ISTANBUL TECHNICAL UNIVERSITY ★ GRADUATE SCHOOL OF SCIENCE ENGINEERING AND TECHNOLOGY

MODIFICATION OF PENDANT ANTHRACENE AND ALLYL FUNCTIONALIZED POLYCARBONATES VIA DOUBLE CLICK REACTIONS

M.Sc. THESIS

Binnaz CANOL

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Thesis Advisor: Prof. Dr. Ümit TUNCA

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İSTANBUL TEKNİK ÜNİVERSİTESİ ★ FEN BİLİMLERİ ENSTİTÜSÜ

ANTRASEN VE ALLİL YAN GRUPLARI İÇEREN POLİKARBONATLARIN İKİLİ 'CLİCK' REAKSİYONLARI İLE MODİFİKASYONU

YÜKSEK LİSANS TEZİ

Binnaz CANOL
(515111003)

Polimer Bilim ve Teknolojisi Anabilim Dalı

Polimer Bilim ve Teknolojisi Programı

Tez Danışmanı: Prof. Dr. Ümit TUNCA

HAZİRAN 2013

Binnaz CANOL, a **M.Sc.** student of ITU **Graduate School of Science Engineering and Technology** student ID 515111003, successfully defended the **thesis** entitled "**MODIFICATION OF PENDANT ANTHRACENE AND ALLYL FUNCTIONALIZED POLYCARBONATES VIA DOUBLE CLICK REACTIONS**", which she prepared after fulfilling the requirements specified in the associated legislations, before the jury whose signatures are below.

Thesis Advisor :	**Prof. Dr. Ümit TUNCA** İstanbul Technical University	.....
Jury Members :	**Prof. Dr. Gürkan HIZAL** İstanbul Technical University	.....
	Assoc. Prof. Dr. Amitav SANYAL Boğaziçi University	.....

Date of Submission : 3 May 2013
Date of Defense : 5 June 2013

To my family,

FOREWORD

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

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Binnaz CANOL
(Chemist)

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ABBREVIATIONS

^{1}H NMR	**:**Hydrogen Nuclear Magnetic Resonance Spectroscopy
^{13}C NMR	**:**Carbon Nuclear Magnetic Resonance Spectroscopy
ATRP	**:**Atom Transfer Radical Polymerization
CH_2Cl_2	**:**Dichloro methane
$CDCl_3$	**:**Deuterated chloroform
CuAAC	**:**Copper catalyzed azide-alkyne cycloaddition
DA	**:**Diels-Alder
EtOAc	**:**Ethylacetate
GPC	**:**Gel Permeation Chromatography
MWD	**:**Molecular Weight Distribution
PEG	**:**Poly(ethyleneglycol)
PC	**:**Poly(carbonate)
PDI	**:**Polydispersity Index
RAFT	**:**Reversible Addition Fragmentation Chain Transfer
NMP	**:**Nitroxide Mediated Polymerization
ROP	**:**Ring Opening Polymerization
TEA	**:**Triethylamine
THF	**:**Tetrahydrofuran
UV	**:**Ultra Violet

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MODIFICATION OF PENDANT ANTHRACENE AND ALLYL FUNCTIONALIZED POLYCARBONATES VIA DOUBLE CLICK REACTIONS

SUMMARY

Biocompatible, biodegradable, or bioresorbable polymers uses in biomedical and environmental applications, such as medical implants and drug-delivery systems. As a kind of surface erosion biodegradable materials, aliphatic polycarbonates are usually derived from ring-opening polymerization (ROP) and have gained increasing interest for their potential use in biomedical and pharmaceutical applications due to their favorable biocompatibility, biodegradability, and nontoxicity.

Nowadays, alternative routes such as Diels-Alder (DA) and the Thiol-ene click reactions which can be classified under the term "click chemistry" have emerged as a powerful tool for the preperation of block and graft copolymers.

One of the most used strategie is copolymerization which has developed as to adjust the properties of polymeric materials. The combination of two polymers into a single entity is generally advantageous because the copolymers may integrate the merits of the original homopolymers. Graft copolymers, also called molecular brushes, have attracted considerable interest for their distinguished conformation and properties.

Ring-opening polymerization (ROP) of carbonates seems of the most effective method to fabricate polycarbonates with good reproducibility and high quality (high molecular weight and low polydispersity). From this point of view, in this thesis, the design and synthesis of graft copolymers of PC-Anth/Allyl with a well-defined molecular architecture and molecular weight was described.

In this study synthesis of anthracene- and allyl-functional cyclic carbonate monomers, anthracen-9-ylmethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate and allyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate, was achieved by the reaction of anthracen-9-ylmethyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate and allyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate with ethyl chloroformate in tetrahydrofuran at room temperature, respectively [1]. The copolymerization of these anthracene- and allyl-functional cyclic carbonate monomers was carried out successfully via ring-opening polymerization (ROP) using benzyl alcohol as initiator, 1,8-diazabicyclo[5.4.0]undec-7-ene and 1-(3,5-bis(trifluorometh1-(3,5-bis(trifluoromethyl))-3-cyclohexyl-2-thiourea, as catalyst system [2]. In the following study, modification reactions of the anthracene- and allyl- functional polycarbonate was accomplished under facile conditions via click reactions (Thiol-ene and Diels-Alder) with model compounds. The composition and molecular weight of the polycarbonates were characterized by ^{1}H NMR and GPC.

ANTRASEN VE ALLİL YAN GRUPLARI İÇEREN POLİKARBONATLARIN İKİLİ 'CLİCK' REAKSİYONLARI İLE MODİFİKASYONU

ÖZET

Biyolojik olarak uyumluluk, kolay parçalanabilme veya yüksek emilim gibi birtakım özellikli polimerlere olan ilgi son zamanlarda artmıştır. Bu polimerler medikal implantlar ve ilaç-taşıma sistemleri gibi biyomedikal ve çevresel uygulama alanlarında kullanılmaktadır. Yüzey erozyonunun bir çeşidi olan biyo çözünür malzemelerin bir çeşidi olan alifatik polikarbonatlar genellikle halka açılma polimerizasyonu (ROP) yoluyla elde edilir. Ayrıca sahip oldukları biyolojik uyumluluk, kolay parçalanabilme ve toksik olmama özelliklerinden dolayı biyomedikal ve ilaç uygulamalarında tercih edilir.

Aşı polimerler sahip olduğu lineer olmayan yapısı, farklı bileşimi ve topolojisi nedeniyle önemli bir ilgiye sahiptir. Dallı yapılarından dolayı genellikle düşük vizkozite değerlerine sahiptir ve bu durumda polimerin işlenme koşullarını kolaylaştırır. Ayrıca, aşı polimerler lineer polimerlere kıyasla daha iyi fiziksel ve kimyasal özelliklere sahiptirler.

Son yıllara kadar, elde bulunan sistemler yaşayan iyonik polimerizasyonlardı (anyonik ve katyonik) . Bu sistemler sayesinde moleküler ağırlığı kontrol edilebilen, well- defined zincir sonu olan ve düşük polidipersiteye sahip polimerler elde edilebilir. Son yıllarda ise kompleks makromoleküllerin sentezinde kullanılan kontrollü/yaşayan polimerizasyon metotlarının kullanımı arttı. İyonik polimerizasyona göre monomerlerin fazla çeşitli olması ve deney koşullarının daha rahat olması bunun başlıca sebebidir.

Kontrollü /yaşayan polimerizasyon tekniklerinden biri olan ATRP kendinden önceki önceki kontrollü radikal polimerizasyon yöntemlerinden (iyonik ,kararlı serbest radikal polimerizasyonu gibi), karmaşık polimer yapıları üretimine izin vermesi ile ayrılır.Bu polimerizasyon yöntemi, sıcaklık gibi reaksiyon parametrelerinin kontrolü ile kolayca durdurulup yeniden başlatılabilir. ATRP'den önce ortaya çıkan kontrollü polimerleşme yöntemlerinde her çeşit monomer kullanılamamasına karşın, ATRP mekanizmasında geniş bir monomer yelpazesine kullanılabilir. Kontrollü ve düzenli büyüyen polimer zinciri ve düşük molekül ağırlığı dağılımı (*polidispersite*), ATRP mekanizması sırasında kullanılan metal bazlı katalizör sayesinde elde edilir.

Halka açılma polimerizasyonu (ROP) siklik monomerin lineer polimer oluşturmak üzere açıldığı tek polimerizasyon yöntemidir. Lactide, carbonate gibi siklik esterlerin halka açılma polimerizasyonu kontrollü poliester sentezinde genel ve etkin bir metottur. Polimerizasyon yöntemlerine ek olarak, düşük polidispersite indisleri ve uç gruplarda yüksek uyumluluk gibi birçok gelişmiş uygulama, ağır metaller gibi istenmeyen kirliliklerin katalizörlerden uzaklaştırılmasını gerektirir. Bu amaçla siklik

esterlerin metalsiz halka açılma reaksiyonlarına organokatalitik yaklaşımlarda bulunulmuştur.

Günümüzde, "click kimyası" terimi altında sınıflandırılan Diels-Alder (DA) ve bakır katalizli azid-alkin siklokatılma (CuAAC) tepkimeleri blok ve aşı 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.

Click kimyası hızlı, etkin, güvenilir ve seçici olmak gibi özelliklere sahip olmasının yanı sıra yeni ilaç araştırma ve biyokimya çalışmalarında geniş olarak kullanılır. Click kimyasında en popüler reaksiyonlardan biri Huisgen 1,3-dipolar siklik katılması reaksiyonudur. Oda sıcaklığında olan azid ve alkin nin reaksiyonunda Cu(I) kataliz olarak kullanılır. Bu reaksiyonun çok tercih edilmesinin sebebi reaksiyon şartlarının basit olması, yan ürün olmaması, verimin yüksek olması ve saflaştırmanın kolay olmasıdır. Bu reaksiyon mekanizması ile ilgili Emrick in yaptığı ilk çalışmalardan bu yana, biyolojik olarak ile ilgili olarak click kimyası ve halka açılma polimerizasyonu metotlarının kullanıldığı bir çok çalışma yapılmıştır. Fakat, click kimyası kullanılarak polikarbonatların modifikasyonun içeren çalışmaların sayısı azdır.

Kopolimerizasyon, polimerik malzemelerin özelliklerini değiştirme ve ayarlama da kullanılan önemli bir yöntemdir. İki polimerin tek olacak şekilde bir araya gelmesi, kopolimerlerin orijinal polimerin meritlerine kadar girebilmesi nedeniyle avantajlıdır. Aşı kopolimerler, moleküler fırça olarak da bilinirler, sahip oldukları özellikler ve şekilleri sayesinde oldukça popülerdirler.

Basit halka açılma kopolimerizasyonu ile kontrollü olarak fiziksel ve mekanik özellikleri belirlenebilen polikarbonat kopolimerler elde edilir. Karbonatların halka açılma polimerizasyonu ile yüksek kaliteli (yüksek moleküler ağırlık ve düşük polidispersite) polikarbonatların elde edilmesi oldukça oldukça efektif bir metottur. Bu çalışmada, belirlenebilir moleküler ağırlığa ve yapıya sahip olan PC-Anth aşı kopolimerlerinin dizaynı ve sentezi konu edilmiştir ve antresan-maleimid-bazlı DA "click reaksiyonu" aşı kopolimer hazırlanmasında kullanılmıştır.

Siklik karbonat monomerlere pentaflorofenilester, azid, allil, alkil halojenür, hidroksil (met)akrilat, stiren, furan, maleimid, ve vinil gibi fonksiyonel grupların eklenmesi, sonuçta elde edilen polikarbonatların fiziksel, kimyasal ve biyolojik özellikleri üzerinde etkin bir denetim sağlar. Ayrıca polikarbonatlardaki bu asılı fonksiyonel grupların yüksek etkinlikli "click" tepkimeleri ile tekrar türevlendirilmeleri iyi tanımlanmış son ürünlerin eldesine yol açacaktır.

Bu çalışmada fonksiyonel alifatik polikarbonat zincirleri sentezlenmiştir ve metal içermeyen ikili 'click' tepkimeleri ile türevlendirilmiştir.Çalışmanın kilit unsuru yeşil kimyadır. Bilindiği gibi yeşil kimyanın önemi günümüzde gittikçe artmaktadır. Sentetik kimyacılar, toksik özellik gösteren metallerin sentezlerde kullanılmalarına alternatif oluşturacak yeni yöntemlerin geliştirilmesi için yoğun çaba sarf etmektedirler. Bu çalışmada da yeşil kimyaya paralel olarak hem polimerin sentezinde, hem de türevlendirilmesinde toksik metal içermeyen yöntemler geliştirilmiştir ve kullanılmıştır.

Çalışmanın ilk bölümünde metalsiz ikili 'click' tepkimelerine olanak tanınlanmıştır, farklı fonksiyonel gruplara sahip (allil, antrasen) siklik karbonat monomerleri sentezlendi ve karakterize edilmiştir. Bu monomerler metal içermeyen katalizör

sistemi ile oda sıcaklığında aynı anda polimerleştirilmiştir ve elde edilen polimer ayrıntılı bir şekilde karakterize edilmiştir. Çalışmanın devamında iki farklı fonksiyonel yan grup içeren alifatik polikarbonat zinciri, biyo uyumlu (metal içermeyen) ikili 'click' tepkimeleri ile türevlendirlmiştir. Böylece, polimerin sentezinde ve türevlendirilmesinde hiçbir şekilde toksik özellik gösteren metal kullanılmamıştır. Burada kullanılan 'click' tepkimeleri Diels-Alder ve tiyol-en tepkimeleridir.

