ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL OF SCIENCE ENGINEERING AND TECHNOLOGY

TRIPLE CLICK STRATEGY FOR THE PREPARATION OF FUNCTIONALIZED POLY(β-HYDROXYL AMINE)S

M.Sc. THESIS

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Department of Polymer Science and Technology

Polymer Science and Technology Programme

JUNE 2013

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ÜÇLÜ KLİK STRATEJİSİ İLE FONKSİYONLANDIRILMIŞ POLİ(β-HİDROKSİL AMİN)LERİN SENTEZİ

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To my family and my friends,

FOREWORD

This master study has been carried out at Istanbul Technical University, Polymer Science & Technology Programme.

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ABBREVIATIONS

$CDCl_3$	**:** Deuterated chloroform
CH_2Cl_2	**:** Dichloromethane
CuAAC	**:** Copper catalyzed azide-alkyne cycloaddition
DA	**:** Diels-Alder
DCC	**:** *N*,*N*'-dicyclohexylcarbodiimide
DMAP	**:** 4-dimethylaminopyridine
DMF	**:** *N*,*N*-dimehthylformamide
GPC	**:** Gel Permation Chromatography
^{1}H NMR	**:** Hydrogen Nuclear Magnetic Resonance Spectroscopy
PDI	**:** Polydispersity Index
PMDETA	**:** *N, N, N',N'', N''*-Pentamethyldiethylenetriamine
Et_3N	**:** Triethylamine
TEMPO	**:** 2,2,6,6-Tetramethylpiperidine-*N*-oxyl
THF	**:** Tetrahydrofuran

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TRIPLE CLICK STRATEGY FOR THE PREPARATION OF FUNCTIONALIZED POLY(β-HYDROXYL AMINE)S

SUMMARY

Efficient and ambient synthesis of functional macromolecules from readily available starting materials has been a significant goal of polymer chemistry. To meet this challenge, the concept of utilizing robust, efficient, and orthogonal (REO) chemical reactions is particularly attractive. In this approach, high yielding chemical reactions that can be carried out under ambient conditions and proceed with high regioselectivity, functional group tolerance, and atom economy are employed. The tolerance and compatibility of these reactions with a variety of functional groups and reaction conditions are an important aspect of the REO concept. This feature can be exploited for facile preparation of multifunctional structures by avoiding the typical functional group protection/deprotection strategies.

In our scheme, the amine−epoxy "click" reaction between a propargylamine and a diglycidyl ether is employed as the polymerization reaction. This process offers many advantages: (i) the polymerization reaction proceeds at room temperature under solvent-less conditions and in the presence of moisture and air; (ii) the process does not require any catalyst/reagent, and hence, simple mixing of the two monomers is needed; (iii) the coupling reaction unmasks a reactive hydroxyl group that is available for further functionalization; (iv) another reactive site is created upon polymerization in the form of tertiary amines that can be transformed into positively charged quaternary structures by protonation/alkylation; (v) a number of amines and epoxides are commercially available, inexpensive, and often in the list of common laboratory chemicals; and (vi) the amine−epoxy coupling process is tolerant to various reactive groups and functionalities such as alkynes and nonconjugated olefins.

The polymerization was carried out at room temperature and under solvent-less conditions. Mechanical stirring of the reactions was deemed necessary due to high viscosity of the polymerization mixture. In this way, a polyaddition reaction between monomers afforded alkyne and hydroxyl-substituted polymer. These polymers represent a novel family of main-chain cationic polymers and are named as poly(β-hydroxyl amine)s.

A simple esterification reaction were done to generate bromine functionalities at the side chain of polymer. TEMPO and Azide functional compounds were clicked to the polymer via Copper (I)-catalyzed azide-alkyne cycloaddition (CuAAC) and Nitroxide radical coupling NRC reactions in one-pot fashion to generate functionalized Poly(β-hydroxyl amine)s.

The polymers were characterized by ^{1}H-NMR and GPC.

ÜÇLÜ KLİK STRATEJİSİ İLE FONKSİYONLANDIRILMIŞ POLİ(β-HİDROKSİ AMİN)LERİN SENTEZİ

ÖZET

Hazırda bulunabilen başlangıç maddeleriyle verimli ve çevreye uyumlu işlevsel makromoleküller sentezlemek polimer kimyasının önemli bir amacı olmuştur. Bu amaca ulaşmak için; dayanıklı, verimli ve ortagonal (REO) reaksiyonlar özellikle tercih edilir. Bu reaksiyonların çeşitli işlevsel gruplarla ve reaksiyon koşullarına olan toleransı ve uyumu REO konsepti için önemlidir. Bu durumdan çoklu işlevsellikteki yapıların akıcı hazırlanmasıyla, tipik işlevsellikteki grup koruma/korumama stratejilerinden kaçınmak için faydalanılabilinir.

Polimerler sentez yöntemlerine göre kondensasyon (kademeli) ve katılma polimerleri olarak ikiye ayrılırlar. Kondenzasyon polimerleri en az iki fonksiyonlu grup (-COOH, -NH_2, -OH) içeren monomerlerin aralarından küçük bir molekülün (H_2O, HCl, NH_3 gibi) ayrılmasıyla oluşurlar. Kondenzasyon polimerizasyonunda iki ya da daha çok fonksiyonel grup bulunduran moleküller arasından küçük bir molekül ayrılmasıyla önce dimer oluşturur. Sonra trimer, tetramer şeklinde zamanla bağlanan birim sayısı ve dolayısıyla mol kütlesi artar. Bu polimerizasyonda monomerik maddelerin birden çok fonksiyonlu grup içermesi gerekir. Katılma polimerleri ise serbest radikal, anyonik, katyonik, koordinasyon polimerleşmesi ile elde edilebilirler. Bu reaksiyonlarda oluşan polimerin temel molekülünün kaba formülü ile monomerin kaba formülü aynıdır

"Click" kimyası 2001 yılında Sharpless tarafından ortaya atılan ve moleküllerin birbirlerine seçici ve hızlı bir şekilde bağlanmasını ve yüksek miktarda ürün elde edilmesini sağlayan reaksiyonları ifade eder. "Click" kimyasında reaksiyon için gereklilikleri karşılamak zor olsa da, birçok "click" prosesi keşfedildi.

• Nükleofilik halka açılma reaksiyonu

• Aldolsüz karbonil kimyası

• Karbon karbon çoklu bağına katılmalar

• Siklik katılma reaksiyonları

Sharpless ve çalışma arkadaşları tarafından ortaya çıkarılan Click Kimyası yüksek oranda ürün eldesi, fonksiyonel gruplara karşı olan toleransları ve seçiciliği ile önemli bir yere sahiptir. Cu(I) katalizli Huisgen 1,3-dipolar siklik katılması da terminal alken ve alkil azid arasında baz katalizörlü oda sıcaklığında gerçekleşen bir reaksiyondur. Bu reaksiyon molekülleri birbirine bağlamada kullanılabilir. Diels-Alder reaksiyonları ise konjuge bir dien ile dienofil bileşiğinin siklo katılması olarak bilinir.

Günümüzde, "click kimyası" terimi altında sınıflandırılan Diels-Alder (DA) ve bakır katalizli azid-alkin siklokatılma (CuAAC) tepkimeleri blok kopolimerlerden karmaşık makromoleküler yapılara kadar değişen birçok polimerik malzemenin

sentezinde başarılı bir şekilde uygulandı ve blok, aşı ve yıldız polimerlerin eldelerinde güçlü bir alternatif yöntem olarak ortaya çıktı.

Buna ek olarak , yine "click kimyası" terimi altında sınıflandırılan nitroksit radikal birleşme reaksiyonları (NRC), moleküllerin birbirlerine seçici ve hızlı bir şekilde bağlanmasını sağlamak amacıyla molekül uçlarında TEMPO ve türevlerinin kullanıldığı bir tepkimedir. ATNRC tepkimesi; farklı topolojilere uygulanabilirliği ve yüksek verimlilikleri nedeniyle iyi tanımlanmış polimerlerin sentezi için potansiyel bir "click" reaksiyonu olarak nitelendirilir. TEMPO uç grubu taşıyan polimer malzemeleri ışık, şok ve ısı değişikliklerine daha az duyarlı olduklarından, azid uç grubu taşıyan polimerlere göre daha kararlıdırlar.

Klik reaksiyonları terminal asetilenler ve azidler arasında gerçekleşen reaksiyonlardır. Klik reaksiyonlarının tercih edilir olmalarının sebepleri arasında; makul reaksiyon koşullarında gerçekleştirilebilmeleri, yüksek verim alınabilmesi, yüksek seçicilik ile gerçekleşmeleri, fonksiyonel grup çeşitliliğine olanak sağlamaları, kısa reaksiyon sürelerine sahip olmaları ve kullanılan çözücülere karşı hassas olmamaları gösterilebilir. Klik reaksiyonlarının uygulama alanları kullanılacak polimer tiplerine bağlı olarak çeşitlendirilebilir.

Bu tez çalışmasında, polikondenzasyon ile klik kimyası yöntemleri kullanılmıştır. Poly(β-hydroxyl amine), brom ve alkin fonksiyonlu polimer, CuAAC ve NRC yöntemleriyle fonksiyonlandırılmış polimer sentezlenmiştir. Bu kopolimerler, üçüncü ve dördüncü bölümlerde ayrıntılı anlatılacaktır.

İlk bölümde, propargilamin ve diglisidil eter arasındaki amin-epoksi klik reaksiyonu, polimerizasyon reaksiyonu olarak kullanılmıştır. Bu yöntem bir çok avantaj sağlamaktadır:

(i) polimerizasyon solventsiz ve oda şartlarında gerçekleşmektedir;
(ii) bu yöntemde katalizöre/reaktife ihtiyaç yoktur bundan dolayı iki monomerin basitçe karıştırılması yeterlidir;
(iii) ileri fonksiyonlandırmaya uygun aktif hidroksil grupları bağlanma reaksiyonu sayesinde ortaya çıkar;
(iv) bir diğer reaktif merkez tersiyer aminlerin polimerizasyonuyla elde edilir. Bunlar protonlama/alkilleme ile pozitif yüklü kuarternize yapılara dönüşür.
(v) çok sayıda amin ve epoksiler ticari olarak mevcut, ucuz ve genellikle bütün laboratuvar kimyasallarında vardır;
(vi) amin epoksi bağlanma süreci, aktif gruplara ve alkinlere ve konjuge olmamış olefinlere karşı toleranslıdır.

