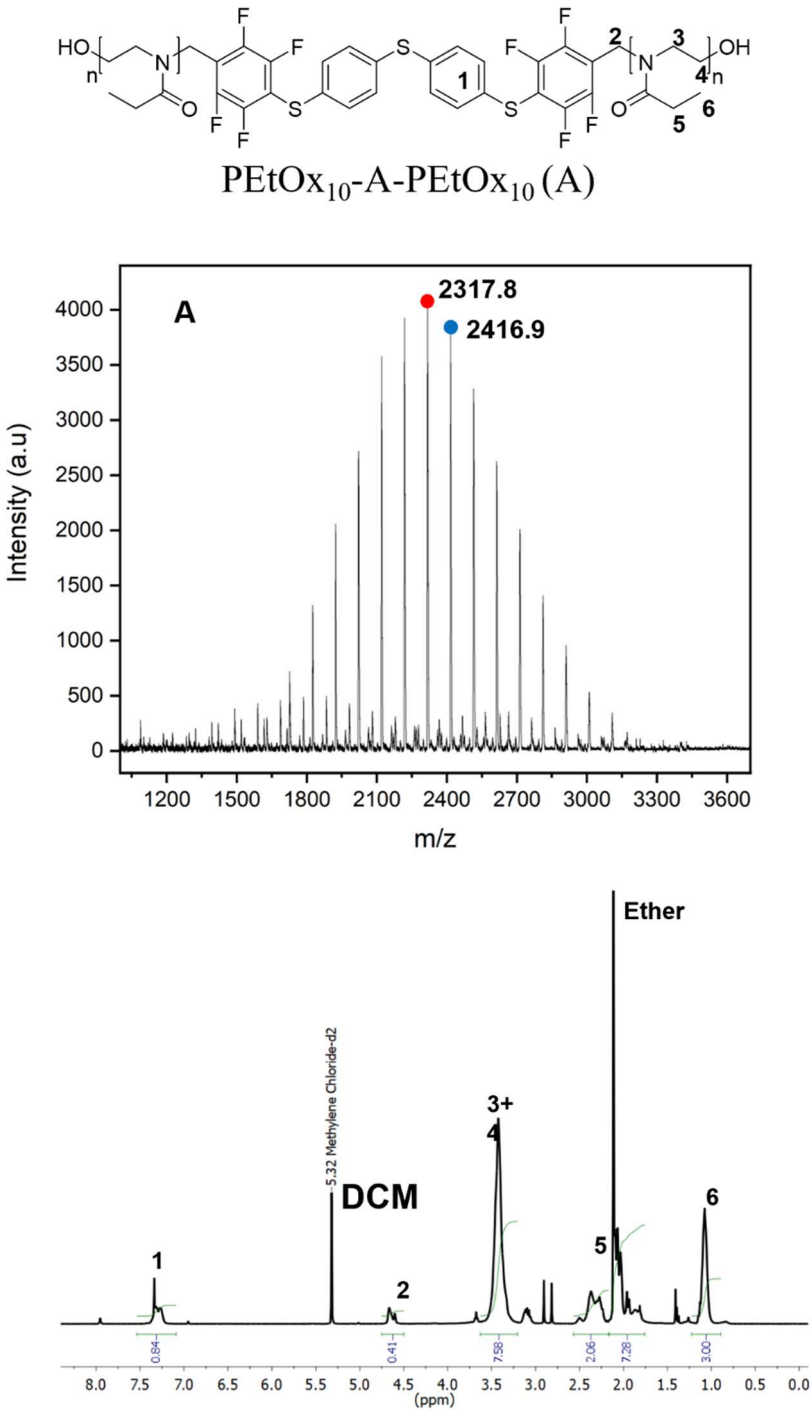
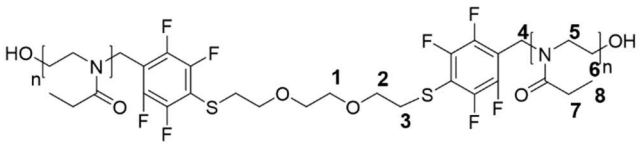


Figure 9. MALDI-ToF and ^{1}H NMR characterisation of PEtOx$_{10}$-A-PEtOx$_{10}$

^{1}H NMR has shown peaks of desired structure, while the MALDI-ToF results showed a major distribution of desired structure. For example, peak 2317.8 fits the theoretical value of a diblock polymer with 17 EtOx units, two hydroxyl end groups, dithiol A as the connection unit and flying in the formation of sodium salt, while the difference between peaks was 99.1 that corresponds to a EtOx unit.



$PEtOx_{10}$-B-$PEtOx_{10}$ (B)

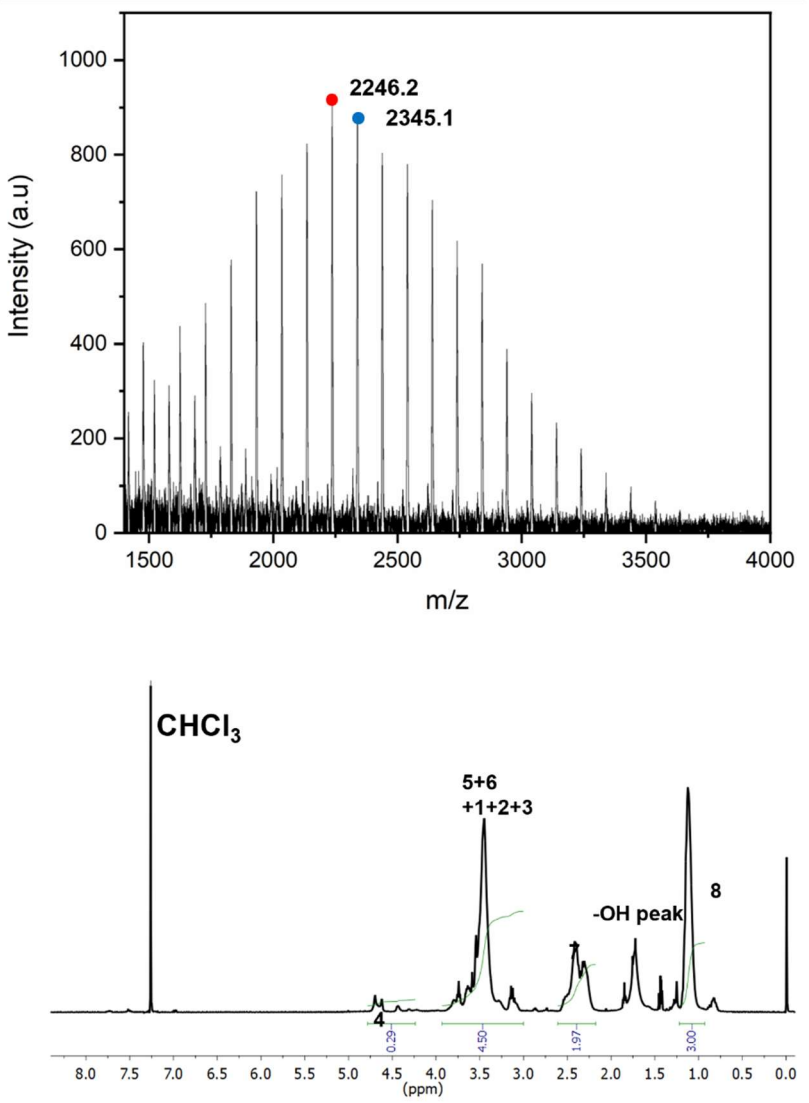


Figure 10. MALDI-ToF and ^{1}H NMR characterisation of $PEtOx_{10}$-B-$PEtOx_{10}$

^{1}H NMR has shown peaks of desired structure, while the MALDI-ToF results showed a major distribution of desired structure. For example, peak 2248.2 fits the theoretical value of a diblock polymer with 17 EtOx units, two hydroxyl end groups, dithiol A as the connection unit and flying in the formation of sodium salt. The difference between peaks was 98.9 that corresponds to a EtOx unit.

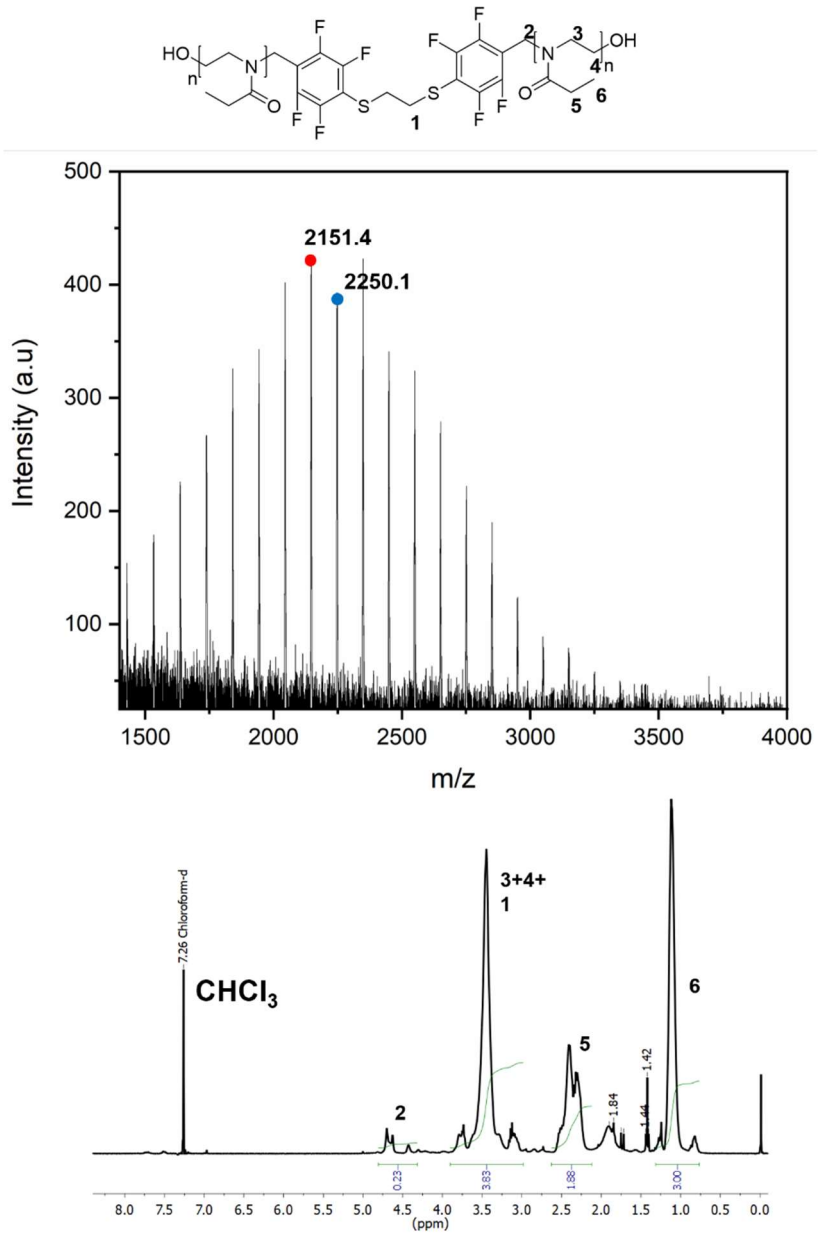


Figure 11. MALDI-ToF and 1H NMR characterisation of $PEtOx_{10}$-C-$PEtOx_{10}$

^{1}H NMR has shown peaks of the desired structure, while the MALDI-ToF results showed a major distribution of desired structure. For example, peak 2151.4 fits the theoretical value of a diblock polymer with 17 EtOx units, two hydroxyl end groups, dithiol A as the connection unit and flying in the formation of sodium salt. The difference between peaks was 98.7 that corresponds to an EtOx unit.

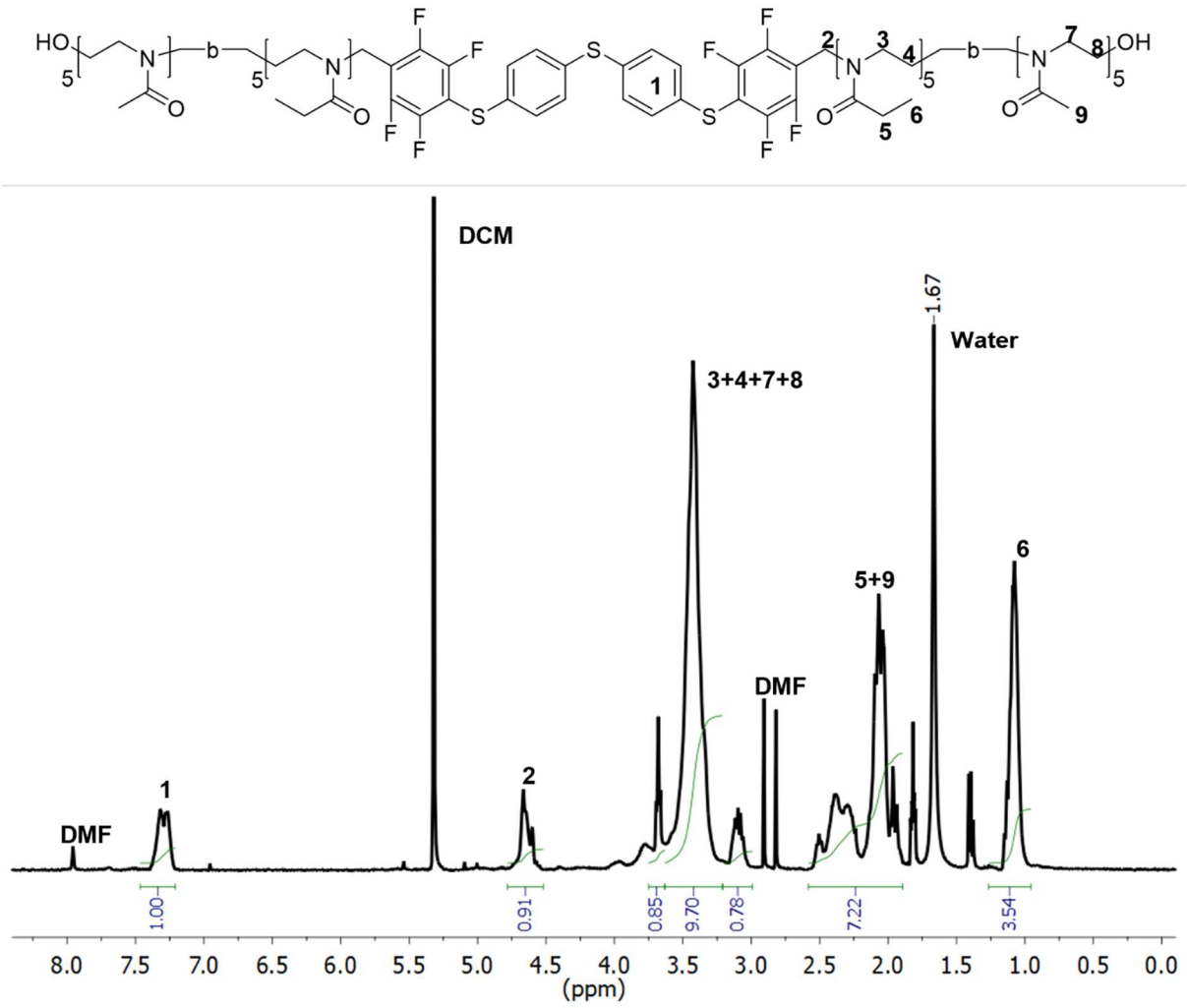


Figure 12. ^{1}H NMR characterisation of tetrablock polymer P(EtOx$_5$-MeOx$_5$)$_2$-A

^{1}H NMR characterisation has shown the formation of desired polymer structure while the integrations suggesting the final product is a mixture of tetrablock polymer and diblock polymer, which shown by the ratio between aromatic peak **1** and -CH_2 peak **2**. Reason might be possible chain transfer in block polymer formation results in reduced chain end fidelity.

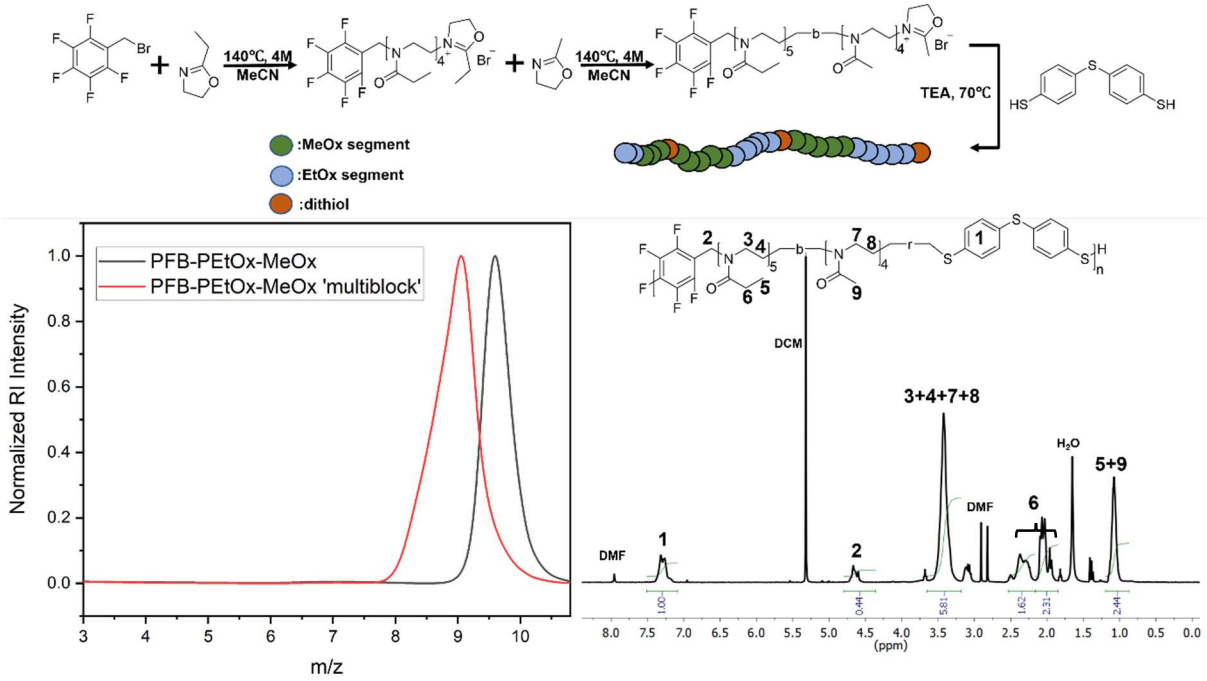


Figure 13. THF GPC traces and ^{1}H NMR characterisation of multiblock P(EtOx-MeOx)

The THF GPC trace has shown a significant hydrodynamic volume change while in the 1H NMR, although the specific peaks have been observed, the distorted ratio between peaks were suggesting that leftover of diblock PEtOx-MeOx existing in the final product. The reason could be the living chain end fidelity was affected during synthesis of block copolymer and the chain transfer during polymerization results in missing α-end functional groups.

3.5 References

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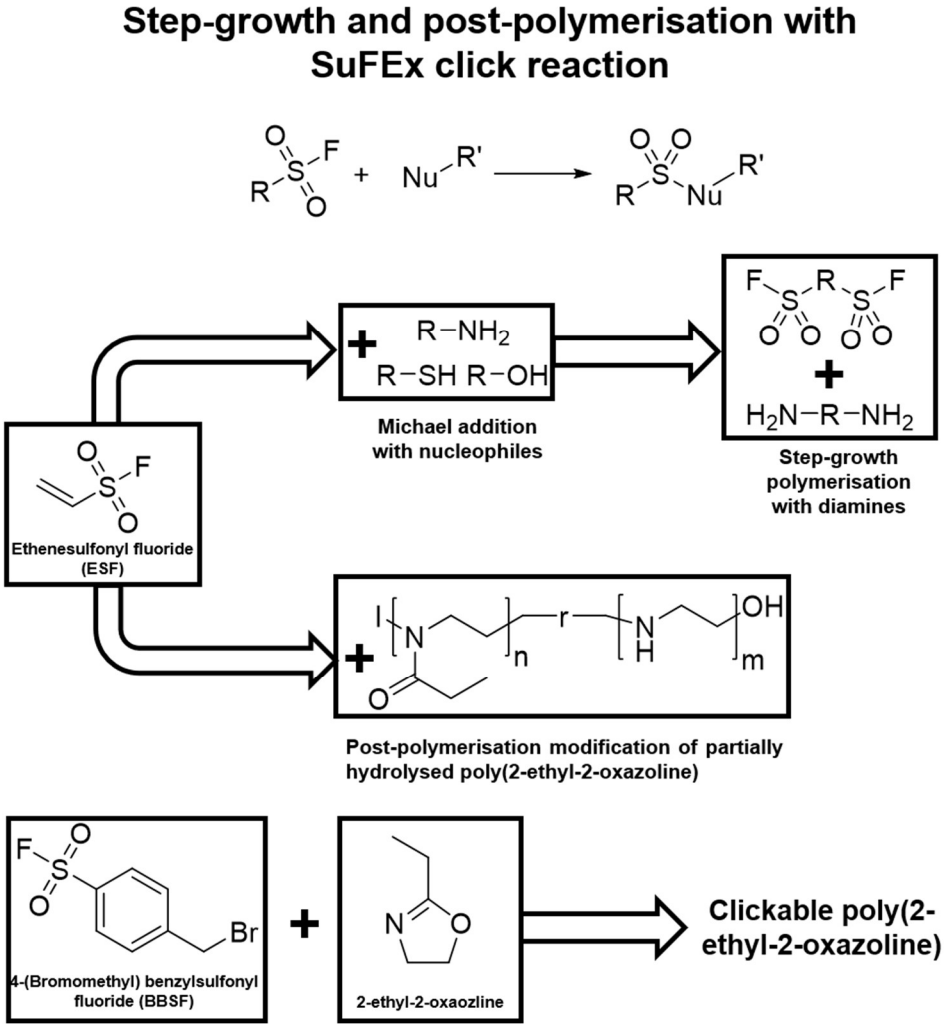
Chapter 4: Click polymerization and post-polymerization modification with Sulfur (VI) fluoride exchange (SuFEx) click chemistry

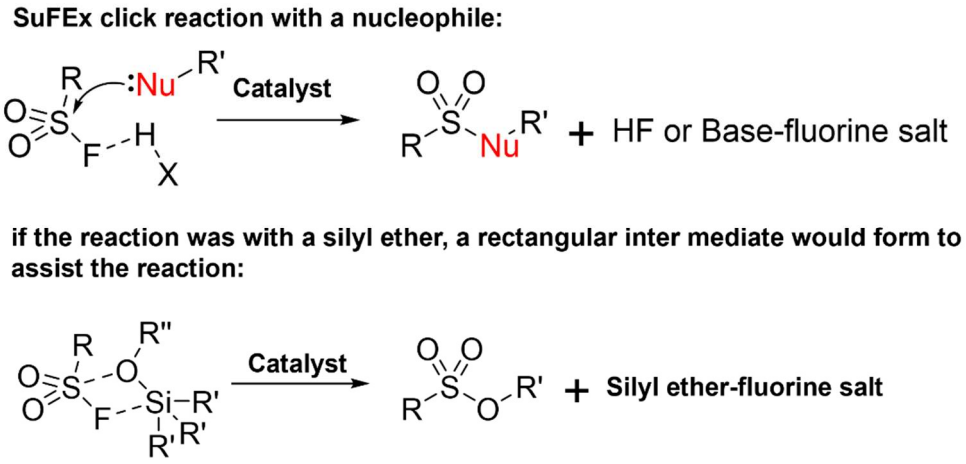


Abstract

Sulfur(VI) Fluoride Exchange (SuFEx) click reaction coined in 2014 by Sharpless has shown great potential in preparation of polysulfate and polysulfonates. However, the SuFEx click polymerization was only investigated with silyl ether groups, and the produced linkage structure was limited. Inspired by the similarity of -SO_2NH- linkage to peptide bonds and encouraged by the lack of reports on creating such linkage with SuFEx click reaction, synthesis of various sulfonylfluoride containing monomers via the Michael addition of primary amine, thiols and hydroxyls with ethenesulfonyl fluoride (ESF) was investigated, followed by the click polymerization of sulfonyl fluoride monomers with diamines. The post-polymerization modification of hydrolysed polyoxazoline with the Michael addition of ESF and subsequent SuFEx click reaction was also investigated. Furthermore, poly(2-ethyl-2-oxazoline) was synthesized utilizing a sulfonyl fluoride containing initiator for possible modifications with SuFEx click reaction.

4.1 Introduction

SuFEx click chemistry is a recently emerged click chemistry that was termed by Sharpless in 2014.[1] This click chemistry is based on the nucleophilic attack of the fluorine on a sulfonyl fluoride group by a nucleophile, the fluorine is removed and forms either HF or fluorine salt and new bond is formed between the sulphur atom and the atom from the nucleophile. (**Scheme 1**) Sharpless and coworkers have utilized this click chemistry in preparation of step-growth polysulfates and polysulfonates.[2,3] Research also showed that the click reaction works with amines and hydroxyls.[1] Benefits from the diversity of commercially available amines and hydroxyls, this reaction should have great potential in click polymerization and PPM.



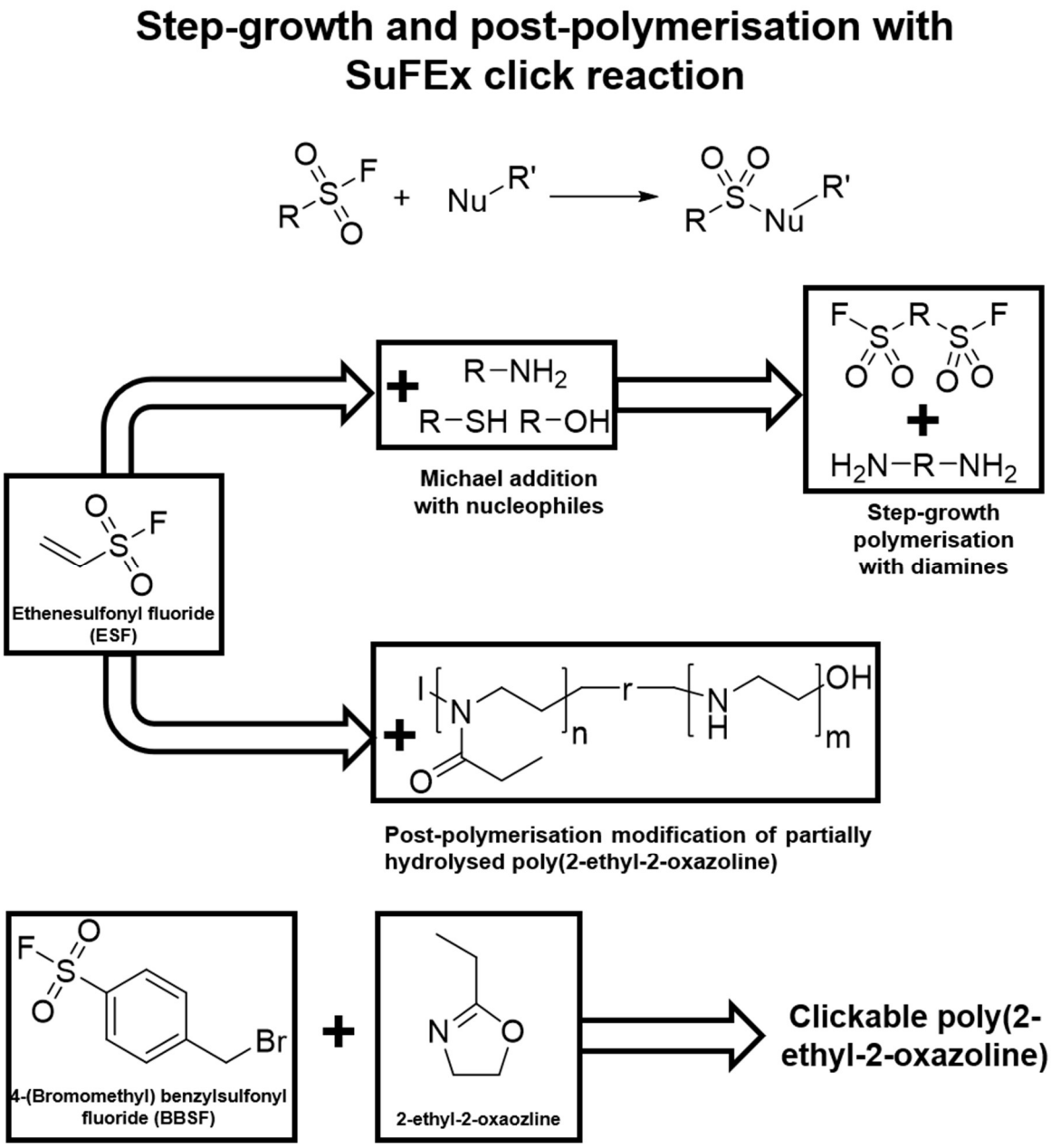
Scheme 1. SuFEx click reaction mechanism with a nucleophile or with a silyl ether. The reaction with silyl ether would form a rectangular intermediate that provides additional benefits for the substitution to happen.