Antresen ve allil fonksiyonlu halkalı karbonat monomerleri, antrasen-9-ol-metil 5-metil-2-okso-1,3-dioksane-5-karboksilat ve allil 5-metil-2-okso-1,3-dioksan-5-karboksil, oda sıcaklığında sırasıyla antrasen-9-ol-metil 3-hidroksi-2-(hidroksimetil)-2-metilpropanat ve allil 3-hidroksi-2-(hidroksimetil)-2-metilpropanatın etil kloroformat ile tetrahidrofuran kullanılarak yapılan reaksiyonları ile sentezlenmiştir [1]. Antrasen ve allil fonksiyonlu halkalı karbonat monomerlerinin kopolimerizasyonu, benzil alkol başlatıcılığında, 1,8-diazabisiklo[5.4.0]undek-7-en ve (1-(3,5-bis(trifloromethil)fenil)-3-siklohekzil tiyoüre) katalizörlüğündeki halka açılma polimerizasyonu ile gerçekleştirilmiştir [2]. Çalışmanın sonraki kısmında antrasen ve allil fonksiyonlu polikarbonat zinciri uygun koşullardaki Click reaksiyonları ile (Tiyol-en and Diels-Alder) model bileşiklerle modifiye edilmiştir.Polikarbonatların molekül ağırlığı ve kompozisyonları ^{1}H NMR ve GPC ile karakterize edilmiştir.

1. INTRODUCTION

Aliphatic poylcarbonates (PCs) have achieved inreasing attention for use in a wide range of different applications such as surgical sutures, bone fixation materials and controlled drug delivery due to their biocompatibilty, very low toxicity and biodegradability. [3,4] PCs are typically synthesized using three different methods, for example, the polycondensation of diol compounds via phosgene or dialkylcarbonates, the copoplymerization of oxiranes with carbondioxide, and the ring opening polymerization (ROP) of cylic carbonate monomers.The latter seems to be the most efficient preparation method when compared with the former, which suffer from many drawbacks such as poor control on the chemical structures, the limitation of molecular weights, and the formation of byproducts [4]. The ROP of cyclic carbonates has been proceeded by anionic polymerization using conventional anionic initiators or coordination-insertion polymerization catalyzed by various organometallic compounds. Recently, metal-free cataylsts such as several amines and phosphines have been extensively used for an efficient synthesis of aliphatic PCs [4-7].

The introduction of functional pendant groups, such as pentafluorophenylester [8], azide [9], allyl [10], alkyl halide [11], hydroxyl [12], (meth)acrylate [13], styrene [14], furan [15], and maleimide [16], vinyl [17] to cyclic carbonate monomers allows a precise cpntrol over the physical,chemical, and bioilogical properties of the resulting PCs. Further reaction on these pendant groups of the resulting PCs that can be realized using highly efficient chemistries, such as click chemistry [18] would lead to PCs with well-defined structures for final needs and applications [9,10,13,15-17]. The thiol-ene and the copper catalyzed azide-alkyne cycloaddition (CuAAC) reactions have been utilized only for the postpolymerization functionalization of PCs. Recently, Dove [10] and Sanyal [16] groups have preperad allyl- and maleimide-functionalized cyclic carbonate monomers, followed by the ROP of these monomers (or with $_{L}$- lactide) using organic catalyst resulting in corresponding well-defined homopolymers (or copolymers). Finally, Michael-addition “thiol-ene” conjugations

were used to modify the pendant allyl or maleimide groups in a quantitive reaction without any obvious degradation of the resulting polymers.However, it is unfortunate that Michael-addition "thiol-ene" is a proper reaction for small organic molecule conjugation rather than polymer o the PC main backbone.

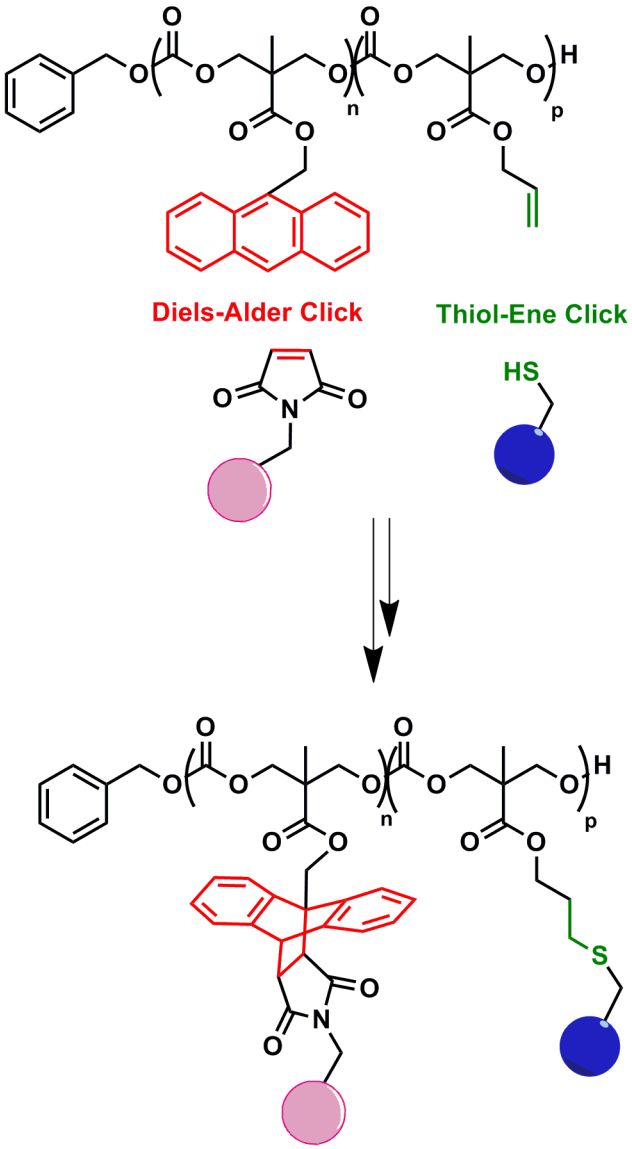


Figure 1.1: Synthesis of graft copolymers via ROP, Diels-Alder click reaction and Thiol-ene click reaction.

Similarly, the azido functionalized PC homopolymer or its copolymer was achieved via ROP of corresponding azido-cyclic carbonates using Sn $(Oct)_2$ as catalyst [9]. Subsequent CuAAC reaction of this pendant azido groups with alkyne-terminated poly(ethylene glycol) (PEG) in the presence of CuBr / Et_3N as catalyst yielded the corresponding graft copolymer in quantitive fashion. However, major drawbacks

here are to employ azido-cyclic carbonates, which have potential explosion risk and the use of toxic copper catalyst in the CuAAC reaction [18]. To overcome these disadvantages, here we used Diels-Alder click reactions, similarly CuAAC fulfill the click criteria related to synthetic polymer chemistry [19].

The copolymerization of anthracene- and allyl-functional cyclic carbonate monomers was carried out successfully via ring-opening polymerization (ROP) using benzyl alcohol as initiator, 1,8-diazabicyclo[5.4.0]undec-7-ene and 1-(3,5-bis(trifluorometh1-(3,5-bis(trifluoromethyl))-3-cyclohexyl-2-thiourea, as catalyst system. In the following study, modification reactions of the anthracene- and allyl-functional polycarbonate was accomplished under facile conditions via click reactions (Thiol-ene and Diels-Alder) with model compounds.

2. THEORETICAL PART

2.1 Living Polymerizations

The considerable attention to the field of living polymerization techniques is due to the increasing demand for well-defined functional polymers with fully controllable molecular characteristics. Living polymerization, the concept of which was first introduced by Szwarc in 1956, is one of the most promising ways for the synthesis of well-defined polymers [20,21]. A living polymerization is defined as a chain polymerization that proceeds in the absence of chain transfer and chain termination as indicated by Szwarc. His pioneering work on the anionic polymerization of St initiated with sodium naphthalenide opened the field of living polymers with controlling the molecular weight and molecular weight distributions as well as the structure of the end-groups.

After the discovery of living anionic polymerization, critical research on cationic polymerization was performed in the "living" era**.** An equimolar mixture of HI/I_2 was the first system used for the initiation of such polymerizations of vinyl ethers [22]**.** In this system, the initially formed adduct of HI to a vinyl ether is activated by iodine. The fast initiation realized ideal living cationic polymerization of alkyl vinyl ethers. Thus, homopolymers and block copolymers with narrow molecular weight distributions were first synthesized in cationic polymerization.

Since then, much progress has been made in these living ionic polymerization techniques and polymerization of various monomers have been examined, for which numerous types of initiators have been developed. While these techniques are undoubtedly successful, they do suffer from rigorous synthetic requirements including the use of very pure reagents and the total exclusion of water and oxygen and incompatibility with a variety of functional monomers. Definitely, with so many parameters to control, such requirements represent a grand challenge to synthetic polymer chemists and some what delay their practical use. Aware of the intrinsic limitations of ionic polymerizations, many efforts have been made to find new routes which could address the development of a free radical polymerization.

This process is tolerant to impurities, very versatile with respect to compatibility with broad range of functional monomers, and relatively easy to implement in an industrial plant.

2.2 Controlled/ ‘‘Living” Polymerizations

Macromolecular engineering of polymers with well-defined and applications through composition, size (molecular weight), uniformity (polydispersity), topology and end-functionality is essential to modern synthetic polymer chemistry research and advanced technological applications [23-29].

Nearly vast part of commercial synthetic polymers is made by using conventional free radical polymerization (FRP), which has so many advantages such as the polymerization of numerous vinyl monomers under mild reaction conditions, requiring an oxygen free medium, also tolerant to water, and a large temperature range (-80 to 250^{o}C) [30]. But it has some limitations, particularly in comparison with living processes [31, 32].

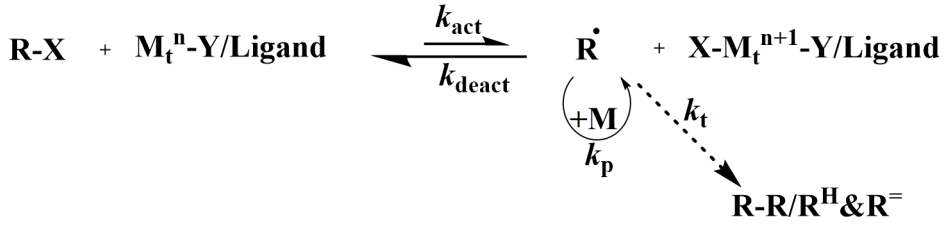
The term of living polymerization is a chain growth polymerization. An ‘’ideal’’ living system is that the growing chain end propagates without chain transfer and termination. Szwarc et al. reported the first living polymerization in 1956, which was the anionic polymerization of styrene with sodium naphthalenide [34, 35]. Well-defined polymers with uniform size, desired functionalities and various architectures have been increasingly achieved via living ionic polymerization. However, ionic polymerizations typically require stringent reaction conditions and have a limited range of (co)polymerizable monomers [33]. Following developments in living anionic polymerization by Michael Szwarc, new approaches towards synthesis of macromolecular engineered materials termed as controlled/’living” radical polymerizations (C/LRP) have been developed [36-38]. Mechanistically, C/LRPs are similar to FRP and proceed through the same intermediates. However, in C/LRPs the equilibrium between active and dormant species allows steadily growth of polymer chains via near instantaneous initiation and chain breaking reactions is minimized [37,39]. There are three classes of C/LRP, i.e. nitroxide mediated polymerization (NMP) [40, 41] atom transfer radical polymerization (ATRP) [42-45], and reversible addition-fragmentation chain transfer (RAFT) polymerization [46, 47].These methods have been known as powerful tools for preparing polymers with

predetermined molecular weights, narrow molecular weight distributions, specific end functionalities, and well- defined architectures [41].

2.2.1 Atom transfer radical polymerization (ATRP)

Thetransition-metal mediated controlled/‘‘living” radical polymerization, reported independently by Matyjaszewski [48], Sawamoto [49] and Percec [50] in 1995, is one of the most powerful techniques to obtain polymers with high control over compositions, architectures, and functionalities. The polymerization, which is mechanistically similar to atom transfer radical addition (ATRA), therefore, is often termed as atom transfer radical polymerization (ATRP).

A general mechanism for ATRP is shown in 2.1. ATRP is based on the reversible homolytic cleavage of carbon-halogen bond by a redox reaction. Homolytic cleavage of the alkyl (pseudo)halogen bond (RX) by a transition metal complex (activator, M_t^n –Y / ligand, where Y may be another ligand or a counterion) in the lower oxidation state generates an alkyl radical ($R^{\bullet}$) and a transition metal complex (deactivator, X–M_t^{n+1}/ ligand) in the higher oxidation state. The formed radicals can initiate the polymerization by adding across the double bond of a vinyl monomer, propagate, terminate by either coupling or disproportionation, or be reversibly deactivated by the transition metal complex in the higher oxidation state to reform the dormant species and the activator.



(2.1)

This process occurs with a rate constant of activation, k_{act}, and deactivation k_{deact}, respectively. Polymer chains grow by the addition of the free radicals to monomers in a manner similar to a conventional radical polymerization, with the rate constant of propagation, k_p. Termination reactions (k_t) also occur in ATRP, mainly through radical coupling and disproportionation; however, in a well-controlled ATRP, no more than a few percent of the polymer chains undergo termination. Typically, no more than 5% of the total growing polymer chains terminate during the initial, short, nonstationary stage of the polymerization. Other side reactions may additionally limit the achievable molecular weights.

This process generates oxidized metal complexes, the deactivators, which behave as persistent radicals to reduce the stationary concentration of growing radicals and thereby minimize the contribution of termination at later stages. A successful ATRP will have not only small contribution of terminated chains but also uniform growth of all the chains; this is accomplished through fast initiation and rapid reversible deactivation.

The ATRP equilibrium (K_{eq}= k_{act}/k_{deact}) essentially mediates the rate of polymerization (R_p), defined by 2.2, by ensuring steady and concurrent growth of all polymer chains, resulting in well-defined polymers with narrow molecular weight distributions. K_{eq} must be low to maintain a low stationary concentration of radicals; thus, the termination reaction is suppressed.

$$R_p = k_p.K_{eq}\frac{[R\text{-}X][M_t^n]}{[M_t^{n+1}]}.[M] \quad (2.2)$$

$$\frac{M_w}{M_n} = 1 + \left(\frac{k_p[R\text{-}X]}{k_{deact}[M_t^{n+1}]}\right)\left(\frac{2}{p} - 1\right) = 1 + \frac{2}{k_{act}[M_t^n]t} \quad (2.3)$$

The rate of ATRP, R_p, has been shown to be the first order with respect to the monomer [M] and initiator [R-X]. The rate of polymerization is also influenced by the ratio of concentrations of the activator to the deactivator, although this may change during polymerization.