Polimerizasyon; oda sıcaklığında, solvent kullanılmayan koşullarda gerçekleştirilmiştir. Polimerizasyon esnasında karışımın yüksek viskozitesinden dolayı reaksiyonlarda mekanik karıştırıcı kullanılması zorunlu ve gereklidir. Bu yol ile ilk olarak monomerler arasındaki poliadisyon reaksiyonu sayesinde alkin ve hidroksil fonksiyonlu polimer elde edilir. Poli(β-hidroksil amin)ler olarak anılan bu polimerler ana zincir katyonik polimer ailesini temsil etmektedir.

İkinci aşamada polimer yan zincirinde brom fonksiyonları oluşturmak için basit esterleşme reaksiyonu yapılmıştır. Brom ve alkin fonksiyonlu polimer elde edilmiştir.

Son olarak da brom ve alkin fonksiyonlu polimerden bakır katalizli azid alkin siklo katılma (CuAAC) ve nitroksit radikal birleşme (NRC) reaksiyonlarıyla TEMPO ve

azit fonksiyonlu Pol(β-hidroksil amin)leri oluşturmak için one-pot sentezi klik reaksiyonları ile kopolimerleri sentezleri gerçekleşmiştir.

Sonuç polimerlerinin karakterizasyonları başarılı bir şekilde gerçekleştirilmiştir. Kopolimerler prosedürlere uygun bir şekilde başarılı olarak sentezlenmiştir. Sentezlenen polimerlerinin Hidrojen Nükleer Magnetik Rezonans Spektroskopisi (^{1}H NMR) ve Jel Geçirgenlik Kromatografisi (GPC) analizleri tartışma ve sonuç bölümünde ayrıntılı bir şekilde anlatılacak, her maddenin sentezlenme prosedürü ayrıntı ile verilecek ve hazırlanma aşamaları detaylı olarak anlatılacaktır.

1. INTRODUCTION

A defining aspect of polymer science is the efficient construction of materials with useful properties from readily available starting materials. Efficient and ambient synthesis of functional macromolecules from readily available starting materials has been a significant goal of polymer chemistry [1,2]. To overcome this difficulty, the concept of utilizing robust, efficient, and orthogonal (REO) chemical reactions is particularly attractive [2,3]. Advances in modern polymerization techniques have allowed access to an ever-increasing array of synthetic polymers and polymeric architectures. However, increasingly complex materials require additional reactions that, for example, can assemble simple preformed polymers into intricate structures that cannot otherwise be constructed. To enable such transformations, there is a need for robust, efficient, and orthogonal (REO) chemical reactions that can meet the high demands of polymer construction and side chain modification [7].

The tolerance and compatibility of these reactions with a variety of functional groups and reaction conditions are an important aspect of the REO concept. This feature can be exploited for facile preparation of multifunctional structures by avoiding the typical functional group protection/deprotection strategies.

The amine−epoxy "click" reaction between a propargylamine and a diglycidyl ether is employed as the polymerization reaction [6]. The choice of epoxy–amine chemistry was governed by two factors: the efficiency of reaction and potential for orthogonality. "Epoxy–amine" coupling possesses many of the attributes of a click reaction. The reaction is highly efficient, can proceed at room temperature in the absence of a catalyst and tolerates a number of functional groups. Importantly for the synthesis of internally functionalized dendrimers, ring opening of the epoxy group leads to the formation of a secondary alcohol. This secondary alcohol can serve as a point of attachment for various kinds of functionalities, while at the same time being orthogonal to subsequent epoxy–amine reactions. The orthogonality and high efficiency of the 'epoxy–amine' reaction results in a lack of byproducts which

allows the dendrimers to be purified by simple precipitation methods with yields greater than 90% [8].

The polymerization was carried out at room temperature, and under solvent-less conditions. Mechanical stirring of the reactions was deemd necessary due to high viscosity of the polymerization mixture. In this way, a polyaddition reaction between monomers afforded alkyne and hydroxyl-substituted polymer. These polymers represent a novel family of main-chain cationic polymers and are named as poly(β-hydroxyl amine)s. Direct functional group manipulations on the prepared poly(β-hydroxyl amine)s give rise to desired multifunctional (2−4 functional sites) structures.

Poly(β-hydroxyl amine) was obtained and a simple esterification reaction were done to generate bromine functionalities at the side chain of polymer. After this reaction copper-catalyzed azide–alkyne cycloaddition (CuAAC) and nitroxide radical coupling (NRC), have been employed extensively as REO processes. Nitroxide radical coupling (NRC) is a reaction in which TEMPO derivatives are used to end-cap polymer chains. NRC also falls under the category of "click" chemistry. When compared with azide group, TEMPO group is less sensitive to light, shock, and thermal changes, which makes the polymer materials stable. TEMPO and Azide functional compounds were clicked to the polymer via azide-alkyne and NRC reactions in one-pot fashion to generate functionalized Poly(β-hydroxyl amine)s.

The polymers were characterized by ^{1}H-NMR and GPC.

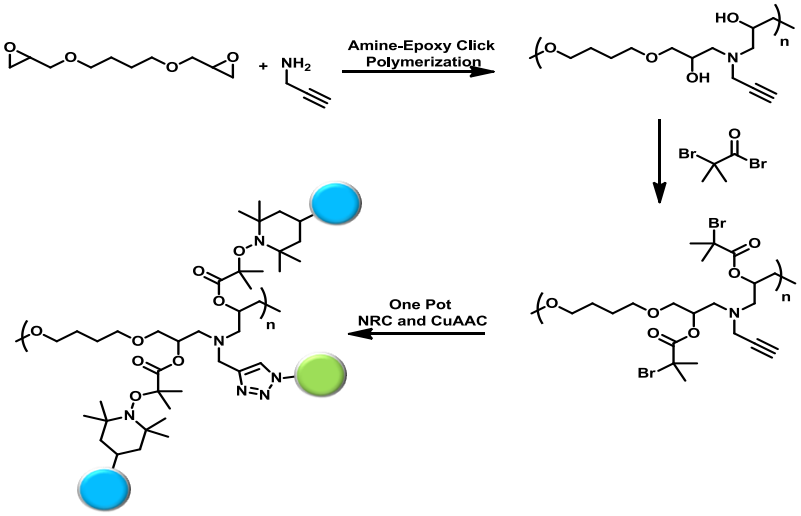


Figure 1.1 : The synthetic pathway for functionalized Poly(β-hydroxylamine)s.

2. THEORETICAL PART

2.1 Condensation Polymerization

2.1.1 Introduction and historical perspective

The application of step-growth polymers could not have achieved such significance without an understanding of the synthetic principles that enable controlled and predictable morphological and mechanical properties of polymers. One unique advantage of step-growth polymerization is the ability to tailor the monomer choice, which directly affects the polymer backbone unlike many conventional free-radical polymers that have a nonfunctional hydrocarbon backbone. The development of novel monomers reenergized research interests and provided a new molecular handle to combine, centered on the fundamental understanding of structure–property–morphology relationships to improve and tailor polymer performance. The ability to design the polymer backbone allows for control of mechanical, thermal, and flexibility of the polymer chain. In addition, multifunctional monomers can be designed to create diverse polymer topology. The understanding of polymer chemical composition and topology promotes morphology control, which relates to various desirable polymer properties such as enhanced mechanical and thermal properties. Polymer research has engaged in an increasing interest toward creating sophisticated, versatile, and multifunctional polymers, which offer 'smart' capabilities such as dynamic assembly, stimuli-responsive, self-healing, and remendable properties.

In addition to creating polymers with tailored physical properties, polymer scientists are becoming increasingly aware of their contribution and responsibility to ameliorate environmental issues. Because step-growth polymers have expanded into various disciplines, global issues, such as diminishing natural resources, human disease, energy crisis, water purification, and climate change, have all been unavoidable concerns which polymer chemists and engineers have been trying to solve. Thus, many of the research efforts have been redirected to some of the first polycondensation polymers that Wallace Carothers studied in 1929, that is, polyesters [9,10]. The revival of polyester synthesis interest stems mainly from the

need to transition away from petroleum-derived monomers and toward renewable resources. In addition, green chemistry promotes research in novel synthetic approaches such as enzyme catalysis, solvent-free, and no by-product polymerizations. The hydrolytically labile ester linkage allows polyesters to find applications not only in recyclable packaging, but also in biodegradable drug delivery devices and biomaterials.

2.1.2 Synthetic principles

Step-growth polymerization involves the reaction of two reactive functional groups to form a new single functional group. For example, an addition–elimination reaction between two monomers, a dicarboxylic acid and a diol, creates a dimer of the two monomers chemically linked through a new ester bond and elimination of the condensate, water. Stepwise reaction of the dimers with subsequent monomers or dimers produces trimers and tetramers, respectively. Because of the sequence of monomer addition, monomers within the reaction are rapidly consumed during the initial stages of the reaction. However, high molecular weight is not initially obtained. The production or absence of a by-product condensate further defines two subclasses of polymers: polycondensation and polyaddition. Polycondensation produces polymers through the elimination of a small-molecule by-product such as hydrochloric acid, water, methanol, acetic acid, and others. Thus, synthesis of step-growth polymers using this approach depends largely on the removal of the condensate in order to drive equilibrium-based polymerization processes toward high molecular weight polymers. On the other hand, polyaddition proceeds without the formation of by-products. Typically, polyaddition requires highly reactive end groups or catalysts to synthesize polymers. Traditional examples of poly-addition polymers are polyurethanes (PUs) and epoxide curing; however, novel click polymers and ionenes are emerging as new modern classes of polyaddition step-growth polymers.

Due to high conversion of monomer requirement for sufficient molecular weight, synthesis of polymers using step-growth polymerization demands reactions that are quantitative. For this reason, synthetic considerations are required to achieve linear high molecular weight linear polymers:

1. high monomer conversion (> 99.9%);
2. difunctional monomers (f =2);

3. monomer stoichiometry of A:B = 1:1;
4. elimination of side reactions such as degradation or cyclization;
5. accessibility of end groups;
6. high monomer purity.