To investigate the step-growth polymerization and post-polymerization modification with SuFEx click chemistry, it is necessary to establish reliable methods to prepare sulfonyl fluoride functionalized monomers and to introduce sulfonyl fluoride groups onto polymer backbones. There are several ways to install sulfonyl fluoride group onto small molecules and polymers. One widely reported way is using sulfuryl fluoride gas, a commercially available fumigant, to react with a variety of functional groups including primary amines, secondary amines and hydroxyls to produce corresponding sulfamoyl fluoride and fluorosulfates.[1] This method has been used intensively in synthesis of polysulfates and polysulfonates as the way to prepare bifunctional sulfonyl fluoride monomers, especially aryl ones.[2,4–6] Manufacturing sulfonyl fluoride functionalized monomer for subsequent side chain modification via SuFEx click reaction has also been reported[7] as well as the end-functionalization.[8] Another convenient way is to use multifunctional connectors to install a sulfonyl fluoride group via reactions orthogonal

to SuFEx click reaction.[1] One good example of multifunctional connectors is ethenesulfonyl fluoride(ESF). Thanks to the electron withdrawn -SO_2F functional group, the double bond in ESF was expected to be very electrophilic and should serve as a good Michael acceptor, which has been quantitatively proved.[9] Plentiful of alkyl bifunctional sulfonyl fluoride compounds have been prepared via the Michael addition of ESF with primary amines in several reports[3,10,11] and following step-growth polymerization and modification have also been studied.

While getting inspired by the efficiency of SuFEx click reaction, it has been noticed that most of the SuFEx click reaction reported was the reaction between sulfonyl fluoride group and silyl ethers. For step-growth polymerization via SuFEx reported polymers were all polysulfates or polysulfonates,[2,3,10,12,13] while the post-polymerization modification via SuFEx click reaction reported on several polymers on side chain[7,11] and end group modification[8,14,15] were also mostly on SuFEx click reaction between sulfonyl fluorides and silyl ethers. As a few reports have shown SuFEx click reaction of sulfonyl fluoride and derivatives with amines and reasonable yields have been claimed,[16,17] step-growth polymerization via SuFEx click reaction with amines and other nucleophiles seems to be an overlooked and interesting research field, while the possible sulfamide (-SO_2NH) linkage obtained in SuFEx-based step-growth polymerization of sulfonyl fluoride and amines might have similar properties as amide linkages and be another candidate for novel pseudo-peptide structures. Besides, the Michael addition of ESF with amines has been proved highly efficient, it would be interesting to study the reaction between ESF and thiols to introduce more sulfur-containing backbone for step-growth polymerizations, while the strong electrophilicity of double bond in ESF might be able to allow addition reactions between weak nucleophiles and ESF, such as hydroxyls.

Thus, a project on investigating SuFEx-based step-growth polymerization and post polymerization modification has been proposed and studied. From investigating addition reactions between ESF and amines, thiols and hydroxyls, to preparation of bifunctional sulfonyl fluoride monomers and subsequent step-growth polymerizations, and also the post-polymerization modification of polyoxazolines with SuFEx click reaction have been studied (**Scheme 2**)and corresponding discussions have been made.



Scheme 2. Investigation on Michael addition of ethenesulfonyl fluoride (ESF) and subsequent step-growth polymerization of di-sulfonyl fluoride compound with diamine, the post-polymerisation modification of partially hydrolysed poly(2-ethyl-2-oxaozline), and the synthesis of clickable poly(2-ethyl-2-oxazoline) with a SuFEx clickable initiator.

4.2 Results and Discussion

4.2.1 Michael addition of ESF with amines, thiols and hydroxyls

To employ the Michael addition approach and prepare bifunctional monomers for subsequent step-growth polymerization study, Michael addition of ESF with amines, thiols and hydroxyls was firstly investigated in two common NMR solvents with distinct polarity: deuterated chloroform and DMSO-d6 to make quick NMR kinetics analysis available. Reactions were executed under room temperature at a 0.5 M concentration and no catalyst was used. In the Michael addition of ESF with primary amines, different mole ratios between ESF and butylamine, which was selected as a candidate of primary amines, were selected including equal amount (1:1), ESF excess (1:0.5) and amine excess (1:2). The aim of using equal amount was to investigate the possibility of preparing mono-adducted compounds which would possess a very interesting structure that has secondary amine and sulfonyl fluoride functional groups, which would be immediately available as an AB-type monomer for step-growth polymerization. For the other two ratios, ESF excess is to make sure a complete Michael addition into double-adducted bi-sulfonyl fluoride product that serves as a bifunctional monomer for subsequent polymerization, while amine excess was aiming to investigate if the primary amine could serve as a base and catalyse the SuFEx click reaction. Butylamine was selected as the model amine to investigate the Michael addition of ESF with amines, obtained results were collected in **Table 1**, corresponding ^{1}H NMR graphs of products were shown in **Figure 1-9**.

Table 1. Addition reactions of ESF with amines, thiols and hydroxyls in deuterated solvents

No.		Mole ratio	Comments
R1	ESF + Butylamine, $CDCl_3$	ESF:Amine = 1:1	Mixed product of mono-adduct (37%) and double-adduct (63%).
R2		ESF:Amine = 2:1	Double-adduct product, yield = 92%
R3		ESF:Amine = 1:2	Mixed product of mono-adduct (53%) and double-adduct(47%).
R4	ESF + Butylamine, DMSO-d6	ESF:Amine = 1:1	Spectrum resolution was bad due to insoluble gel formation in NMR tube.

R5		ESF:Amine = 2:1	Double-adduct product, yield = 91%
R6		ESF:Amine = 1:2	Spectrum resolution was bad due to insoluble gel formation in NMR tube.
R7	ESF + 1-butanethiol DMSO-d6	ESF:Thiol = 1:1	Complete consumption of ESF
R8	ESF+ 1-butanethiol DMSO-d6	ESF:Thiol = 1:2	Complete consumption of ESF, no further reaction.
R9	ESF + 1-butanethiol $CDCl_3$	ESF:Thiol = 1:1	No reaction
R10	ESF + cysteamine	ESF:cysteamine = 1.2:0.5	Selective reaction on amine
R11	ESF+ 1-butanol $CDCl_3$	ESF:hydroxyl = 1:1	Slow reaction

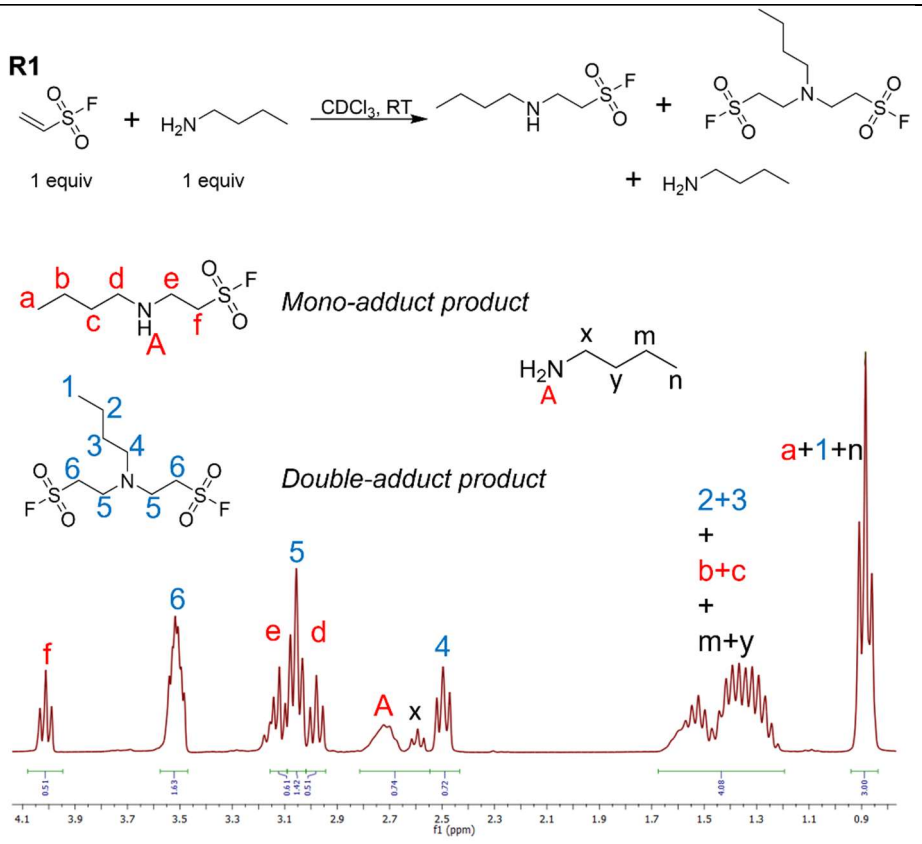


Figure 1. ^{1}H NMR characterisation of Michael addition of ESF and butylamine under the mole ratio of 1:1(ESF:Amine). The ratio of mono-substituted product and double-substituted product were determined by the ratio of peak **f** and peak **6**.

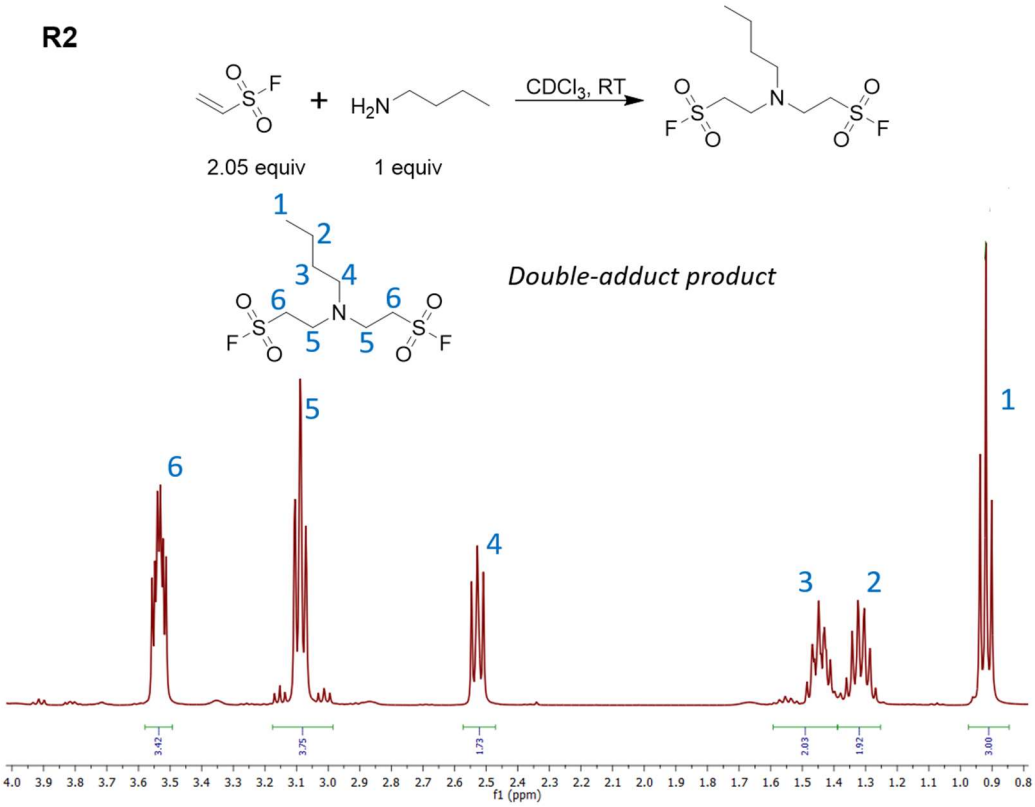


Figure 2. 1H NMR characterisation of Michael addition of ESF and butylamine under the mole ratio of 1.1:0.5(ESF:Amine) in $CDCl_3$. Double-substituted product was observed and corresponding peaks were assigned.

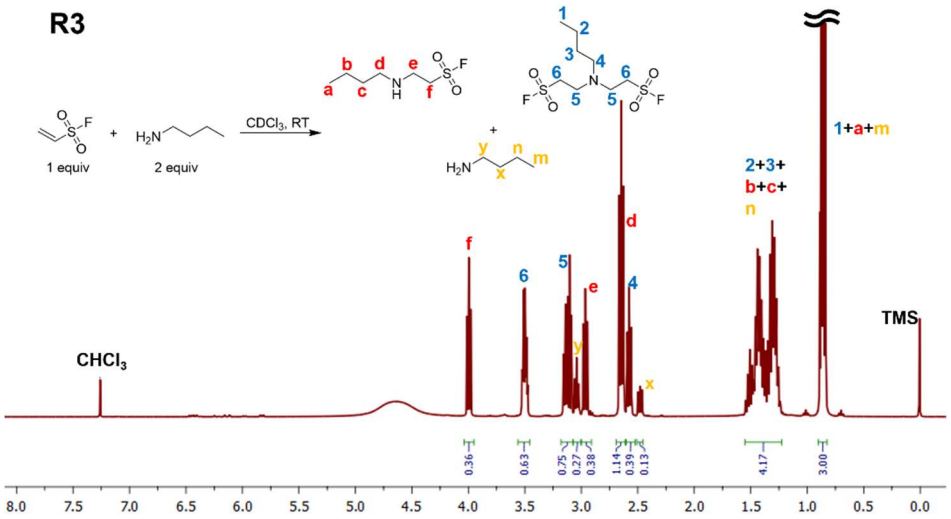


Figure 3. [1]H NMR characterisation of Michael addition of ESF and butylamine under the mole ratio of 1:2(ESF:Amine) in $CDCl_3$. Mono-substituted, double-substituted and leftover

butylamine were observed in the spectrum. The ratio between mono-substituted and double-substituted product were calculated with the ratio between peak **f** and **6**.

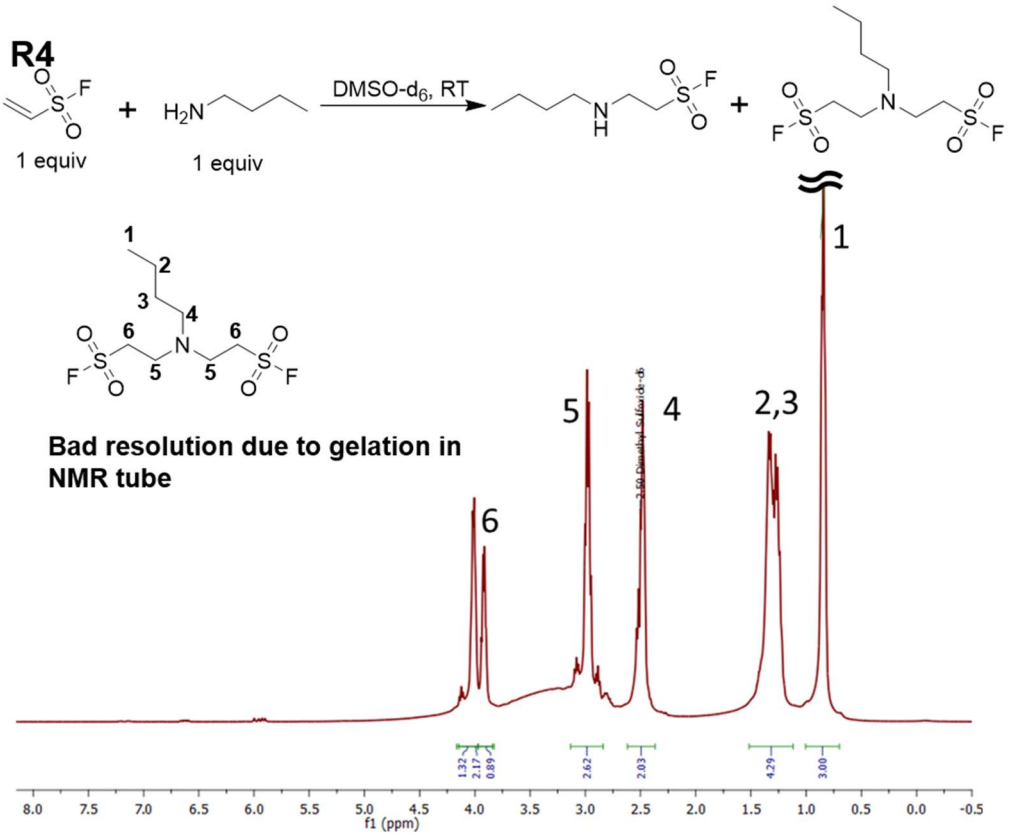


Figure 4. ^{1}H NMR characterisation of Michael addition of ESF and butylamine under the mole ratio of 1:1(ESF:Amine) in DMSO-d6. The resolution of the spectrum was bad, broad peaks shown in the spectrum and insoluble gel was observed in the NMR tube, indicating possible side reactions like SuFEx click reaction might happened or strong hydrogen bonding was presented to produce a gel structure.

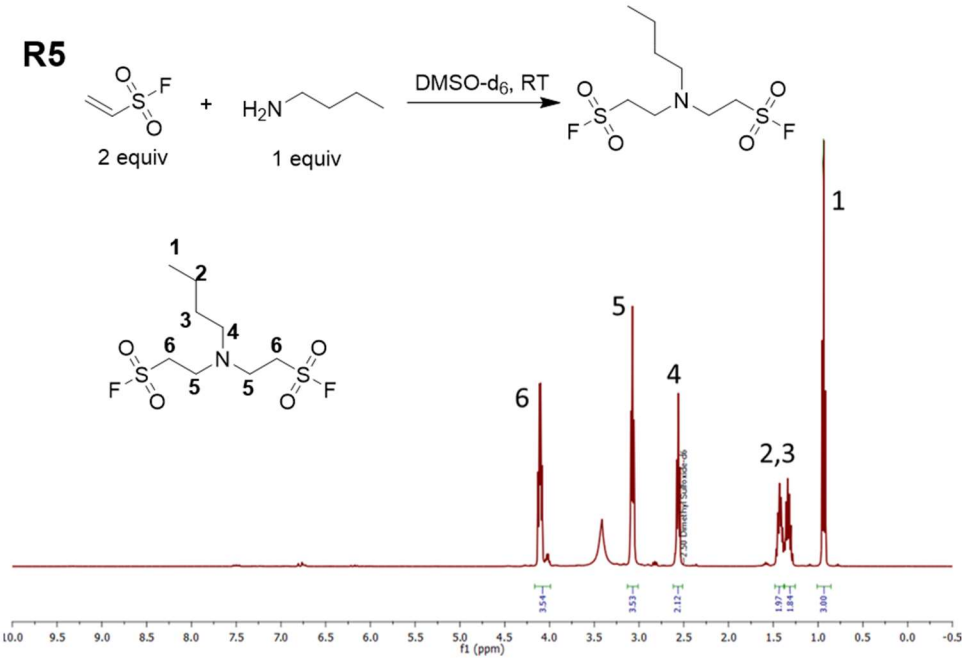


Figure 5. ^{1}H NMR characterisation of Michael addition of ESF and butylamine under the mole ratio of 1:0.5(ESF:Amine) in DMSO-d6. Double-adduct product has been observed in the NMR spectrum based on the integration, corresponding peaks were assigned.

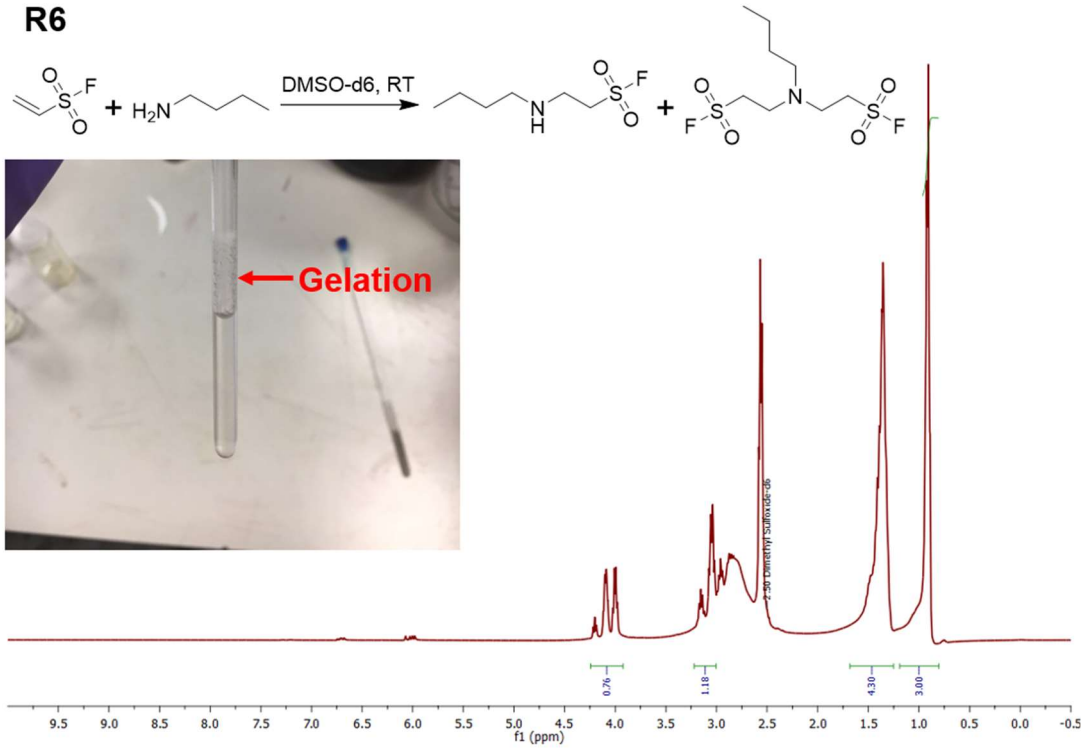


Figure 6. ^{1}H NMR characterisation of Michael addition of ESF and butylamine under the mole ratio of 1:2(ESF:Amine) in DMSO-d6. The resolution of the spectrum was bad, broad peaks was observed in the spectrum and insoluble gel was observed in the NMR tube, indicating side

reactions, most likely SuFEx click reaction, might happened and resulting in crosslinked structure.

Results have shown that the Michael addition of ESF with primary amines are quite efficient under several reactant ratios, as the first NMR kinetics sample, which was supposed to be t0, have shown complete consumption of ESF in both solvents (**Figure 1-6**). This indicates the Michael addition happens in minutes, while the insoluble gel formation in DMSO when the ratio of ESF to butylamine was larger than 1:0.5 shown that further SuFEx click reaction might happen under the catalysis of butylamine but is only possible in very polar solvents like DMSO. This suggests the step-growth polymerization of bifunctional sulfonyl fluoride and bisamine might be possible. Mixed products of mono-adduct and double-adduct has been observed in reactions **R1, R3** while for **R4** and **R6** the spectrum resolution was not good enough to identify products, the existence of mixed products indicates no selectivity of Michael addition was shown under selected reaction condition. While taking **R1** as an example, the percentage of obtained mono-adduct product and double-adduct product can be calculated as 37% and 63%, based on ^{1}H NMR integrations of signature peaks **f** and **6**. (**Figure 1**) These results suggest the Michael addition of ESF with primary amines under the ratio of ESF to amine equal to 1:0.5 could be an efficient way to synthesis bifunctional sulfonyl fluoride monomers for step-growth polymerization via SuFEx click reactions.

Apart from aza-Michael addition of ESF, the thiol-ene reaction of ESF with 1-butane thiol was investigated under ratios of ESF to thiol equal to 1 to 1 or 1 to 2 in DMSO-d6(**R7, R8**). Again, the use of excess thiol was to investigate if SuFEx click reaction could happen under such reaction condition, using extra thiol as a catalyst. Based on the efficiency of Michael additions, the assumption was the thiol-ene reaction should be at least equally efficient. ^{1}H NMR results of **R7** and **R8** were collected in **Figure 7-8**. The thiol-ene reaction in DMSO-d6 at 1:1 ratio(**R7**) has shown a complete consumption of ESF in minutes, similar to previously studied Michael addition, and all corresponding hydrogens of the product have been assigned, while the reaction at a 1:2 ratio only shown the thiol-ene addition product and leftover thiols, indicating SuFEx click reaction did not happen under selected reaction condition with thiol as the catalyst. However, when trying to study the thiol-ene reaction in deuterated chloroform at a 1:1 ESF to thiol ratio, ^{1}H NMR results has demonstrated no reaction has happen (**Figure 9**), all double

bond hydrogens from ESF were still in the reaction system, while the thiol hydrogens remain unreacted as well. Chances are in the rather apolar deuterated chloroform solvent system the thiyl radical generated in the free-radical addition process was stabilized. This solvent effect provides the possibility of selective Michael addition of ESF to certain functional groups like amine.

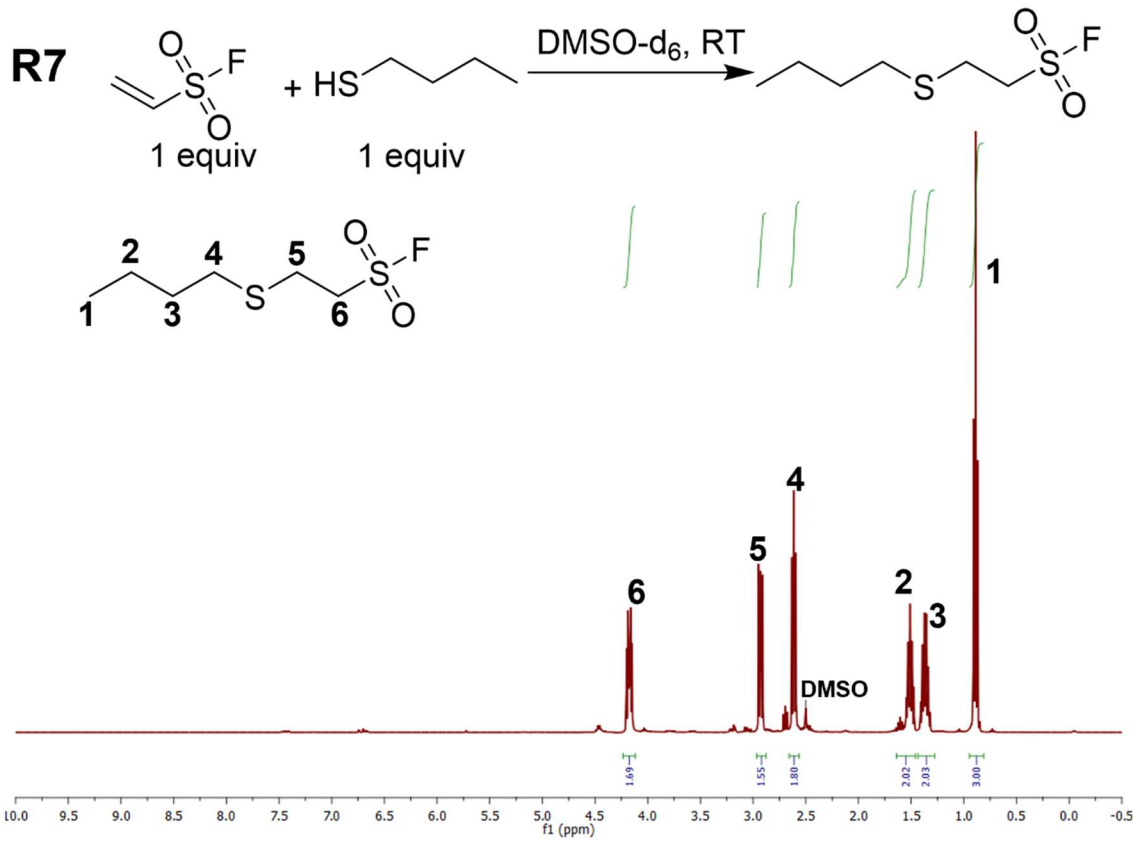


Figure 7. ^{1}H NMR characterisation of Michael addition of ESF and 1-butanethiol under the mole ratio of 1:1(ESF:Thiol) in DMSO-d6. Desired product was observed, and corresponding peaks were assigned.