Equation 2.3, which shows how the polydispersity index in ATRP (in the absence of chain termination and transfer) relates to the concentrations of initiator (RX) and deactivator (M_t^{n+1}), the rate constants of propagation (k_p), deactivation (k_{deact}), and monomer conversion (p). Lower polydispersities are obtained at higher conversion, higher k_{deact} relative to k_p, higher concentration of deactivator, and higher monomer to initiator ratio, $[M]_0/[I]_0$ [51, 52, 53].

An ATRP system consists of the monomer, an initiator, and a catalyst composed of a transition metal species complexed with any suitable ligand. A detailed discussion of the basic components of ATRP is elucidated extensively in the following sections.

Monomers

A variety of monomers, including styrene, acrylonitrile, (meth) acrylates, (meth) acrylamides, 1,3-dienes, and 4-vinylpyridine, undergo ATRP. The less reactive monomers, such as ethylene, vinyl chloride, and vinyl acetate, have not been polymerized by ATRP. Some other monomers may be difficult to polymerize since they exhibit side reactions. An example of such a monomer is 4-vinyl pyridine (4-VP), which can undergo quaternization by the (alkyl halide) initiator [54]. The most common monomers in the order of their decreasing ATRP reactivity are methacrylates, acrylonitrile, styrenes, acrylates, (meth)acrylamides [55].

Initiators

Generally, initiators used in ATRP are alkyl halides (RX) (or pseudohalides,) with α-phenyl, vinyl, carbonyl, cyano groups and multiple halogen atoms as well as any compound with a weak halogen-heteroatom bond, such as sulfonyl halides. The primary role of the initiator is to determine the number of dormant chains and to provide the end groups of the polymer chains.

To obtain well-defined polymers with narrow molecular weight distributions, the (pseudo) halide group, X, must rapidly and selectively migrate between the growing chain and the transition metal complex. Thus far, bromine and chlorine are the halogens that afford the best molecular weight control. Iodine works well for acrylate polymerizations; however, in styrene polymerizations the heterolytic elimination of hydrogen iodide is too fast at high temperatures. Fluorine is not used because the carbon–fluorine bond is too strong to undergo homolytic cleavage. As for other X groups, some pseudohalogens, specifically thiocyanates, have been used successfully in polymerization of acrylates and styrenes [56-58].

Initiator efficiency is of prime importance for succesful ATRP. Generally, alkyl halides RX with resonance stabilizing substituents are efficient initiators for ATRP. Often, the structure of the initiator is analogous to the structure of the halogenated polymer chain end to obtain similar reactivity of the carbon-halogen bond. For example, styrene polymerizations often incorporate 1-phenylethyl chlorides or bromides as the initiators [59]. However, this guideline does not always hold as demonstrated in the polymerization. The use of sulfonyl chlorides as universal initiator in ATRP of styrene and methacrylates was reported [60].

The initiator can not only be a small molecule, but also a polyfunctional small molecule, or a macromolecule, which would produce end-functional polymers, star polymers, and graft copolymers, respectively.

Catalysts

Catalyst is the most important component of ATRP. It is the key to ATRP since it determines the position of the atom transfer equilibrium and the dynamics of exchange between the dormant and active species. There are several prerequisites for an efficient transition metal catalyst. An efficient catalyst should be able to expand its coordination sphere and oxidation number upon halogen abstraction from an initiator (alkylhalide) or dormant polymer chains. The metal center should have reasonable affinity toward a halogen. Additionally, the catalyst should not participate in any side reactions which would lower its activity or change the radical nature of the ATRP process.

Various transition metals, such Re [61], Ru [62], Rh [63], Fe [64-69], Ni [70,71], Pd [72] and Cu [73,74] has been successfully used as catalysts for ATRP. Among them, Cu seems to be the most efficient metal as determined by the successful application of its complexes as catalysts in the ATRP of a broad range of monomers in diverse media [75].

Ligands

Ligands solubilize the transition metal salt in organic media and adjust the redox potential of the metal center for appropriate activity. For copper catalysts, bidentate and multidentate, but not monodentate, nitrogen ligands work best. Bridged and cyclic ligands as well as branched aliphatic polyamines yield more active catalysts than do simple linear ligands. 4,4-Dialkyl-2,20-bipyridines and tris-(2-dimethylaminoethyl)amine are examples of active ligands [76,77].

Ligands for ATRP systems include multi dentate alkylamines, pyridines, pyridine imines, phosphines, ethers or half-metallocenes pecies. Copper complexes with various multi dentate N-containing ligands are most of ten used as ATRP catalyst ssuch as PMDETA, and tris[2-(dimethylamino) ethyl]amine (Me6-TREN) [77].The ATRP catalytic activity of Cu(I) complexes increases in the order bipyridine (bpy)<1, 1, 4, 7, 10, 10- hexamethyl triethylene tetramine (HMTETA)<

PMDETA<tris(2-pyridylmethyl)amine (TPMA)< Me6-TREN<dimethylcross-bridgecyclam (DMCBCy). The most active complex known to date is derived from the cross-bridged cyclam ligand DMCBCy [51].

While nitrogen ligands are typically used for copper-based ATRP, phosphorus-based ligands are used for most other transition metals in ATRP.

Solvents

ATRP has been carried out in bulk, solution, suspension, and aqueous emulsion. A range of solvents have been used for solution polymerization, including toluene, ethyl acetate, alcohols, water, ethylene carbonate, DMF, and supercritical carbon dioxide. Apart from the usual considerations, one needs to consider if a solvent interacts with and affects the catalyst system, such as by displacement of ligands. Some polymer end groups (e.g., polystyryl halide) can undergo substitution or elimination in polar solvents at polymerization temperatures.

ATRP can be carried out in aqueous heterogeneous systems (suspension and emulsion) with proper choice of the components of the reaction system (initiator, activator, deactivator). The components need to be chosen so that they are stable in the presence of water and soluble in the organic phase with minimal solubility in the aqueous phase [76,77].

2.2.2 Nitroxide mediated radical polymerization (NMP)

Nitroxide mediated radical polymerization (NMP) is a living polymerization process. It is capable of producing well-defined polymers with narrow molecular weight distribution (MWDs) and predictable molecular weights (MWs).

It is interesting to note a similarity between the iniferter mechanism and the general outline of a successful living free radical mechanism (Figure 2.1).

The identity of the mediating radical, $R^{\cdot}$, is critical to the success of living free radical procedures and a variety of different persistent, or stabilized radicals have been employed. These range from (arylazo)oxy [81], substituted triphenyls,[82] verdazyl [83], triazolinyl [84], nitroxides [85] etc. with the most widely studied and certainly most successful class of compounds being the nitroxides, especially 2,2,6,6-tetramethylpiperidinoxy (TEMPO), and their associated alkylated derivatives, alkoxyamines.

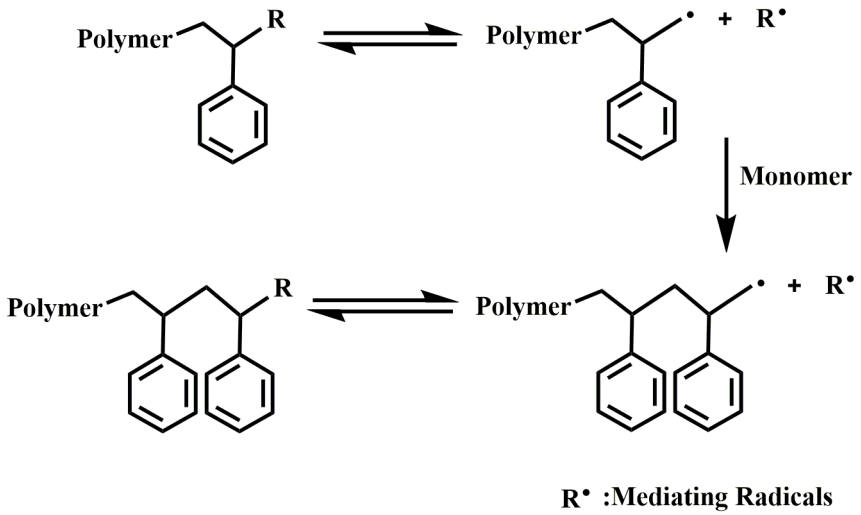


Figure 2.1: General mechanism of nitroxide mediated radical polymerization.

The 2,2',6,6'- tetramethylpiperidine-1-oxyl radical (TEMPO) was used as the nitroxide component in these initial studies. The alkoxyamine is formed in situ during the polymerization process [86]. Although NMP is one of the simplest methods of living free radical polymerization (LFRP), it has many disadvantages. Many monomers will not polymerize because of the stability of the dormant alkoxyamine that forms. Also, since the reaction is kinetically slow, high temperatures and bulk solutions are often required. Also, the alkoxyamine end groups are difficult to transform and require radical chemistry.

The chain end functionalization of polymers synthesized by NMP is a significant problem because dormant chains containing alkoxyamines can regenerate terminal radicals which can depolymerize at high temperatures. A very interesting chain end functionalization process has also been discovered by Hawker et. al. which involves the controlled monoaddition of maleic anhydride or maleimide derivatives to the alkoxyamine chain end. The alkoxyamine can then be easily eliminated and other functional groups can be introduced [87] to initiator ratio, $[M]_0/[I]_0$ [78,79,80].

2.2.3 Reversible-Addition fragmentation chain transfer (RAFT)

The most recent report of a controlled/"living" free radical polymerization has been reported by Haddleton and co-workers as well as Thang et al. Reversible addition-fragmentation chain transfer (RAFT) is achieved by performing a free radical

polymerization in the presence of dithio compounds, which act as efficient reversible addition-fragmentation chain transfer agents [88].

Reversible addition-fragmentation chain transfer (RAFT) incorporates compounds, usually dithio derivatives, within the living polymerization that react with the propagating center to form a dormant intermediate. The dithio compound can release the alkyl group attached to the opposite sulfur atom which can then propagate with the monomer. The greatest advantage to RAFT is the incredible range of polymerizable monomers. As long as the monomer can undergo radical polymerization, the process will most likey be compatible with RAFT. However, there are many major drawback that arise when using this process. The dithio end groups left on the polymer give rise to toxicity, color, and odor and their removal or displacement requires radical chemistry. Also, the RAFT agents are expensive and not commercially available [89].

2.3 Ring-Opening Polymerization (ROP)

Polylactones and polylactides can be prepared by two different approaches, by the polycondensation of hydroxycarboxylic acids or by the ring-opening polymerization. The polycondensation technique is less expensive than ROP. However, it is hard to get high molecular weight polymers, to success specific end groups, and to prepare well-defined copolyesters [90]. Ring-opening polymerization (ROP) is a unique polymerization process, in which a cyclic monomer is opened to generate a linear polymer. It is fundamentally different from a condensation polymerization in that there is no small molecule byproduct during the polymerization. Polymers with a wide variety of functional groups can be produced by ring-opening polymerizations. Preparation of cyclic monomers, studies of catalysis and mechanisms are active areas of research both in industry and academia [91-94].

Nowadays, increasing attention is paid to degradable and biodegradable biocompatible polymers for applications in the biomedical and pharmaceutical fields, primarily because after use they can be eliminated from the body via natural pathways and also they can be a solution to problems concerning the global environment and the solid waste management. Aliphatic polyesters are among the most promising materials as biodegradable polymers.

The most remarkable aspect of ROP was theoretically cleared by Flory; the invariant number of propagating chains in the ROP results in the generation of polymerization (DP). the advanteges of ROP in conjuction with a “living” method have facilitated the controlled synthesis of block, graft, and star polymers, which leads to a present consensus that living ROP is a powerful and versatile addition-polymerization method [95].

Tradationally, mechanisms for ROP are divided into cationic and anionic polymerization in terms of the ionic charge of active propagating species. A special case is “coordination-insertion” mechanism, which involves metal-catalyzed ROPs. this mechanism is formed from coordination of monomer to metal of a catalyst and insertation of the monomer to the to the metal-oxygen bond [95].

2.3.1 Controlled Ring-Opening Polymerization of Cyclic Esters

The ring opening polymerization (ROP) of lactones and lactides to produce poly(ester)s provides versatile biocompatible and biodegradable polymers possessing good mechanical properties.

These advantages have seen aliphatic poly(ester)s receive increasing attention over the last few years driven by their application as biodegradable substitutes for conventional commodity thermoplastics and applications in the biomedical field [96].

There are some reasons for studying the polymerization of cyclic esters. Firstly, to take advantage of the potential of preparing variety of polymers with control of the major variables affecting polymer properties in synthetic polymer. In addition, there are some important factors such as economy, toxicology, and technical apparatus development. Secondly, ROP facilitates to synthesise various advanced macromolecules, involving homopolymers with well-defined structures or end groups, or copolymers such as block, graft or star copolymers[90].

If aliphatic poly(ester)s are synthesized by polycondensation of hydroxyl-carboxylic acids, yield of resulting polyesters is low molecular weight polyesters (M_n<30.000) with poor control of specific end groups [97].In contrast, high molecular weight aliphatic polyesters can be prepared in short periods by ROP. There has been much research directed towards the controlled ROP of commercially available cyclic esters

including glycolide, lactide and ε-caprolactone resulting in aliphatic poly(ester)s with high molecular weights [98].

In practice, the ROP of lactones and lactides requires an appropriate catalyst to proceed in reasonable conditions and to afford polymers with controlled properties (2.3).

Since the pioneering work of Kleine et al. in the 1950s metal-based catalytic systems have been the focus of considerable attention for the polymerization of cyclic esters, and numerous studies have been carried out to elucidate the mechanism of such coordination polymerizations. Through variation in the nature of the metal center and of the surrounding ligands, a broad range of initiators have been prepared and evaluated [99,100,101,102].

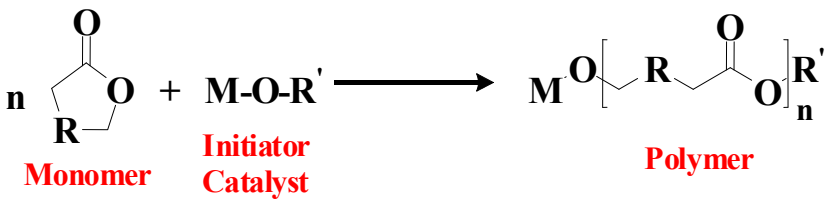


Figure 2.2: Schematic reprensantation of the ROP of a cyclic ester R=$(CH_2)_{0-3}$ and/or (CHR').