These conditions are required to achieve high molecular weight linear polymers.

Variations of monomer functionality as well as monomer composition afford polymers with tailored performance. Unlike chain-growth polymerization which contains a hydrocarbon polymer backbone, step-growth polymers incorporate the added advantage of a tailorable polymer backbone composition. Design of novel step-growth polymers often involves the synthesis of novel monomers. Typical limitations of commercial step-growth polymerization arise from the lack of available monomers and the cost of manufacturing the appropriate monomers for desired polymer properties.

Step-growth polymerization demands specific reaction considerations to ensure high molecular weight polymers. The reactivity of end groups becomes critical to achieve high molecular weight for optimal properties. In addition to the reactivity of the end group, the concentration and accessibility of the end groups also affect the reaction rate. The species within the polymerization will transition from high monomer and end group concentrations to oligomers and lower concentrations of end groups. This change in reactive species will inherently alter the kinetics of polymerization. Changes in reaction polarity, volume, and viscosity ultimately impact the reaction [11]. As the polymerization reaches high conversions, the viscosity will increase dramatically and limit the mobility of the polymer end groups, and thus their statistical likelihood of reactions.

Some step-growth polymerizations proceed through an equilibrium reaction. The forward reaction promotes the growth of the polymer chain, and the reverse reaction encourages depolymerization. As the reaction toward polymers occurs, there is an inherent equilibrium-driven reverse reaction. Depending on the reaction, the removal of the condensate can drive the reaction forward. In addition, long reaction times are often required because high extent of conversion is necessary for high molecular weight polymers. Thus, many step-growth reactions require the aid of catalysts.

One of the fundamental problems facing polymer chemists today and throughout history is to understand and predict how structural changes will impact the physical, mechanical, chemical, and thermal properties of polymers. This is no simple task due to different aspects of a polymer's structure which play a significant role in deciding its ultimate properties. For example, polymers comprised of identical repeating unit will display dramatic differences in properties based on its molecular weight, topology, morphology, and thermal history. As expected, differences in chemical structure determine polymer properties. For example, nylon-6,6 exhibits dramatically different properties than the polyester formed from reacting 1,6-hexane diol with adipic acid. The only structural difference exists in the linkages between the repeating units, amides in the case of polyamides and esters in the case of polyesters. This minor structural difference contributes to significant variations in the physical properties of the two polymers. Understanding these differences and intelligently utilizing these molecular properties to design polymers with tailorable bulk properties is a challenge that the polymer chemistry community continues to address. Many recent advances in understanding of structure–property relationships within step-growth polymers will be discussed herein, but many unsolved challenges remain.

2.1.3 Molecular weight control

Molecular weight is arguably the single most important polymer parameter. Low molecular weight polymers have lower tensile strength, impact strength, toughness, and mechanical strength than their high molecular weight counterparts. As such, an understanding and control of molecular weight is crucial in the synthesis and development of step-growth polymers. Fortunately, a theoretical approach exists for predicting molecular weight for linear step-growth polymerizations as a function of conversions [12].

2.1.4 Synthesis of step-growth polymers

Step-growth polymerization occurs in 'steps' to form new chemical bonds.. There are two types of step-growth polymerization processes: polycondensation and polyaddition. Both classes of polymerizations proceed in the same fashion of monomer to dimer to tetramer and high molecular weight polymer. The differences in the two classes of step-growth polymers as well as examples of these polymers are described in the following sections.

2.1.5 Polycondensation polymers

Polycondensation polymers are a class of step-growth polymers in which the formation of a new functional group results in the elimination of a small-molecule by-product. Classical examples of polycondensation polymers include polyesters, polyamides, polyimides, and poly(arylene ethers) (PAEs). These polymers utilize organic reactions such as addition– elimination chemistry to afford polymers with specific functional linkages. The resulting polymer linkages provide properties such as hydrolyzability, hydrogen-bonding interactions, and dipolar interactions. Careful monomer selection and polymer topology further tailor the mechanical properties of these polymers. The immense amount of established research demonstrates the expanding impact of polycondensation polymers in commercial industry.

2.1.6 Polyaddition

Polycondensation polymers are a class of step-growth polymers in which the formation of a new functional group results in the elimination of a small-molecule by-product. Classical examples of polycondensation polymers include polyesters, polyamides, polyimides, and poly(arylene ethers) (PAEs). These polymers utilize organic reactions such as addition– elimination chemistry to afford polymers with specific functional linkages. The resulting polymer linkages provide properties such as hydrolyzability, hydrogen-bonding interactions, and dipolar interactions. Careful monomer selection and polymer topology further tailor the mechanical properties of these polymers. The immense amount of established research demonstrates the expanding impact of polycondensation polymers in commercial industry.

2.1.7 New Strategies for step-growth polymers

In the previous sections, the discussion has primarily revolved around many of the ‘classical’ step-growth polymers and synthetic techniques. Some of the most exciting work performed in the last decade on polycondensations and polyadditions has been in nontraditional step-growth polymers. A recurring theme in these new synthetic techniques is to utilize high-yielding and highly specific organic reactions to synthesize novel step-growth polymerizations. In many cases, orthogonal reactions are elicited to improve the reaction efficiency and expand the available functional groups in a polymer system [13,14,15]. Orthogonal reactions are defined as ‘a set of completely independent classes of protecting groups… [in which] each class of

groups can be removed in any order and in the presence of all other classes'[16]. These highly specific reactions introduce an array of functional groups available for step-growth polymerizations that were previously unachievable. In many cases, these methods utilize functional groups that are not typically considered traditional step-growth functional groups. The principles of 'standard' step-growth polymerization methodologies, nevertheless, provide a foundation to discover new polymeric architectures using nontraditional step-growth polymerization.

2.2 Click Chemistry

The term "click chemistry" concept encompasses a wide range of highly efficient and specific organic reactions that can be conducted in a range of environments (Figure 2.1). Click reactions are characterized by being modular, wide in scope, giving very high yields, generating only inoffensive byproducts that are capable of removal by nonchromatographic methods, and contain regiospecificity. The chemical process must include simple reaction conditions, readily available starting materials, the use of without solvent or a benign solvent, simple product isolation, and a thermodynamic driving force of at least 20 kcal/mol [17]. The click reactions commonly include to form a carbon-heteroatom bond such as: *nucleophilic substitution chemistry* - especially ring opening reactions of strained heterocyclics such as epoxides, aziridines, aziridinium ions, and episulfonium ions; *nonaldol carbonyl chemistry* – formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones, and amides; *additions to carbon-carbon multiple bonds* – epoxidation, dihydroxylation, aziridination, sulfenyl halide addition, and Michael additions; *cycloadditions of unsaturated species* – 1,3-dipolar cycloaddition reactions, and Diels-Alder type reactions. These reactions have been employed for many years to bring about a range of chemical transformations. But nowadays Cu(I) catalyzed azide–alkyne cycloaddition, Diels–Alder cycloaddition and the thiol-ene reaction receive particular attention as they are easy and elegant synthetic approaches to the coupling of chemical compounds.

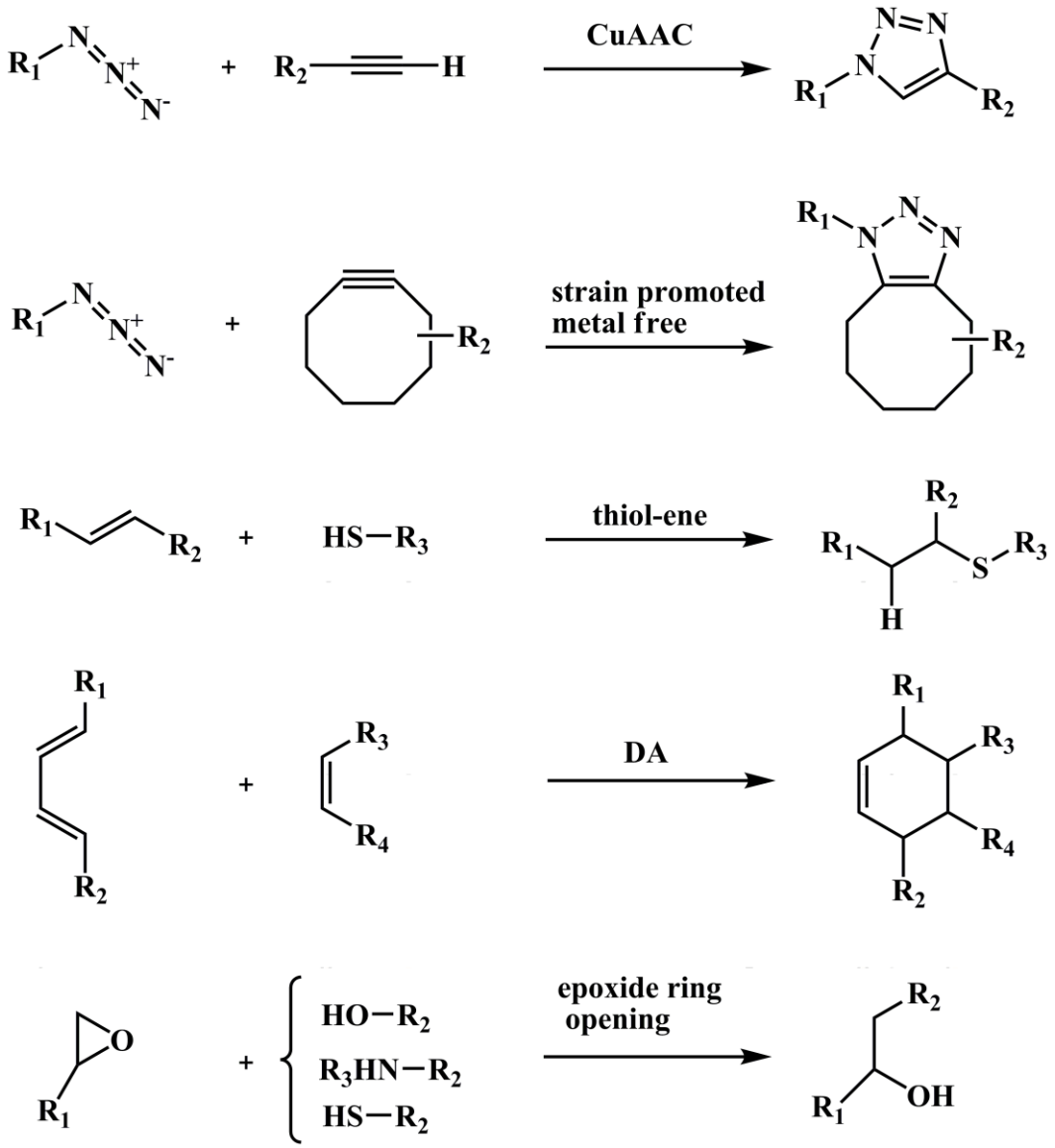


Figure 2.1 : General representation of click reactions cell [17].