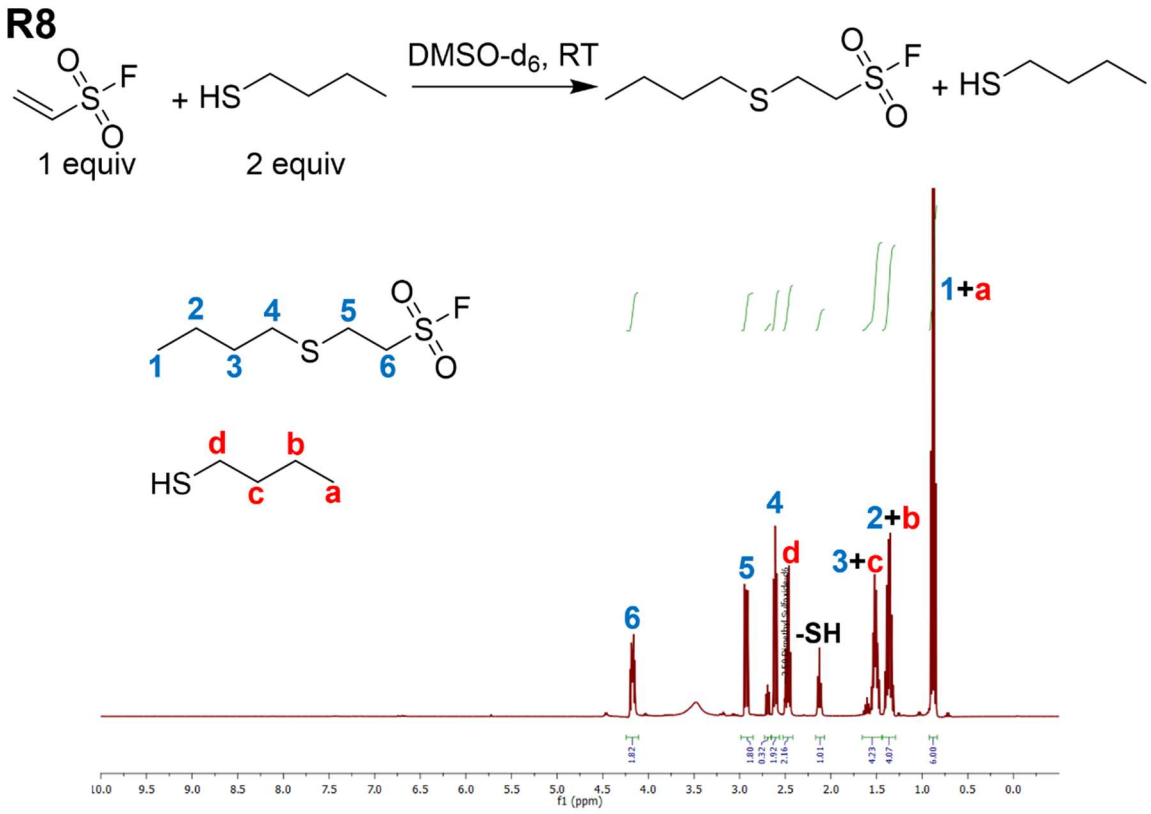


Figure 8. ^{1}H NMR characterisation of Michael addition of ESF and 1-butanethiol under the mole ratio of 1:2(ESF:Thiol) in DMSO-d6. Desired product and leftover thiols were observed, indicating no further click reactions happen in this reaction system, and corresponding peaks were assigned.

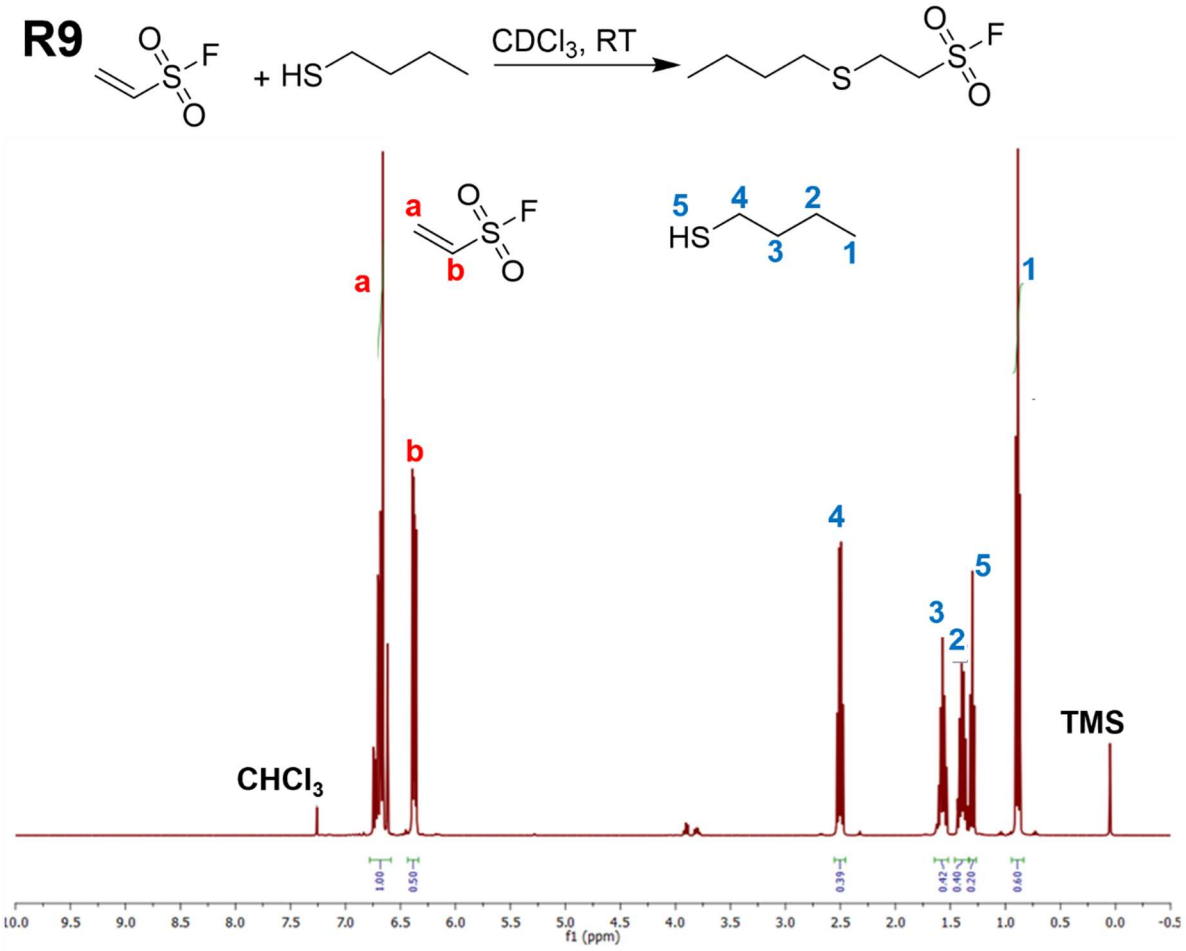


Figure 9. ^{1}H NMR characterisation of Michael addition of ESF and 1-butanethiol under the mole ratio of 1:1(ESF: thiol) in $CDCl_3$. The NMR spectrum has shown no reaction happened between ESF and thiol.

Based on this solvent effect presented, it was natural to pick cysteamine, a compound with a primary amine and a thiol functional group, to investigate if the amines can be selectively reacted in deuterated chloroform. The reaction was executed under the same condition as the Michael addition reactions while the mole ratio of ESF to cysteamine was set at 1.2:0.5(**R10**). This ratio was set to investigate which functional group would react faster than another. ^{1}H NMR results comparison (**Figure 10**) has shown that the primary amine has been reacted and desired bifunctional sulfonyl fluoride compound was produced, while according to ESF residue shown in the ^{1}H NMR, indicated by the remaining double bond peaks, the thiol group was not reacted with the ESF double bond. This selectivity might provide a chance to prepare a multifunctional monomer for either orthogonal click chemistry or the preparation of polymer networks.

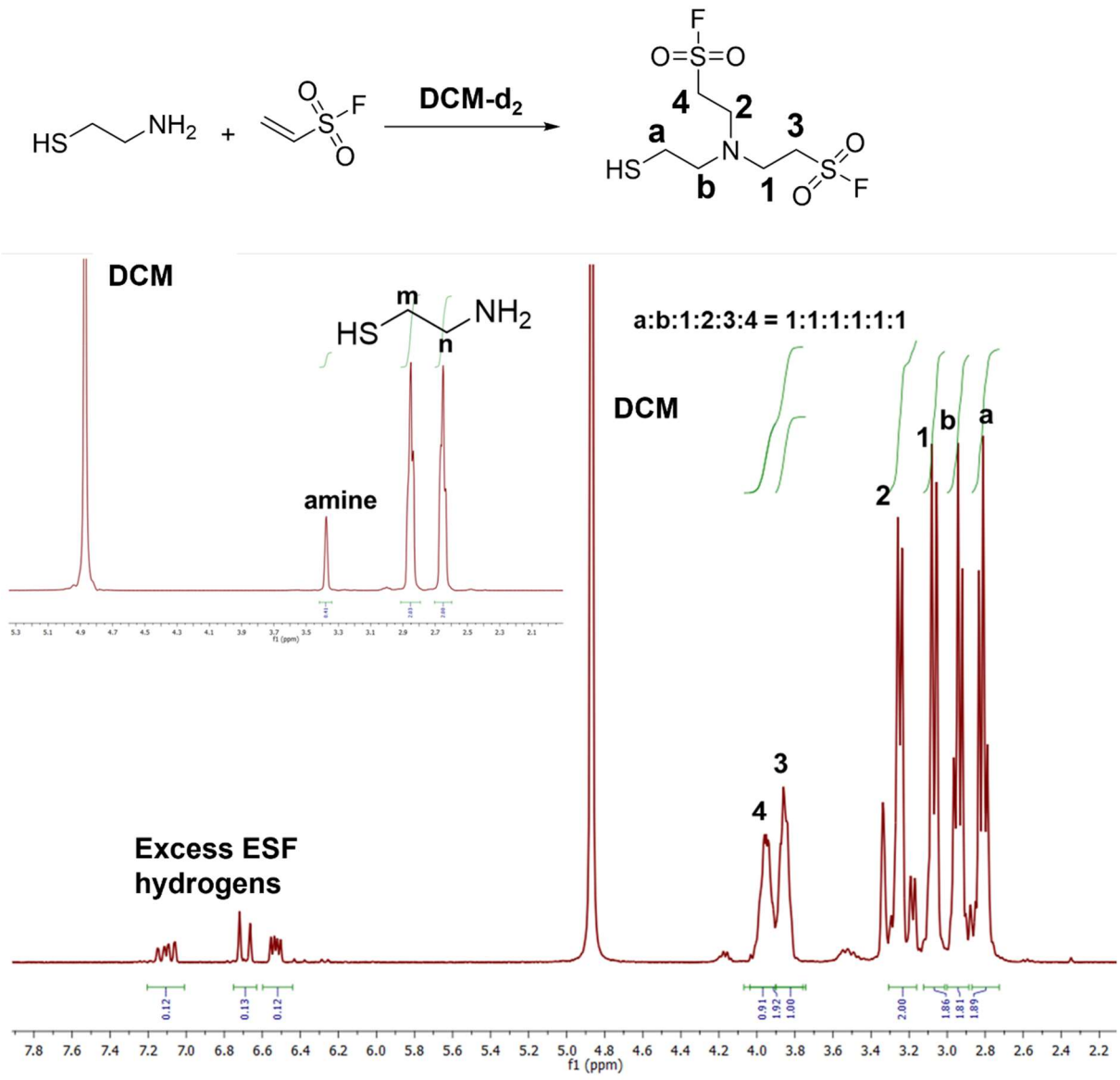


Figure 10. ^{1}H NMR characterisation of selective Michael addition of ESF with cysteamine. The integration of 3 and 4 indicates only two -CH_2 pairs was near the sulfonyl fluoride group, while excess ESF hydrogens indicating no further reactions beyond the double-adduct onto the cysteamine primary amine.

Apart from mono-thiol compounds, the thiol-ene reaction between ESF and two dithiol compounds have also been investigated to produce bifunctional sulfonyl fluoride compounds. 4,4-Thiobisbenzene thiol and 1,3,4-thiadiazole-2,5-dithiol were selected as dithiol candidates. The reaction was done at 0.5M concentration in DMSO-d6 only as solubility issues were observed for 4,4-thiobisbenzene thiol in deuterated chloroform. The mole ratio of ESF to dithiol was set at 1:0.5 to produce bifunctional sulfonyl fluoride compounds. The reaction

between ESF and 4,4-thiobisbenzene thiol have shown promising results, ^{1}H NMR characterisation (**Figure 11**) indicating the formation of a bifunctional sulfonyl fluoride compound, proved by the elimination of ESF double bond hydrogens and the generation of hydrogen peaks between 3.0-4.5. However, the integration between peak 3 and 4 was distorted, the integration of peak 4 was significantly higher than the theoretical number 4.0. This might be the consequence of side reactions of the ESF double bond. For the reason with 1,3,4-thiadiazole-2,5-dithiol, an insoluble yellow rubber-like crosslinked solid was obtained. Possible reason is the tertiary amine ring was somehow opened, the amine participated in the addition reaction and make the dithiol tetra-functionalized hence the crosslinking product.

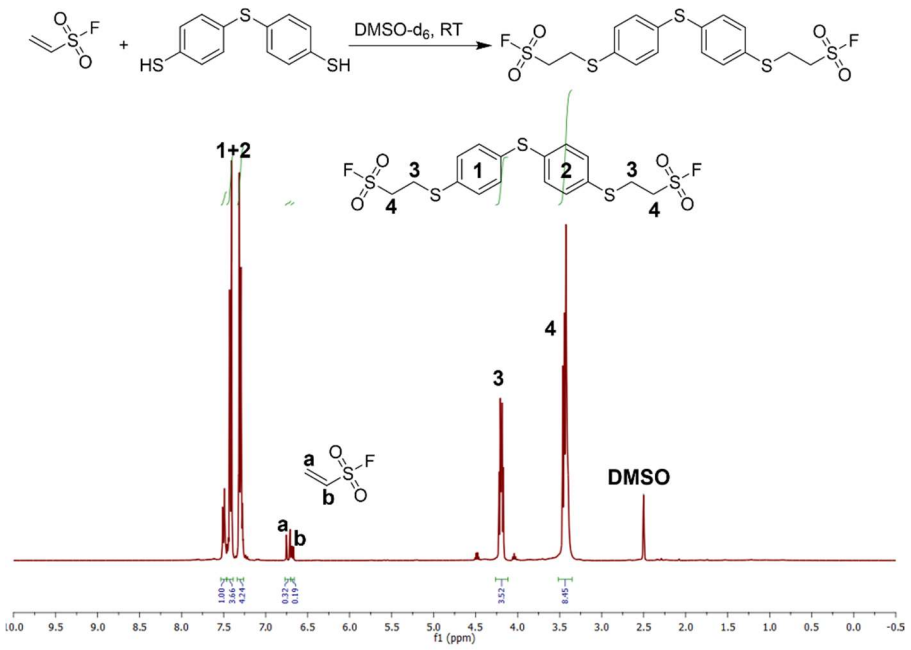


Figure 11. ^{1}H NMR characterisation in DMSO of thiol-ene addition between ESF and 4,4-thiobisbenzene thiol under the ratio of 1:0.5 of ESF to dithiol. Desired bifunctional fluoride was generated evidenced by the consumption of ESF and the generation of peak 3 and 4.

For reaction with hydroxyl compounds, the stoichiometry mole ratio of triphenylphosphine (PPh_3) was used as a catalyst to compensate weak nucleophilicity of hydroxyl compounds. The reaction between ESF and 1-butanol was performed in deuterated chloroform at a 1 to 1 ratio of ESF to 1-butanol (**Figure 12**). ^{1}H NMR result at t0 has shown the reaction is happening, evidenced by the newly emerged hydrogen peaks from 3.7-4.3. However, a large amount of remaining ESF hydrogens and 1-butanol hydrogens indicated the reaction is not complete, hence, the reaction was allowed to stir for another 8 hours. The ^{1}H NMR result at t(8 hours) has shown only a slight increase of extent of reaction basing on the decrease of ESF hydrogens

and the increase of integration of hydrogen peaks from 3.7-4.3. Picking the peaks of PPh_3 as the reference peak while knowing the initial mole amount of PPh_3 was 0.25mmol, the difference of integration of ESF peaks between 6.2-7.0 was calculated and the conversion after 8 hours were 30%.

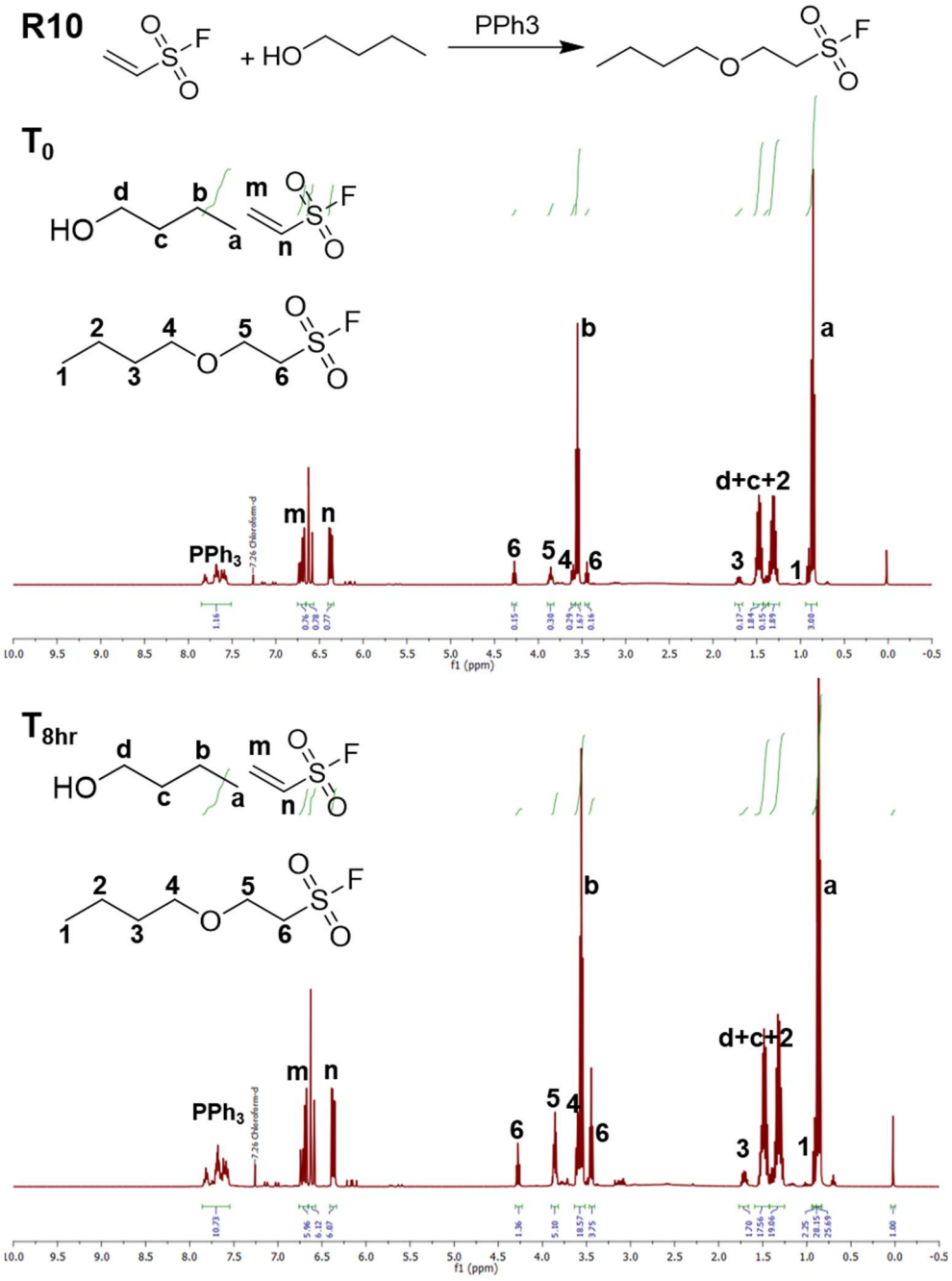


Figure 12. ^1H NMR characterisation of Michael addition of ESF and 1-butanol under the mole ratio of 1:1(ESF:hydroxyl) in $CDCl_3$. Comparison of NMR spectrum at t(0) and t(8hour) has shown the reaction happened between ESF and 1-butanol but at a very slow rate.

After briefly investigation of the Michael additions of ESF with amine, thiol and hydroxyls, the highly efficient reaction between primary amines and ESF has been shown as a solid way to synthesis bifunctional sulfonyl fluoride monomers. Thus, two bifunctional sulfonyl fluoride monomers, derived from butylamine and benzylamine, respectively, were synthesized via Michael addition of primary amine with ESF. The procedure was shown in **section 4.5.3, general procedure**. The existence of the desired compound was proved by ^{1}H NMR.

Step-growth polymerization of bifunctional sulfonyl fluoride with silyl ether compounds to produce polysulfates and polysulfonates has been well studied and reported by Sharpless's research group in 2014.[1] The mechanism suggested was a nucleophilic attack process of base catalyst on the S-F bond. A possible explanation for the high efficiency is strong driving forces were involved in this reaction including a temporary rectangular structure of -O-Si- and S-F bonds as well as the formation of a fluoro-silyl salt which is enthalpy favoured. Apart from silyl ether compounds, reactions of sulfonyl fluoride group with other nucleophiles have also been reported, although mostly the reaction of SO_2F_2 with a nucleophile. A few reports studied the reaction between amines and sulfonyl fluoride groups and claims a good yield. Thus, investigating the step-growth polymerization of bifunctional sulfonyl fluoride and bisamines seems to be an interesting way to discover step-growth polymers with unique sulfamide linker and a large library of available side chain functionalities.

4.2.2 Investigation on step-growth polymerization of bifunctional sulfonyl fluoride with bisamines

Two bifunctional sulfonyl fluoride monomers derived from butylamine and benzylamine were prepared and employed in the step-growth polymerization study, ^{1}H NMR shown the formation of the desired structure. (**Figure 13**) 1,6-Hexanediamine and 1,12-diamino dodecane were used as

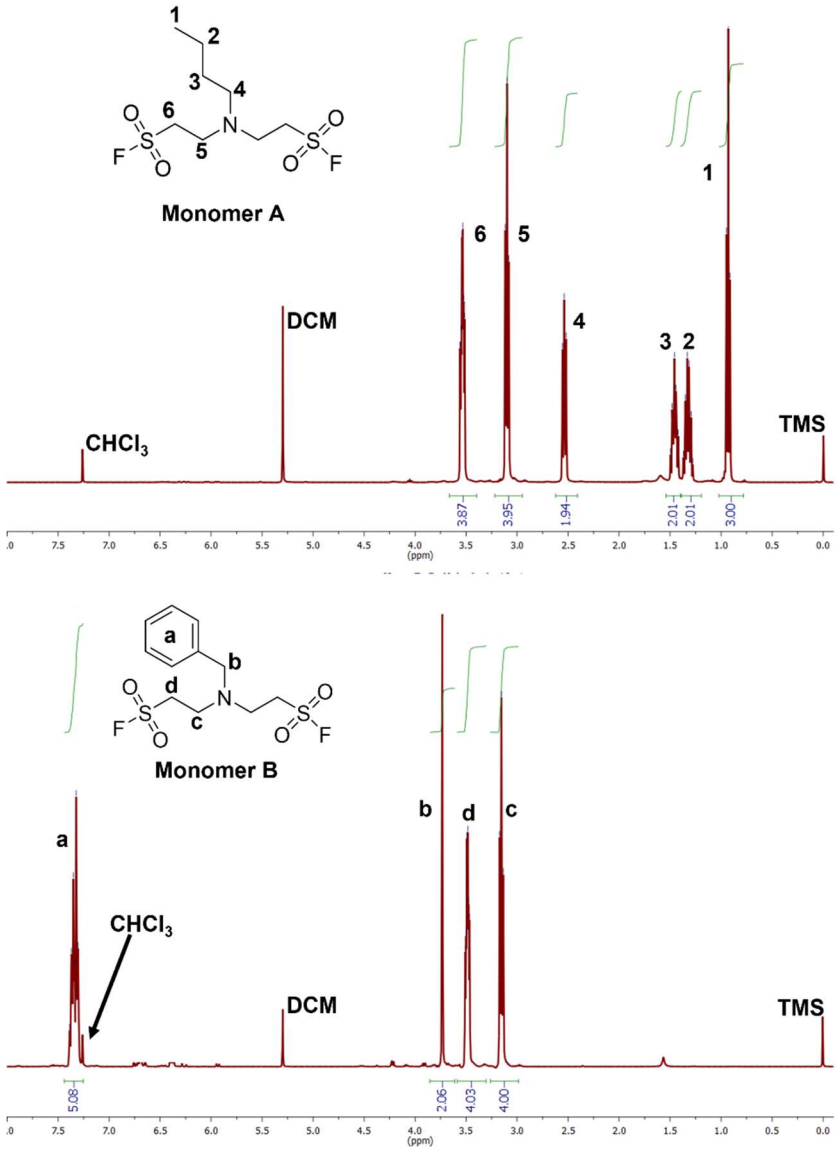


Figure 13. ^{1}H NMR characterisation of reaction crude of preparation of monomer A and monomer B. The integrations shown the desired hydrogen with correct values. See peaks in **section 5.5**.

the bisamine monomers. The reaction was initially done at 1M concentration with a 1:1 mole ratio of both monomers under an inert atmosphere to prevent possible interruption from moisture that leads to undesired termination and varying of stoichiometry. Dry DMF was used

as the solvent and 2.1mol% of distilled DBU was used as the catalyst. Comparing to reported step-growth polymerization via SuFEx click reaction, excess DBU was used because differing from SuFEx reaction with silyl ether compounds where fluoride ions were captured by the silyl ion to produce stable salt, HF scavenger must be employed in the reaction with amines for safety reasons. Both monomers were dissolved in dry DMF in an oven-dried microwave vial with a magnetic follower, the vial was then sealed, freeze and thawed three times and leave to purge under nitrogen flow for 30 minutes, distilled DBU was then added to the reaction mixture, the vial was placed in 80℃ oil bath and allowed to stir overnight. A crude sample of the reaction mixture was taken and analysed with GPC and obtained results were collected in **Figure 14**. It was shown that the reaction did not produce polymers with high molecular weight in all four attempts. The molecular weight was low, and the molecular dispersity was also low, indicating the step-growth polymerization is limited to very low conversion, which would be the consequence of either low reaction efficiency or side reactions. The polymerization was also executed for bifunctional sulfonyl fluorides and 4,4 thiobisbenzene thiol, but no significant polymer peak was observed in THF GPC.