Besides the coordination-insertion mechanism, alternative strategies based on anionic, nucleophilic, or cationic promoters have also been recently (re)evaluated, the preliminary results reported in these fields being rather promising [103,104].

Catalysts

A large variety of organometallic compounds, such as metal alkoxides and metal carboxylates, has been studied as initiators or catalysts in order to achieve effective polymer synthesis [100]. The covalent metal alkoxides with free p or d orbitals react as coordination initiators and not as anionic or cationic initiators [105]. The most widely used complex for the industrial preparation of polylactones and polylactides is undoubtedly tin(II)2-ethylhexanoate, commonly referred as stannous octoate [$Sn(Oct)_2$]. It has been approved as a food additive by the American Food and Drug Administration (FDA) [90]. It is also commercially available, easy to handle and soluble in common organic solvents and in melt monomers. It is highly active and

allows for the preparation of high-molecular-weight polymers in the presence of an alcohol [106]. Aluminum alkoxides have also proved to be efficient catalysts for the ROP of cyclic esters. The common example, namely, aluminum (III) isopropoxide, $Al(Oi\text{-}Pr)_3$, has been largely used for mechanistic studies. However, it has been revealed to be significantly less active than $Sn(Oct)_2$ [107]. Moreover, an induction period of a few minutes is systematically observed with $Al(Oi\text{-}Pr)_3$ attributed to aggregation phenomenon [108].

For all these reasons, $Al(Oi\text{-}Pr)_3$ is much less used for the preparation of biodegradable polyesters, and especially since aluminum ions do not belong to the human metabolism and are suspected of supporting Alzheimer's disease.

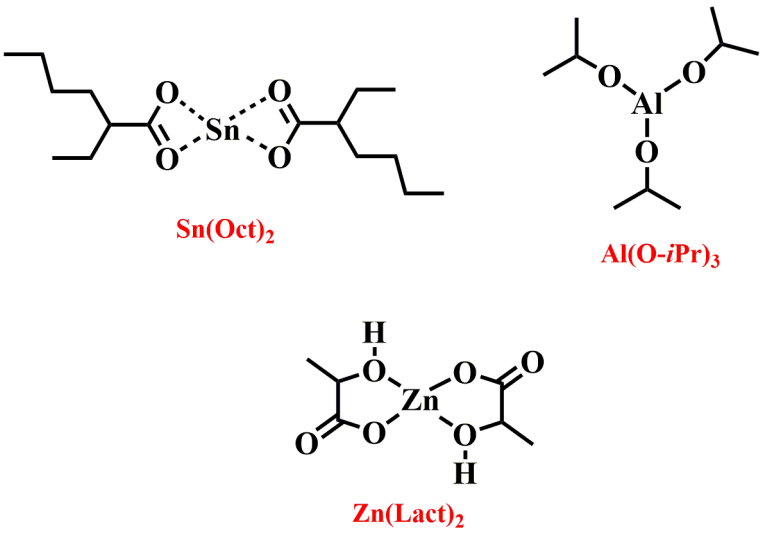


Figure 2.3: Catalysts of Ring Opening Polymerization.

Much interest has been devoted to zinc derivatives as potential nontoxic catalysts. Zinc powder itself is a relatively good polymerization catalyst that is used industrially [109]. With reaction times of several days at 140 °C in bulk, it is roughly as active as $Al(Oi\text{-}Pr)_3$. Numerous zinc salts have also been investigated [110].

Although polymerization of alifatic cyclic carbonetes has been reported using organometallic catalysts (MAO, IBAO, $Sn(Oct)_2$ and $Al(Oi\text{-}Pr)_3$) and as well as enzymes, there are some metal-free catalysts polymerizations of carbonetes and other cyclic monomers such as lactones.

Simple organic molecules like 4-dimethylaminopyridine (DMAP), 4-pyrrolidinopyridine (PPY) and some phosphines have shown to support ROP of cyclic monomers in the presence of a proper nucleophilic initiator. Most of these

catalysts have the advantages of being commercially available or readily synthesized [111-113].

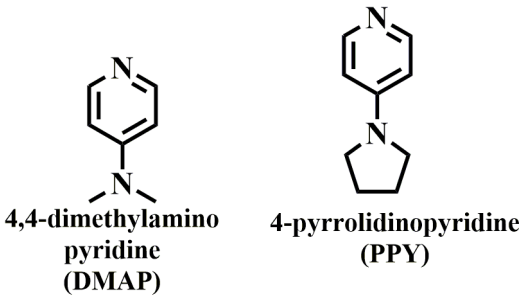


Figure 2.4: Metal-free Catalysts of Ring Opening Polymerization.

N-heterocyclic carbenes (NHCs) become a new class of highly active catalysts owing to their high nucleophility. Their important reactivity for transesterification reactions are manifested in their ability to catalyze ROP of lactones and carbonates [113].

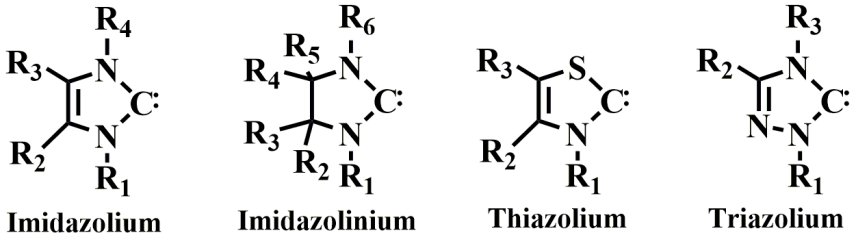


Figure 2.5: N-heterocyclic Carbenes Catalysts for Ring Opening Polymerization.

Other organic catalysts have been developed that supply electrophilic and nucleophilic activations. Amine substituted ureas and thioureas proved to be highly selective for the ROP of cyclic carbonetes to give predictable molecular weights, narrow polydispersities along with end-group fidelty.

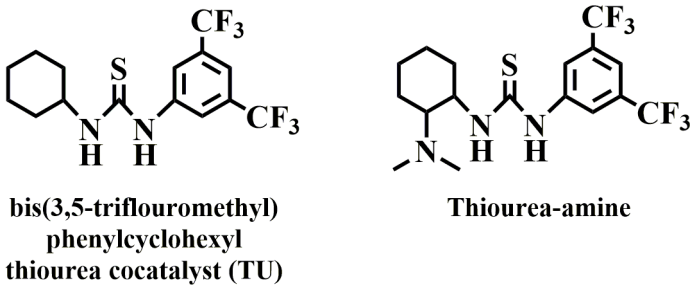


Figure 2.6: Amine Substituted Ureas and Thioureas Catalysts for ROP.

Both using bis(3,5-triflouromethyl) phenylcyclohexyl thiourea cocatalyst (TU) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) caused to quantitative monomer conversion in much shorter times while maintainng the excellent control over the polyester molecular parameters [113].

2.3.2 Cationic Ring-Opening Polymerization

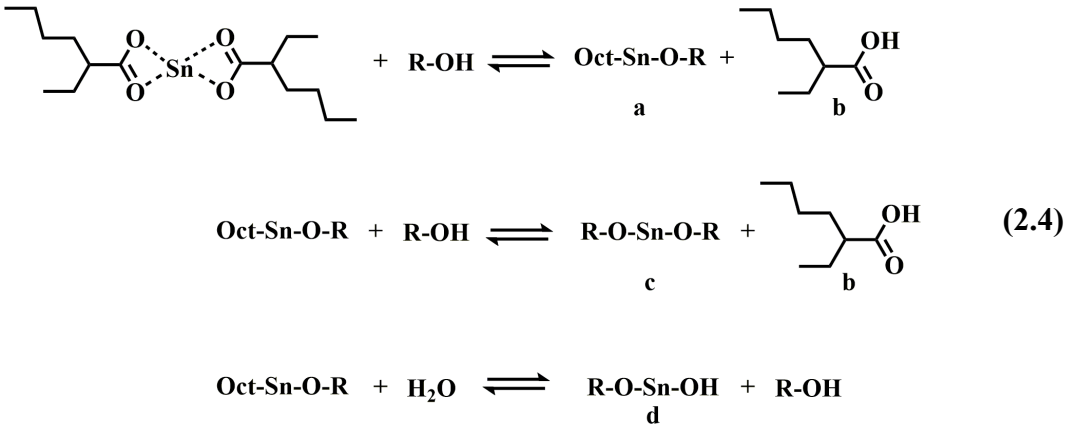
For the ROP of a variety of cyclic heterocycles, cationic polymerization has been applied. the cationic ROP of lactones has been achieved using alkylating agents, acylating agents, Lewis acids, and protic acids. Early 1970s, it was reportted by Dittrich and Schultz that LA polymerization with cationic compounds were unsuccessfull. In 1986, Kricheldorf and co-workers screened a variety of acidic compounds, among which triflouromethanesulfonic acid (triflic acid, HOTf) and methyl triflate (MeOTf) proved to be useful initiators for cationic ROP of LA [110].

2.3.3 Anionic Ring-Opening Polymerization

The anionic polymerization of lactones with Li or K alkoxides is well-known. However, less work has been done on the anonic ROP of strained heterocycles with organic counterions [110].

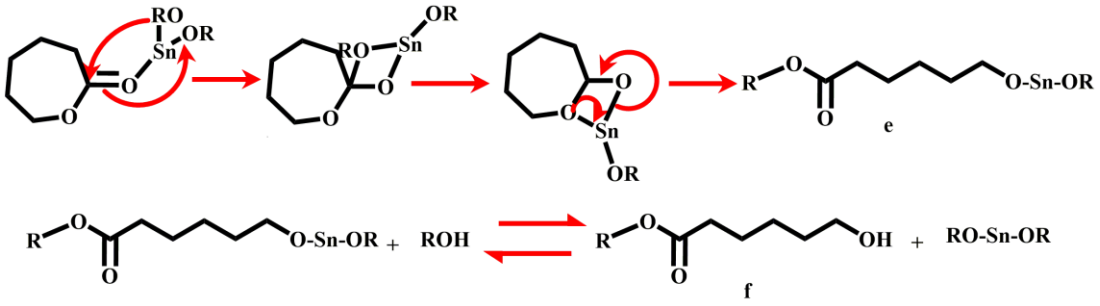
2.3.4 Coordination-Insertion Ring-Opening Polymerization

Covalent metal carboxylates, particularly tin(II) bis(2-ethylhexanoate) usually referred to as tin(II) octanoate, $Sn(Oct)_2$ belong to the most frequently used initiators for polymerization of cyclic esters due to its low cost, low toxicity, and high efficiency. Although, there are controversial reports in the literature about the nature of $Sn(Oct)_2$ activity in the polymerization of lactones, two basic types of mechanism have been proposed. The first one is directly catalytic type where the catalyst serves to activate monomer through coordination with its carbonyl oxygen [114, 115]. The second mechanism is the monomer insertion type mechanism where the catalyst acts as co-initiator along with either purposely added or adventitious hydroxyl impurities, and polymerization proceeds though an activated stannous alkoxide bond [116,117].



(2.4)

Kricheldorf and co-workers have recently illustrated how the structure of the alcohol initiator may influence the strength of the catalyst/alcohol interaction [115, 117]. According to these authors, this interaction, in the early stages of reaction, is responsible for formation of the "true" initiating species, subsequent ring opening, and formation of the active, propagating chain end. Prior to the beginning of polymerization, adventitious hydroxyfunctional impurities (e.g., water) or purposely added alcohol first complex and subsequently react with $Sn(Oct)_2$ producing a stannous alkoxide species (a) and free 2-ethylhexanoic acid (b) as shown in 2.4. Further reaction with a second equivalent of alcohol produces the stannous dialkoxide initiator (c) and releases a second equivalent of 2-ethylhexanoic acid (b) as depicted in 2.4 [116, 117]. Adventitious water, meanwhile, serves mainly as a catalyst deactivator via a reversible reaction with a or c, thereby decreasing the concentration of active initiator and producing a stannous alcohol derivative (d), such as shown in 2.4, which is more thermodynamically stable than the stannous dialkoxide and is less efficient as an initiator [117].



(2.5)

Reaction of c with monomer by means of coordination- insertion generates the first actively propagating chain end (e) consisting of not only the initiating alcohol fragment but also the active propagating center derived from the first monomer unit and stannous alkoxide. The e species may either propagate or undergo rapid intermolecular exchange of the stannous alkoxide moiety for a proton from either hydroxyl groups of initiator (if remaining) or another hydroxy chain end, either e or polymeric in nature. This rapid exchange of protons and stannous alkoxide moieties results in a dynamic equilibrium between activated and deactivated chain ends as depicted in 2.6, where R=unreacted alcohol initiator or hydroxy chain ends generated in situ. This process eventually consumes the remaining unreacted alcohol initiator not involved in the initial formation of c. ROP based on coordination-insertion

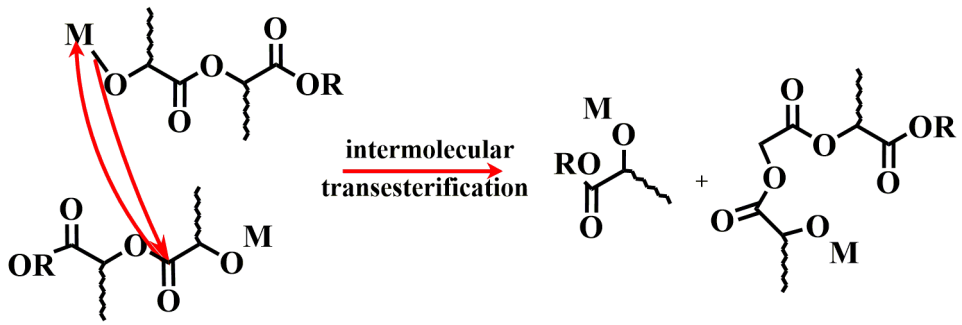
mechanism has been thoroughly investigated since it may yield well-defined polyesters through living polymerization [107, 118].