2.2.1 Diels-alder click reaction (DA)

The Diels-Alder (DA) reaction is a concerted [4π+2π] cycloaddition reaction of a conjugated diene and a dienophile, which [18-19] has been one of the best methods for the preparation of six-membered carbocycles. The typical [4+2]-cycloaddition condenses a diene moiety onto an alkene or alkyne system (dienophile) to afford a cyclohexene or cyclohexadiene derivative. The Diels-Alder reaction's name comes form Professor Otto Diels [20] and his student, Kurt Alder [21]. DA reaction was arising from the reaction of cyclopentadiene with quinone denotes a historic event in the field of chemistry [18].

According to the Woodward-Hoffmann rules, the concerted suprafacial [π4s + π2s] cycloaddition of a diene and a dienophile is thermally allowed. The theory predicts

that the rate and regioselectivity of cycloadditions are controlled by either the HOMO of the diene and the LUMO of the dienophile in the normal Diels-Alder and by the HOMO of the dienophile and the LUMO of the diene in the inverse electron-demand Diels-Alder [22]. In Diels-Alder reactions, the stereoselectivity is generally high due to the "*cis* principle", which states that Diels-Alder reactions require a cisoid conformation for the diene and suprafacial-suprafacial mode of reaction, meaning that both ends of the diene attack from the same face of the dienophile in a *syn* fashion. The Diels-Alder addition of dienophiles to dienes quite often gives the *endo* adducts [23,24]. This is the "*endo* rule", first proposed by Alder and Stein [25]. The "*endo* rule" is usually rationalized as a result of the principle of "maximum accumulation of unsaturation" (Figure 2.2).

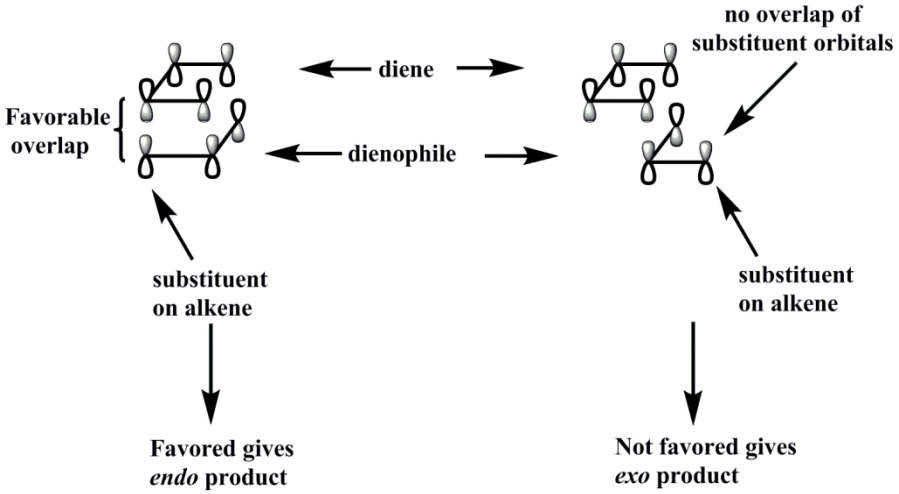
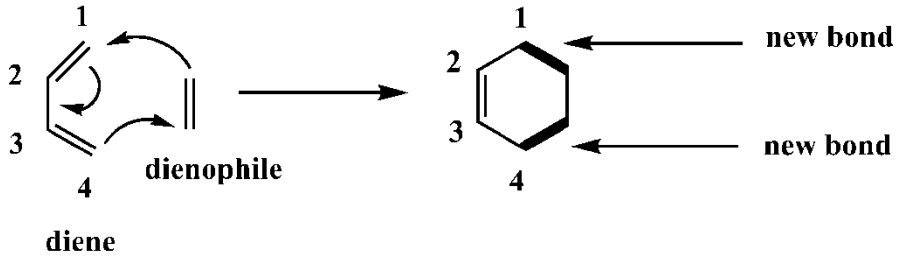


Figure 2.2 : *Endo* and *exo* steroselectivity of Diels–Alder Reactions

The polarizability of the diene and dienophile creates dispersive forces making the *endo* transition state more stable than the *exo* transition state. Secondary orbital overlaps are possible, leading to secondary binding forces that stabilize this transition state [26-27]. Solvents other than water have little effect on the *endo* selectivity [28-29]. Diels-Alder reaction possess characteristics of click techniques like being specific, atom-economical, and highly efficient. This reaction has been employed in organic chemistry for many years, but its increased use in the area of macromolecular structures has led to the emergence of click chemistry concepts. In contrast to the majority of click reactions that create carbon-heteroatom bonds formation, traditional Diels-Alder reactions form new carbon-carbon bond between dienes and electron-deficient dienophiles (2.1).

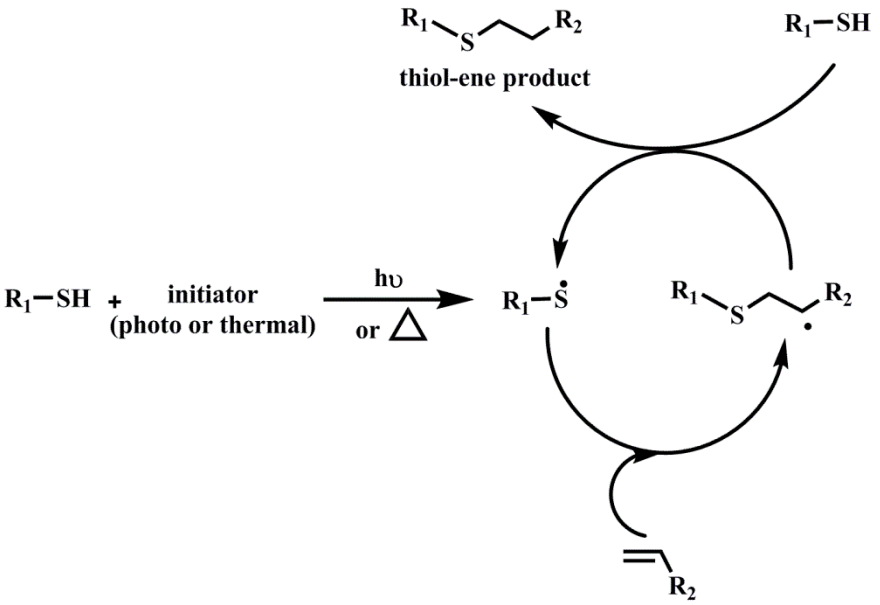


(2.1)

2.2.2 Thiol-ene reaction

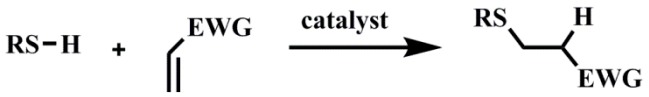
The thiol-ene reaction, well-known for over 100 years, [30] is, simply, the hydrothiolation of a C=C bond (reaction 2.3). Hoyle and Bowman groups have been most widely employed this method for preparing near-perfect networks and films which is arguably the latest and newest attempts in polymer/materials fields [31]. The click status of this reaction is due to its highly efficient and orthogonal character to a wide range of functional groups, as well as for being compatible with water and oxygen. The thioether linkage, formed after thiol-ene reaction shows greater stability to a wide range of chemical environments, such as strong acid and basic media as well as oxidizing and reducing conditions.

Generally, the thiol-ene reaction has been conducted under radical conditions, photochemically and thermally induced [30-32]. Under such conditions, it proceeds via a typical chain process with initiation, propagation and termination steps. Initiation involves the treatment of a thiol with an initiator, under irradiation or heat, resulting in the formation of a thiyl radical, $RS^{\cdot}$, plus other by products (reaction 2.2). Simple thermallysis of the S–H bond can also be employed as a means of generating thiyl radicals. Propagation is a two step process involving first the direct addition of the thiyl radical across the C=C bond yielding an intermediate carbon-centred radical followed by chain transfer to a second molecule of thiol to give the thiol-ene addition product, with anti-Markovnikov orientation, with the concomitant generation of a new thiyl radical. Possible termination reactions involve typical radical–radical coupling processes.



(2.2)

In addition to the radical mediated thiol-ene reactions, hydrothiolations can be readily accomplished under mild base or nucleophilic catalysis such as NEt_3, primary/secondary amines or certain phosphines [33]. Such reactions are slightly less versatile than the radical-mediated thiol-ene reaction since to be effective the C=C must be activated, *i.e.* electron deficient (reaction 2.3).



(2.3)

EWG (Electron Withdrawing Group) = ester, amide, cyano

Figure 2.3 shows some examples of suitable activated ene substrates, and includes (meth)acrylates, fumarate esters and maleimide derivatives.