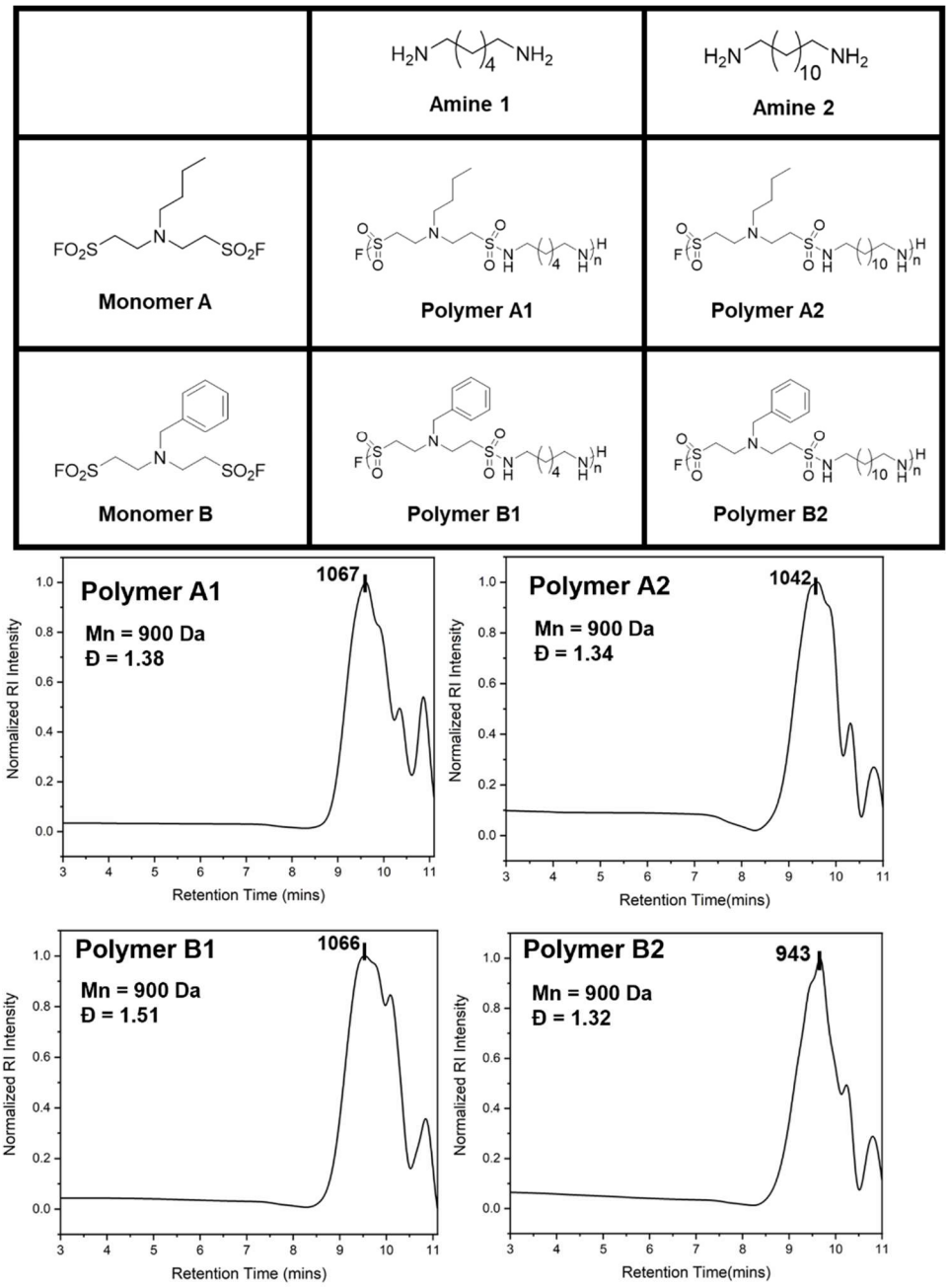


Figure 14. THF GPC traces of step-growth polymerization of bifunctional sulfonyl fluoride monomers with diamines. In all four polymerization attempts, there were no high molecular weight polymers shown, while for both monomer and amine the resulting M_n of polymers were about the same, indicating a universal mechanism problem prevents the chain propagation, most likely side reactions that affect the chain end fidelity. It is worthy to notice that the polymer peaks are out of calibration range, thus the integration value might not be reliable.

As the polymer growth seems to be limited, MALDI-ToF analysis was employed to check the chain end functionality and if desired backbone structure was obtained. The latter one was determined by observing the distance between polymer peaks and check if they fit the molecular weight of monomers and desired repeating units. The MALDI-ToF samples of these polymer crudes were prepared following the general procedure in section 4.5.3. The quality of MALDI-ToF signals was poor for all polymers, indicating the polymer was difficult to ionise. ^{1}H NMR was also used to analyse the polymers. However, as the molecular weight of polymer crude was too low, there were not broad polymer backbone peaks shown in the spectrum.

The polymer growth was significantly limited, one possible reason is side reactions happened, changed the chain end fidelity and terminated the chain growth. About this, Sharpless has provided a strong point in two publication in 2017.[3,10] A side reaction of dehydrofluorination of the α-hydrogen of alkyl sulfonyl fluoride would result in generating a reactive sulfene intermediate(**Figure 15**), which would then react with any active species like moisture or oxygen and hence limit the chain growth polymerization. In their reports the largest polymer was only 7.5kDa and obtained with 5mol% of DBU and elongated heating time of 24 hours. To prove this assumption, a stability test was executed. The bifunctional sulfonyl fluoride monomer derived from butylamine was mixed with 2 equivalents of DBU in $CDCl_3$ and left for 24 hours to measure an ^{1}H NMR. Results obtained were shown in **Figure 15** where the ratio between peak 1 and 6 should be 3 to 4, but in this NMR spectrum the ratio was only 3 to 2, indicating two hydrogens was deprotonated and thus the decrease in integral.

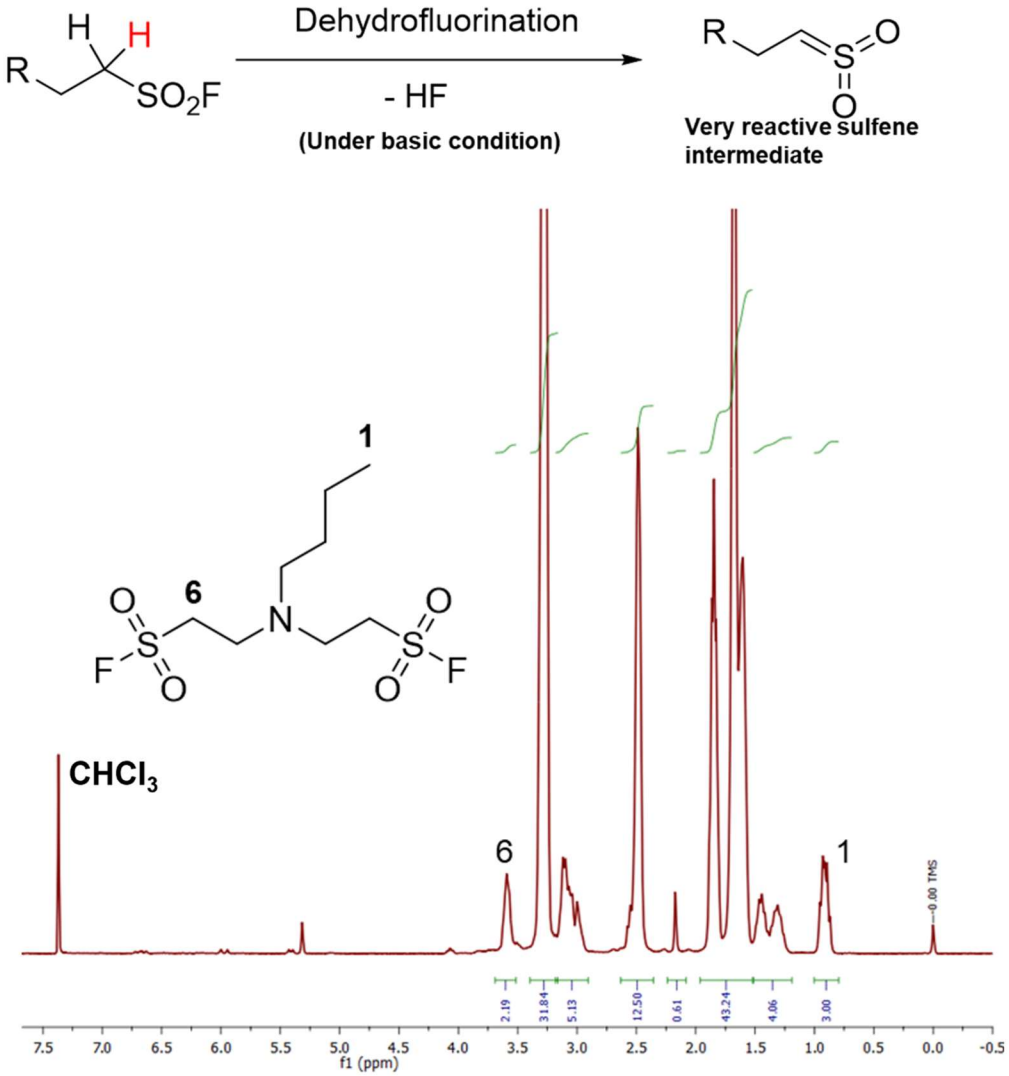


Figure 15. Stability test of bifunctional sulfonyl fluoride monomer in CDCl3 with 2 equivalents of DBU. Noted that the ratio of integration number of peak 6 to peak 1 should be 4 to 3, while under the treatment of DBU it is 2 to 3, indicating the dislocation of α-hydrogens.

4.2.3 Post-polymerization modification of partially hydrolysed poly(oxazoline) with ESF

Poly(oxazoline)s have been well studied as a versatile polymer in biomedical applications. While restrained by the elegant but delicate cationic ring opening polymerization (CROP) process, limited functionalities could be directly obtained via polymerization of functional oxazoline monomers. Thus, the post-polymerization modification of polyoxazolines, include α and ɯ end-functionalization using functional initiators or terminating agents, and side chain modification by CROP-tolerable functional oxazolines, naturally become an important and intense research field. However, the hydrolysis of polyoxazolines, which release functional

secondary amines on polyoxazoline backbone, remains unfavoured in the field of post-polymerization modification of polyoxazoline. Most published reports on hydrolysed poly(oxazoline)s were reporting it as a copolymer of poly(ethylenimine) and poly(oxazoline)[18–20] and investigating the biological applications of it such as RNA binding[21] and antifouling.[22] Possible reasons include the steric hinderance of poly(oxazoline) side chains prevent reactions like Michael addition and Ugi-4 component reaction to happen and reach high yield on hydrolysed poly(oxazoline), and the shielded secondary amine on polyoxazoline backbone might not be a good donor or nucleophile. Nevertheless, ethenesulfonyl fluoride might be a solution to the difficulties on modification of hydrolysed poly(oxazoline)s, as ESF is a very strong Michael acceptor and a very small molecule. Thus, it might be possible to efficiently modify partially hydrolysed poly(oxazoline) with ESF and introduce functional groups via SuFEx click chemistry subsequently.

To investigate the post-polymerization modification of hydrolysed poly(oxazoline)s, partially hydrolysed poly(2-ethyl-2-oxazoline) (PEtOx) has been obtained from a collaborator, the degree of hydrolysis, 13.7%, was determined by ^{1}H NMR (**Figure 16**). Extra water can be removed by freeze-drying for 48 hours. The Michael addition of ESF with partially hydrolysed poly(oxazoline) was then executed in DCM at 0.2M, the concentration was set to accommodate the solubility of hydrolysed PEtOx. The ratio of secondary amine to ESF was set at 1 to 2, ESF was used in excess to increase reaction efficiency. The reaction mixture was allowed to stir at room temperature for 3 hours and the obtained polymer was precipitated in cold diethyl ether, dried under a high vacuum. ^{1}H NMR was employed to determine if the reaction is successful (**Figure 16**).

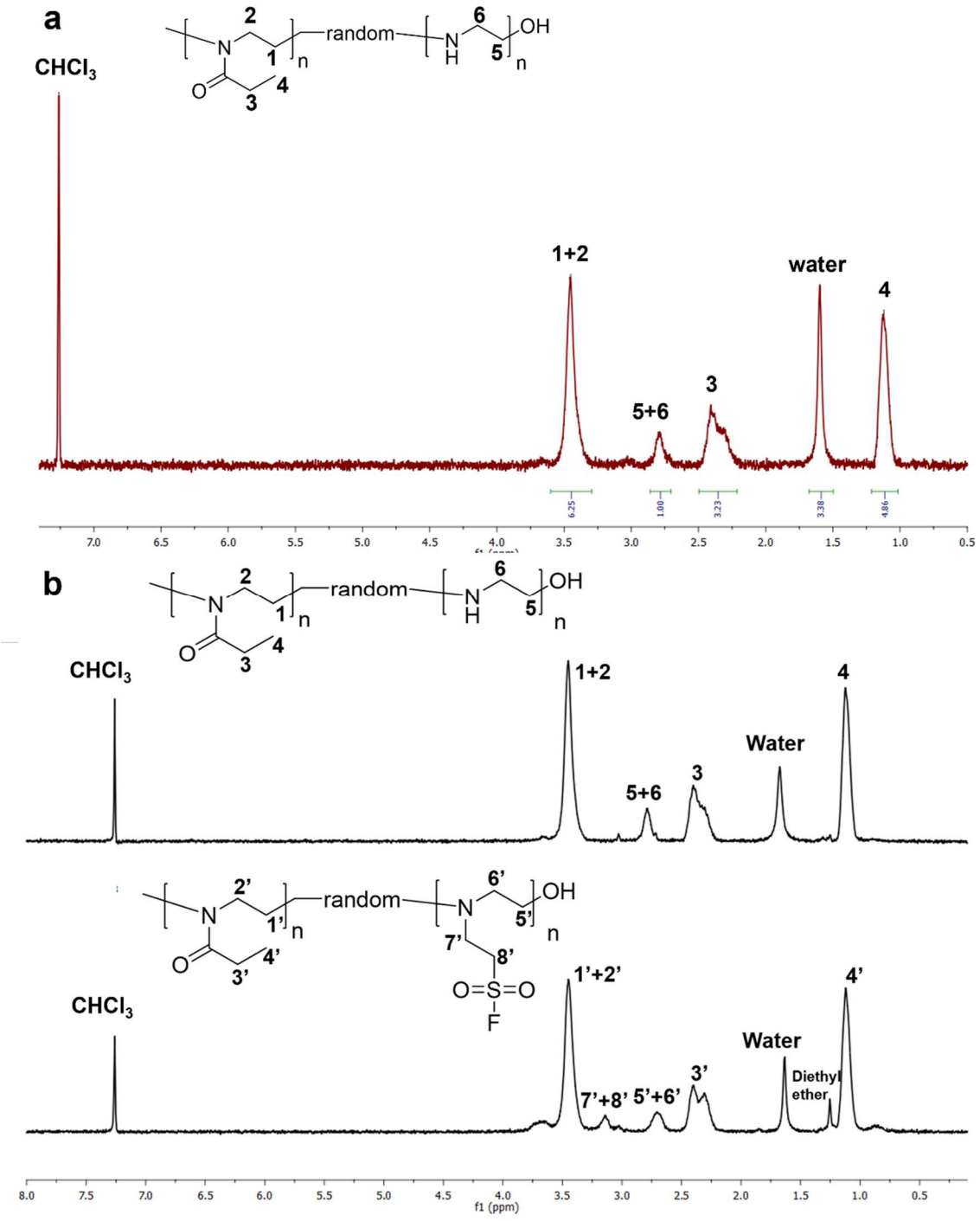


Figure 16. Room temperature Michael addition of ESF to partially hydrolysed poly(2-ethyl-2-oxazoline). The ratio of peak 5+6 to peak 1+2 in **a** shown the degree of hydrolysis as 13.7%. After the Michael addition, the extent of reaction can be calculated by ratio of peak 7'+8' to 5'+6', which is 80% in this case.

The extra peaks shown as 7' and 8' represents the connection -CH_2CH_2- generated after the Michael addition of ESF with backbone secondary amines, while the degree of reaction can be

easily determined by calculating the ratio between the integration number of 7' + 8' to 5' + 6', which was 81% under current reaction condition. It surely can be improved by adding a catalyst and elevate reaction temperature based on the mechanism of Michael addition. However, before the optimisation of Michael addition procedure, further investigation on SuFEx click reaction with sulfonyl fluoride side chain was executed to get some preliminary results. Benzylamine was selected as the candidate as aromatic peaks would be easy to identify. The reaction was executed under 80ºC at 0.5M concentration in DMF with 1.1 equivalent of DBU as the catalyst, the reaction crude was then precipitated in cold diethyl ether, obtained solid was then dried in a vacuum oven and then analysed with THF GPC and ^{1}H NMR (**Figure 17**).

In the THF GPC and ^{1}H NMR, shifting of GPC trace towards larger hydrodynamic volume and generation of peaks 7' + 8' all suggest the successful Michael addition between ESF and the backbone secondary amines. However, the click reaction does not have very strong evidence to support the success. Although aromatic peaks 10 have shown in the spectrum, the corresponding -CH_2 peaks have not shown as a significant peak on the spectrum to integrate on and identify the degree of reaction. Besides, in the THF GPC trace, the peak has shifted towards smaller hydrodynamic volume as well as split, while peaks are shown in low molecular weight region. As the functional group expected was an aromatic ring which theoretically does not result in a decrease of hydrodynamic volume, a possible explanation is the dehydrofluorination mentioned previously has occurred here, resulting in partially installation of benzyl group and partially degeneration of sulfonyl fluoride end groups, which makes this side-chain modification method not practicable.

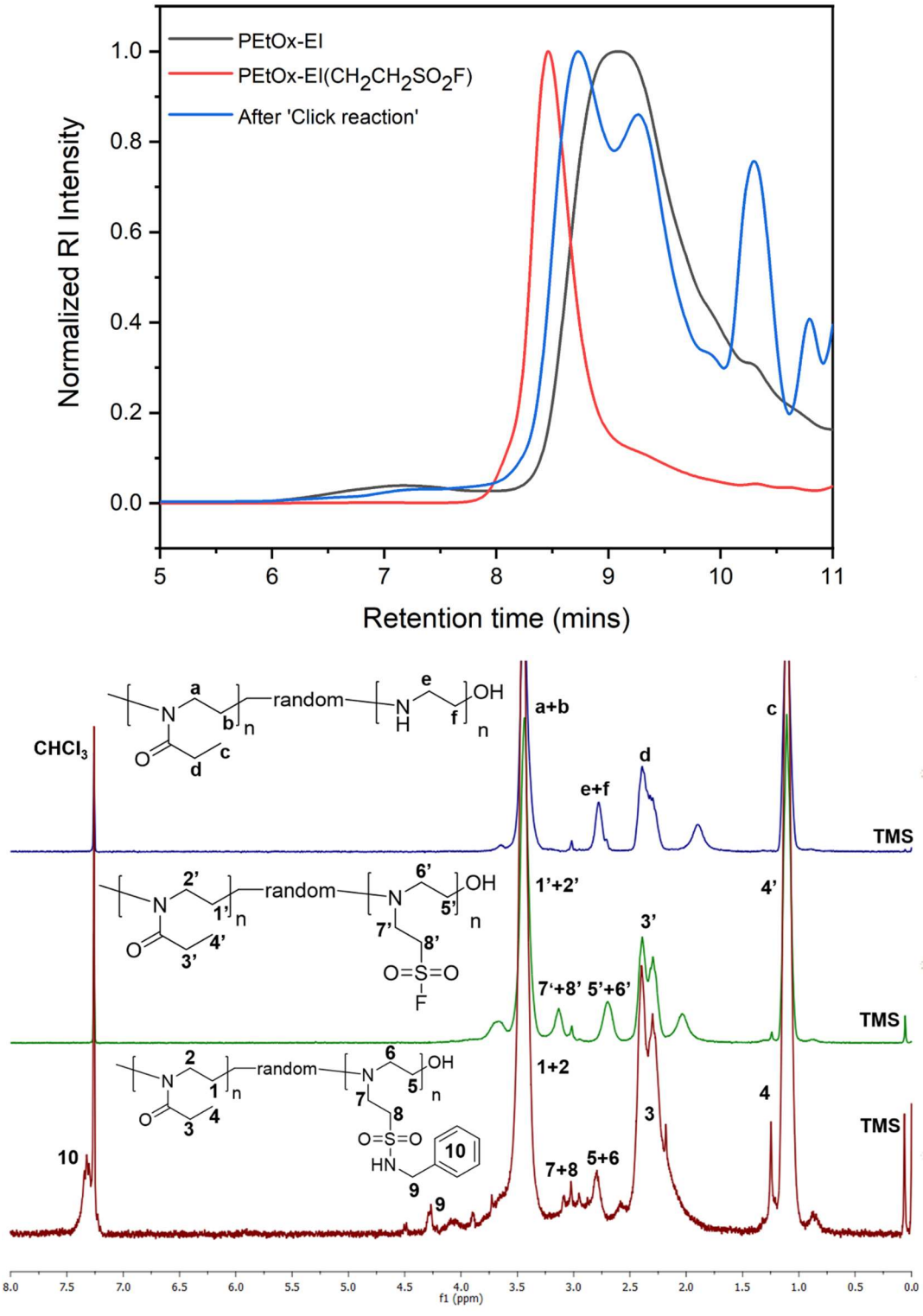


Figure 17. THF GPC and 1H NMR comparison of partially hydrolysed P(EtOx), PEtOx after Michael addition and the SuFEx click reaction attempt.

4.3 Health and safety of using ESF as a sulfonyl fluoride source

Ethenesulfonyl fluoride is a chemical of high hazard level. It is a colourless, odourless violate liquid that is a strong hydrogen fluoride releaser as well as a very toxic compound that can be absorbed through the skin. It is also a lachrymator which could cause a serious problem if handled improperly. Thus, a complete risk assessment must be done before handing this compound. The complete risk assessment that has been done for this study to be performed in Becer group lab, department of chemistry, University of Warwick will be shown in section 5.6.

As using this compound has a huge health and safety risk, based on current evidence on step-growth polymerization and side-chain functionalization, it is necessary to find a possibly more efficient, safer, and novel way to introduce the clickable sulfonyl fluoride for step-growth polymerization and post-polymerization modification. Inspired by the other project summarized in chapter 3 of this thesis, sulfonyl fluoride functionalized benzyl bromide might be an interesting compound to study, while the comparison between SuFEx click reaction and PFTR click reaction can be easily established this way.

4.4. Sulfonyl fluoride functionalized poly(oxazoline) and study of the coupling efficiency

As a possible reason for the low efficiency of step-growth polymerization and the reduced hydrodynamic volume in the post-polymerization modification attempt was the dehydrofluorination of the acidic hydrogen on the α-carbon of the sulfonyl fluoride group. Employing a SuFEx linker that does not have acidic hydrogens on the α-location, like -OSO_2F, -Ar-SO_2F, or the hydrogen on α location is more stable than alkyl ones, like -NH-SO_2F, [78] is necessary to explore the most stable coupling properties of this reaction. Based on the experience in using pentafluoro benzyl bromide as the initiator of CROP of polyoxazolines and the subsequent study on polymer coupling and step-growth polymerization, 4-(bromomethyl) benzenesulfonyl fluoride has been selected as a candidate to investigate if this compound can be used as a functional initiator for CROP of polyoxazolines, and the efficiency of subsequent coupling reaction would be investigated if the polymerization is feasible.

Initial investigations started from the polymerization of 2-ethyl-2-oxazoline with 4-(bromomethyl) benzenesulfonyl fluoride (BBSF) as the initiator to give some preliminary

results. Due to consideration of sulfonyl fluoride group stability, the initial reaction was performed at 120℃ with microwave-assisted heating under an inert atmosphere in MeCN, the monomer concentration was set at 4.0 M and the degree of polymerization was set at DP10 (**Figure 18**). As the counter ion stays the same in BBSF and pentafluoro benzyl bromide, assumptions were made that the reaction rate should be roughly the same and the reaction time was thus set at 24 mins at selected conditions. The reaction was quenched in a sodium hydroxide methanol solution to provide a fully hydroxyl functionalized end group. THF GPC, ^{1}H NMR and MALDI-ToF analysis was executed to investigate if the polymerization has been successful, and the end-functionalization has been quantitative. Results were collected in **Figure 18**.

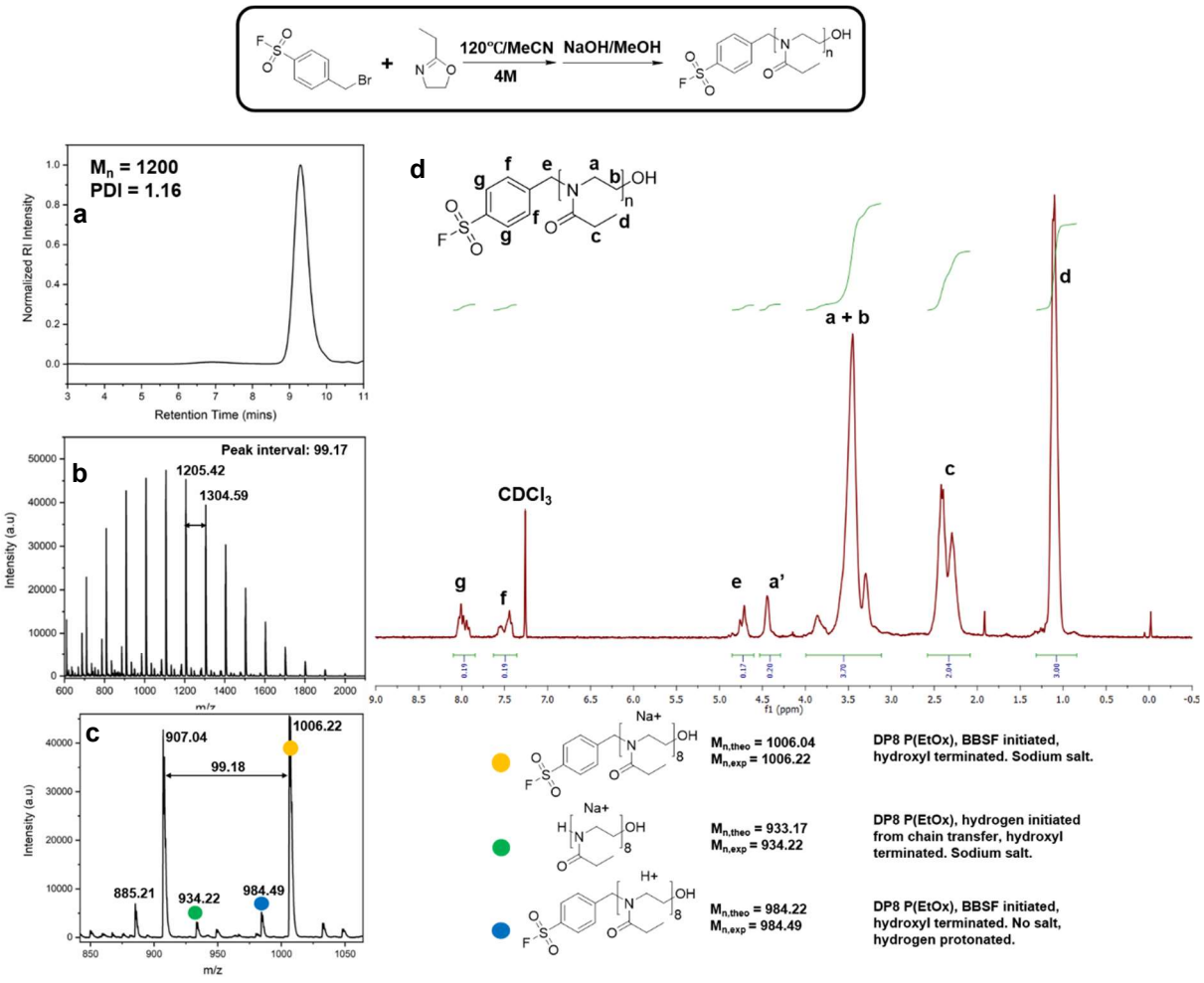


Figure 18. Synthesis and THF GPC(**a**), MALDI-ToF (**b, c**) and ^{1}H NMR(**d**) characterisation of clickable poly(2-ethyl-2-oxazoline) with 4-(Bromomethyl) benzenesulfonyl fluoride (BBSF).