In such coordination-insertion polymerizations, the efficiency of the molecular-weight control depends from the ratio $k_{propagation}/k_{initiation}$ but also from the extent of transesterification side reactions. These transesterification reactions can occur both intramolecularly (backbiting leading to macrocyclic structures and shorter chains) and intermolecularly (chain redistributions) [119].

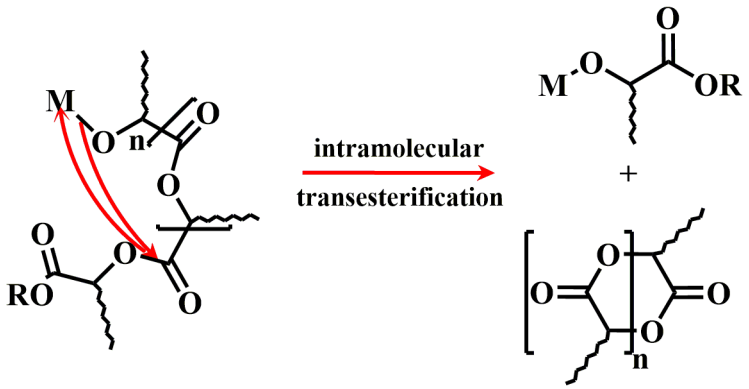
Intermolecular transesterification reactions modify the sequences of copolylactones and prevent the formation of block co-polymers. Intramolecular transesterification reactions cause degradation of the polymer chain and the formation of cyclic oligomers.

The polymerization/depolymerization equilibrium should also be taken into account as a particular case of intramolecular transesterification reaction. All of these side reactions result in broader molecular-weight distributions, sometimes making the molecular weights of the resulting polymers irreproducible. The extent of these undesirable transesterification reactions was found to strongly depend on the metallic initiator [109]. Side reactions occur from the very beginning of the polymerization with $Sn(Oct)_2$, leading to rather broad MWD (PDI indexes around 2) but only at high or even complete conversion with $Al(O\textit{i}\text{-}Pr)_3$, yielding lower PDI indexes (less than 1.5) [109,120].

Parameters that influence the number of transesterifications are temperature, reaction time, and type and concentration of catalyst or initiator. Depending on the metal used, the initiator is more or less active towards transesterification reactions [120].



(2.6)



(2.7)

The promising results obtained with $Sn(Oct)_2$, $Al(O\textit{i}\text{-}Pr)_3$, and $Zn(Lact)_2$ have given rise to a growing interest in metal-based initiators that would display higher catalytic activity and better control the extent of the undesirable transesterification reactions.

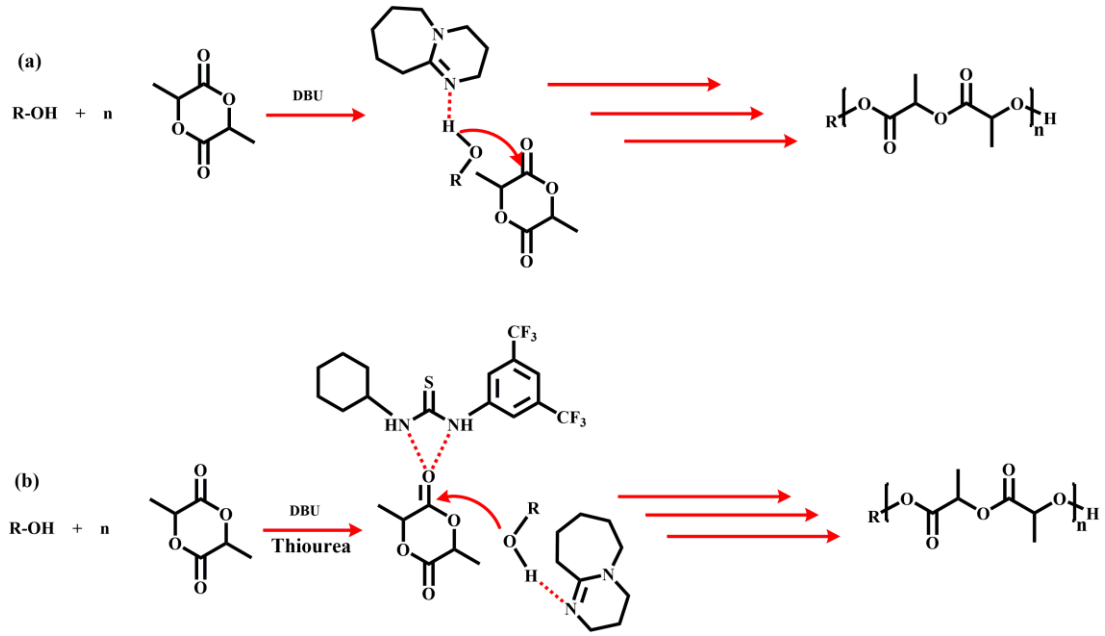


Figure 2.7: (a) Chain-end/general base activation in the presence of LA and DBU and **(b)** bifunctional activation of LA in the presence of ROH from an equimolar mixture of thiourea and DBU [113].

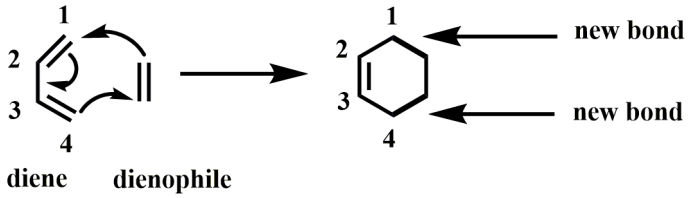
2.4 Click Chemistry

"Click chemistry" is a chemical term introduced by Sharpless in 2001 and describes chemistry tailored to generate substances quickly and reliably by joining small units together [123]. Click chemistry can be summarized only one sentence: Molecules that are easy to make. Sharpless also introduced some criteria in order to fullfill the requirements as reactions that: are modular, wide in scope, high yielding, create only

inoffensive by-products, are stereospecific, simple to perform and that require benign or easily removed solvent. Nowadays there are several processes have been identified under this term in order to meet these criterias such as nucleophilic ring opening reactions; non-aldol carbonyl chemistry; thiol additions to carbon–carbon multiple bonds (thiol-ene and thiol-yne); and cycloaddition reactions. Among these selected reactions, copper(I)-catalyzed azide-alkyne (CuAAC) and Diels-Alder (DA) cycloaddition reactions and thiol-ene reactions have gained much interest among the chemists not only the synthetic ones but also the polymer chemists.

2.4.1 Diels-Alder Reaction

The Diels-Alder (DA) reaction is a concerted [4π+2π] cycloaddition reaction of a conjugated diene and a dienophile. This reaction is one of the most powerful tools used in the synthesis of important organic molecules. The three double bonds in the two starting materials are converted into two new single bonds and one new double bond to afford cyclohexenes and related compounds (2.8). This reaction is named for Otto Diels and Kurt Alder, who received the 1950 Nobel prize for discovering this useful transformation [114-116].

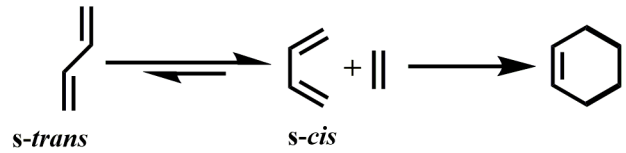


(2.8)

Typically, the DA reaction works best when either the diene is substituted with electron donating groups (like -OR, -NR2, etc) or when the dienophile is substituted with electron-withdrawing groups (like -NO2, -CN, -COR, etc) [117].

2.4.1.1 Stereochemistry of Diels-Alder Reaction

There are stereochemical and electronic requirements for the DA reaction to occur smoothly. First, the diene must be in an s-cis conformation instead of an s-trans conformation to allow maximum overlap of the orbitals participating in the reaction (2.9).

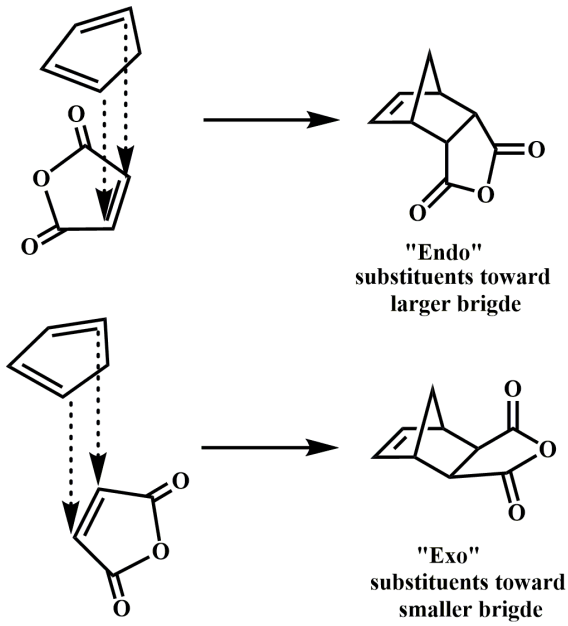


(2.9)

The "s" in s-cis and s-trans refers to "sigma", and these labels describe the arrangement of the double bonds around the central sigma bond of a diene. Dienes often exist primarily in the lower energy s-trans conformation, but the two conformations are in equilibrium with each other. The s-cis conformation is able to react in the DA reaction and the equilibrium position shifts towards the s-cis conformer to replenish it. Over time, all the s-trans conformer is converted to the s-cis conformer as the reaction proceeds.

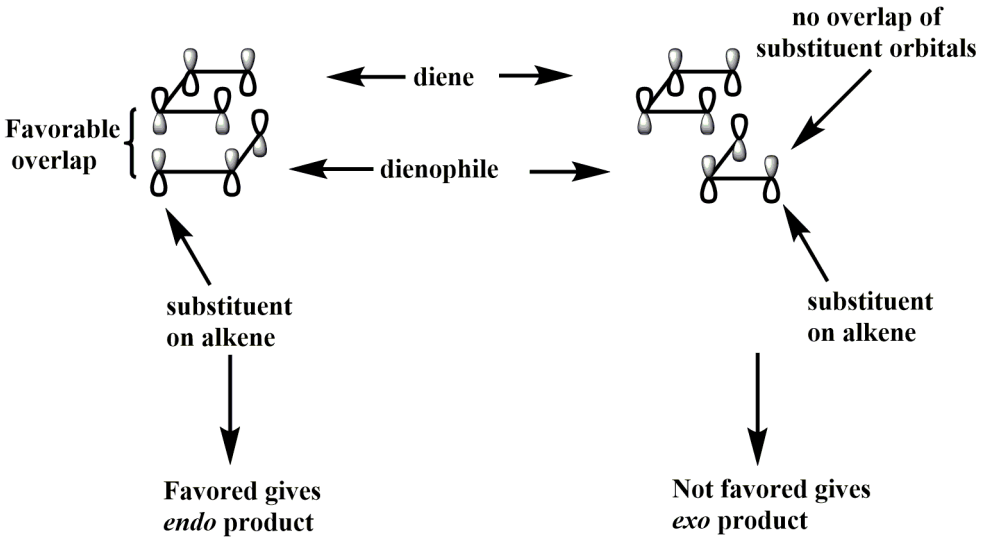
A unique type of stereoselectivityis observed in DA reactions when the diene is cyclic. In the reaction of maleic anhydride with cyclopentadiene, for example, the endo isomer is formed (the substituents from the dienophile point to the larger bridge) rather than the exo isomer (the substituents from the dienophile point away from the larger bridge) (2.10).

The preference for endo–stereochemistry is "observed" in most DA reactions. The fact that the more hindered endo product is formed puzzled scientists until Woodward, Hoffmann, and Fukui used molecular orbital theory to explain that overlap of the p orbitals on the substituents on the dienophile with p orbitals on the diene is favorable, helping to bring the two molecules together [118,119].



(2.10)

Hoffmann and Fukui shared the 1981 Nobel Prize in chemistry for their molecular orbital explanation of this and other organic reactions. In the illustration below, notice the favorable overlap (matching light or dark lobes) of the diene and the substituent on the dienophile in the formation of the endo product (2.11):



(2.11)

Oftentimes, even though the endo product is formed initially, an exo isomer will be isolated from a DA reaction. This occurs because the exo isomer, having less steric strain than the endo, is more stable, and because the DA reaction is often reversible under the reaction conditions. In a reversible reaction, the product is formed, reverts to starting material, and forms again many times before being isolated. The more stable the product, the less likely it will be to revert to the starting material. If the reaction is not reversible under the conditions used, the kinetic product will be isolated. However, if the first formed product is not the most stable product and the reaction is reversible under the conditions used, then the most stable product, called the thermodynamic product, will often be isolated.

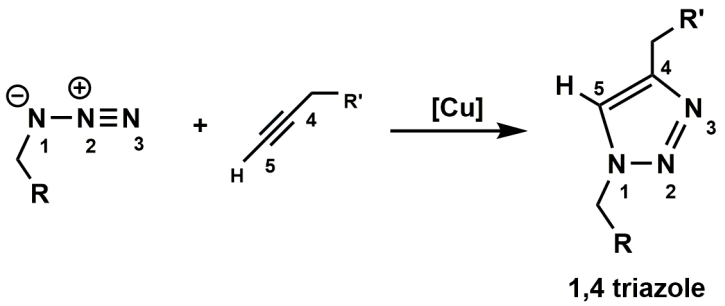
2.4.2 Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC)

Huisgen's 1,3-dipolar cycloaddition of alkynes and azides yielding triazoles is, undoubtedly, the premier example of a click reaction [120]. Recently, 1,3-dipolar cycloadditions, such as reactions between azides and alkynes or nitriles, have been applied to macromolecular chemistry, offering molecules ranging from the block copolymers to the complexed macromolecular structures [121].

Sharpless and co-workers have identified a number of reactions that meet the criteria for click chemistry, arguably the most powerful of which discovered to date is the Cu(I)-catalyzed variant of the Huisgen 1,3-dipolar cycloaddition of azides and alkynes to afford 1,2,3-triazoles [122]. Because of Cu(I)-catalyzed variant of the Huisgen 1,3-dipolar cycloaddition of azides and alkynes reactions' quantitative yields, mild reaction condition, and tolerance of a wide range of functional groups, it is very suitable for the synthesis of polymers with various topologies and for polymer modification [123]. Because of these properties of Huisgen 1,3-dipolar cycloaddition, reaction is very practical. Moreover, the formed 1,2,3-triazole is chemically very stable [124].