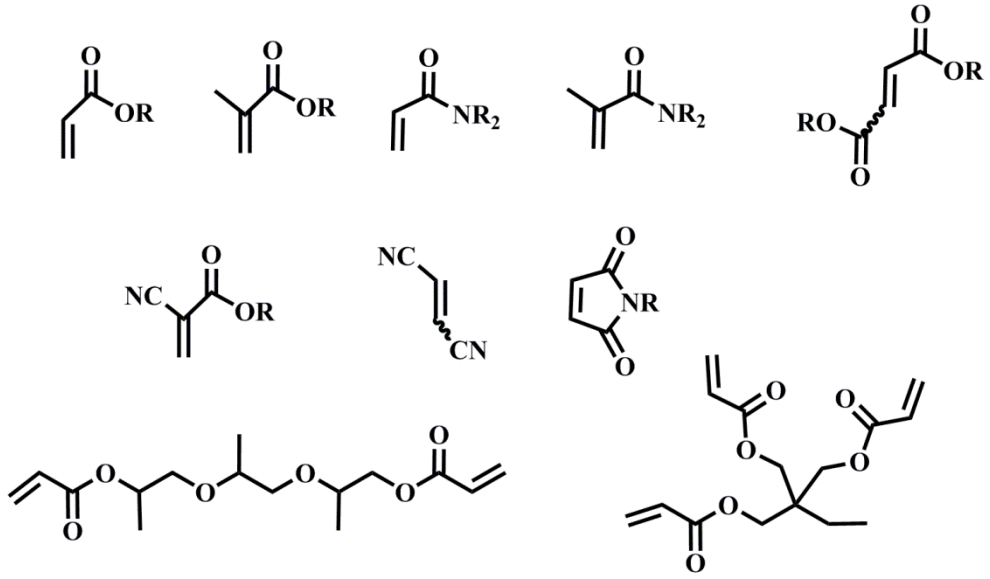
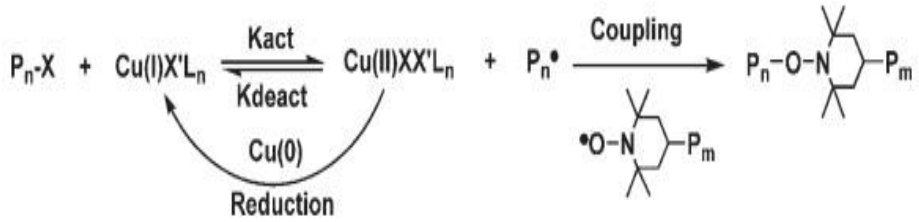


Figure 2.3: Examples of activated substrates susceptible to hydrothiolation via a base/nucleophile-mediated process

Maleimides are common activated substrates for such thiol-ene reactions and deserve a special comment. Due to the presence of two activating carbonyl groups in a *cis*-conformation coupled with ring-strain/bond angle distortion, the C=C bond in maleimides is especially reactive and as such, thiol-ene reactions occur extremely rapidly. Indeed, the high efficiency of these reactions is evident from their widespread use as a bioconjugation tool [34-35].

2.2.3 Nitroxide radical coupling click

A new reversible coupling strategy termed atom transfer nitroxide radical coupling (ATNRC) [36-37] has the attributes of a "click" reaction. In which the bromine end-functional group of one polymer served as oxidant is reduced to bromine anion and carbon radical is formed. The Cu^{1+} is oxidized to Cu^{2+} in the presence of CuBr/ ligand. Then polymeric radical is immediately captured by another 2,2,6,6-tetramethyl-piperidinyl-1-oxy (TEMPO) end-functional polymer, and alkoxyamine is formed between the two polymers [38] (2.4). In ATNRC reaction, CuBr participated in the reaction was served as reactant and its action was quite different from the ATRP. If some Cu(0) was added, the Cu(0) would react with the formed Cu^{2+} and the Cu^{+} was regenerated, which promoted the reaction completely. Thus, under the ATNRC conditions (such as the Cu(0)/CuBr/PMDETA system), the graft, [39] the star-shaped, [40] and the linear copolymer [41] were prepared successfully with high efficiency.



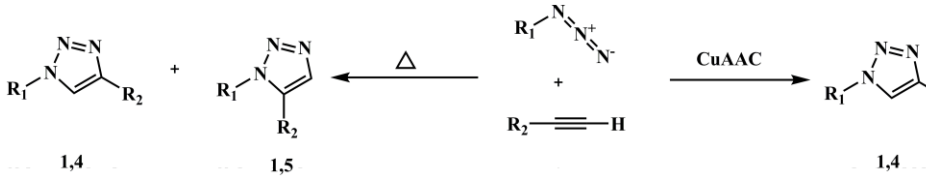
(2.4)

This reaction involves formation of a carboncentered radical by an atom transfer reaction with Cu(I)Br and trapping of this radical with a persistent nitroxide radical at close to diffusion-controlled rates. The unique aspect of this reaction is its reversibility, in which the product alkoxyamine can readily be converted to the starting incipient radical and parent nitroxide at elevated temperatures (>100 ^{0}C when TEMPO-type nitroxides are used) [42-43]. This methodology has been used to synthesize degradable and reversibly coupled linear multiblock copolymers, block and graft copolymers in the presence of a 10-fold molar excess of copper species per

halide end group [44]. The rate determining step in the coupling reaction is the speed (kact) at which the halide end groups on the polymer chains convert (or are activated) to the carbon-centered radical via atom transfer reactions with Cu(I) species.

2.2.4 Copper (I)-catalyzed azide-alkyne cycloaddition (CuAAC)

The thermal reaction of organic azides with terminal or internal alkynes has been known for more than a century, the first 1,2,3-triazole being synthesized by A. Michael from phenyl azide and diethyl acetylene dicarboxylate in 1893. The reaction has been investigated in detail by Huisgen and coworkers during 1950s–70s in the course of their studies of the larger family of 1,3-dipolar cycloaddition reactions [45]. The Huisgen 1,3-dipolar cycloaddition reaction of alkynes and organic azides [46] has gained considerable the most attention of any click reaction since 2001, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) was realized independently by the Meldal and the Sharpless laboratories [47,48]. The conventional Huisgen cycloaddition of azides and alkynes is not appropriate the criterion of a click reaction, by reason of the high temperatures necessary (>110 °C) and the lack of regiospecificity, with a racemic mixture of 1,4- and 1,5-triazole products (2.5) [45]. The copper catalyzed reaction allows to proceed much faster under much milder conditions and produces only the 1,4-regiosomer triazole [49,50]. The great success of the Cu(I) catalyzed reaction is actually a virtually quantitative, very robust, insensitive, general, and orthogonal ligation reaction.



(2.5)

The CuAAC rate is increased by a factor of 10^7 relative to the Huisgen 1,3-dipolar cycloaddition [51], so it considerably fast at and below room temperature. The reaction is not significantly affected by the steric and electronic properties of the groups attached to the azide and alkyne centers, and primary, secondary, and even tertiary, electron-withdrawing and electron-donating, aliphatic, aromatic, and heteroaromatic azides usually react well with variously substituted terminal alkynes. The reaction realizes in many protic and aprotic solvents, including water, and is unaffected by most organic and inorganic functional groups. The 1,2,3-triazole has

the advantageous properties of high chemical stability, strong dipole moment (4.8–5.6 Debye), aromatic character, and hydrogen bond accepting ability [52]. A stepwise mechanism [48,51] of CuAAC (Figure 2.4) consist of three key steps [53]:

(1) activation of a terminal alkyne as copper acetylide

(2) formal cycloaddition to produce cuprated triazole

(3) protiolysis of to release triazole.

The alkyne first coordinates to copper(I), forming a π-complex in which the acetylenic proton is more acidic by up to 9.8 units [51]. Coordination of the azide's nearby nitrogen to copper establishes the regiochemistry of the overall reaction and produces cupracycle. Ring contraction of forms (1,2,3-triazol-5-yl) copper species, which undergoes protiolysis to form triazole. Protonation of triazole-copper derivative followed by dissociation of the product ends the reaction and regenerates the catalyst.

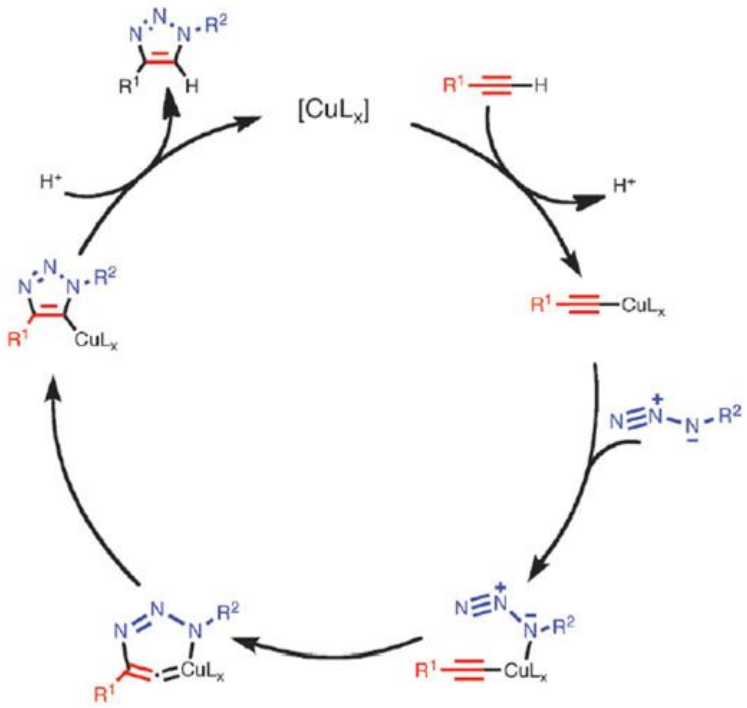


Figure 2.4 : Triazole ring formation mechanism by copper catalyzed

To date, copper is noticeable as the only metal for the dependable, easy, and 1,4-regiospecific catalysis of the azide–alkyne cycloaddition. Indeed, other metals known to catalyze various transformations of alkynes have not so far provided efficient catalysts for producing to 1,4-triazoles. Investigatios of complexes of all of the first-row transition elements as well as complexes of Ag(I), Pd(0/II), Pt(II), Au(I/III), and

Hg(II), among others, have all failed to produce triazoles in synthetically useful yields; their effect on the rate and selectivity of the cycloaddition was at best marginally noticeable. Only ruthenium cyclopentadienyl complexes were found to catalyze the formation of the 1,5-disubstituted triazole from azides and terminal alkynes, and also to engage internal alkynes in the cycloaddition.