Obtained results suggesting a successful preparation of sulfonyl fluoride functionalized PEtOx with BBSF as the initiator. ^{1}H NMR has shown the corresponding peaks while the ratio between peak g and peak d indicating the experimental degree of polymerization was 10.5 which fits the theoretical degree of polymerization of 10. This suggests a good initiator efficiency of BBSF, MALDI-ToF analysis has shown desired end groups as a major distribution, while the secondary distribution fits the polymer produced via chain transfer process. This polyoxazoline synthesized has the potential of being modified with SuFEx click reaction on the α-end, while the ɯ-end could be tuned with different termination agents, which could open the avenue to more bifunctional polyoxazolines for post-polymerization modification.

4.4 Summary and outlook

In this chapter, the efficiency of Michael addition of ESF with amines, thiols and hydroxyls, the feasibility of using ESF to prepare bis-sulfonyl fluoride compounds and subsequently the synthesis of step-growth polymers of bis-sulfonyl fluorides and bisamines have been investigated. The Michael addition of ESF with nucleophiles has been shown as highly efficient, while solvent effect presents in the addition reaction of ESF with thiols. However, the click polymerisation of bis-sulfonyl fluorides derived from bisamine and bisamines failed to give polymers with reasonable molar mass. A possible reason is the dehydrofluorination of α-hydrogens in alkyl sulfonyl fluoride groups results in loss of chain-end functionality that disallow proper step-growth polymerization to happen. The failure of click reaction also shown in the post-polymerisation modification of partially hydrolysed poly(2-ethyl-2-oxazoline) study. Reports have shown using bifluoride acidic catalysts[3,10] could over come this problem and results in decent polymers. However, the preparation of bifluoride acidic catalysts requires harsh reaction conditions and extremely toxic reagents such as hydrogen fluoride, while the cost of commercially purchase is high. Thus, before performing any further study on preparing such step-growth polymers, the health and safety concern should be taken into account firstly. The successful preparation of poly(2-ethyl-2-oxazoline) with BBSF as the initiator shown a potential way of introducing SuFEx click reaction into the field of poly(oxazoline) chemistry, which could be further explored to prepare poly(oxazoline) copolymers or bio-conjugated poly (oxazoline)s.

4.5.1 Materials and methods

Ethenesulfonyl fluoride (ESF) (Aldrich, 95%), Butylamine (Aldrich, 99.5%), 1-Butanethiol (Aldrich, 99%), 1-Butanol (Aldrich, ≥99.0%), Cysteamine (Aldrich, ≥95.0%), 4,4′-Thiobisbenzenethiol (Aldrich, 98%) were selected as starting materials of Michael addition studies. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (Aldrich, 98%) were used to activate the SuFEx click reaction. 4-(Bromomethyl) benzylsulfonyl fluoride (BBSF) (Aldrich, 97%) and 2-ethyl-2-oxazoline (Aldrich, 99%) were used for investigation of synthesis of clickable poly(2-ethyl-2-oxazoline), while the 2-ethyl-2-oxazoline was distilled prior to polymerisation.

N,N-Dimethylformamide (DMF, Aldrich), chloroform (Aldrich), tetrahydrofuran (THF, Aldrich) were used as the solvent for Michael addition and step-growth polymerisation. Deuterated $CDCl_3$, DMSO-d_6 and DCM-d_2 (Aldrich) were used as the solvent of Michael addition of ESF with nucleophiles and the ^1H NMR characterisation.

Triphenyl phosphine (Aldrich 99%) was used in the Michael addition of ESF to hydroxyls to accelerate the reaction.

4.5.2 Instrumentation

Nuclear Magnetic Resonance (NMR) spectroscopic measurements were performed on 300 or 400 MHz Bruker instruments in 5 mm NMR tubes. Residual solvent signals of $CHCl_3$ (δH = 7.26 ppm, δC =77.2 ppm) was used as reference. ^{19}F NMR chemical shifts are given relative to a $CFCl_3$ standard. Gel permeation chromatography (GPC) measurements were conducted on an Agilent 1260 infinity system operating in THF with 2% TEA and equipped with refractive index detector and variable wavelength detector, 2 PLgel 5 μm mixed-C columns (300 × 7.5 mm), a PLgel 5 mm guard column (50 × 7.5 mm) and an autosampler. The instrument was calibrated with linear narrow PS standards. All samples were filtered through 0.2 μm PTFE filters before analysis. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-ToF MS) was performed on a Bruker Autoflex Speed mass spectrometer using a nitrogen laser delivering 2 ns pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The matrix used was trans-2-[3-(4-tertbutylphenyl)-2-methyl-2-propylidene]malonitrile (DCTB) dissolved in THF. Sodium trifluoroacetate used as a cationic agent (solution in acetonitrile). The compound (diluted in THF) was applied after separate loadings of DCTB and sodium trifluoroacetate. Samples were

measured in reflective or linear mode and calibrated against poly(methyl methacrylate) standards.

4.5.3 General procedures and characterisations.

General procedure of preparing double-substituted bifunctional sulfonyl fluoride compound from Michael addition of ESF with alkyl primary amines

To a well-stirred solution of the primary amine (0.5 equivalent) in DCM (0.5M concentration), ESF (1.1 equivalent) was slowly added through 5 minutes to avoid sudden exothermic action. The reaction mixture was then allowed to stir for 2 hours to overnight. The reaction crude was concentrated with rotavap and left under high vacuum overnight to receive desired bifunctional sulfonyl fluoride compound.

Preparation of MALDI-ToF samples of polymers

Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF MS) was performed on a Bruker Autoflex Speed mass spectrometer using a nitrogen laser delivering 2 ns pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The matrix used was trans-2-[3-(4-tertbutylphenyl)-2-methyl-2-propylidene]malonitrile (DCTB) dissolved in THF. Sodium trifluoroacetate used as a cationic agent (solution in acetonitrile). The compound (diluted in THF) was applied after separate loadings of DCTB and sodium trifluoroacetate. Samples were measured in reflective or linear mode and calibrated against poly(methyl methacrylate) standards. 25mg/ml solution of MALDI matrix DCTB in THF, 0.5 mg/ml solution of polymer crude solution in a THF-miserable volatile solvent, for instance chloroform, and 0.5 mg/ml solution of sodium trifluoroacetate in THF were made. A PMMA standard with reasonable molar mass was used as the calibration standard. MALDI spots was made by mixing 0.5µl of each solution together and take 0.5µl and spot on a 384 stainless steel MALDI plate.

1H NMR characterisation of Monomer A and B

Monomer A (400MHz, $CDCl_3$): δ 3.56-3.51 (m, J = 3.6 Hz, 3.2 Hz, 3.2 Hz, 3.6 Hz, 3.6 Hz, 4H, -CH_2-SO_2F), 3.12-3.08 (t, J = 6.8 Hz, 6.8 Hz, 4H, -CH_2-), 2.56-2.51 (t, J = 7.2 Hz, 7.6 Hz, 2H, -CH_2-), 1.50-1.42 (m, J = 6.8 Hz, 8 Hz, 7.2 Hz, 7.6Hz, 2H, -CH_2-), 1.37-1.27 (m, J = 7.2 Hz, 7.6 Hz, 7.6 Hz, 7.2 Hz, 2H, -CH_2-), 0.95-0.91 (t, J = 7.2 Hz, 7.2 Hz, 3H, -CH_3)

Monomer B (400MHz, $CDCl_3$): δ 7.39-7.30 (m, J = 6.8 Hz, 7.2 Hz, 5.2 Hz, 6.0 Hz, 7.6 Hz, 5H, aromatic, C_6H_5), 3.73 (s, 2H, (C_6H_5)-CH_2-), 3.51-3.46 (m, J = 3.6 Hz, 3.2 Hz, 3.6 Hz, 3.2 Hz, 3.6 Hz, 4H, -CH_2-), 3.17-3.13 (t, J = 7.2 Hz, 6.8 Hz, 4H, -CH_2-)

4.6 Risk assessment of using ESF

As ESF was identified as a highly toxic chemical which possess a high hazard level, a proper risk assessment has been done aiming to minimize the risk of using ESF in the chemistry labs in the department of chemistry, University of Warwick. It is presented here to provide more information for future ESF users to understand how to work safely with this chemical.

WARWICK
THE UNIVERSITY OF WARWICK

Risk Assessment Form

Title of Risk Assessment	Use of Ethenesulfonyl fluoride in lab C303	Date of assessment	21/05/2019
Department	Chemistry	Date review due	

Description of Task/Process	Ethenesulfonyl fluoride(ESF) will be used in Michael addition[1,2] reactions with amines, alcohols and thiols. Reactions will be carried out in lab C303, typically in 10-20 mg (0.007-0.014ml) scale while in some scale-up synthesis up to 500mg (0.3ml) of ESF will be used in compatible organic solvent systems including dichloromethane, chloroform, dimethyl sulfoxide, methanol, and dimethylformamide at room temperature (25°C). Generally, the chemical will be transferred with glass pipettes (normally used)/syringe and needles with luer locks (only used for very small amount, like below 10mg, use will be minimised once Eppendorf pipettes is available)/Eppendorf pipettes (used for very small amount), from the manufacturer container bottle to an oven dried clean microwave tube where another reactant, usually a nucleophile, is pre-dissolved in organic solvent mentioned above and ready for Michael addition. The concentration of reactants will be 0.5M. ESF will be added slowly(dropwise) to the system to prevent the exothermic feature of Michael addition causes undesired evaporation of ethenesulfonyl fluoride. The system will be sealed with 20mm aluminum seals with 0.125-inch thick, blue PTFE/white silicone septa to prevent any possible pressure caused break of reaction vial and accidental release of ethenesulfonyl fluoride. Yield of the Michael addition is 88%-96%, based on solvent and nucleophile efficiency. Upon completion of reaction, the reaction mixture will pass a deprotected rink amide resin column to capture all ESF residue. 1H NMR will be used to detect the sole existence of desired product.
Assessment carried out by	Tieshuai Zhao

Risk assessment of ESF

Additional information

Sulfur fluoride exchange (SuFEx) click reaction, coined by Sharpless in 2014[3], has been reported as an efficient approach to synthesize high-molecualr-weight polysulfates/polysulfonates with excellent mechanical, optical, oxygen-barrier and flash-memory properties[4]. Most reported examples of polysulfate/polysulfonate synthesis are based on Bis-phenol A(BPA) derived monomers to mimic backbone structure of polyether ether ketone(PEEK) polymers to gain similar thermal and mechanical properties. Although some pendant groups could be installed on BPA derived monomers, the backbone and side chain diversity is still limited due to the limited number of available BPA derivatives and the aromatic nature of monomers.[4,5] Attempts shown the feasibility of preparation of aromatic-aliphatic alternative polysulfates[6], but investigation on full aliphatic backbone polysulfates is still absence.

Full aliphatic backbone polysulfates possess very similar backbone structure to nylon 6/6, which indicates this kind of polymer, although lack of investigation, might also possess good mechanical strength, rigidity and processability if high-molecular-weight polymer could be prepared using SuFEx click reaction. The C-S-N-backbone with –SO_2NH- linkage is also a good structural mimic to γ-peptides with unique sulfur-including backbone, more hydrogen bonding sites and large side chain diversity which might be useful in bioconjugation studies (Figure 1).

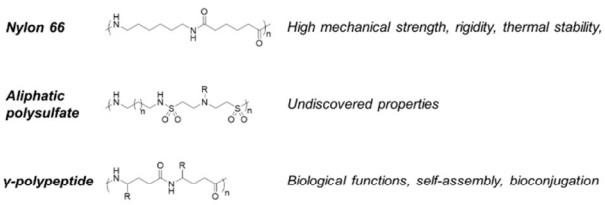


Figure 1| Structure comparison of Nylon 66, aliphatic polysulfate and γ-polypeptide.

Synthesis of full aliphatic backbone polysulfates via SuFEx click reaction can be achieved by step-growth polymerization between bis-sulfonyl fluoride monomers and bis-nucleophile compounds under the catalyse of a base. While bis-nucleophile compounds, include bis-amine, bis-thiols, are usually commercial available, the synthesis of aliphatic bis-sulfonyl fluoride monomers becomes the current research focus.

ESF is used as a linker for effectively introducing sulfonyl fluoride groups(-SO_2F)[3] onto aliphatic backbone while

other reported linker, including sulfuryl fluoride(SO_2F_2)[3], thionyl tetrafluoride(SOF_4)[7] are all reactive toxic gas[8,9] which have more risk while handling. These gas linkers are also not capable of creating a C-SO2F terminus. Michael addition of ESF with primary amines has been firstly reported in 1970s, shown that mild conditions and proper solvent selection leads to double-adduct product and good conversion of ESF, while moderate heating is required for some delocalisation stabilized nucleophiles. This reaction has been reported with more examples in 2014, provides evidence of using dichloromethane as solvent at room temperature, Michael addition of 2 equivalents of ESF with one equivalent of aliphatic amine gives bis(alkylsulfonyl fluorides) product with near quantitative yield. Another recent publication from Sharpless's group regarding polysulfonate synthesis also provides various examples of amine/aniline ESF adducts. Based on these existing research, synthesis of six different bis(alkylsulfonyl fluorides) via Michael addition of ESF and aliphatic primary amines(Figure 2) has been planned for subsequent aliphatic polysulfate synthesis.

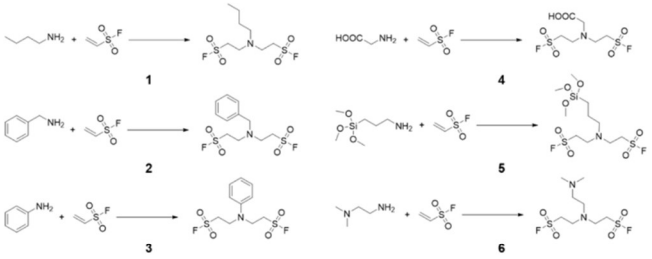


Figure 2|Six designed Michael addition reaction between ESF and primary amines.

Ethenesulfonyl fluoride(ESF) will be used in Michael addition with primary amines using reported literature procedures[2,3,4,6]. From previous experience, this chemical is packed in aluminium package, 1g(0.75ml) contained in amber poly bottle. The chemical is a clear colourless liquid. For each Michael addition, typically 50-100mg(0.038ml-0.076ml) or maximum 500mg(0.38ml) of ethenesulfonyl fluoride will be used. The reaction will be carried out at room temperature (25°C) in microwave reaction vials sealed with 20mm aluminum seals with 0.125-inch thick, blue

PTFE/white silicone septa to prevent any possible pressure caused break of reaction vial and accidental release of ethenesulfonyl fluoride in a well-ventilated fumehood.

ESF has been identified as a danger, flammable poisonous and toxic substance, HF releaser and lachrymator, with multiple toxicity via several approaches[10]. The severity of risk should be identified as MAJOR due to its toxicity thus the purpose of this risk assessment is to ensure that the risk of using ESF is minimised to a safe level for the purchasing, storage, handling and disposal of ESF.

Hazard and precautionary statement codes of ESF[10] are:

Hazard statements: H226-H301+H311+H331-H314-H335-H341

Precautionary statements: P261-P280-P301+P310-P305+P351+P338-P310

These codes indicate that ESF should be categorised as hazard level high and Group R for storage[11]. Thus, bottles of ESF will be contained in a lockable plastic container that labelled clearly with the name, amount, hazards and warning on the outside of the container (Figure 3). This container will be placed in a lockable safety cupboard for the storage of ESF only. The location will be updated on quartzy as 'ESF cupboard'.

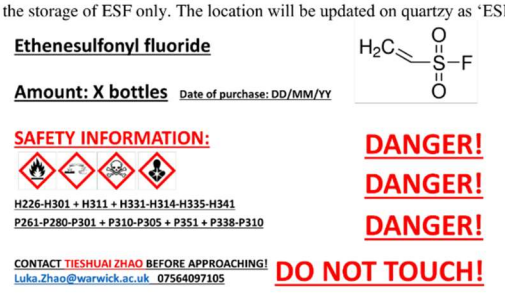


Figure 3|Labelling of ESF container

The major routes of exposure to ESF is the inhalation of ESF vapour and skin contact with the liquid. Circumstances of these exposure take place would be:

1: Mishandling of the liquid while weighing and transferring using glass pipettes/syringes caused spillage of drops of ESF onto skin.

2. Spillage of ESF liquid in lab atmosphere during transferring from the safety cupboard to the fumehood, causing the release of ESF liquid and vapour.

3. False closure of the ESF bottle, causing the release of ESF vapour into ventilated or not ventilated atmosphere.

4. Accidental breakage of the ESF bottle, causing the release of ESF liquid and ESF vapour.

5. Flammable risk of ESF.

To minimise the likelihood of harm, from previous experience on handling this chemical, some general controlling measures are listed below:

2. Full PPE will be used: protective clothing (lab coat), two layers of protective gloves (satisfy the standard EN 374)[10], tightly fitting safety goggles. Used gloves will be disposed using a specific solid waste bucket, soaked with 3M aqueous NaOH solution*,[12] to remove any remaining sulfonyl halides before disposal. If spilled on gloves, the glove should be immediately take off and disposed in NaOH bath. Lab coats will be instantly take off and soak in 3M aqueous NaOH solution if contaminated, the contaminated part will stay inside the fumehood while taking off the lab coat. Safety shower is in the lab C303.

3. The handling of ESF will be carried out in a clean and empty fumehood to avoid accidental mishaps that might cause spillage. A 3M NaOH bath will be placed in the fumehood. Any glassware or syringes will be soaked overnight in the NaOH solution before disposal[8].

4. The chemical will be keep away from high temperature resources to avoid any possible fire.

* The 3M NaOH solution is stored in a 9L polypropylene plastic container, the container is always less than half-full (1L-2L) with lockable lids on to avoid spillage. The container is labelled with the name of chemical, hazards and

warning (Figure 4). As the total amount of ESF will be used in this project would be under 0.1mol. 2L of 3M NaOH aqueous solution should be considered as huge excess for removing sulfonyl fluoride residue on used glassware.

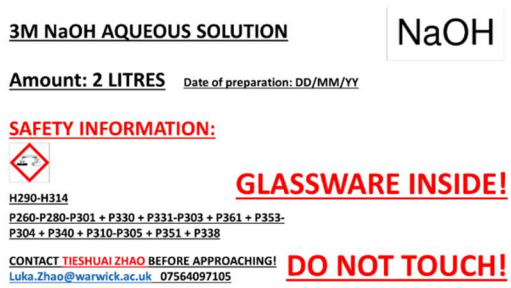


Figure 4|Labelling of 3M NaOH aqueous solution

5. A first aid folder, including emergency treatment of HF, MSDS of ESF, paper regarding the poisonous of ESF, is available for any possible first aid measure required.

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Hazards and how they may cause harm	Who may be at Risk?	Existing Control Measures	Current Risk Level (VL,L,M,H,VH)	Where current risk is M, H or VH, what additional Control Measures are required?	Action required by whom & by when?	Final Risk Level
Serious injury through oral intake	Tieshuai Zhao (main user) Becer group Members visitors	No eating/drinking in the lab! Labelling correctly to inform people the toxicity. Storage in a lockable container where only informed lab members can access.	L	Inform other members of the group the toxicity of this chemical.	Tieshuai Zhao Executed on 14th May 2019	L
Serious injury through skin contact	Tieshuai Zhao (main user) Becer group Members Chemistry department members	PPE:protective clothing (lab coat), two layers of protective gloves (satisfy the standard EN 374) (7), tightly fitting safety goggles will be properly equipped to avoid skin exposure. Small amount of chemical (below 500mg, 0.5ml) will be used in each reaction to minimise the risk.	M	Inform other members of the group the toxicity of this chemical.	Tieshuai Zhao Before and during the use of ESF, From 14th May 2019	L
Serious injury through breathing vapour	Tieshuai Zhao (main user) Becer group members	The chemical is stored in a well-ventilated safety cupboard. The bottle will always be tightly sealed before moving from one ventilated place to another. The chemical is stored away from any acid bottle in case of accidently reaction and release acid vapour. Any glassware/syringe used will be soaked in 3M NaOH solution to remove any sulfonyl halide before disposal.	M	Purchasing **a small lockable amber plastic container**, store it in a ventilated lockable safety cupboard near the fumehood to minimise the risk of leakage during transportation. Once the chemical is delivered and collected from stores it will be stored in the lockable container in fumehood.	Tieshuai Zhao Before the purchase of ESF, Date TBD by Chemtech officers	L
Sharps injury from Glassware/Needles	Tieshuai Zhao (main user) Becer group members	Handle with extra caution, use as few needles as possible in reaction. Always use syringes with luer lock system. Check the integrity of glassware before use. All the glassware and syringes used will be decontaminated and placed in corresponding sharp containers.	M	Purchasing Eppendorf pipettes for ESF transfer use only to replace syringe and needles for small scale (under 10mg) transportation.	Tieshuai Zhao Before the purchase of ESF, Date TBD by Chemtech officers	L

Hazards and how they may cause harm	Who may be at Risk?	Existing Control Measures	Current Risk Level (VL,L,M,H,VH)	Where current risk is M, H or VH, what additional Control Measures are required?	Action required by whom & by when?	Final Risk Level
Spillage during experimentation and transportation	Tieshuai Zhao (main user) Becer group members Chemistry department members	The container of ESF will be tightly sealed during any transportation. In the fumehood of handling 3M NaOH solution will always be available to react spilled ESF to avoid any further risk. Small amount of ESF is used in each experiments to minimise the spillage. ESF comes in a plastic bottle which decreased the risk of a shuttering. If spilled, the spillage part should be covered with glycine immediately to capture the ethenesulfonyl fluoride, lab members will be evacuated immediately, lab C303 will be locked down. To clean the spillage, following 'Section 6: Accidental release measures' from the MSDS of ESF, the spillage will be contained, collected with an electrically protected vacuum cleaner or by wet-brushing and place in halogenated container for disposal.	L	Talk with stores if there is sealed carriage containers could be used for the transportation of ESF.	Tieshuai Zhao Before the purchase of ESF Date TBD, after the talk with ChemTech members	L
Exposure to chemical during emergency	Tieshuai Zhao (main user) Becer group members First aider	HF first aid antidote gel is in place near the fumehood. Trained first aiders are located in C-Block. Safety shower is placed in lab C303.	M	Inform Matt Donald, Andrea Lotierzo, Andrew Marsh in C-Block about the use of this chemical and the possible risk of HF hazard and lachrymator hazard. Make sure that necessary first aid equipment (e.g:	Tieshuai Zhao Before the purchase of ESF Date TBD, after the talk with ChemTech members	L

Hazards and how they may cause harm	Who may be at Risk?	Existing Control Measures	Current Risk Level (VL,L,M,H,VH)	Where current risk is M, H or VH, what additional Control Measures are required?	Action required by whom & by when?	Final Risk Level
				breathing respirator) is in place. One member of Becer research group, Ben Drain, will become a first-aider for emergency treatment.		
Exposure to chemical during transport(storage, waste removal)	Tieshuai Zhao (main user) Becer group members	The chemical is stored in a tightly sealed plastic bottle. The bottle come in double-wrapped with bubble wrap and sigma standard aluminium package. All glassware/syringe/bottle used would be soaked in a 3M NaOH bath overnight to remove sulfonyl fluoride before any disposal. Before disposal of the NaOH bath solution, an NMR will be executed to detect if there is any sulfonyl fluoride residue.	M	Discussion with ChemTech team regarding the proper approach of disposal and the feasibility of store this chemical in a lockable container in a fumehood.	Tieshuai Zhao Before the purchase of ESF Date TBD, after the talk with ChemTech members	L

Work should not be carried out until the assessment is completed and all required control measures are in place.

Overall Final Risk Rating (Highest level in final column above)	L

Additional Comments from Risk Assessor (e.g. funding or practical implications)	

Approved By		Position	

Date	

Please print a copy, sign it and keep for your records

	Severity				
Likelihood	Superficial	Minor	Serious	Major	Extreme
Unlikely	Very low	Very low	Low	Low	Moderate
Possible	Very low	Low	Low	Moderate	High
Likely	Low	Low	Moderate	High	Very high
Very likely	Low	Moderate	High	Very high	Very high
Extremely likely	Moderate	High	Very high	Very high	Very high

See 'Matrix for risk evaluation' for further guidance.