In recent years, triazole forming reactions have received much attention and new conditions were developed for the 1,3-dipolar cycloaddition reaction between alkynes and azides [125]. 1,2,3-triazole formation is a highly efficient reaction without any significant side products and is currently referred to as a click reaction [126].

Copper(I)-catalyzed reaction sequence which regiospecifically unites azides and terminal acetylenes to give only 1,4-disubstituted 1,2,3 triazoles (2.12).



(2.12)

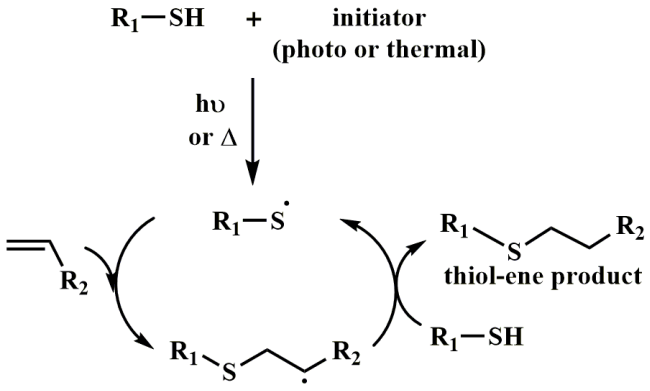
In fact, the discovery of Cu(I) efficiently and regiospecifically unites terminal alkynes and azides, providing 1,4-disubstituted 1,2,3-triazoles under mild conditions, was of great importance. On the other hand, Fokin and Sharpless proved that only 1,5-disubstituted 1,2,3-triazole was obtained from terminal alkynes when the catalyst switched from Cu(I) to ruthenium(II) [124].

2.4.3 Thiol-ene click reaction

The thiol-ene reaction is an emerging synthetic tool that is considered to be a "click" reaction because the reaction has many of the attributes of the "click" reaction, for

example, quantitative yields, rapid reaction rates, mild reaction conditions, and tolerant of various solvents and functional groups.

The thiol-ene chemistry, which involves the hydrothiolation of a C=C bond, can be induced photochemically or thermally at ambient temperatureto mainly give an anti-Markownik-type product. Generally, the thiol-ene reaction follows a radical-mediated process, with initiation, propagation and termination steps. Initiation involves the treatment of a thiol with an initiator, under irradiation or heat, subsequently generating a thiyl radical, $RS^{\cdot}$, via hydrogen abstraction, plus other byproducts (2.13). Propagation then occurs in two step which involves first the direct addition of the thiyl radical to the C=C bond producing an intermediate thioether carbon radical followed by chain transfer to a second molecule of thiol to give the thiol-ene addition product with the concomitant generation of a new thiyl radical. Termination is believed to ocur through the radical-radical recombination of the thioether carbon and/or thiyl radicals. Although thiol–ene "click" reaction has mainly been focused on a radical-mediated version to non-activated alkenes, this reaction can also proceed via nucleophilic (Michael) addition, especially when the vinyl group is alpha to an electron withdrawing moiety.



(2.13)

The Michael addition applies to α, β-unsaturated carbonyl compounds such as acrylate, maleimido, etc., and an intermediate thioanion is usually generated owing to the usage of a base or nucleophilic catalysis such as Et_3N, primary/secondary amines or certain phosphines for the reaction.

The thiol-ene ''click'' reactions, through either a radical or nucleophilic mechanism, provide efficient hydrothiolation routes across virtually any double bond [125-129].

Over the years, the thiol-ene ''click'' reaction has been extensively exploited in polymer chemistry since it can be conducted under various conditions without any

metal catalyst. The UV-induced crosslinking of unsaturated polymers (photocuring) by reaction with multifunctional thiols is currently employed in surface coating owing to a number of advantages over other curing methods. Biomaterials for application in medicine, especially dentistry, have been prepared by using this process. Only recently, however, has the "click" aspect of the thiol-ene ''click'' reaction been fully appreciated in the field of polymer science. The use of thio-Michael addition as a "click" reaction was recently reported by Lowe et al. for the synthesis of star polymers [130]. The great potential of thiol–ene chemistry was exploited by Hawker and co-workers in the synthesis of poly(thioether) dendrimers [131].Consequently, numerous examples are available in the literature for polymer end group and backbone modification [132-134], many of which are covered in various excellent reviews [135,136].

2.5 Topology

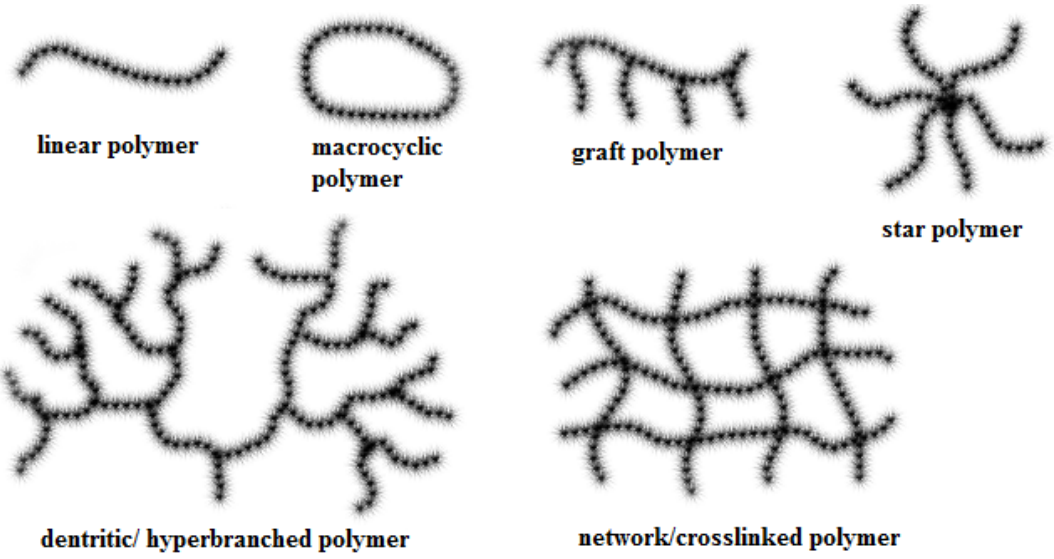


Figure 2.8 Illustration of polymers with various topologies.

2.5.1 Block copolymers

Block copolymers display remarkable phase behavior and are industrially important as thermoplastic elastomers, [126] impact modifiers, [127] compatibilization agents, [128] and surfactants [129]. The novel properties that arise in block copolymers when compared to random copolymers result from microphase separation of the components. A generally recognized prerequisite for well-defined phase behavior is

to have low PDIs for each of the blocks (generally PDI < 1.3), and especially precise synthetic techniques are required for control of molecular weight and PDI.

In particular, anionic polymerization has been successfully applied for block copolymer synthesis [130] Several other routes have been realized as well, including controlled radical polymerization [131-133], living cationic polymerization [134-136],group transfer [137-139], metathesis polymerization [140,141], ring-opening polymerization [142-144] or combinations of these techniques. Recently, block copolymers and, in particular, block co- (polyesters) have shown great promise in both nanoscale patterning of microelectronics and biomedical applications, due to the variety of two- and three-dimensional morphologies that can be constructed and the (bio)degradability of polyester segments. Organocatalytic strategies that avoid introducing any metallic catalysts appear highly advantageous.

2.5.2 Graft copolymers

The synthesis of graft copolymers can be accomplished through one of three routes: "grafting from" reactions (utilizing polymerization of grafts from a macroinitiator with pendant functionality), "grafting through" processes (operating by homo- or copolymerization of a macromonomer) and "grafting onto" (occurring when the growing chain is attached to a polymer backbone). The first two methods have been used in conjunction with ATRP in the design of graft copolymers and underscore the versatility of this controlled radical polymerization technique to synthesize a variety of (co) polymers.

2.5.2.1 "Grafting from " method

In the "*grafting from*" method, a polymer backbone (macroinitiator) with a predetermined number of initiation sites is generated, followed by grafting the side chains from the macroinitiator. The number of grafted chains can be controlled by the number of initiation sites generated along the backbone assuming that each one participates in the formation of one branch.

The "*grafting from*" approach has been extensively used in the synthesis of well-defined macromolecular grafts and brushes. For instance, PI-*g*-PS and PBd-*g*-PS well-defined copolymers were synthesized several years ago employing anionic polymerization [145, 146].

2.5.2.2 “Grafting trough ” method

The "grafting through" method (or macromonomer method) is one of the simplest ways to synthesize graft copolymers with well defined side chains. In a "grafting through" copolymerization the reactivity ratio of monomers and macromonomers may be affected by micro-inhomogeneity of the reaction mixture in addition to the reaction mechanism. This has often been observed in macromonomer copolymerization, or "grafting through" copolymerization for preparation of graft copolymers that would be expected to undergo phase separation. [147].

Typically a low molecular weight monomer is radically copolymerized with a (meth)acrylate functionalized macromonomer. This method permits incorporation of macromonomers that have prepared by other controlled polymerization processes into a backbone prepared by a CRP.

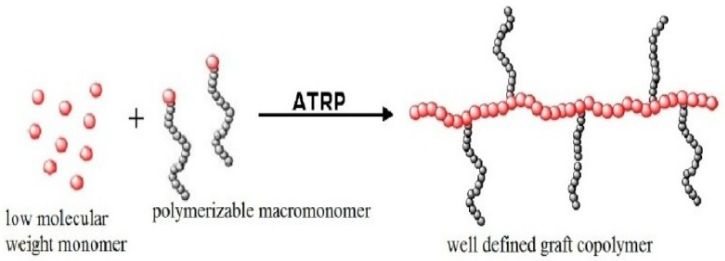


Figure 2.9: Synthesis of well-defined graft copolymer via grafting through method.

Macromonomers are short polymer chains possessing a polymerizable group at one terminus. A great variety of methods involving living polymerization techniques, chain transfer reactions, and end chain modifications have been developed to synthesize such species. In this case the macromonomer comprises the branch of the copolymer, and the backbone is formed in situ. The number of branches per backbone can be generally controlled by the ratio of the molar concentrations of the macromonomer and the comonomer. Several other factors have to be considered. Among them the most important one is the copolymerization behavior of the macromonomer and the comonomer forming the backbone.

2.5.2.3 “Grafting onto ” method

Due to steric congestion between reactive polymeric sidechains and backbones, the grafting density of polymeric brushes (number-average ratio of brush sidechains to backbone monomer units) prepared by the “grafting onto” method is usually low

[148]. An excess of reactive sidechains can be employed to increase the grafting density, although it is not easy to purify the final brush polymers by repeated fractionation to remove the unreacted linear chains. In order to increase the grafting density during the “grafting onto” synthesis, two factors should be considered. One is to use a reactive polymeric sidechain with a “thinner” structure, which can decrease the steric hindrance during grafting reactions. The other is to perform an organic reaction with high efficiency, which assures a fastcoupling reaction between reactive sidechains and backbones.

2.6 Functional Polycarbonates

Biodegradable polymers have been widely used and have greatly promoted the development of biomedical fields because of their biocompatibility and biodegradability. Synthetic biodegradable polymers have found more versatile and diverse biomedical applications because of their tailorable designs or modifications.

Most commonly used degradable materials for the preparation of clinical devices are aliphatic polyesters and copolyesters. From this point, aliphatic polycarbonates are good materials because they have functionalizable side chains (OH, NH_2, COOH, etc.) can easily meet the need for functionalization of biomaterials.

Furthermore, aliphatic polycarbonates have good biocompatibility, low toxicity and good biodegradability [149,150]. High molecular weight aliphatic polycarbonates can be prepared by the ROP of cyclic carbonates.

The most commonly used cyclic carbonates for ROP are five- ans six-membered cyclic monomers. A great variety of functional cyclic carbonate monomers have been successflly used for homopolymerization and copolymerization with various heterocyclic monomers through ROP [151].

Recently, Hedrick et. al. surveyed a Lewis base (1,8-diazabicyclo[5.4.0]undec-7-ene, DBU) for the ROP of trimethylenecarbonate (TMC) based on organocatalysis and synthesized a variety of functional polycarbonates. Since DBU is purely organic, it is particularly suitable for use in the synthesis of biomaterials [152].

In this thesis, aliphatic polycarbonate chains are synthesized via ring opening polymerization. In the literature, it is mentioned that, a lot of scientists used some

tecniques to synthesize aliphatic polycarbonate chains. These tecniques will shortly summarized by next examples.

Jianwen Xu and coworkers syntesized well-defined functional polycarbonates and poly(ester-carbonates), in this study, they prepared azido-functionalized cyclic carbonate monomer, AzDXO, that exhibited controlled/"living" ring-opening polymerization kinetics under the catalysis of 1,8-diazabicyclo[5.4.0]undec-7- ene. Homopolymerization of AzDXO and copolymerization of AzDXO with lactide resulted in polycarbonate and poly(ester-carbonates) with well-defined composition and narrow polydispersity. Further side-chain functionalizations of these polymers were accomplished under facile conditions via coppercatalyzed or copper-free strain-promoted azido-alkyne cyclcoaddition [93].

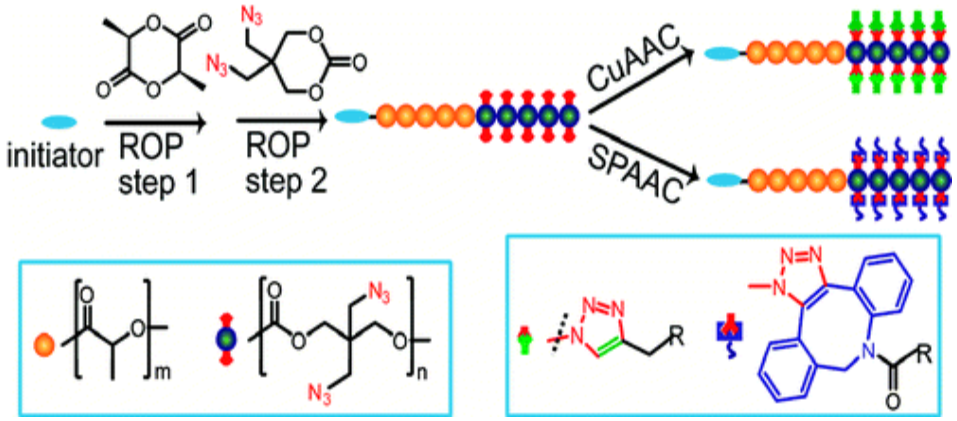


Figure 2.10 : Synthesis of azido-functionalized polycarbonate via controlled/"living" ring-opening polymerization and functionalized with coppercatalyzed or copper-free strain-promoted azido-alkyne cyclcoaddition [93].