3. EXPERIMENTAL WORK

3.1 Materials and Chemicals

Propargylamine (98%, Aldrich), 1,4-butanediol diglycidyl ether (%95, Aldrich), α-bromoisobutryl bromide (98%, Aldrich), triethylamine (Et_3N, 99.5%, Aldrich), 4-dimethylaminopyridine (DMAP, 99%, Aldrich), 1,1,1-tris(4-hydroxyphenyl)ethane (99%, Aldrich), CuBr (99.9%, Aldrich), Cu(0),. *N*, *N*, *N*', *N*'', *N*''-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich) was distilled over NaOH prior to use. Tetrahydrofuran (THF, 99.8%, J.T. Baker) was dried and distilled from benzophenone-Na. Dichloromethane (CH_2Cl_2, 99%, J. T. Baker) was dried and distilled over and P_2O_5. Diethyl ether (99.7%, Aldrich), toluene (99.8%, Aldrich), methanol (99.8%, Aldrich) were used without further purification. Hexane were in technical grade and distilled prior to use.

3.2 Instrumentation

The ^1H NMR (500 MHz) spectra were recorded on Agilent VNMRS 500 MHz NMR Spectrometer in $CDCl_3$. The conventional Gel Permeation Chromatography (GPC) measurements were carried out with an Agilent instrument (Model 1100) consisting of a pump (0.3 mL/min), refractive index, and UV detectors. Four Waters Styragel columns (HR 5E, HR 4E, HR 3, HR 2), (4.6 mm internal diameter, 300 mm length, packed with 5 μm particles) were used in series. The effective molecular weight ranges were 2000-4.000.000, 50-100.000, 500-30.000, and 500–20.000, respectively. THF was used as eluent at a flow rate of 0.3 mL/min at 30 °C. Toluene was used as an internal standard. The molecular weight of the polymers were calculated on the basis of linear PS standards (Polymer Laboratories), whereas linear PMMA standards (Polymer Laboratories) were only used for the molecular weight determination of the PMMA homopolymer using PL Caliber Software from Polymer Laboratories.

3.3 Synthesis Methods

3.3.1 Synthesis of 2-azido ethanol

To a 100 mL of round bottom flask was added 2-bromo ethanol (5 g, 40 mmol) in 50 mL of water/acetone (1/4, v/v). NaN_3 (4 g, 60 mmol) was added in one portion to the reaction and the mixture was stirred at 60 ^oC for overnight. After acetone was removed, remaining liquid was dissolved in CH_2Cl_2 and extracted with water. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and combined organic layers were dried over Na_2SO_4. Solvent was removed under vacuum and 1 was obtained as pale yellow oil. Yield=95%. ^1H NMR ($CDCl_3$, δ) 3.75 (t, 2H, CH_2O), 3.44 (t, 2H, CH_2N_3).

3.3.2 Synthesis of Poly(β-hydroxyl amine)s (Synthesis of hyroxyl and alkyne functional polymer)

To a 25 mL of round bottom flask, 1,4-butanediol diglycidyl ether (1 g, 15m mol, 1 eq) and propargylamine (0.27 g, 69 mmol) was added stirred under nitrogen atmosphere with the help of a mechanical stirrer at room temperature for three days. After this period, 300 mL diethyl ether was added to the crude polymerization mixture and stirred vigorously. The polymer product was recovered by precipitation into 300 mL diethyl ether. The dissolution–precipitation procedure was repeated two times. The material was allowed to settle on the glass surface. The diethyl ether was decanted and polymer dissolved in chloroform and transferred into a glass vial and dried. Yield = 0.9 g 70%. ^1H-NMR (δ, ppm, 500 MHz, $CDCl_3$): 3.86 (m, 2H, OCH_2CH), 3.52-3.36 (m, 10H, OCH_2CH_2, OCH, OCH_2CH, CH_2CCH), 2.72 (m, 2H, NCH_2CH), 2.59 (m, 2H, NCH_2CH), 2.24 (s, 1H, CH_2CCH), 1.65 (s, 4H, OCH_2CH_2); GPC (THF): M_n =6400, M_w = 9500, PDI (M_w/M_n) = 1.5.

3.3.3 Synthesis of hydroxy substituted Poly(β-hydroxyl amine)s (Synthesis of bromine and alkyne functional polymer)

Poly(β-hydroxyl amine)s (1.0 g, 4 mmol) and DMAP (1.43 g, 12 mmol) were dissolved in 50 mL of THF, and Et_3N (6.48 mL, 47 mmol) was added. The reaction mixture was then cooled to 0 ^oC), α-bromoisobutryl bromide (2.88 ml, 23 mmol) was added dropwise within 30 minutes to this solution. The reaction mixture was stirred for 15 min. at 0 ^oC then for overnight at room tempeature. The ammonium salt was filtered off and the solvent was evaporated under reduced pressure. The remaining

residue was extracted with CH_2Cl_2, and saturated aqueous $NaHCO_3$. The aqueous phase again extracted with CH_2Cl_2, and combined organic phases dried over Na_2SO_4. Excess CH_2Cl_2 was evaporated under reduced pressure and the remaining solution was precipitated into cold methanol. Yield: 0.8 g (85%). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.06 (bs, 2H, OC*H*), 3.48 (m, 10H, OC*H*$_2$CH$_2$, OC*H*$_2$CH, C*H*$_2$CCH), 2.81 (m, 4H, NC*H*$_2$CH), 2.21 (m, 1H, CH$_2$CC*H*), 1.93 (bs, 12H, C(C*H*$_3$)$_2$), 1.59 (s, 4H, OCH$_2$C*H*$_2$) ; GPC (THF): *M*n =10800, *M*w = 15000, PDI (*Mw*/*Mn*) = 1.4.

3.3.4 Functionalization of hydroxy substituted Poly(β-hydroxyl amine)s through CuAAC and NRC in one pot fashion

Poly(β-hydroxyl amine)s functionalized (1 g, 1,8 mmol) was dissolved in DMF (10 mL) in a 25 mL of Schlenk tube. 2-azido ethanol (0.17g, 2.0 mmol) and TEMPO (0.62 g, 4.0 mmol) was added to this solution. The mixture was stirred at room temperature for 10 min. Next, Cu(0) (1.26 g, 20 mmol), CuBr (0.57 g, 4.0 mmol), and PMDETA (0.83 mL, 4 mmol) were immediately added to the Schlenk tube. The reaction mixture was degassed by three Freeze-Pump-Thaw cycles, left in vacuum, and stirred for 24 h at room temperature. The mixture was diluted with THF, filtered through a column filled with neutral alumina to remove the copper complex, and precipitated in cold methanol. The crude product was purified by dissolution–precipitation in THF-cold MeOH. (Yield: 0.49 g, 87 %. ^{1}H NMR (*δ*, ppm, 500 MHz, CDCl3): 7.70 (bs, 1H, CHC*H*N), 5.01 (bs, 1H, CH$_2$C*H*CH$_2$), 4.46 (bs, 2H, NC*H*$_2$CH), 4.00 (bs, 2H, NC*H*$_2$CH$_2$), 3.85 (bs, 2H, CH$_2$C*H*; GPC (THF): *M*n =18400, *M*w = 25500, PDI (*Mw*/*Mn*) = 1.4.

4. RESULTS AND DISCUSSION

Cationic polymers are of immense utility in a myriad of applications. Some prominent examples include gene delivery, [14] DNA sensing, [15] and antimicrobial applications [16]. The reaction of amines with diglycidyl-terminated small molecules might present a simple synthetic pathway for the preparation of main-chain ammonium- based cationic structures[18−20]. To examine this possibility, initially 1,4-butanediol diglycidyl ether and propargylamine were employed as the monomers. A polyaddition reaction between monomers afforded polymer 1.

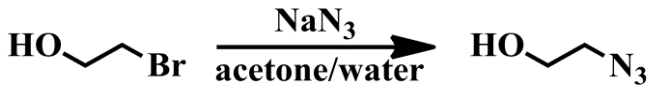
The polymerizations were carried out at room temperature and under solvent-less conditions. Due to the high viscosity of the polymerization mixture mechanical stirrer used. The polymer yield ranged from 75% to 80% with some material loss that was inevitable due to the highly viscous nature of the materials and strong adherence of the polymers to the glass surfaces. In addition, some fractionation may also be the reason for low polymer yields. Figure 4.2 shows the ^{1}H NMR spectra of polymer 1. The molecular weights of the polymers were determined against polystyrene standards. Monomer stoichiometry plays a central role in defining the molecular weights of the polymers in AA-BB-type of step-growth polymerization. Hence, a stoichiometric imbalance of the reactive functional groups in the polymerization media is a likely reason for the low molecular weights of the present polymers.

Polymer 1 was found to be soluble in a range of typical organic solvents but insoluble in water. However, upon protonation, polymer 3 can be transformed into ionic polymer and can become completely water-soluble.

To investigate the availability of the other reactive site on the polymer chain, the hydroxyl units of polymer 1 were subjected to a postpolymerization modification reaction using bromine (Polymer 2) and 2-azido ethanol, TEMPO (Polymer 3).

4.1 Synthesis of 2-Azido Ethanol

2-azido ethanol was obtained quantitatively via nucleophilic substitution reaction using 2-bromo ethanol and NaN_3 in the presence of acetone/water mixture as seen in Equation 4.1.



(4.1)

It was observed from ^{1}H NMR spectrum, a signal related to methylene protons next to Br atom at 4.52 ppm completely disappeared and a new peak linked to -N_3 unit was observed at 3.44 ppm as seen in Figure 4.1.