Risk Level	
Very low	Acceptable risk - no action required
Low	Tolerable risk - further control measures not required, but status must be monitored
Moderate	Further control measures required to reduce risk as far as is reasonably practical
High	Urgent action required to allow activity to continue
Very high	Risk intolerable - activity must cease until the risk has been reduced

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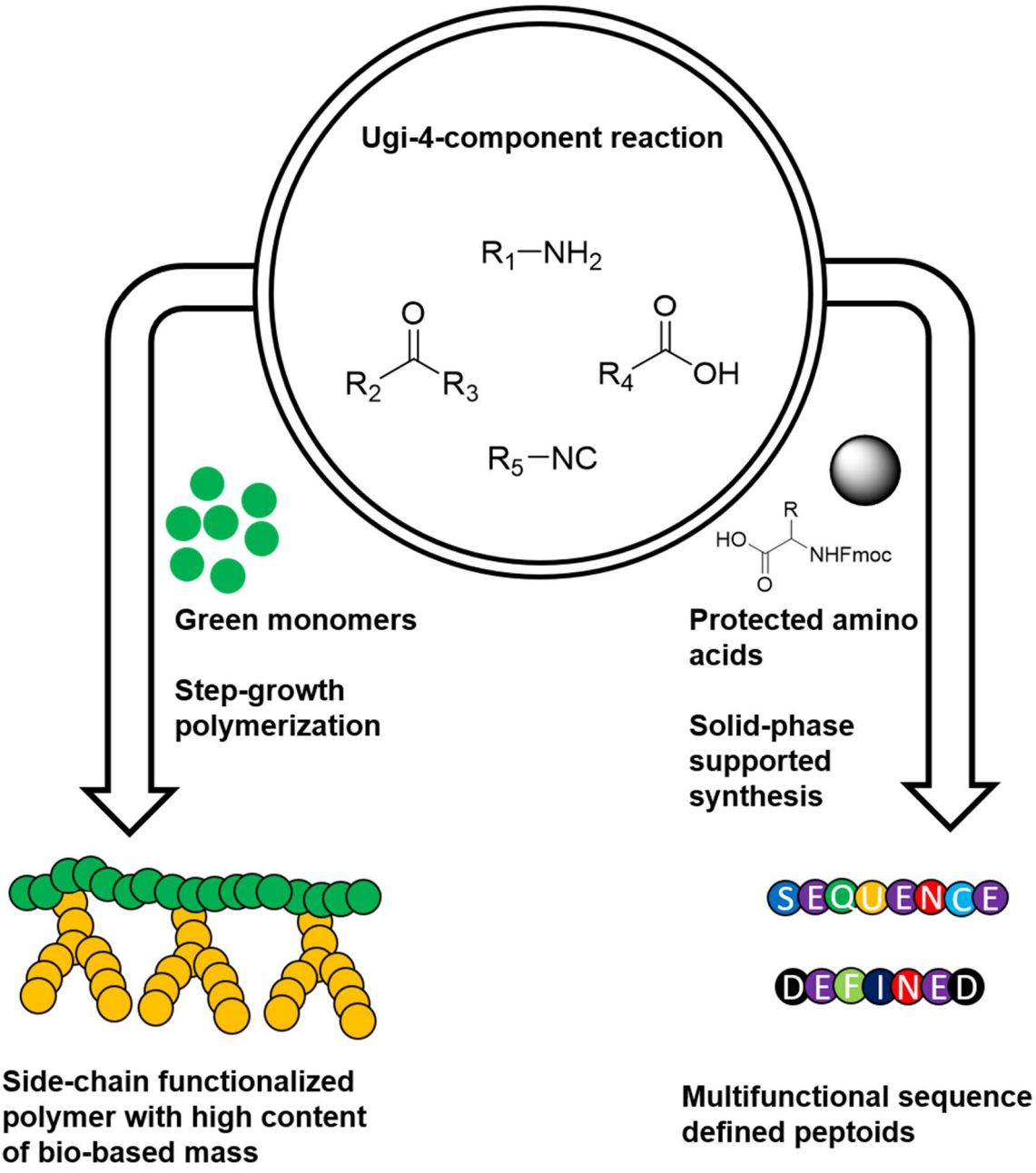
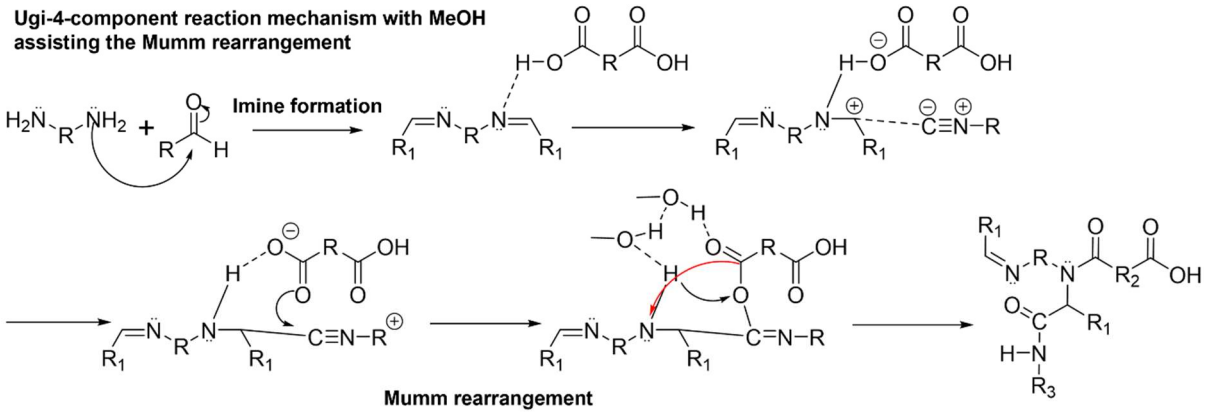
Chapter 5: Step-growth and sequence-defined polymers via Ugi-4-component reaction.



Multicomponent reactions have been recognised in organic chemistry for decades while their application in the polymer chemistry field was only developed in the last ten years. Ugi-4-component reaction, a well-known and intensively studied multicomponent reaction, can produce substituted amide structures, or namely peptoid structures, that has three functional groups on one repeating unit, with commercially available reactants. Thus, it has great potential for preparing multifunctional peptoid structures, or multifunctional polymers for large scale synthesis. Herein, the preparation of side-chain functionalised polymers with high bio-content mass, and the synthesis of sequence defined multifunctional peptoids were presented. Polymers with bio-content mass up to 84% and tuneable thermal behaviours as well as sequence defined peptoid hexamers were reported.

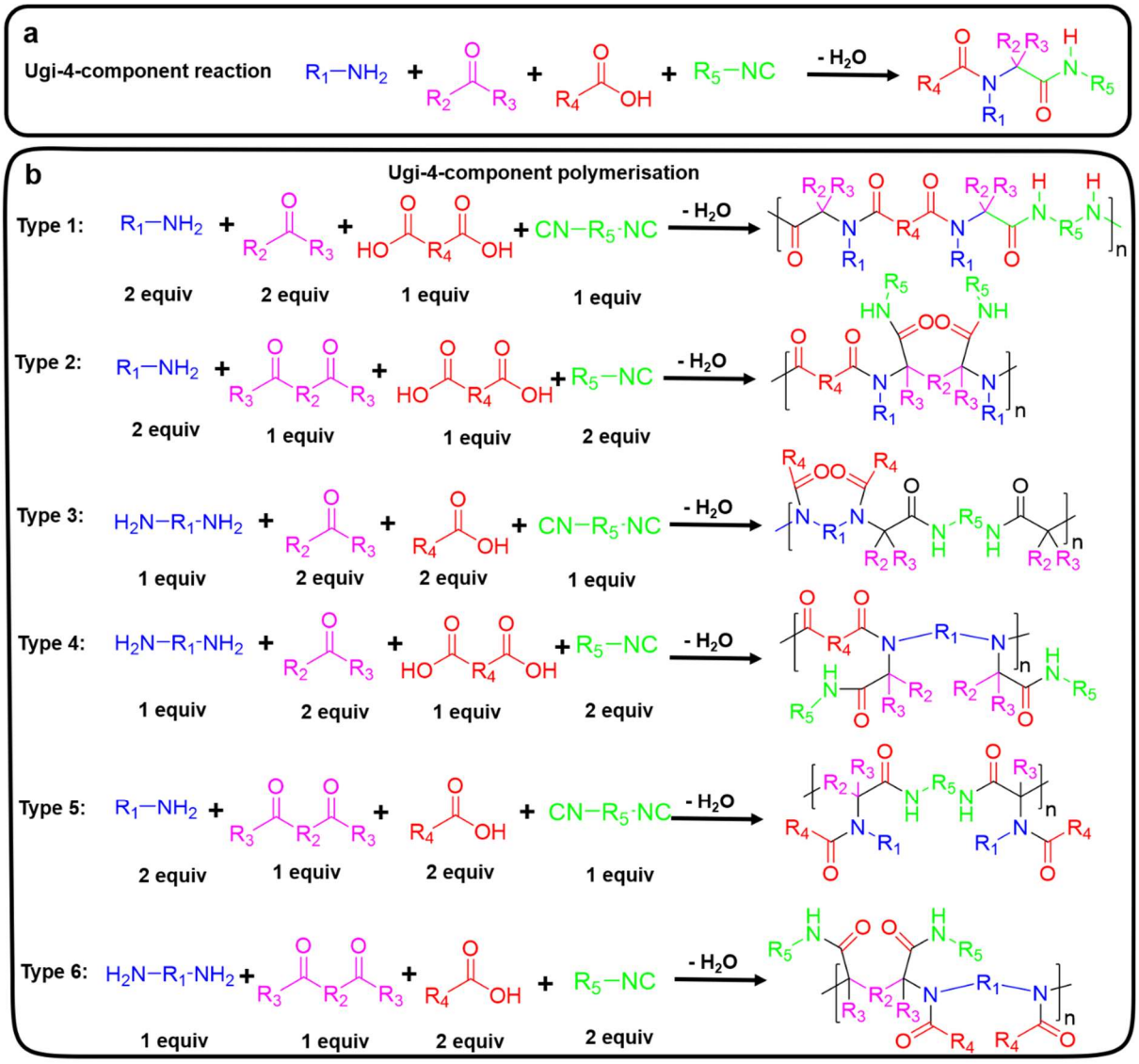
5.1 Introduction

Apart from click reactions, another kind of reaction that is often termed as highly-efficient, modular and possess high atom efficiency, is multicomponent reactions. These reactions were defined as reactions involving more than two starting materials, and initially designed to simplify the preparation of complex structures, transferring multi-step synthesis and purification to one-pot reactions in order to increase the overall yield and simplify the procedure.[1] Several multicomponent reactions have been developed in decades since their inception, such as the Biginelli reaction,[2] Passerini reaction[3] and Ugi reaction,[4,5] whilst the Ugi-4-component reaction has been intensively studied and arguably becoming the most reported multicomponent reaction. The Ugi-4-component reaction (Ugi-4CR) is the reaction of an amine, an aldehyde or ketone, a carboxylic acid, and an isocyanide to form a N-substituted amide structure, the mechanism is shown in **Scheme 1**. The N-substituted amide structure was also known as the peptoid structure, which normally has a N-substituted glycine repeating unit that is more flexible comparing to the peptide backbone due to the lack of charity, while N-substituted and C-substituted backbone structure is available via Ugi-4-component reaction. (**Scheme 2, a**) Several useful features of this reaction were reported such as highly-efficient, using readily available reactants from large libraries, and progress under room temperature. These features have led the Ugi-4CR to be widely studied with application in the synthesis of macrocycles,[6,7] modification of polymers[8,9] and synthesis of designed multi-functional molecules.[5,10,11]



Scheme 1. Ugi-4-component reaction mechanism with MeOH assisting the Mumm rearrangement.

However, the Ugi-4-component reaction was not exploited in the field of polymer chemistry until 2014, where Sehlinger *et al.* delivered a comprehensive report on the synthesis of substituted polyamides with Ugi-4-component reaction.[12] All six possible combinations for step-growth polymerization via Ugi-4CR where any two of the four components were bifunctional (**Scheme 2, b**) have been investigated with different solvent compositions, stoichiometric ratios and temperatures. A complementary report from Gangloff *et al*. in 2015 also studied the Ugi-4CR polymerisation with emphasis on aromatic monomers,[13] where the acceleration effect of adding water as the catalyst has been revealed. Since then, Ugi reaction has been recognized by polymer chemists and several studies of preparing novel polymers *via* the Ugi-4CR reaction have been reported.[4,14–17]



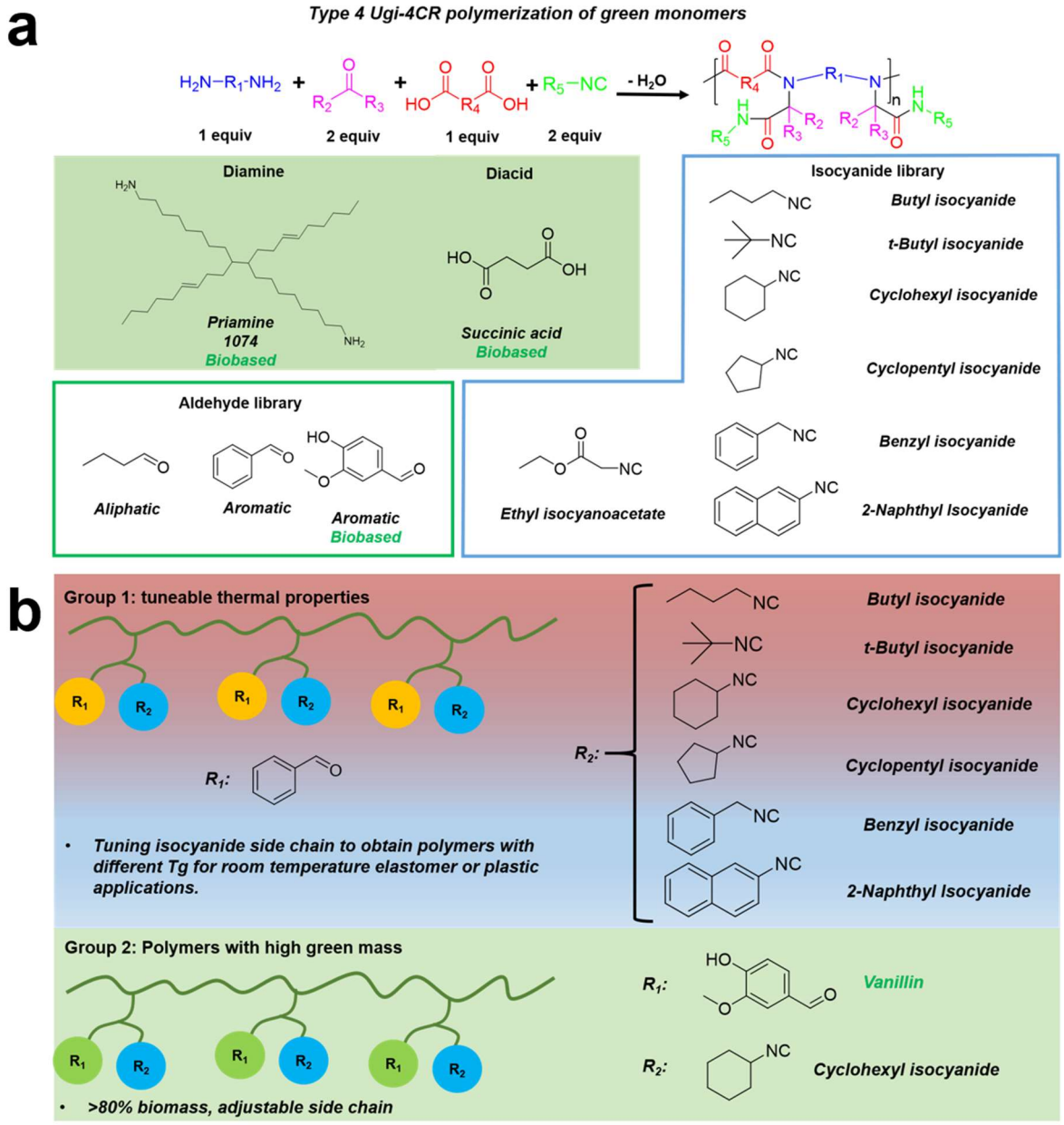
Scheme 2. Reaction scheme of Ugi-4-component reaction (**a**) and corresponding six possible ways of Ugi-4-component polymerisation. (**b**)

As the only by-product of Ugi reaction is benign water, while the reaction can be performed in MeOH, which has been reported as a relatively 'green' solvent,[18] and the reaction is producing a substituted polyamide structure which can be termed as a peptidomimetic product and showing promising thermal properties, the Ugi reaction has been recognised as a valuable candidate in preparing sustainable polymers and peptide mimicking polymers. One good example of the preparation of sustainable polymers was the direct polymerization of levulinic acid with Ugi-4CR reported by Hartweg *et al.* in 2016,[19] where polymers with M_n values from 5000 to 12000 were obtained *via* the Ugi-4CR of levulinic acid, a diamine and a diisocyanide. A unique polymer backbone with embedded cyclic structure was obtained, and corresponding thermal properties were thoroughly studied with DSC and TGA. This work has shown the potential of applying Ugi reaction in the synthesis of polymers with bio-sourced mass, given the large library of commercially available bio-sourced acids and amines that already been used in organic synthesis.[20–22] However, in this report, all cases the biomass content of the obtained polymers did not excess 59%, as the diamine and the diisocyanide used were not from a bio-source or prepared in a sustainable way. The prepared polymers also lacked side chain functionality, the advantage of modularity of Ugi reaction hence becoming futile. Nevertheless, inspired by this report, the idea of investigation on preparing polymers with more bio-sourced mass while using the side chain functionality provided by Ugi reaction to tune certain properties has become appealing. Although the isocyanide component remains non-renewable, the utilisation of commonly available isocyanides over much more difficult to access diisocyanides could facilitate the reaction to be feasible on a large scale with readily available monomers with a high overall biomass content, and potential future routes for the sustainable production of isocyanides were reported.[23]

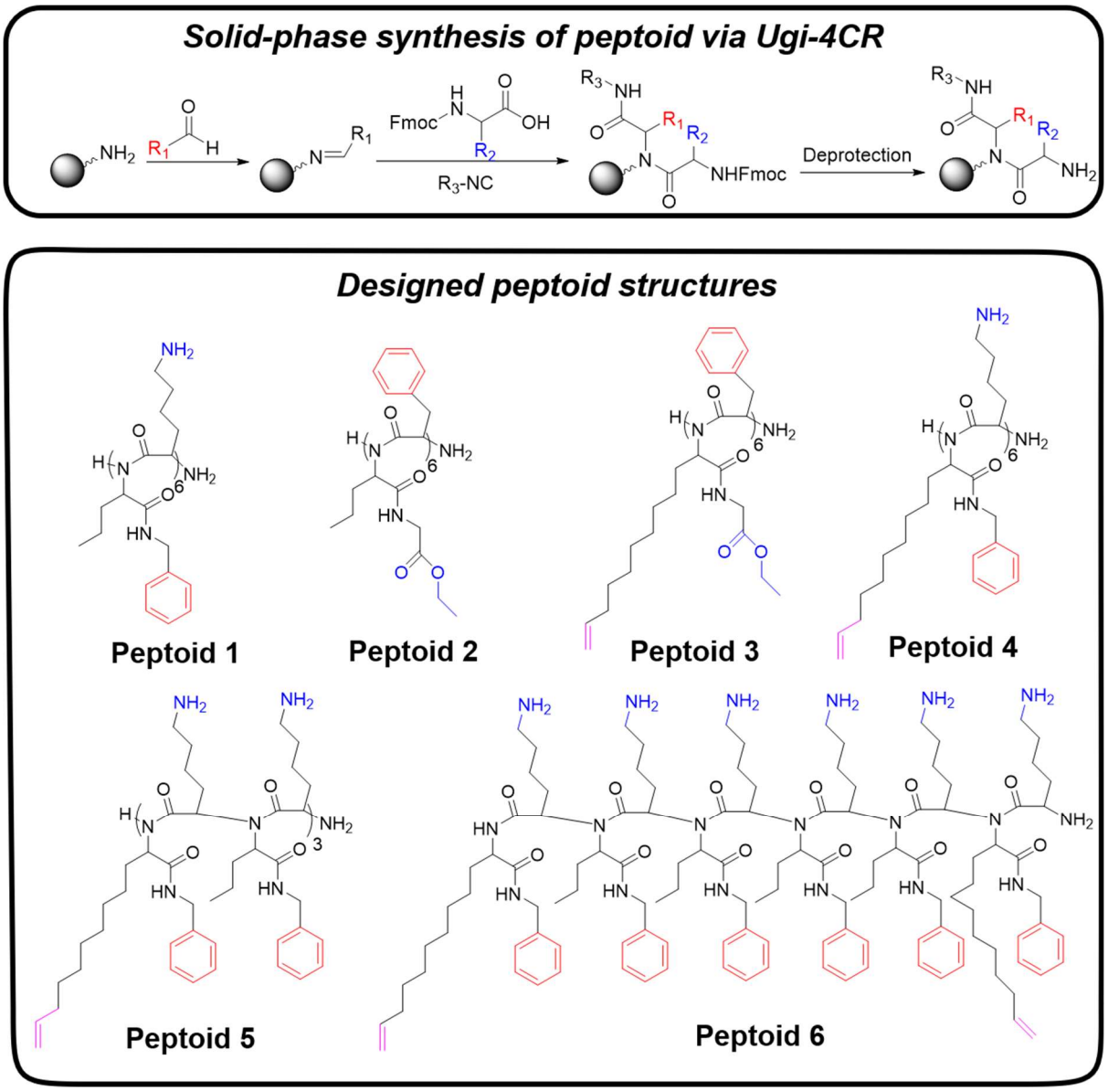
Reports on preparing peptidomimetic oligomers with Ugi reaction can date back to 2008, where cyclic peptoid pentamers possessing RGD (arginine-glycine-aspartic acid) functionalized side chains were prepared with consecutive Ugi 4-component reactions.[7] Although the self-assembly properties were not examined in this study, it shown the feasibility of preparing peptidomimetic polymers with Ugi-4-component reaction. Zhang *et al* reported the preparation of peptoid polymers with the Ugi-4-component polymerization of natural amino acids, an aldehyde and an isocyanide in 2016.[24] This report demonstrated an efficient way to prepare polypeptoids without the tedious synthesis of a N-substituted α-amino acid N-carboxyanhydrides (NNCAs) precursor. Inspired by this study, the preparation of alternating

peptide-peptoid polymer and sequence defined peptide-peptoid hybrid polymer assisted by solid-phase supported synthesis were reported.[14,17,25,26] Side chain protected amino acids were employed in these studies to introduce Ugi reaction intolerable functional groups such as amines. However, the side chain functionality introduced by Ugi reaction was not thoroughly investigated in these reports. Three functional groups could be introduced onto one peptoid repeating unit, while modularity was promised by the large library of commercially available aldehydes and isocyanides. Utilizing different functional groups, especially Ugi reaction tolerable ones like alkyne and alkene, to either produce peptoid polymers with compounded properties or allow further modification of peptoid polymers into desired applications could be very interesting. Besides, as sequence defined polypeptoid could be prepared with solid-phase supported synthesis method, by precisely controlling the location and density of functional groups, which has been reported as important factors and well-reviewed in the field of glycopolymer,[27–29] properties of obtained polypeptoids could be fine-tuned.

Herein, inspired by existing reports mentioned above, the study on utilizing Ugi reaction to synthesize step-growth polymers with sustainable monomers (**Scheme 3, a and b**), and prepare sequence-defined peptoids with designed side chain functionality (**Scheme 4**) were designed and performed. Results were summarized in following sections. The study presented here should provide novel information on ways of preparing polymers with bio-sourced mass and multifunctional peptidomimetic compounds.



Scheme 3. Designing on preparation of polymers via Ugi-4CR polymerization of green monomers. The reaction scheme and monomer library were shown in **a**, where grouping polymers for investigation on tuning thermal properties with different side chain functional group as well as preparation of polymer with high bio-mass content were shown in **b**.



Scheme 4. Designing on preparation of multifunctional peptoid oligomer via solid-phase synthesis via Ugi-4CR. Peptoid 1 and 2 were designed to have charged and aromatic groups for providing driving force for self-assembly or being utilised in bioactivities such as RNA binding. Peptoid 3 to 6 were designed to have different spacing between clickable side chains, which allows following modification with thiol-ene click reaction and investigate the spacing effect.

5.2 Results and discussion

5.2.1 Preparation of Ugi-4CR step-growth polymers with bio-sourced diamine and diacid

5.2.1.1 Confirming Reaction Viability

The two bifunctional components in Ugi 4CR polymerization form the polymer backbone, and as such the six available combinations of bifunctional and monofunctional monomers provide 6 different polymer architectures. As bio-sourced diacids and diamines are far more accessible than diisocyanides and dialdehydes, this study utilised succinic acid (SA) and Priamine 1074 (P74), a 99% pure linear diamine with flexible carbon linkers, as the bifunctional monomers to study the Ugi 4CR polymerization. P74 was initially analysed with electrospray ionisation mass spectrometry (ESI-MS) to confirm the supplier's data of molecular weight as 532 was correct, while the mass of Priamine 1074 was shown as 532.5 as expected. (**Figure 1, a**) To confirm that the Ugi-4CR would occur as intended, a non-polymer analogue of our intended polymerisation reaction was completed. This also allowed us to double-confirm the molecular weight of our diamine, P74, as an accurate stoichiometric ratio is vital for achieving high molecular weights in step growth polymerisation. P74, benzaldehyde, benzoic acid and tert-butyl isocyanide were used to perform a Ugi-4-component reaction and resulting crude product was analysed with ESI-MS. (**Figure 1, b**) Obtained results showed the desired peaks corresponding to the desired product ionised with sodium ion or hydrogen ion were observed, whilst peaks corresponding to single Ugi-4CR reaction product and fragmentation were also observed. However, there are still extra significant peaks **1** (m/z: 876.5), **2** (m/z: 996.8) and **3** (m/z: 1192.6) shown in the ESI-MS results. As these peaks did not fit to any side reaction products, like Passerini reaction product (m/z: 311.23) and Ugi-3-component reaction product (m/z: 928.26), or possible salt-ionised products. The most possible reason for these peaks to be detected is the products formed ionized complex with remaining compounds in the ESI-MS detection region.

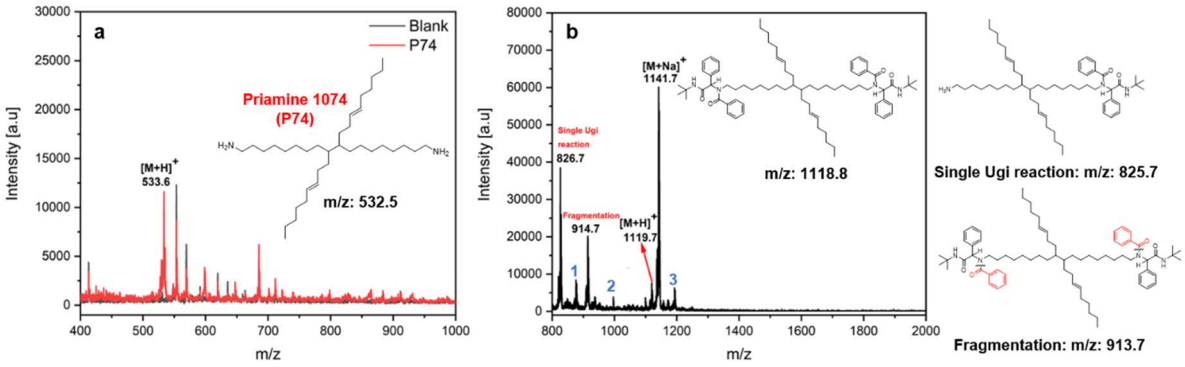


Figure 1. ESI-MS analysis of P74 (**a**) and Ugi-4CR reaction product of P74, benzaldehyde, benzoic acid and tert-butyl isocyanide.(**b**) The molecular weight of P74 was confirmed in **a**, and the applicability of Ugi-4CR reaction with P74 was shown in b, for the fragmentation structure, red-coloured structure was removed to give a fragmentation with m/z = 913.7. Possible structures were analysed in **b** whilst peak 1,2 and 3 does not fit to reasonable assumptions. Possible explanations of appearance of these peaks were ionised complex of product with remaining compound in the ESI-MS detection region.

5.2.1.2 Initial polymerisation reactions

Following the confirmation of the molecular weight of P74, as well as the reaction proceeding as expected the Ugi-4-component polymerization of P74 and SA was then investigated with different aldehydes and isocyanides. The reaction scheme is shown in **Scheme 2, a**. The initial design of the project was to prepare polymers with a bio-sourced backbone, with functionalized side chains providing different properties, despite not necessarily being themselves bio-sourced. The first Ugi 4CR polymerization of P74 and SA was performed at 1.0 M concentration in MeOH under 100°C in a sealed microwave vial with butyraldehyde and ethyl isocyanoacetate. The initial intention was to vary the carbon chain length of the aldehyde to control the glass transition temperature and solubility of the polymer products, while utilising the acetate group *via* deprotection to give carboxylic acid functionality, either for possible surface activation properties, or to use for post-polymerization modification.