Diels–Alder click reaction for the preparation of various types of aliphatic polycarbonates (PCs) were synthesized by Tunca-Hizal group. They first prepared a novel anthracene-functionalized cyclic carbonate monomer, anthracen-9-ylmethyl 5-methyl-2- oxo-1,3-dioxane-5-carboxylate, followed by ring-opening polymerization of this monomer to prepare PC with pendant anthracene groups (PC-anthracene) using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)/1-(3,5-bis(trifloromethyl)phenyl)-3- cyclohexylthiourea (TU) as the catalyst and benzyl alcohol as the initiator in CH_2Cl_2 at room temperature. Subsequently, the resulting PC-anthracene was grafted with a linear a-furan protected-maleimide terminated- poly(methyl methacrylate) (PMMA-MI), or poly(ethylene glycol) (PEG-MI) or a mixture of PMMA-MI and PEG-MI to yield well-defined PC graft or hetero graft copolymers or PC-g-PEG, or

PC-g-(PMMA)-co-PC-g-(PEG) , respectively, using Diels–Alder click reaction in a grafting-onto methodology [19].

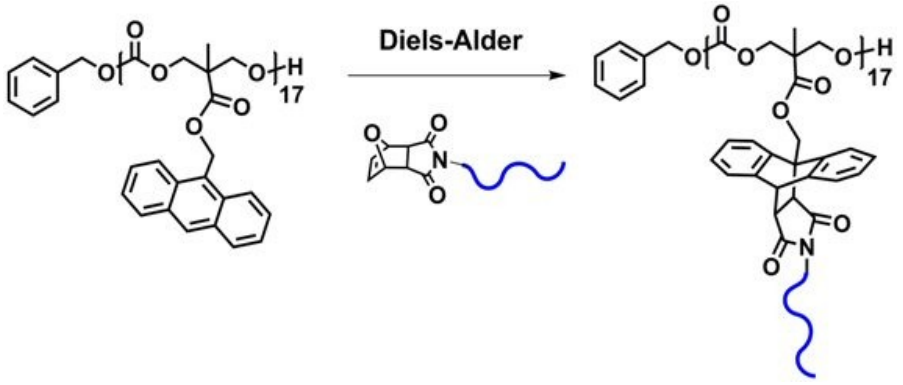


Figure 2.11: Diels–Alder click reaction for the aliphatic polycarbonate (PC) [19].

Tunca-Hizal group prepared well-defined polycarbonate (PC)-block copolymers with Diels-Alder reaction as a click reaction strategy .A well-defined anthracene-terminated polycarbonate (PC-anthracene) was prepared using 9-anthracene methanol as an initiator in the ring opening polymerization of benzyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate in CH_2Cl_2 at room temperature for 5 h. Next, a well-defined a-furan protected maleimide-terminated-poly(ethylene glycol),-poly(methyl methacrylate) and-poly(e-caprolactone) were clicked with the PC anthracene at reflux temperature of toluene to yield their corresponding PC-based block copolymers (PC-b-PEG, PC-b-PMMA, and PC-b-PCL). The homopolymer precursors and their block copolymers were characterized by using the GPC, NMR and UV analysis [153].

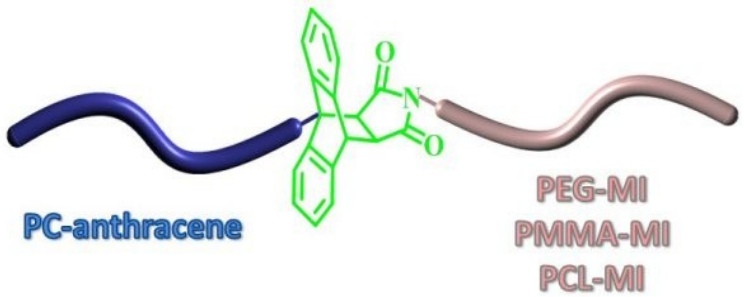


Figure 2.12: PC-based block copolymers (PC-*b*-PEG, PC-*b*-PMMA and PC-*b*-PCL) [153].

Daniel P. Sanders and coworkers developed an improved two-step synthetic route to functionalized cyclic carbonate monomers that features a novel cyclic carbonate intermediate with an active pentafluorophenyl ester group ($MTCOPhF_5$). The active pentafluorophenyl ester of $MTCOPhF_5$ is amenable to further substitution with

suitable nucleophiles such as alcohols and amines to generate functionalized cyclic carbonates in high yields. The substitution reaction was tolerant of a wide variety of functionalities, including various hydrophobic and hydrophilic groups, reactive functionalities (via thiol-ene click chemistry or alkyl halides), and protected acids, alcohols, thiols, and amines. In view of the ever-increasing need for biodegradable and biocompatible polymers, this new methodology provides a simple and versatile platform for the synthesis of new and innovative materials [154].

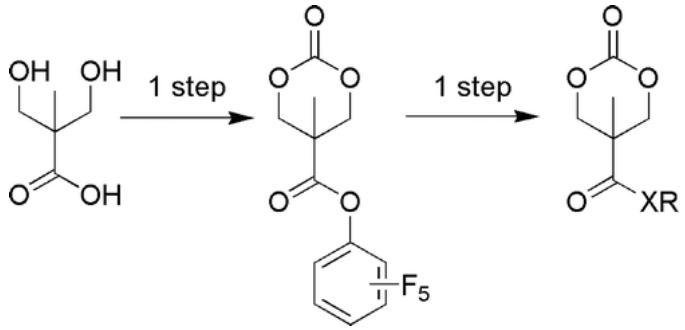


Figure 2.13: General synthetic route to functionalized cyclic carbonate monomers using pentafluorophenyl ester intermediate [154].

A novel six membered cyclic carbonate monomer with azido groups, 2,2-bis(azidomethyl)trimethylene carbonate (ADTC), was synthesized by cyclization of 2,2-bis(azidomethyl)propane-1,3-diol with ethyl chloroformate using triethylamine as a base in dry THF at room temperature in 80% yield by Xiaojin Zhang and coworkers. Then, azido polycarbonates PADTC and PADTC-co-PDTC were gained via ROP of ADTC and 2,2-dimethyltrimethylene carbonate (DTC) with 1,6-hexanediol as an initiator and $Sn(Oct)_2$ as a catalyst. Finally, azido copolycarbonates PADTC-co-PDTC were reacted with various alkynyl compounds, i.e., alkynyl-terminated poly(ethylene glycol) monomethyl ether (propargyl-PEG), propargyl alcohol, dimethylpropargylamine, and propargyl methacrylate, via click chemistry catalyzed by CuBr-Et_3N in THF at 35℃ to afford the polycarbonates with pendant groups or chains [155].

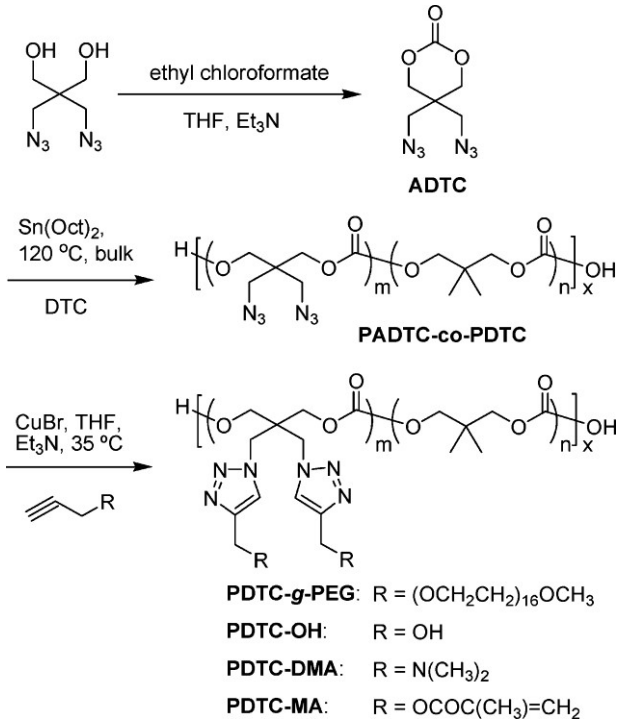


Figure 2.14: Synthesis of azido copolycarbonates PADTC-*co*-PDTC and their functionalization via the the click reaction [155].

Bio-inspired stabilization of aliphatic polycarbonate-based hydrogels were synthesized by Christophe Bartolini and coworkers.The study has been carried out by the metal-free ring-opening co-polymerization (ROP) of 6-membered cyclic carbonates containing,respectively, protected guanidine and carboxylic acid functions. Polyethylene glycol (PEG) bound tomethylcarboxy trimethylene carbonate at each extremity was used as the cross-linker, and thecopolymerizations were performed in CH_2Cl_2 for 24 h in the presence of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and N-(3,5-trifluoromethyl)phenyl-N-cyclohexylthiourea (TU), the catalyst andco-catalyst, respectively. Well-defined hydrogels of various compositions and presenting a high gelfraction were obtained. HR-MAS NMR has been successfully employed to validate our purification technique as well as to assess the selective de-protection of the guanidine and carboxylic acid functions. Evidence of self-assembling properties has been attested by differential scanning calorimetry (DSC), HR-MAS NMR analysis and swelling test experiments in aqueous buffered solutions at pH 4 and 8 [156].

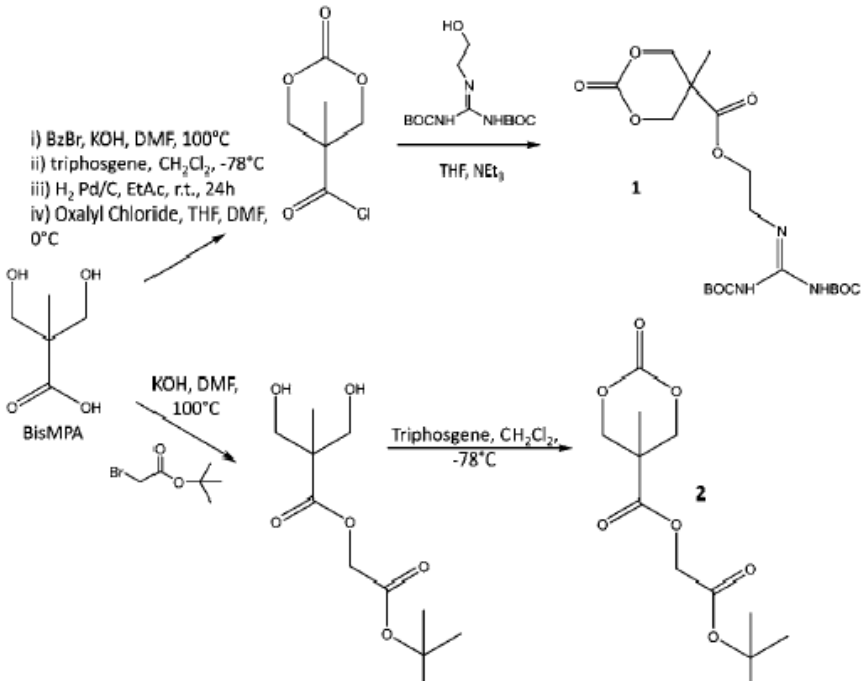


Figure 2.15: Synthesis of trimethylene carbonate-5-methyl-5-carboxyethyl guanidine 1,3-tert-butyloxy carbonyl (MTC-GuaBOC) and trimethylene carbonate-5-methyl-5-carboxy-tert-butylacetate (MTC tBAc) [156].

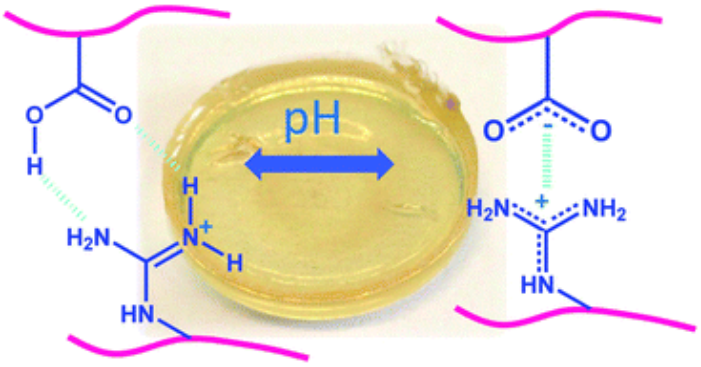


Figure 2.16: Bio-inspired stabilization of aliphatic polycarbonate-based hydrogels.

Dove and coworkers synthesized well-defined propargyl-functional poly(carbonate)s via the organocatalytic ring-opening polymerization of 5-methyl-5-propargyl oxycarbonyl-1,3-dioxan-2-one (MPC) using the dual catalyst system of 1-(3,5-bis(trifluoromethyl)phenyl)-3-cyclohexyl thiourea (TU) and 1,8 diazabicyclo[5.4.0]undec-7-ene (DBU). The resulting homopolymers showed low dispersities and high end-group fidelity,with the versatility of the system being demonstrated by the synthesis of telechelic copolymers and block copolymers. The synthesized homopolymers with varying degree of polymerization were

functionalized with a range of azides via copper-catalyzed Huisgen-1,3-dipolar addition or thiols viaradical thiylation, to produce functional aliphatic poly(carbonate)s from a single polymeric scaffold [157].