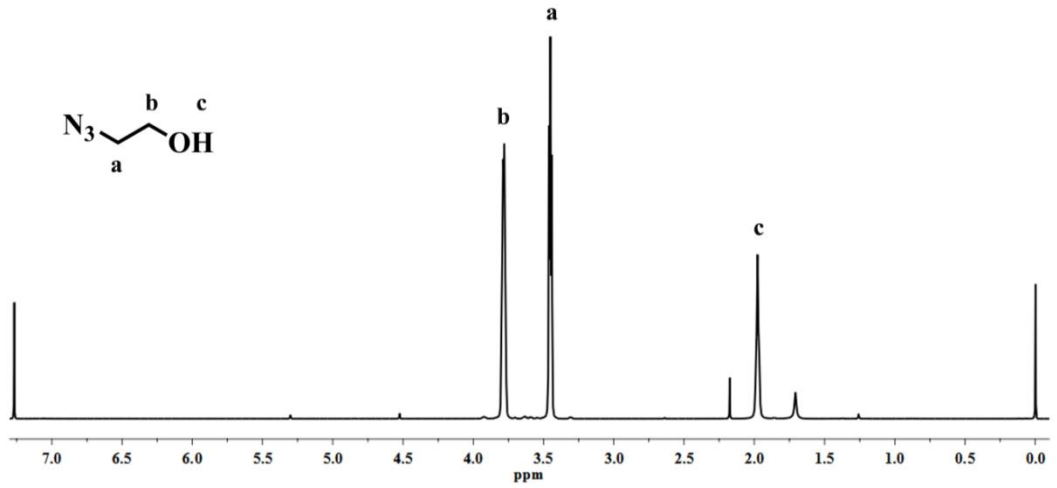
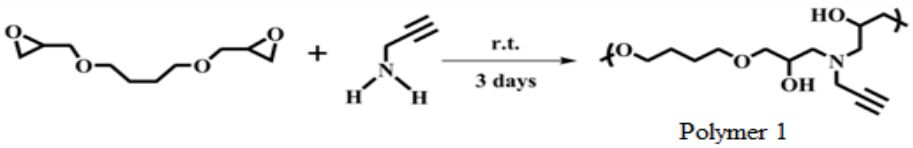


Figure 4.1 : ^{1}H NMR spectrum of the multifunctional linking agent.

4.2 Synthesis of the Poly(β-hydroxyl amine)

Poly(β-hydroxyl amine) was synthesized via amine-epoxy click polymerization with reaction of 1,4-butanediol diglycidyl ether and propargylamine. The polymerization was carried out at room temperature for 3 days using a mechanical stirrer. The resulting polymer has both hydroxyl and alkyne functionalities (Equation 4.2).



Polymer 1

(4.2)

Table 4.1: The solvent effect to the reaction of 1 g 1,4-butanediol diglycidyl ether (1 eq) and 0.32 mL propargylamine (1 eq).

Solvent	***Day***	$M_{w,GPC}$ **(g/mol)**	$M_{n,GPC}$ **(g/mol)**	M_w/M_n
-	3	1800	1600	1.13
1ml THF	10	6700	5500	1.20
2ml THF	18	3900	2700	1.41
3ml THF	25	6500	5100	1.28

The process was tried with solvent in order to use magnetic stirrer. Polymerization occurred but time decreed and we couldn't obtain high yield results. Mechanical stirrer decided to use (Table 4.1).

The compound Polymer 1 was simply purified by precipitation into the diethyl ether and its structure was identified by ^{1}H NMR spectroscopy (Figure 4.2). ^{1}H NMR spectroscopy confirmed clearly the structure of Polymer 1 by appearance of characteristic signals such as acetylene protons (δ 2.24). Also the disappearance of NH protons and the shift on epoxy protons are a proof for amine-epoxy click reaction**..**

The number-average molecular weight obtained by GPC ($M_{n,GPC}$ = 6400 g/mol, relative to linear PS standards). Moreover, M_w/M_n = 1.5 calculated from GPC displays relatively narrow molecular weight distribution. $M_{n,NMR}$ can not be calculated because there is no reference proton for the calculation.

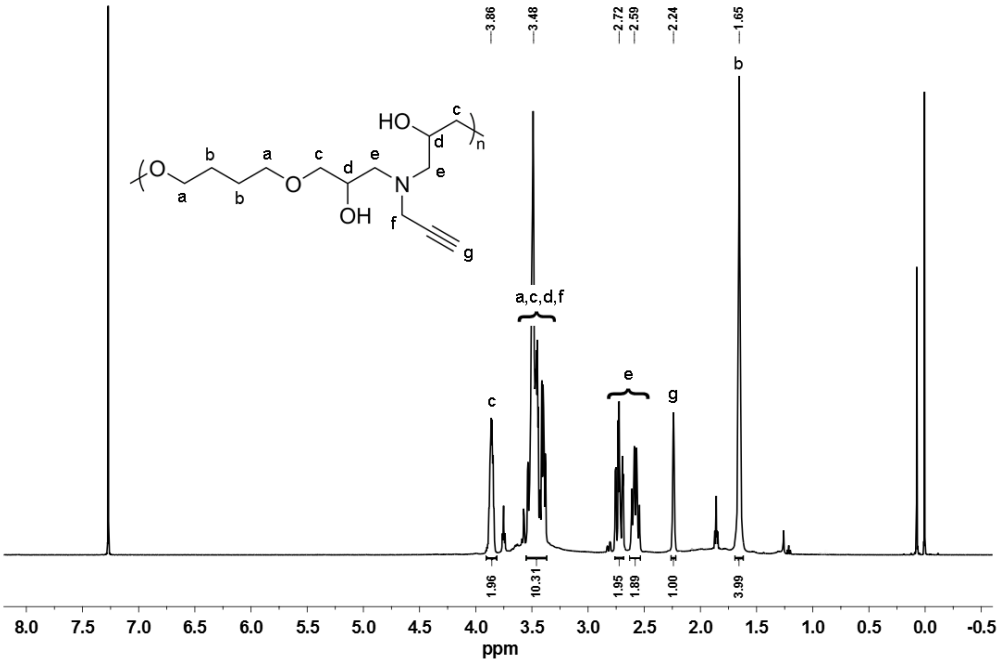
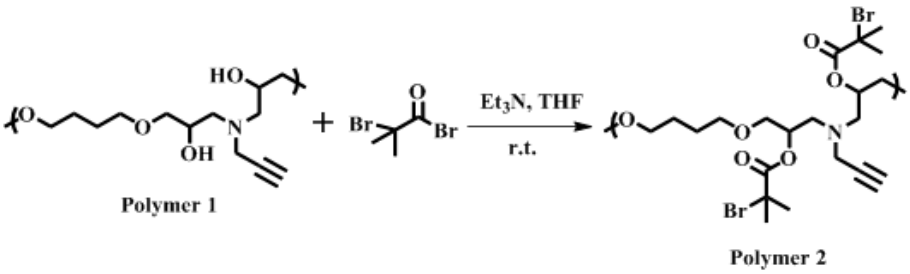


Figure 4.2 : ^{1}H NMR spectrum of Poly(β-hydroxyl amine) in $CDCl_3$.

4.3 Synthesis of Bromine and Alkyne Functional Polymer

Poly(β-hydroxyl amine) was then reacted with α-bromoisobutyryl bromide in THF to introduce the bromine functionality to the polymer which can be used in the synthesis of macromolecules with various structures (Equation 4.3). After esterification, the reaction mixture was filtered and extracted with CH_2Cl_2 and combined organic phases dried over Na_2SO_4. Excess of CH_2Cl_2 was evaporated and concentrated. Then precipitated into cold methanol two times. The resulting polymer has both alkyne and bromine functionality which can be used in click reactions.



(4.3)

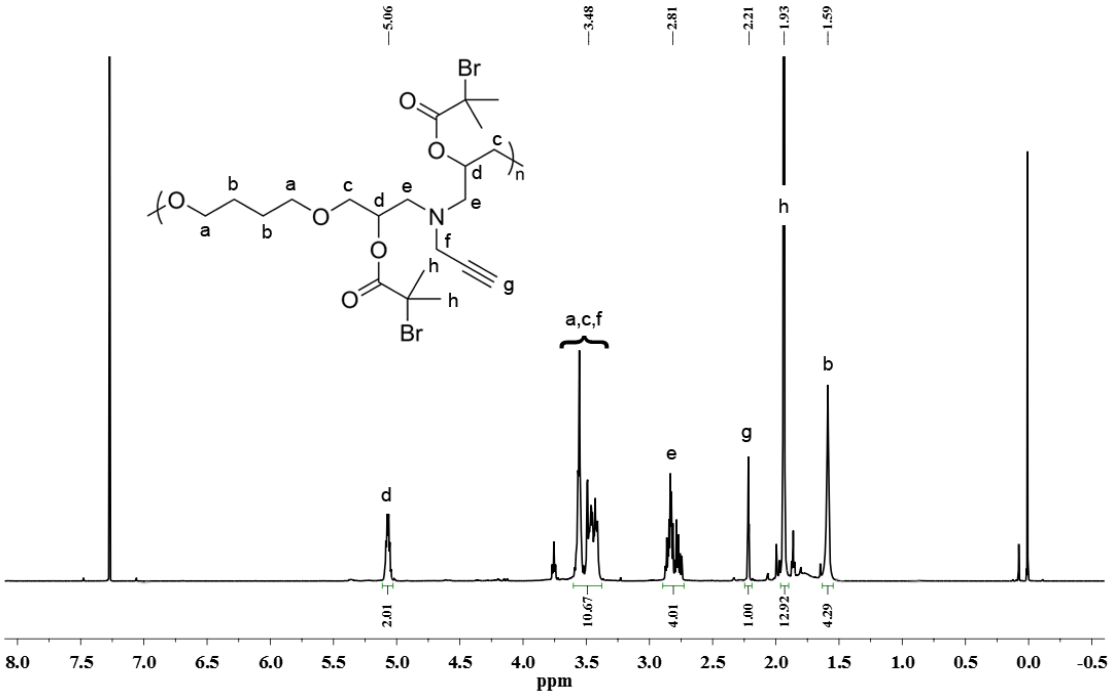


Figure 4.3 : ^{1}H NMR spectrum of Bromine and Alkyne Functional Poly(β-hydroxyl amine) in $CDCl_3$.

Polymer 2 ^{1}H NMR spectrum indicated that the d protons adjacent to hydroxyl group were shifted to downfield because of the esterification reaction. The appearance of aliphatic h protons are proved the addition of the bromine group and it is clearly seen that the methyl protons next to Br were detected at 1.93 ppm.