The reaction mixture was heated under 100°C with microwave assisted heating for 2 hours and the resulting polymer (**P1, Table 1)** was analysed with THF GPC. A bimodal peak was observed, with the secondary peak significantly decreasing the obtained Mn value. (**Figure 2, a**) Further heating for 60 hours did not reduce the secondary peak. It has been reported that

aldehydes with α-hydrogens increase the chance of cyclisation,[12] which might be responsible for the observed secondary peak. Thus, the aldehyde of choice was changed to benzaldehyde, an α-blocked aldehyde, and ethyl isocyanoacetate (for synthesis of polymer **P2**) and cyclohexyl isocyanide (for synthesis of polymer **P3**) was used to investigate if different isocyanides result in different polymer sizes. The effect of conventional heating versus microwave heating, changing temperature, elongate reaction time and adding 0.5 mol% of water as catalyst were also investigated with **P2** as the model reaction. Notably, obtained GPC traces showed the secondary peak was present in every Ugi 4CR polymerisation attempted, albeit to varying degrees. (**Figure 2**, **b and c**) Polymer **P3** has a significantly larger hydrodynamic volume comparing to polymer **P2**. The possible reasons for the secondary peak are the cyclisation product, side reaction products, leftover monomer, or oligomers. Notably, most reports on Ugi polymerization report similar findings and identify it as the cyclic product.[12,13] As cyclic product was mostly produced at low concentration of reactants, synthesis of P3 was repeated in bulk (**Figure 2**, **c**). However, even smaller polymer was obtained, which might be the consequence of large viscosity of the bulk reaction mixture reduced the mobility of oligomers. These results indicating using different isocyanide does have a effect on the extent of polymerization, while elevated temperature with microwave assisted heating would be beneficial for obtaining large polymer. Elongated heating and bulk reaction would not enhance the polymerisation. Thus, the general reaction condition was then determined as 1.0 M of bifunctional monomers in MeOH, 100℃ microwave assisted heating for two hours.

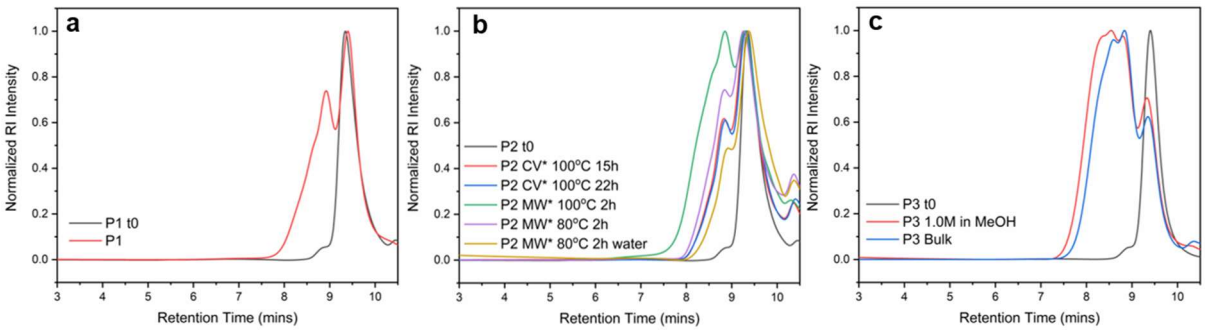
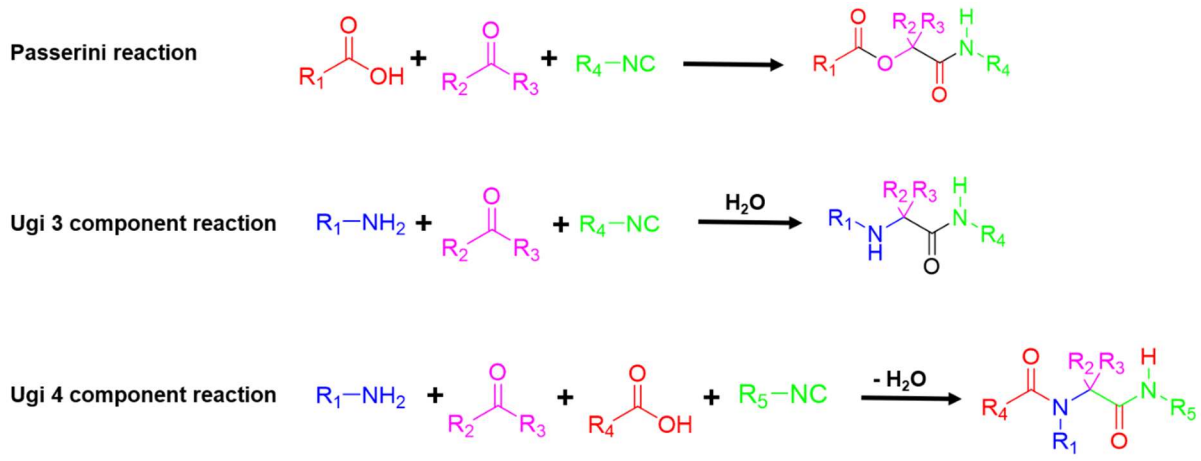


Figure 2. Initial investigation on Ugi-4CR polymerization with different aldehydes, isocyanides, heating pattern and effect of water and solvent. **a**: Ugi-4CR polymerisation of P74, SA, butyraldehyde and ethyl isocyanoacetate. **b**: Ugi-4CR polymerisation of P74, SA, benzaldehyde and ethyl isocyanoacetate with investigation on effect of heating pattern, temperature and adding water as catalyst. **c**:Ugi-4CR polymerisation of P74, SA, benzaldehyde and cyclohexyl isocyanide, with investigation on the effect of bulk reaction.

5.2.1.3 Identifying and reducing the secondary peak

After the secondary peak was observed, our next goal became identifying and reducing it. The polymerization of P74, SA, benzaldehyde, and cyclohexyl isocyanide (synthesis of polymer P3) was selected as the model reaction to investigate how to minimize and separate the secondary peak and increase the molecular weights of obtained polymers. Firstly, the polymerization procedure was optimized to minimize the possible side reactions: the Passerini reaction and the Ugi-3-component reaction. (**Scheme 5**) The former can be easily avoided via an imine formation step between the diamine and aldehyde, prior to the addition to succinic acid and isocyanide, and has been reported in several studies of the Ugi reaction. The latter, which is the reaction between an amine, a carbonyl and an isocyanide, was avoided by a delay between the addition of the SA to the imine and isocyanide to the subsequent reaction mixture. As the imine formed in the polymerization appears as an insoluble white slurry in a MeOH solvent system, which might be the consequence of loss of polarity from the imine formation, a homogenous reaction mixture is observed soon after the addition of SA under stirring, indicating the successful protonation of the imine intermediate due to the dissolution of the previously insoluble slurry. The mechanism used here was based on recently reported investigation on Ugi-4CR reaction mechanism, which was slightly different from what Ugi proposed more than 50 years ago.[30] The isocyanide could then be added, beginning the polymerisation process. However, this improved reaction procedure did not reduce the amount of secondary peak, suggesting the possible side reactions were not responsible.



Scheme 5. Reaction scheme of Ugi-4CR and two common side reactions, Passerini reaction and Ugi-3-component reaction, while doing Ugi-4CR.

Table 1. Synthesis of polymers with different aldehyde and isocyanide starting materials via Ugi-4CR polymerisation and solvent effect investigation.

	Aldehyde	Isocyanide	Solvent	$M_{n,GPC}$ (g/mol)	$M_{w,GPC}$ (g/mol)	PDI	Bio-content*(%)
P1	Butyraldehyde	Ethyl isocyanoacetate	MeOH	2200	2700	1.26	65.9
P2	Benzaldehyde	Ethyl isocyanoacetate	MeOH	2600	3400	1.32	61.7
P3A	Benzaldehyde	Cyclohexyl isocyanide	MeOH	2800	5300	1.88	62.2
P3B	Benzaldehyde	Cyclohexyl isocyanide	MeOH/THF (4:1)	3800	6600	1.71	62.2
P3C	Benzaldehyde	Cyclohexyl isocyanide	MeOH/THF (2:1)	4100	7600	1.84	62.2
P3D	Benzaldehyde	Cyclohexyl isocyanide	MeOH/THF (1:1)	3900	6700	1.73	62.2
P3E	Benzaldehyde	Cyclohexyl isocyanide	MeOH/THF (1:2)	2700	4900	1.82	62.2
P3C**	Benzaldehyde	Cyclohexyl isocyanide	MeOH/THF (2:1)	4100	7600	1.84	62.2
P4	Benzaldehyde	Benzyl isocyanide	MeOH/THF (2:1)	3000	5800	1.94	61.2
P5	Benzaldehyde	Cyclopentyl isocyanide	MeOH/THF (2:1)	4200	7400	1.76	63.9
P6	Benzaldehyde	n-Butyl isocyanide	MeOH/THF (2:1)	3400	7000	2.04	65.4
P7	Benzaldehyde	Tert-butyl isocyanide	MeOH/THF (2:1)	3000	5400	1.82	65.4
P8	Benzaldehyde	2-Naphthal isocyanide	MeOH/THF (2:1)	2400	4500	1.90	57.3
P9	Benzaldehyde	Ethyl isocyanoacetate	MeOH/THF (2:1)	2800	3600	1.28	61.7
P3C**	Benzaldehyde	Cyclohexyl isocyanide	MeOH/THF (2:1)	4100	7600	1.84	62.2
P3C, P	Benzaldehyde	Cyclohexyl isocyanide	MeOH/THF (2:1)	7100	11700	1.63	62.2
P10	Vanillin	Cyclohexyl isocyanide	MeOH/THF (2:1)	3300	5000	1.53	83.9

*: Bio-content (%) was calculated by sum of molecular weight of sustainable monomer divided by the molecular weight of desired one-mer.

** Duplicated from **P3C** for comparison.

5.2.1.4 Optimising the solvent system

SA has poor solubility in MeOH, best results were obtained following addition in bulk to the reaction system; a pre-dissolved SA in hot MeOH solution results in reduced polymer size and increased secondary peak due to the tendency of SA to crash out during addition, resulting in inconsistent reaction stoichiometry. (**Figure 3, a**) Adding SA in bulk to the imine reaction mixture in selected solvent system was shown as the suitable procedure. The polymer stopped growing at 2 hours of reaction time, whilst the secondary peak intensity increasing after 2 hours. The explanation was formed polymer has poor solubility in MeOH and results in a heterogenous reaction system, while the concentration of reactive chain ends decreased significantly in the solution and led to increased cyclisation product, hence the increase of secondary peak intensity. A preliminary kinetics study was conducted with a 1-hour time intervals, which showed that no further polymer growth was observed after two hours. (**Figure 3, b**) The secondary peak was firstly largely reduced from 1 hour to 2 hours but increased after 2 hours. Based on this kinetics study, the assumption of the secondary peak is a mixture of cyclic product and oligomer product, as the part of secondary peak reduced from 1 hour to 2 hours should indicate oligomers forming larger polymers. As the observation indicates that the crude product is not a homogenous solution after 2 hours, a possible reason for the increase of secondary peak intensity after 2 hours might be large polymers become less soluble in MeOH and formed the gel-like phase while in remaining liquid phase, the concentration of reactive chain was significantly reduced, which promoted the formation of cyclic structure. Thus, optimising the solvent system to assist the dissolution of the reaction mixture and thus increase both the concentration of polymer chains in the reaction solution and the mobility of oligomers presented a solution to both possible issues.

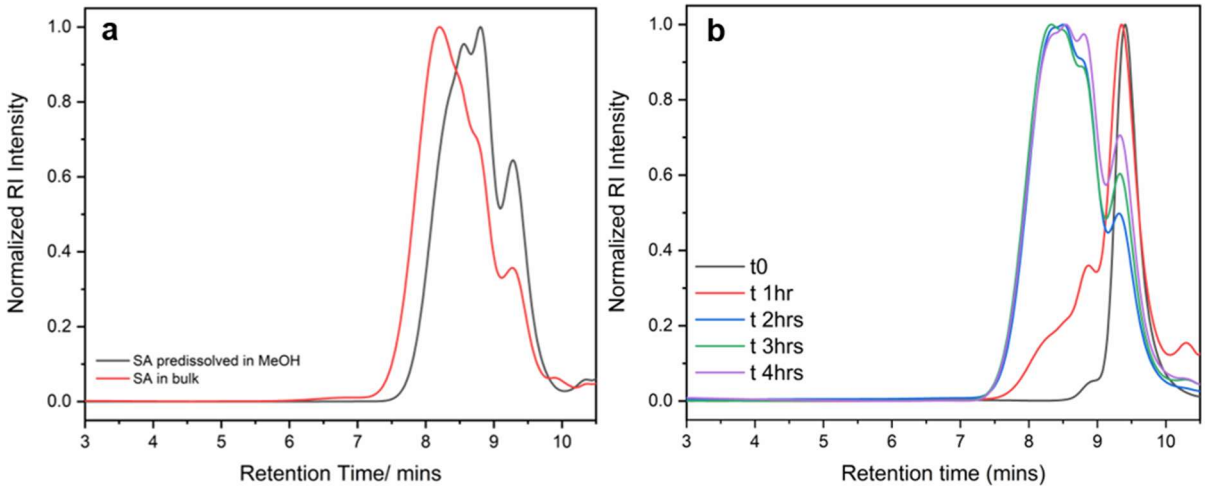


Figure 3. Investigation on effect of the addition procedure of SA(**a**) and the preliminary kinetics investigation to determine optimised reaction time.(**b**)

Cyclisation is unavoidable in step-growth polymerisation but is more prominent at lower concentrations due to the decreased chance of polymer chains meeting each other. Thus, the reaction solvent system was adjusted from pure MeOH to a MeOH/THF mixture system to assist the polymer dissolution. The polymerization of P74, SA, benzaldehyde and cyclohexyl isocyanide was repeated at 1.0 M concentration (with respect to P74 and SA) at 100℃ for 2 hours in different MeOH/THF solvent systems, with the obtained polymers (**P3A-P3E**) analysed with THF GPC in **Figure 4 a**. The MeOH/THF (2:1) system, **P3C**, performed best, with the least secondary peak. The Ugi reaction is thought to require MeOH to progress efficiently, while the polymers are soluble in THF. The optimised ratio contains enough THF to solubilise the products, increasing the mobility of oligomers to react with each other and form longer chains, while maintaining a large fraction of MeOH to retain the efficiency of the Ugi 4CR polymerization. Notably, MeOH is considered a green solvent, but THF is not, so from a sustainability perspective it is also ideal to use only the minimal amount of THF that enables a homogenous reaction mixture even at high molecular weights.

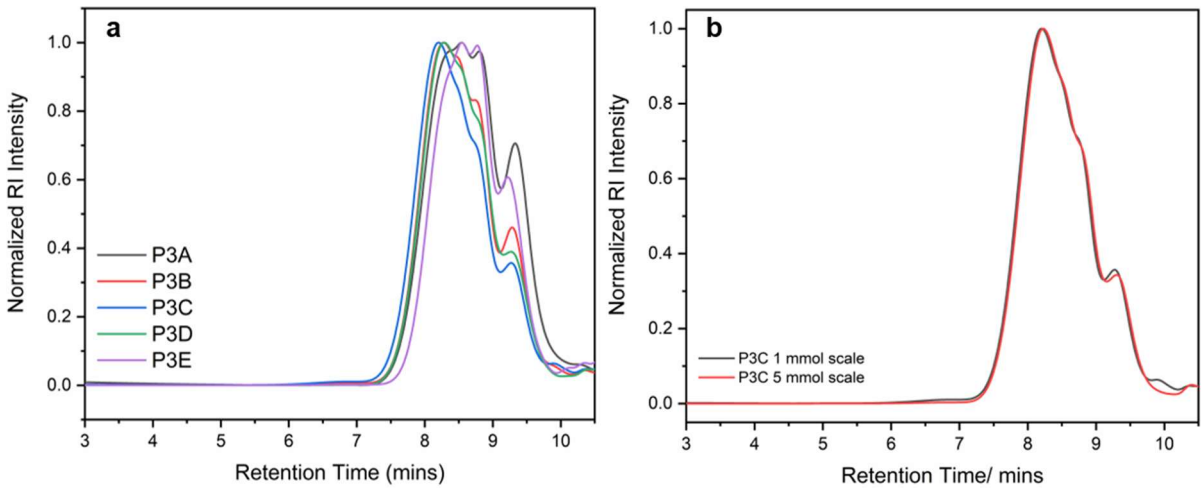


Figure 4. Optimisation on solvent composition of Ugi-4CR polymerisation of P74, benzaldehyde, SA and cyclohexyl isocyanide (**a**) and 5 mmol scale-up reaction of P74, benzaldehyde, SA and cyclohexyl isocyanide (**b**). The MeOH/THF (2:1) solvent system (**P3C, a**) was shown to be the best solvent system and change of reaction scale does not impact the size of polymer obtained.

Scale-up

Following the optimisation of the reaction procedure and the solvent system, the previous model reaction in the MeOH/THF (2:1) optimised solvent system, **P3C**, was repeated at a 5 mmol scale, with respect to P74 and SA, resulting in over 4 grams of polymer with 83% yield. (**Figure 4, b**) This indicates the potential of synthesis of multi-gram scale polymers with the Ugi-4CR polymerization of P74 and SA.

5.2.1.5 Precipitation of polymers

While isolating the crude polymer products, it was found that the polymers of P74, SA, benzaldehyde and cyclohexyl isocyanide (**P3** series) could be precipitated into cold water or MeOH to remove unreacted monofunctional reagents. A second precipitation of the scaled-up **P3C** product into dry ice cooled diethyl ether allowed separation of the low molecular weight secondary peak into the liquid phase, leaving a high molecular polymer as the precipitate (**P3C, P**) with 59% yield. (**Figure 5, a**) Obtained **P3C, P** has a significantly higher $M_{n,GPC}$ and $M_{w,GPC}$ comparing to **P3C**.(**Table 1**) The separated low molecular weight peak product was then dried and analysed with ESI-MS and MALDI-ToF. However, both methods did not provide a clear result, while chances were remaining high molecular weight species prevented low molecular weight species from being ionised and got recognised in both techniques. Possible solution is purifying isolated low molecular weight peak product with a preparative HPLC system and

identify components. Dry-ice cold diethyl ether precipitation was applied to other polymers (**P4-P9**), however, only polymer **P3C** and **P5** were shown to precipitate as a nice solid in dry-ice cold ether with elevation in $M_{n,GPC}$ and $M_{w,GPC}$. For polymer **P7** precipitation in cold MeOH could partially remove the secondary peak and elevate $M_{n,GPC}$ from 3400 to 5000. For other polymers, none of the precipitation removes secondary peaks.

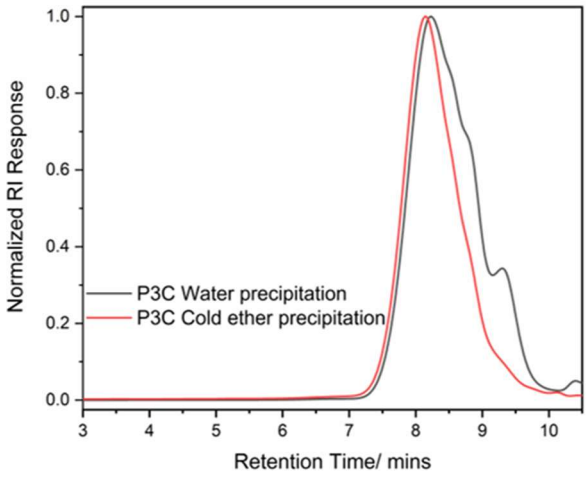


Figure 5. Removal of low molecular weight peak via precipitation of polymer **P3C** in dry-ice cold diethyl ether. Significant change in $M_{n,GPC}$ and $M_{w,GPC}$ was observed and recorded in **Table 1**.

5.2.1.6 Kinetic Study

Once the solvent system had been optimised, a more detailed kinetics study was conducted. The model reaction, **P3C**, was repeated over a two-hour period with 20-minute time intervals between sampling, with each aliquot characterised with THF GPC. (**Figure 6**) The THF GPC results suggested that the secondary peak was slightly shifted towards higher molecular weight compared to the large single peak seen in the t_0 sample. Also, the intensity of the secondary peak was initially appeared to decrease over the two hours but remained unchanged between the last two time points. That can serve as another evidence that the secondary peak could be a combination of leftover oligomers and cyclic products, with the increased solution viscosity at the late stages of the reaction possibly responsible for these oligomers not forming longer chains. MALDI-ToF was also employed as the characterisation method to identify the secondary peak. However, obtained polymers did not provide a significant response in both reflective and linear mode MALDI-ToF analysis. Possible explanations are long alkyl side chain and backbone from the Priamine added difficulty to the ionisation of polymer.

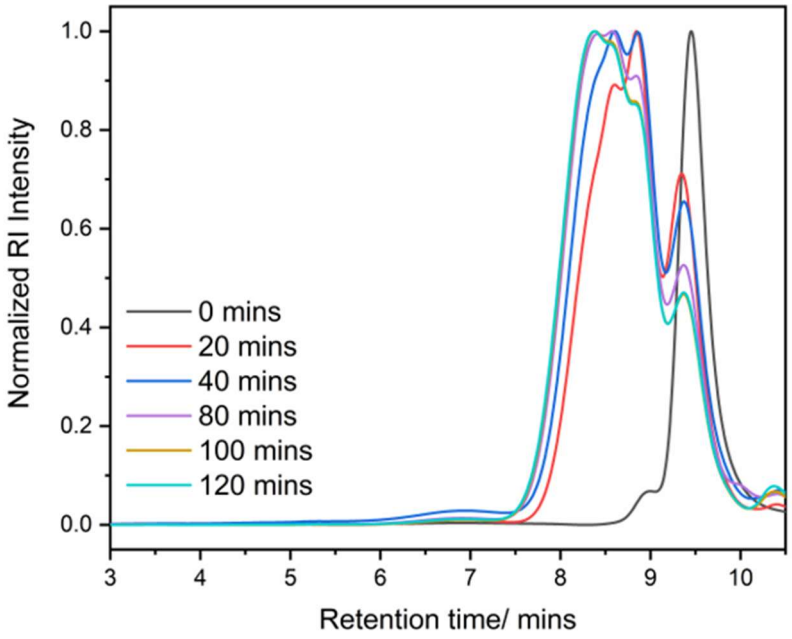


Figure 6. Kinetics investigation of preparation of polymer **P3C** in MeOH/THF (2/1) solvent system under 100℃ microwave assisted heating for 2 hours. Time interval was 20 minutes. It is notably that t (100 min) and t (120 min) curve overlapping completely, indicated no more chain growth after 100 minutes. The decrease of secondary peak before 100 mins indicates the secondary peak is a mixture of oligomer and cyclic product.

5.2.1.7 Varying side chain groups to adjust the thermal properties

Following the identification of the secondary peak and all the reaction optimisations, the Ugi 4CR polymerisation was conducted with benzaldehyde, P74, SA, and a range of isocyanides to study the potential tuneability of the thermal properties of the polymer products (**P3C*, P4-P8, Table 1**). The isocyanides used were intended to provide comparable results. For example, **P3C** with the cyclohexyl side chain could be compared with **P4** which possess aromatic side chain to investigate the effect of π-π stacking force on the glass transition behaviour of polymers. Obtained polymer was isolated by precipitation first in water, and then in cold diethyl ether. However, the separation of the secondary peak during the second precipitation was not consistent across all of the polymers, with only **P8** and **P9** giving solid products in the second precipitation. The other products failed to yield solid products and had to be precipitated only in either cold water or cold methanol. The thermal properties were then studied *via* thermogravimetric analysis (TGA) and differential scanning calorimetry(DSC), with the obtained results shown in **Figure 7 a**, **b** and **Figure 8**.

For TGA, polymer **P3C** and its precipitation product with less secondary peak, and polymer **P8** were studied to investigate the decomposition temperature of polymers, and if the secondary peak or the side chain composition affects the decomposition behaviour. The TGA data show similar degradation temperatures at around 405℃ for all the polymer products, with the decomposition temperature not affected by the prior separation of the secondary peak or the side chain composition. However, the prior separation of the secondary peak did change the remaining mass of polymer in TGA, which might be the consequence of the low molecular weight product was easier to break down and removed from the pan during heating. The degradation temperatures were calculated by the average of temperature at the turning points of the first derivative of TGA curves.

The DSC analysis of polymers (**Figure 8**) shown that the glass transition temperature of the obtained polymer was lower than room temperature in most cases, while varying side chains from butyl to 2-naphthyl groups, shown in **Figure 8 e and g**, does not have a significant impact on glass transition temperature. Possible reasons are the long flexible alkyl backbone and side chains of P74 dominated the packing behaviour of polymers and reduced the glass transition temperature significantly, whilst the aromatic side chains used does not provide strong enough driving force to have a significant impact on thermal behaviour. The polymer produced with tert-butyl isocyanide (**P7, Figure 8, f)** surprisingly have a higher glass transition temperature than other polymers apart from polymers with cyclic structure on their side chains. (**P3, P3CP and P5**) That might because the tert-butyl isocyanide has the smallest side chain steric hindrance, hence eased the packing of polymer chains. It is notable that for **P3C, P3CP** and **P5**, (**Figure 8, a, b, d**) where cyclohexyl or cyclopentyl side chain was employed, these polymers possess glass transition temperatures from 7.0℃ to 26.2℃, as well as an exothermic peak at a higher temperature. That might be the consequence of partial crystallization of polymers during cooling from the melt, while it is interesting that the crystallization peak only appears in these polymers with a cyclic alkyl side chain, rather than polymers with aromatic side-chain where extra driving force for packing would be expected. The undefined sharp peak in every sample was possibly an artefact due to discharge of static electricity in the system. These results indicate to tune the glass transition temperature of polymers, isocyanides, or

aldehydes with longer alkyl side chain, like C12 or C16 or bulkier functional group should be used to actually have an impact on polymer's thermal behaviour.

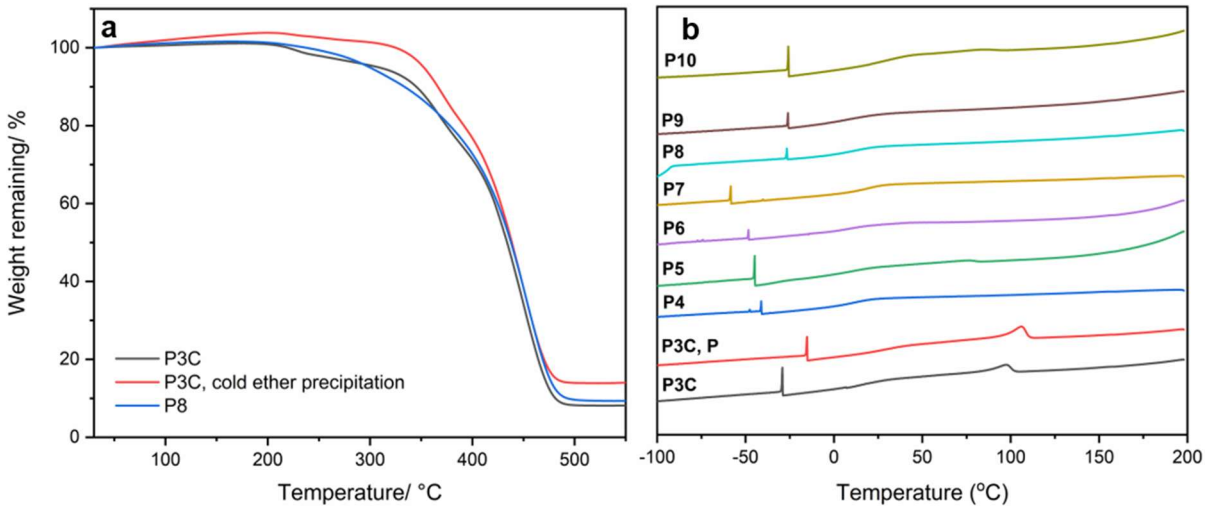


Figure 7. Representative TGA analysis investigating the impact of low molecular weight peak and how would changing side chain affect the decomposition behaviour. (**a**) Stacked DSC diagrams of all prepared polymers. (**b**)

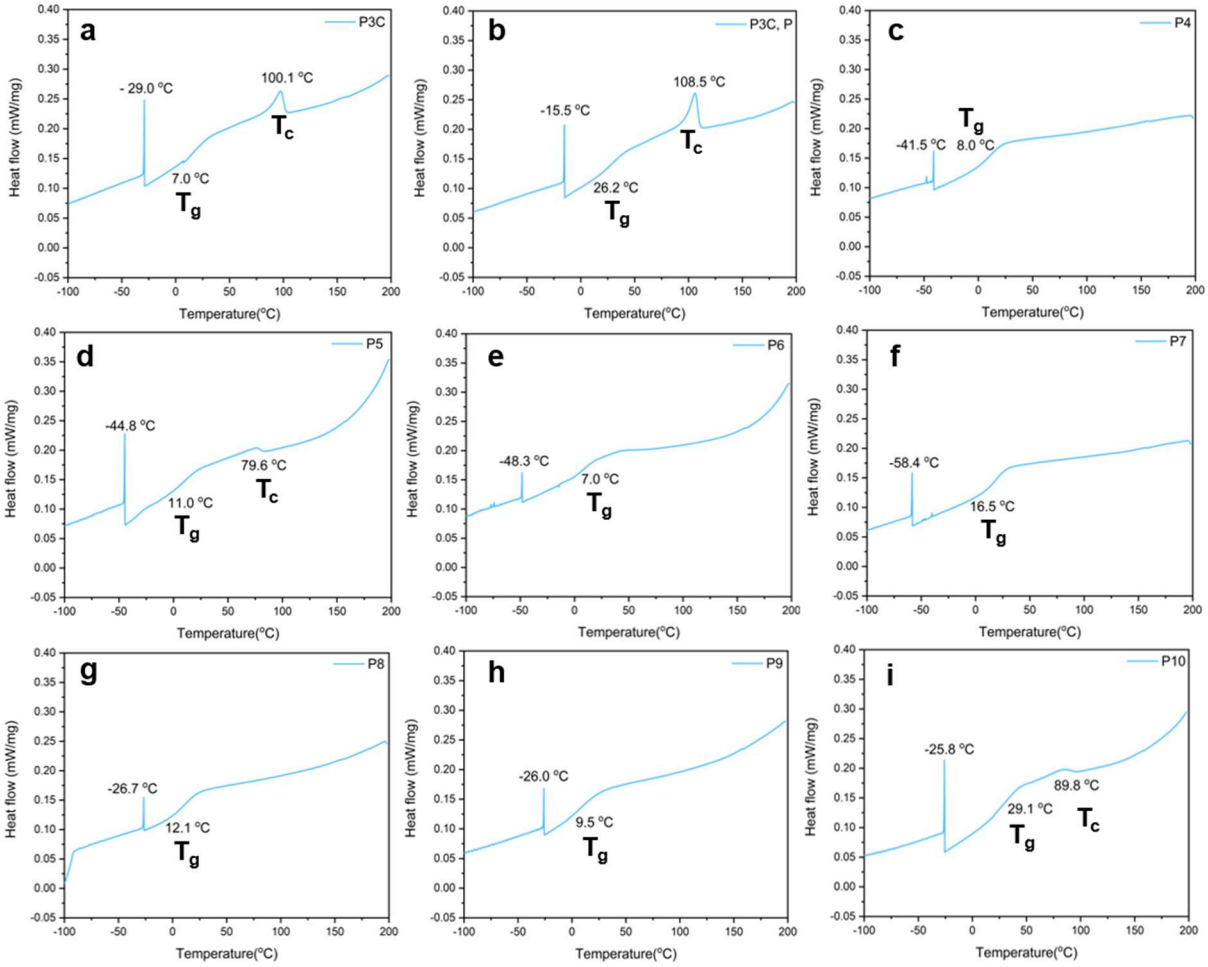


Figure 8. DSC curves of second cooling cycle of **P3C**, **P3C, P** and **P4-P10.** Glass transistion temperatures (T_g) were identified by calculating the 1st deriviative and 2nd derivatitve of the obtained curve. Crystallisation temperatures were presented in samples with cyclic alkyl side chains **P3C, P3C,P P5** and **P10.**

5.2.1.8 Maximising the bio-mass content

As the aldehydes used were not bio-sourced, we explored the utilisation of vanillin, a commercially available bio-sourced aldehyde with a structure similar to benzaldehyde. The polymer of P74, SA, vanillin and cyclohexyl isocyanide, **P10**, was prepared at a 1 mMol scale, with a biomass content of 84%. Obtained polymer **P10** (**Figure 9**) precipitated out in cold MeOH to give a pale-yellow solid with a yield of 73%. The glass transition behaviour of **P10** was studied with DSC and presented in **Figure 8, i**. Combined with the previously mentioned 5 mMol scale-up reactions and the previously discussed possible method to synthesize isocyanides in a more sustainable manner, this emphasises the potential of the Ugi 4CR in the synthesis of functionalised polyamides with tuneable side chains and thermal properties, without catalyst, in a green solvent, almost entirely from bio-sourced monomers.

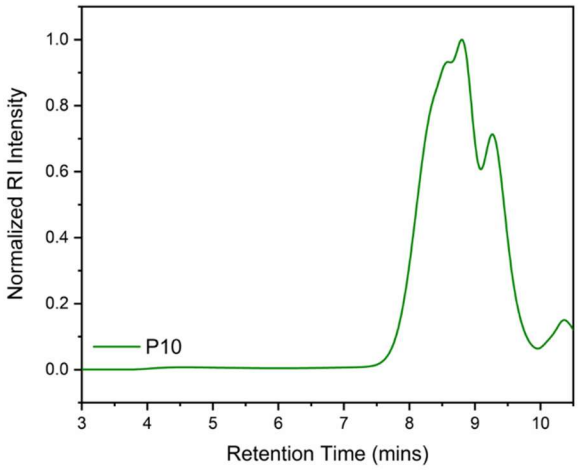


Figure 9. THF GPC trace of polymer **P10** with bio-based vanillin as the aldehyde source.

5.2.1.9 Summary and Outlook

Based on obtained results, the preparation of step-growth polymers with green monomers via Ugi-4CR polymerization was shown to be feasible. Polymers with up to 84% bio-content mass were prepared. The reaction condition and procedure, like the addition of reagents and solvent composition, were optimized, while more optimisations would be required to produce polymers with higher molecular weight. Polymers with different side chain were prepared and their thermal properties were investigated with DSC and TGA. These substituted polyamides were shown to be thermally stable with decomposition temperature above 400℃. To tune the glass transition temperature, large side-chain groups were required as the long alkyl chain from P74 would dominate the thermal behaviour and results in room temperature elastomers. By using cyclic alkyl isocyanides, or possibly aldehydes, polymers with crystallisation behaviour could be prepared.

The $M_{n,GPC}$ and $M_{w,GPC}$ of obtained polymers were low, as the secondary peak presented affected the integration significantly, while removal of the secondary peak results in a significant increase of $M_{n,GPC}$ and $M_{w,}$GPC. Identifying and finding a universal approach to removal of the secondary peak would be the focus for the next stage, while preparative HPLC purification might be required for identifying the secondary peak. By controlling the

stoichiometry and adjusting the end group of polymers, the avenue of chain extension with amine or carboxylic acid end groups could be opened and provide larger polymers.

5.2.2 Preparation of sequence-defined peptoids via solid-phase support synthesis

As designed in **Scheme 4**, peptoids that have hydrophobic, charged, aromatic and clickable side chains were synthesized via solid-phase supported Ugi-4-component reaction. Butyl aldehyde and 10-undecenal was employed to provide hydrophobic or clickable side chains and serves as the aldehyde source. Fmoc-protected lysine and phenylalanine were used as carboxylic acid sources, while their functional groups provide positively charged, and aromatic side chain. Fmoc-protected primary amines from the amino acids can be deprotected and allow further chain extension. Two isocyanides, benzyl isocyanide and ethyl isocyanoacetate, were selected to provide aromatic side chains and negatively charged side chains by removing the protecting ethyl group after the peptoid synthesis. A general procedure was developed for solid-phase supported synthesis of these peptoids, and the procedure is shown in section **5.2.3**. After the preparation and cleavage, isolated crude peptoid was characterized with MALDI-ToF and the obtained results were shown in **Figure 10**.

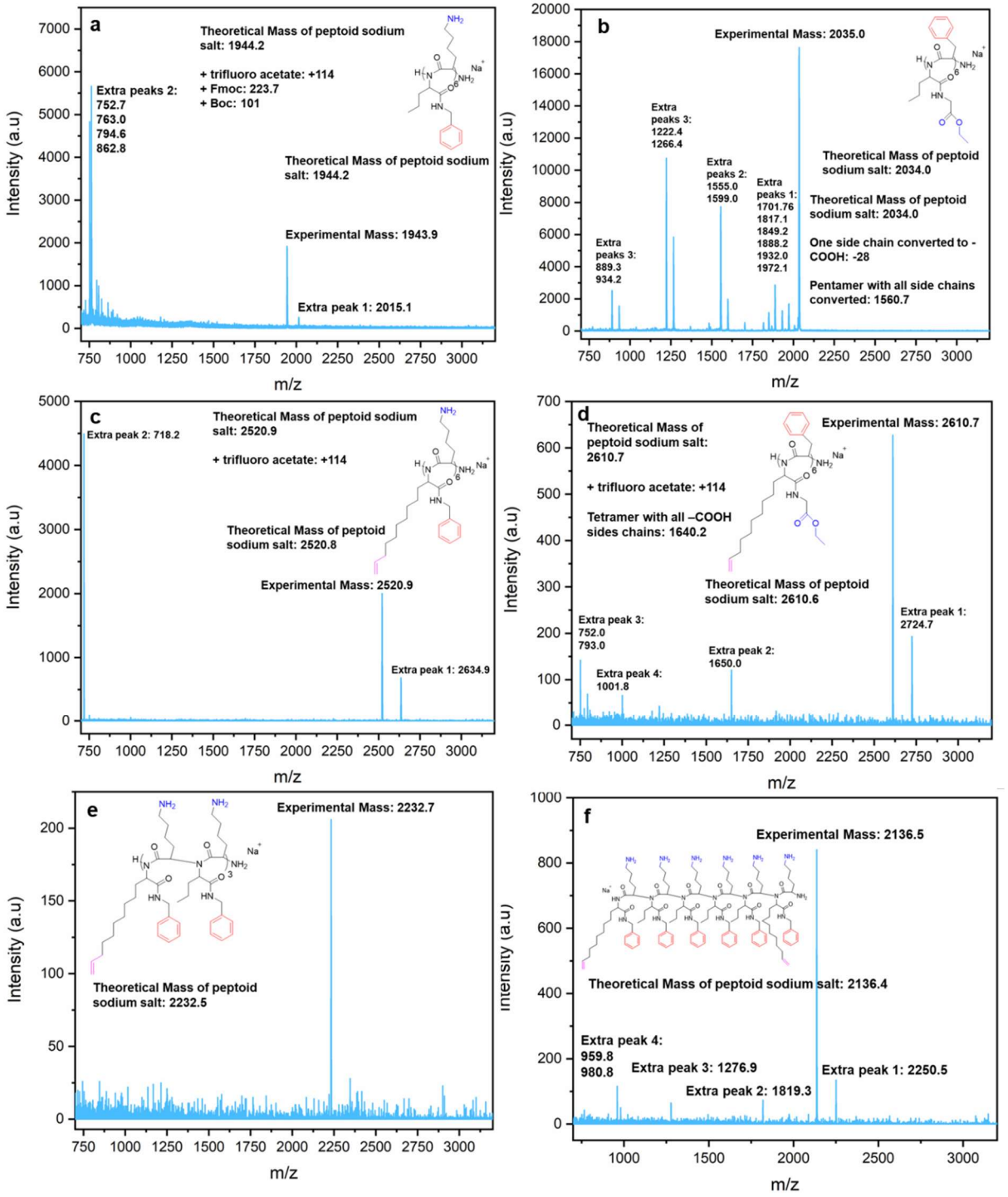


Figure 10. MALDI-ToF analysis of peptoid prepared. Mass of desired structures were found in presence of secondary peaks, indicating side reactions might happened and further purification would be necessary before any investigation on peptoid properties.

MALDI-ToF results suggesting that the desired peptoid structure was found in crude product of corresponding peptoids (**Figure 10, a**) while secondary structures were also found. Most of the secondary peaks were from trifluoroacetate ionised polymer chains or shorter oligomers,

while the former one could be simply removed by redissolve peptoid in water and following with neutralization with base such as sodium carbonate. The existence of shorter oligomers indicating the Ugi coupling might not be 100% completed in some cases, for example the preparation of peptoid 2. (**Figure 10, b**) Possible reasons are steric hindrance affected the chain extension process and thus results in different length of peptoids. In previous sections ethyl isocyanoacetate was shown having a poor performance while preparing step growth polymers, which could be another reason that the Ugi-4CR reaction did not reach full conversion. These peptoid structures should be analysed and purified with analytical HPLC and preparative HPLC before any further investigation on self-assembly or click reaction modification.

5.3 Conclusion and outlook

Step-growth polymers with high bio-sourced mass and sequence defined function-rich peptoids were synthesized via Ugi-4CR reaction. Produced step-growth polymers were shown to have good thermal stability, tuneable glass transition behaviour and functional side chain groups. However, identifying the secondary peak presented in polymers and further increase the size of polymer obtained by optimisation of reaction conditions or using obtained polymer as macromonomer for chain extension with other bio-based monomers should be considered as the next stage study, and ultimately to produce polymers with high bio-sourced mass and high molecular weight for further potential processing and manufacturing. Sequence defined peptoids were also prepared via solid-phase supported Ugi-4-component reaction. These peptoids have high density of functional groups thus would be interesting to either design them as multi-functional centres or investigate the orthogonal modification. The function-rich nature also would assist study on self-assembly of short oligomers. However, proper analysis and purification with analytical HPLC and preparative HPLC system would be required before any further action. These peptoids could be an interesting addition to the current research field of sequence-defined polymers.

5.4 Experimental

5.4.1 Materials and methods

Priamine 1074 (Croda, 99%), Succinic acid (Aldrich, 99%), B%), Butyraldehyde (Aldrich, 98.0%), Benzaldehyde (Aldrich, ≥99%), Vanillin (Aldrich, 99%), Ethyl isocyanoacetate

(Aldrich, 95.0%), Cyclohexyl isocyanide (Aldrich, 98.0%), Cyclopentyl isocyanide (Aldrich, 98.0%), Benzyl isocyanide (Aldrich, 98.0%), 2-Naphthyl isocyanide (Aldrich, 95%), n-Butyl isocyanide (Aldrich, 97%), t-Butyl isocyanide (Aldrich, 98%) were selected as monomers for Ugi-4CR step-growth polymerisation. Rink Amide MBHA resin (100-200 mesh) (Aldrich, 0.78mmol/g), 10-undecenal (Aldrich, ≥95%, FG, stabilized), Fmoc-Lys(Boc)-OH (Aldrich, ≥98%, Novabiochem®), Fmoc-Phe-OH (Aldrich, ≥98%, Novabiochem®), Piperidine (Aldrich, ReagentPlus®, 99%) were used for sequence defined peptoid synthesis.

N,N-Dimethylformamide (DMF, Aldrich), chloroform (Aldrich), dichloromethane (Aldrich), tetrahydrofuran(THF, Aldrich), diethyl ether(Aldrich) and methanol (Aldrich) were used as the solvent for polymerization, precipitation and characterisation. Trifluoro acetic acid (Aldrich, 99%) were used for peptoid cleavage.

5.4.2 Instrumentation

Nuclear Magnetic Resonance (NMR) spectroscopic measurements were performed on 300 or 400 MHz Bruker instruments in 5 mm NMR tubes. Residual solvent signals of $CHCl_3$ (δH = 7.26 ppm, δC =77.2 ppm) was used as reference. Gel permeation chromatography (GPC) measurements were conducted on an Agilent 1260 infinity system operating in THF with 2% TEA and equipped with refractive index detector and variable wavelength detector, 2 PLgel 5 μm mixed-C columns (300 × 7.5 mm), a PLgel 5 mm guard column (50 × 7.5 mm) and an autosampler. The instrument was calibrated with linear narrow PS standards. All samples were filtered through 0.2 μm PTFE filters before analysis. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF MS) was performed on a Bruker Autoflex Speed mass spectrometer using a nitrogen laser delivering 2 ns pulses at 337 nm with positive ion ToF detection performed using an accelerating voltage of 25 kV. The matrix used was trans-2-[3-(4-tertbutylphenyl)-2-methyl-2-propylidene] malonitrile (DCTB) dissolved in THF. Sodium trifluoroacetate used as a cationic agent (solution in acetonitrile). The compound (diluted in THF) was applied after separate loadings of DCTB and sodium trifluoroacetate. Samples were measured in reflective or linear mode and calibrated against poly(methyl methacrylate) standards. Thermalgravimetric analysis (TGA) and differential scanning calorimetry (DSC) was performed on a Mettler Toledo TGA/DSC with a heating rate of 10°C/min under nitrogen. Electrospray ionisation mass spectrometry (ESI-MS) was performed on an Agilent 6130B single Quad mass spectrometry instrument.

5.4.3 General procedures

General procedure of Ugi-4CR polymerisation with P74, SA and different aldehyde and isocyanide candidates.

Priamine 1074 (532mg, 1mmol or any calculated amount, 1 equiv) was weighed into a microwave vial with stirring bar and dissolved in 1 ml of select solven system, like MeOH or MeOH/THF mixture, to give a 1.0M solution. Selected aldehyde (2 equiv) was added to the vial with vigorous stirring applied, and white precipitation was then observed in seconds. The reaction mixture was sealed and allowed to stir at room temperature for 30 minutes to allow the imine formation process to complete thus avoid Passerini reaction as the side reaction. Succinic acid (118mg, 1 equiv) was then added to the reaction mixture, the reaction vial was then heated in an oil bath at 40℃ for 5 minutes or the time when the mixture becomes homogenous. Selected isocyandie (2 equiv) was then added to the reaction mixture. The vial was then resealed and heated with microwave assisted heating for 2 hours or any designed reaction time.

General procedure of solid-phase supported synthesis of peptoids

Resin swelling

Step 1. Rink amide resin (0.5 mmol, 0.78 mmol/g, 641mg) was added into a peptide synthesizer tube. 4ml of DCM was added to the resin to make the resin swell. The tube was put onto a peptide shaker, sealed and shake for 3 minutes, then sit still for 10 minutes.

Fmoc Deprotection of solid phase

Step 2. DCM was removed from swelled resin by applying vacuum to the tube, 4ml DMF was added to the resin, the tube was sealed and shake for 5minutes, DMF was then removed by applying vacuum to the tube.

Step 3. Add DMF to the resin, shake for 3 minutes, remove DMF, repeat 3 times.

Step 4: Add 5ml of DMF/piperidine (4:1) solvent to the resin. Seal the tube, put on shaker and shake for 10 minutes.

Step 5: Remove DMF/piperidine by applying vacuum to the tube. Add 8ml of DMF/piperidine to the resin. Seal the tube, put on shaker and shake for 10 minutes.

Step 6: Remove DMF/piperidine by applying vacuum to the tube Add 8ml of DMF to the resin. Seal the tube and sit still for 5 minutes, put on shaker and shaker for 10 minutes.

Step 7: Remove DMF by applying vacuum, add 5ml DMF to the resin. Seal the tube and put on shaker, shake for 5 minutes, remove DMF, repeat three times.

Step 8: Remove DMF by applying vacuum, add 5ml DCM to the resin, sit still for 5 minutes, put on shaker and shake for 10 minutes, remove DCM. Add 5ml DCM to the tube and repeat three times.

Repeating unit addition

Step 9: Add 5ml $CHCl_3$/MeOH (3:1) mixture to resin, allow it to swell for 10 minutes.

Step 10: Remove $CHCl_3$/MeOH (3:1) mixture by vacuum, add 5ml $CHCl_3$/MeOH (3:1) mixture to the resin. Allow it to swell for 5 minutes. Add aldehyde (1 mmol) to the swelled resin. Seal the tube and shake for 30 minutes for imine formation.

Step 11: Add Fmoc protected amino acid(1mmol) and isocyanide (1mmol) into the system. 1ml $CHCl_3$/MeOH (3:1) mixture can be added to assist the dissolution of amino acid. Seal the tube, put it to the peptide shaker and shake 24 hours to allow the Ugi reaction to take place.

Repeat Fmoc deprotection and repeating unit addition section until desired peptoid length is achieved. It is necessary to notice that one Fmoc deprotection section needs to be done after desired peptoid length is achieved to release the amine end group of peptoid.

Peptoid cleavage and isolation

Step 12: Solid phase loaded with desired peptoid was swelled in 5ml DCM for 5 minutes. The tube was sealed and shake for 10 minutes, DCM was then removed by applying vacuum. Repeat 4 times.

Step 13: Obtained resin was dried by running air through and transferred into a scintillation vial. 5ml of cleavage cocktail (e.g. 95% aqueous TFA) was added to the resin, sit for 1 minutes and then shake for 2 hours.

Step 14: The resin cocktail mixture was filtered and the solid residue was washed with 2ml of cleavage cocktail. The filtered liquid was dried by blowing a gentle air stream through it overnight.

Step 15: Obtained crude oil was dissolved in a 5:5 acetonitrile/water mixture, vortexed to assist the dissolution and freeze dried to obtain either fluffy powder or yellow oil as the crude peptoid.

MALDI ToF analysis of crude peptoid

Solutions of crude peptoid in THF (1mg/ml), *trans*-2-[3-(4-*tert*-Butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) in THF (25mg/ml), and sodium trifluoro acetate in ethanol (0.5mg/ml) were freshly prepared. 1 µl of each solution were mixed in a 1.5ml Eppendorf tube and vortexed for 1 minute. 0.7µl of mixed solution were spotted onto a MTP 384 ground steel MALDI plate and dried for subsequent analysis.

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Chapter 6: Conclusion and outlook

The main goal of this thesis was to investigate the preparation and post-polymerisation modification of functional polymers with click reactions and multicomponent reactions, as these two kinds of reactions are highly efficient, have no or benign by-product and introduce multiple functional linkages or side chain groups, they could be considered as ideal candidates for preparing functional polymers, especially in a step-growth polymerisation manner.

Following the review of previous reports on utilizing click reactions and multicomponent reactions to synthesize functional polymers in **Chapter 1**. Para-fluoro thiol and thiol-bromo click reaction were employed as the candidates to synthesis step-growth polymers with commercially available dithiols and 2,3,4,5,6 pentafluoro benzyl bromide (PFBB) in a dual-click reaction fashion in **Chapter 2**. It was found that the step-growth polymerization can proceed at room temperature while based on the nucleophilicity of dithiol compounds the completion could be reached in 10 minutes. Stoichiometric amount of base activates the synthesis of a linear polymer and milder base allows formation of longer polymer chains. DMF acts as the optimum solvent for the polymerization, although a sequential addition of DMF into a $CHCl_3$ solvent system provides further polymer growth during elongated reaction time. Obtained polymers have a good thermal resistance up to 300℃ and hydrophobic character was measured by water contact angle measurements. These polymers, as synthesized in a highly-efficient manner with commercially available reagent, might have potential in large-scale synthesis to produce polymers for manufacturing. The high-aromatic and fluorinated aromatic content in these polymers also might have potential in the field of conductive polymers. Subsequent studies should be proceed in focus of manufacturing and processing of these polymers.

To further explore the dual-clickable compound PFBB, the benzyl bromide structure was used for the polymerisation of oxazolines in **chapter 3**, where the kinetics study has shown the practicability of using PFBB as a clickable initiator in oxazoline polymerisation, which enriched the library of clickable initiators for poly(oxazoline). The clickable α-end of prepared polymers were exploited, polymers were coupled together using commercially available dithiols as linked to produce diblock, tetrablock and star polymers. Furthermore, by utilizing the highly efficient chain termination process in cationic ring opening polymerisation of poly(oxazoline)s, multiblock poly(oxazoline)s, which is rarely reported, were successfully

synthesized in a one-pot fashion. The whole process can take only 10 minutes in certain cases. Prepared polyoxazolines were shown to be able to self-assemble into nanoparticles which shown in TEM. As the thermal responsiveness of poly(oxazoline)s was a well-known property, by tuning the length of poly(oxazoline) blocks in prepared amphiphilic polymers, or adjusting the hydrophilicity by partially hydrolyse these polyoxazolines, could lead to controlled thermal responsiveness in desired temperature region. This should be the next step for this study if any further investigation would be performed.

Another click reaction, which is only been coined in the last ten years, SuFEx click reaction, was investigated in **Chapter 4**, where a commercially available sulfonyl fluoride containing compound ethenesulfonyl fluoride (ESF) was used initially to prepare bis-sulfonyl fluoride compounds via Michael addition with amines, thiols and hydroxyls. The Michael addition of ESF with amines and thiols were efficient and finish in minutes, while a solvent effect presents in ESF-thiol addition reaction, allowing selective reaction of amine with ESF. However, the step-growth polymerisation did not perform well and give only short polymers. The reason is the dehydrofluorination of α-hydrogens on the methylene group next to sulfonyl fluoride, which was proved by ^{1}H NMR as well as reported by the Sharpless group. The post-polymerisation modification of partially hydrolysed poly(2-ethyl-2-oxazoline) was not successful due to the same reason. However, another sulfonyl fluoride containing compound that does not possess an α-hydrogen, 4-(bromomethyl) benzylsulfonyl fluoride (BBSF), was used for the cationic ring opening polymerisation of 2-ethyl-2-oxazoline and shown successful preparation of SuFEx clickable poly(2-ethyl-2-oxazoline). Naturally, following study will be focusing on utilizing BBSF as the clickable initiator, and prepare various poly(oxazoline)s for possible bio-conjugation studies, and researchers from our research group has already started working on it.

Finally, in **Chapter 5**, the well-known Ugi-4-component reaction has been investigated for its application in synthesis of step-growth polymers and sequence defined polymers. Step-growth polymers with high bio-sourced mass and sequence defined function-rich peptoids were synthesized via Ugi-4CR reaction. Produced step-growth polymers were shown to have good thermal stability, tuneable glass transition behaviour and functional side chain groups. However, identifying the secondary peak presented in polymers and further increase the size of polymer obtained by optimisation of reaction conditions or using obtained polymer as

macromonomer for chain extension with other bio-based monomers should be considered as the next stage study, and ultimately to produce polymers with high bio-sourced mass and high molecular weight for further potential processing and manufacturing. Sequence defined peptoids were also prepared via solid-phase supported Ugi-4-component reaction. These peptoids have high density of functional groups thus would be interesting to either design them as multi-functional centres or investigate the orthogonal modification. The function-rich nature also would assist study on self-assembly of short oligomers. However, proper analysis and purification with analytical HPLC and preparative HPLC system would be required before any further action. These peptoids could be an interesting addition to the current research field of sequence-defined polymers.

As the library of click reactions and multicomponent reactions keeps enlarging, utilizing these reactions to construct novel heteroatom polymer backbones and provide functionality on polymer side chains for desired properties or post-polymerisation modification uses should be an important part of the polymer chemistry field. The reaction efficiency and orthogonality of click reactions would benefit the design and preparation of polymers. In the future where more click reaction and multicomponent reactions were developed, these reactions should be introduced into polymer chemistry immediately to prepare novel functional polymers. Overall, the work presented here would open the avenue for design and preparation of perfluoro aromatic polymers, preparation and post-polymerisation modification of telechelic poly(oxazoline)s, and the preparation of novel sustainable and sequence-controlled polymers. These polymers play important roles in fields like conductive materials, smart drug delivery vehicles, and information storage applications, and the chemistry explored in this thesis should be helpful for designing and developing novel materials in these fields in the future.