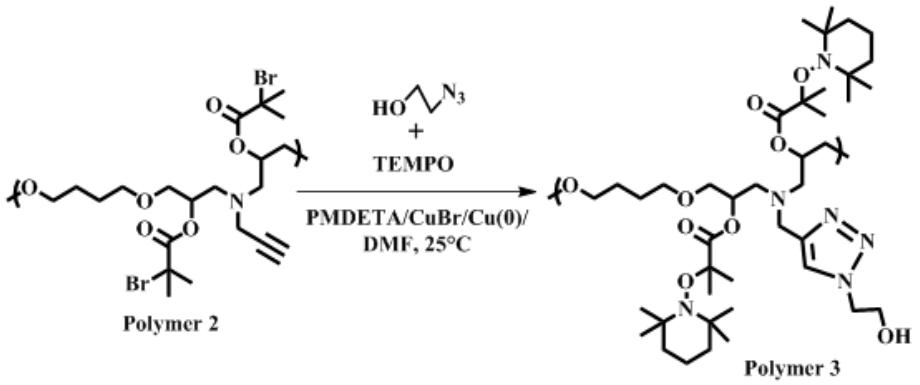
The number-average molecular weight obtained by GPC ($M_{n,GPC}$ = 10800 g/mol, relative to linear PS standards). Moreover, M_w/M_n = 1.4 calculated from GPC displays relatively narrow molecular weight distribution.

4.4 Functionalization of Hydroxy Substituted Poly(B-Hydroxyl Amine)s Through CuAAC and NRC in One Pot Fashion

The new bromine and alkyne functional polymer was then clicked with model compounds for the functionalization of the backbone. As the polymer has both bromine and alkyne functionalities, the NRC and CuAAC reactions can be used in one pot fashion for the functionalization. For doing this azido ethanol and TEMPO were used as model compounds.

The double click reactions were performed in DMF with the polymer 2 and model compounds with the presence of Cu(0), CuBr and PMDETA in one pot fashion (Equation 4.4).

After the reaction polymer 3 was diluted with THF, filtered through a column filled with neutral alumina to remove the copper complex, and precipitated in cold methanol. The crude product was purified by dissolution–precipitation in THF-cold MeOH.



(4.4)

^{1}H NMR spectroscopy confirmed clearly the structure of polymer 3 by appearance of characteristic signals such as triazole protons (δ 7.70). Also the disappearance acetylene protons is a proof for the click reactions. a signal related to methylene protons next to Br atom at 1.93 ppm completely shifted to upfield, as the stronger elektronegative group (Br) disappears and new peaks linked to $N_3CH_2CH_2OH$ unit was observed at 3.85 and 4.00 ppm as seen in Figure 4.4. These results confirmed that the synthesis of 3 was achived.

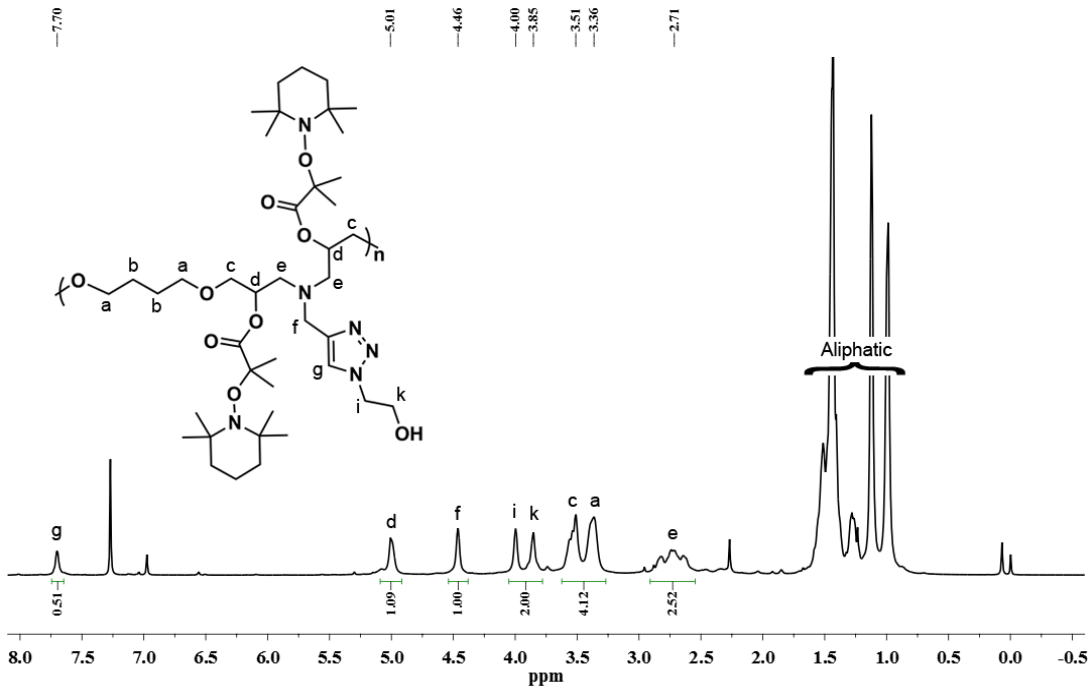


Figure 4.4 : ^{1}H NMR spectrum of functionalized hydroxy substituted Poly(β-hydroxyl amine)s in $CDCl_3$.

The number-average molecular weight obtained by GPC (M_n,GPC = 18300 g/mol, relative to linear PS standards). Moreover, M_w/M_n = 1.4 calculated from GPC displays relatively narrow molecular weight distribution.

4.5 The GPC Evaluations

The GPC traces of all polymers exhibited a monomodal distribution and completely shifted to the higher molecular weight region as compared with their starting polymers, proving the successful synthesis of brush copolymers as depicted in Figure 4.5, and furthermore the molecular weight distributions are relatively narrow and in the range of 1.20-1.54 from the conventional GPC. On the other hand, it was observed that the GPC trace of the Functonalized Hydroxy Substituted Poly(β-

hydroxyl amine)s using CuAAC and NRC in one pot fashion (Polymer 3) shifted to the higher retention time compared to Bromine and Alkyne Functional Poly(β-hydroxyl amine) (Polymer 2). This may be attributed to a decrease in the hydrodynamic volume after modification.

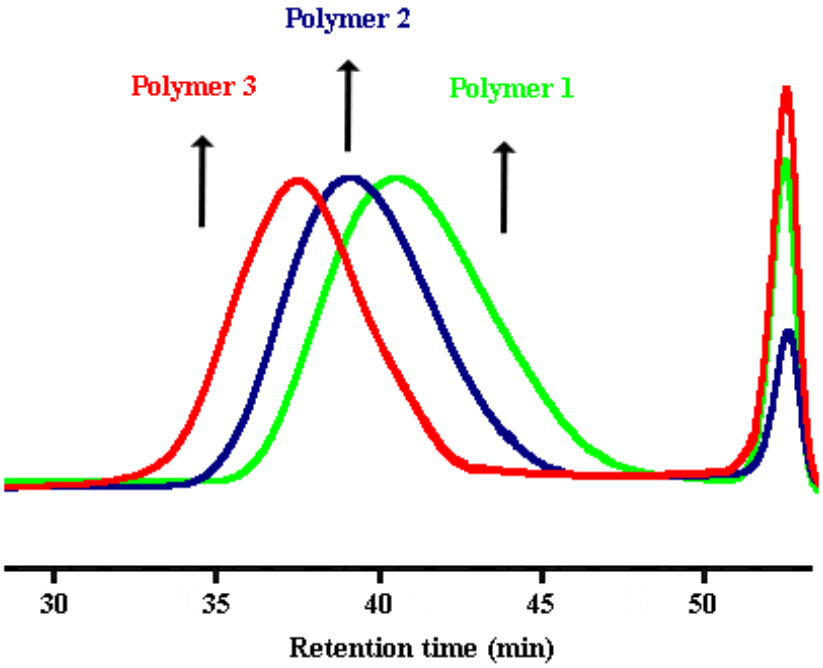


Figure 4.5 : GPC traces of Polymer 1, Polymer 2 and Polymer 3 using RI detector in THF at 30 ^{o}C.

5. CONCLUSION

A novel family of main-chain cationic polymers, poly(ß-hydroxyl amine)s, were prepared by the amine−epoxy click polymerization at ambient conditions and from readily available small molecular building blocks. By using the REO concepts, a number of chemically distinct reactive sites, in their chemically free form, could be incorporated during the construction of the polymer chains. Postpolymerization modifications of these reactive sites in a sequential manner afforded multifunctional cationic structures. The orthogonal nature of the applied chemistries allowed a protection/deprotection free synthetic scheme to be developed while the efficiency of the involved processes resulted in near quantitative modifications of the reactive sites. The modification sequence could be altered due to the orthogonality of the selected set of reactions.

The opportunity of functionalization bodes well for various applications in which the cationic polymer chain has to be modified to achieve optimum properties. For example, hydrophobic modifications of the cationic polymers are shown to improve gene delivery efficiency by enhancing the cellular uptake of the modified polymer by lipophilic cell membranes. The prospect of introducing more than one functional group in the present work suggests that not only can one add a hydrophobic site for better cellular uptake but also incorporate, for example, a targeting ligand and an imaging agent in a chemically well-defined manner. In summary, the versatile, ambient, efficient, and practically simple synthetic strategy from commercially available inexpensive building blocks and the opportunity for multiple functionalizations of the presented new class of main-chain cationic polymers hold significant promise for the development of high-performance biomaterials for potential use in antimicrobial and gene delivery applications.

As a conclusion, the amine-epoxy click polymerization generated Poly(β-hydroxyl amine) was used as a versatile main backbone for functionalization of the main chain hydroxyl and alkyne groups. All polymers as evidenced via NMR and GPC measurements were found to be compatible with expected structures and displayed

monomodal traces with low molecular weight distributions. Therefore, we have shown here that the triple click reaction strategy involving CuAAC, and NRC reactions is a highly efficient process for the synthesis of hydroxy substituted Poly(β-hydroxyl amine).

The comparison among the integrated signals in the ^{1}H-NMR spectrum proved that most of monomers are present in equimolar amounts in the random copolymers. It is noted that $M_{n,NMR}$ is consistent with $M_{n,GPC}$ which provided to synthesized random copolymers.

All in all, triple click strategy includes click polimerization then, modification with one pot double click reactions of the polymer.

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PRESENTATIONS

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