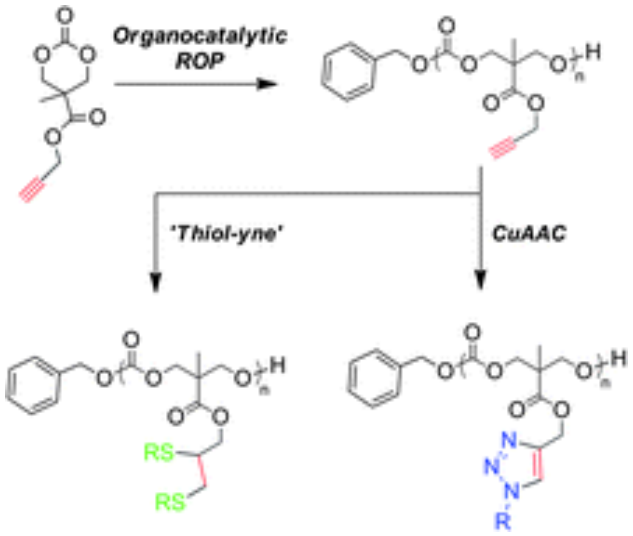


Figure 2.17: Propargyl-functional poly(carbonate)s via the organocatalyticring-opening polymerization [157].

Sanyal and coworkers described a novel strategy to synthesize and functionalize maleimide containing thiol reactive biodegradable polymers by the organocatalyzed (co)polymerization of a novelfuran-protected maleimide-functional carbonate monomer. Polymers obtained via ROP have pendant groups containing furan-protected maleimide units which, upon subjection to thermal cyclo reversion reaction, yields maleimide groups that are ready to react with thiol containing molecules [158].

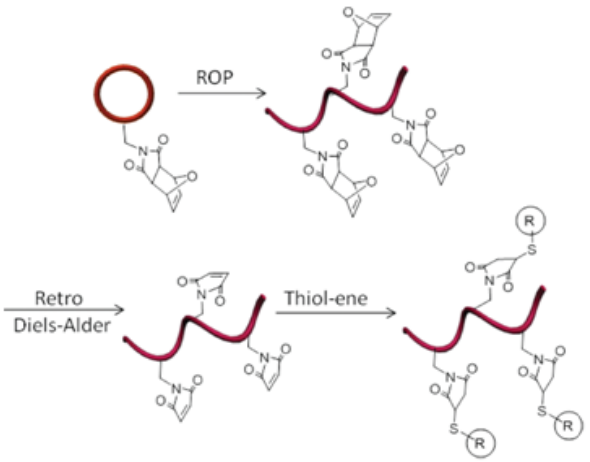


Figure 2.18: Illustrative scheme outlining the synthesis of maleimide containing polymers [158].

3. EXPERIMENTAL WORK

3.1 Materials

9-anthracene methanol (97%, Aldrich), triethylamine (Et_3N, 99.5%, Aldrich), *N,N'*-dicyclohexylcarbodiimide (DCC, 99 %, Aldrich), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 99%, Aldrich),succinicanhydride (97%, Aldrich), allyl alcohol (97%, Aldrich), furan (99%, Aldrich), maleic anhydride (99%, Aldrich), ethanolamine (99.5%, Aldrich), 1,4-dioxane (99.8%, Aldrich), 4-dimethyl amino pyridine (DMAP, 99 %, Acros), were used as received. Poly(ethylene glycol monomethyl ether) (PEG-OH) (M_n= 550 g/mol, Acros) was dried over anhydrous toluene by azeotropic distillation. Dichloromethane (CH_2Cl_2, 99.9 %, Aldrich) was used after distillation over P_2O_5. Tetrahydrofuran (THF, 99.8 %, J.T. Baker) was dried and distilled.Solvents unless specified here were purified by conventional procedures. All other reagents were purchased from Aldrich and used as received without further purification.

3.2 Instrumentation

^1H and ^{13}C NMR spectra were recorded on an Agilent VNMRS 500 (500 MHz for proton and 125 MHz for carbon). The conventional gel permeation chromatography (GPC) measurements were carried out with an Agilent instrument (Model 1100) consisting of a pump, refractive index (RI), and ultraviolet (UV) detectors and four Waters Styragel columns (guard, HR 5E, HR 4E, HR 3, and HR 2), (4.6 mm internal diameter, 300 mm length, packed with 5 μm particles). The effective molecular weight ranges are 2000-4,000,000, 50-100,000, 500-30,000, and 500-20,000, respectively. THF and toluene were used as eluent at a flow rate of 0.3 mL/min at 30 °C and as an internal standard, respectively. The apparent molecular weights ($M_{n,GPC}$ and $M_{w,GPC}$) and polydispersities (M_w/M_n) were determined with a calibration based

on linear PS standards using PL Caliber Software from Polymer Laboratories. UV spectra were recorded on a Shimadzu UV-1601 spectrophotometer in CH_2Cl_2.

3.3 Synthetic Procedures

2,2,5-trimethyl-[1,3]dioxane-5-carboxylic acid (1), anthracen-9-ylmethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (2), anthracen-9-ylmethyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate (3), anthracen-9-ylmethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (4), allyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (5), allyl 3-hydroxy-2-(hydroxymethyl)-2- dioxane-5-carboxylate (6), allyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (7), 1-(3,5-bis(trifloromethyl)phenyl)-3-cyclohexylthiourea (TU) (8), 4,10-Dioxatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione (9), 4-(2-hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5- dione (10), 2-bromo-2-methyl propionic acid 2-(3,5-dioxo-10-oxa-4- azatricyclo [5.2.1.$0^{2,6}$] dec-8-en-4-yl) ethyl ester (11), 4-(2-(1,3-dioxo-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindol-2(3H)-yl)ethoxy)-4-oxobutanoic acid (12),furan-protected maleimide-end-functionalized PEG (PEG_{550}-MI) (13), anthracene and allyl functionalized polycarbonate (PC-Anth/Allyl) (14), Diels-Alder click reaction between PC-Anth/Allyl and furan-protected maleimide (MI-Br) (15), thiol-ene click reaction of PC-g-MI with N-acetyl-L-cysteine methyl-ester (16), Diels-Alder click reaction between PC-Anth/Allyl and PEG_{550}-MI (17), thiol-ene click reaction of PC-g-PEG with N-acetyl-L-cysteine methyl-ester (18).

3.3.1 Synthesis of 2,2,5-trimethyl-[1,3]dioxane-5-carboxylic acid (1)

The 2,2-bis(hydroxymethyl)propanoic acid (16 g, 119.2 mmol) along with *p*-TSA (0.9 g, 4.64 mmol), and 2,2-dimethoxypropane (22.4 mL, 178.8 mmol) dissolved in 80 mL of dry acetone, and stirred 2 h at room temperature. In the vicinity of 2h, while stirring continued the reaction mixture was neutralized with 12 mL of totally NH_4OH (25%), and absolute ethanol (1:5), filtered off by-products and subsequent dilution with dichloromethane (240 mL), and once extracted with distilled water (80 mL). The organic phase dried with Na_2SO_4, concantrated to yield 14.8 g (71%) as white solid after evaporation of the solvent. ^{1}H NMR ($CDCl_3$, δ) 4.18 (d, 2H, CC*H*$_2$O), 3.63 (d, 2H, CC*H*$_2$O), 1.38 (s, 3H, C*CH*$_3$) 1.36 (s, 3H, C*CH*$_3$), 1.18 (s, 3H, C=OC(CH_2O)$_2$*CH*$_3$).

3.3.2 Synthesis of anthracen-9-ylmethyl 2,2,5-trimethyl-[1,3]dioxane-5-carboxylate (2)

9-Anthracene methanol(6.5 g, 31.25 mmol) was dissolved in 100 mL of CH_2Cl_2 and **1** (6.5 g, 37.4 mmol), and DMAP (5.5 g, 45.13 mmol) were added to the reaction mixture in that order. After stirring 5 minutes at room temperature, DCC (9.25 g, 44.9 mmol) dissolved in 50 mL of CH_2Cl_2 was added. Reaction mixture was stirred overnight at room temperature and urea byproduct was filtered. Solvent was evaporated and the remaining product was purified by column chromatography over silica gel eluting with hexane/dichlorometane (4:1) to give pale yellow oil (Yield = 9.22 g; 81 %). ^{1}H NMR ($CDCl_3$, δ) 8.50 (s, 1H, Ar*H* of anthracene), 8.32 (d, 2H, Ar*H* of anthracene), 8.02 (d, 2H, Ar*H* of anthracene), 7.60-7.45 (m, 4H, Ar*H* of anthracene), 6.2 (s, 2H, *CH*$_2$-anthracene), 4.14 (d, 2H, CC*H*$_2$O), 3.58 (d, 2H, CC*H*$_2$O), 1.38 (s, 3H, C*CH*$_3$), 1.35 (s, 3H, C*CH*$_3$), 1.08 (s, 3H, C=OC(CH_2O)$_2$*CH*$_3$).

3.3.3 Synthesis of anthracen-9-ylmethyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate (3)

9-anthrylmethyl 2,2,5-trimethyl-1,3-dioxane-5-carboxylate (9.22 g, 25.3 mmol) was dissolved in a mixture of 100 mL of THF and 100 mL of 1 M HCl. The reaction mixture was stirred for 2 h at room temperature. The precipitated product was filtered off and reaction mixture was concentrated and extracted with 480 mL of CH_2Cl_2 and 80 mL of water. The combined organic phase was dried with Na_2SO_4 and concentrated. Hexane was added to the reaction mixture and it was kept in deep freeze overnight to give white solid (Yield = 8.2 g, 89 %). ^{1}H NMR ($CDCl_3$, δ) 8.52 (s, 1H, Ar*H* of anthracene), 8.30 (d, 2H, Ar*H* of anthracene), 8.03 (d, 2H, Ar*H* of anthracene), 7.60-7.45 (m, 4H, Ar*H* of anthracene), 6.2 (s, 2H, *CH*$_2$-anthracene), 3.85 (d, 2H, C*H*$_2$OH), 3.66 (d, 2H, C*H*$_2$OH), 2.17(br, 2H, OH), 1.01 (s, 3H, C*CH*$_3$).

3.3.4 Synthesis of anthracen-9-ylmethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (4)

In a 250 mL of three-neck round bottom flask were added **3** (8.2 g, 25.5 mmol) in100 mL of THF. The solution was cooled to0 °C, and a solution of ethyl chloroformate (4.82 mL,44 mmol) in 25 mL of THF was added dropwise to the reaction mixture. Then a solution of triethylamine (10.56 mL, 10.5 mmol) in 25 mL of THF was added dropwise (20 min). The whitesuspension was stirred for 2 h at 0

°C and subsequently at ambienttemperature for overnight. The ammonium salt was filtered off and the solvent was removed under reduced pressure to give a yellow residue that was further purified by crystallization from dry THF to give white powder. Yield: 6.8 g (83%). ^{1}H NMR ($CDCl_3$, δ) 8.5 (s, 1H, Ar*H* of anthracene), 8.2 (d, 2H, Ar*H* of anthracene), 8.0 (d, 2H, Ar*H* of anthracene), 7.60-7.50 (m, 4H, Ar*H* of anthracene), 6.2 (s, 2H, CH_2-anthracene), 4.6 (d, 2H, CCH_2OC=O), 4.1 (d, 2H, CCH_2OC=O), 1.2 (s, 3H, C=OC(CH_2O)$_2$$CH_3$). ^{13}C NMR ($CDCl_3$, δ) 171.2 (Anth-$CH_2$O*C*=O), 147.7 (O*C*=OO), 131.3 (Ar*C* of anthracene), 131 (Ar*C* of anthracene), 129.7 (Ar*C* of anthracene), 129.2 (Ar*C* of anthracene), 127 (Ar*C* of anthracene), 125.2 (Ar*C* of anthracene), 124.8 (Ar*C* of anthracene), 123.4 (Ar*C* of anthracene), 72.9 (*C*H_2OC=OO), 60.7 (Anth-*C*H_2), 40.4 (*C*CH_2OC=O), 17.6 (C*C*H_3).

3.3.5 Synthesis of allyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (5)

Allyl alcohol(3.54 ml , 71.37 mmol) was dissolved in 100 mL of CH_2Cl_2 and **1** (9.9 g, 56.89 mmol), and DMAP (1.27 g, 10.39 mmol) were added to the reaction mixture in that order. After stirring 5 minutes at room temperature, DCC (11.72 g, 56.81 mmol) dissolved in 50 mL of CH_2Cl_2 was added. Reaction mixture was stirred overnight at room temperature and urea byproduct was filtered. Solvent was evaporated and the remaining product was purified by column chromatography over silica gel eluting with hexane/ethylacetate (9:1) to give bright liquid (Yield = 7.4 g; 85 %). ^{1}H NMR (500 MHz, $CDCl_3$, δ) 5.89 (m, 1H, CH_2=C*H*), 5.32-5.24 (m, 2H,CH_2=CH), 4.64 (d, 2H, vinylic H), 4.19 (d, 2H,C=OC(CH_2)(CH_3)), 3.64 (d, 2H,C=OC(CH_2)(CH_3)), 1.42 and 1.38 (s, 3H, COC(CH_3), s and 3H, COC(CH_3)), 1.21 (s, 3H, C=OC(CH_2)$_2$(CH_3)).

3.3.6 Synthesis of allyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate (6)

Allyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (7.4 g, 34.6 mmol) was dissolved in a mixture of 80 mL of THF and 80 mL of 1 M HCl. The reaction mixture was stirred for 2 h at room temperature. The precipitated product was filtered off and reaction mixture was concentrated and extracted with 360 mL of CH_2Cl_2 and 60 mL of water. The combined organic phase was dried with Na_2SO_4 and concentrated. Ethyl acetate was added to the reaction mixture and it was kept in deep freeze overnight to give bright liquid (Yield = 6.36 g, 86 %). ^{1}H NMR (500 MHz, $CDCl_3$, δ)5.91(m, 1H, CH_2=C*H*), 5.35-5.24 (m, 2H,CH_2=CH), 4.66 (d, 2H, vinylic H), 3.90 (d, 2H,

C*H*$_2$OH), 3.73 (d, 2H,C*H*$_2$OH), 2.94 (s, 2H, CH$_2$O*H*), 1.08 (s, 3H, C=OC(CH$_2$)$_2$(C*H*$_3$)).

3.3.7 Synthesis of allyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (7)

In a 250 mL of three-neck round bottom flask were added **6** (6.3 g, 36.2 mmol) in100 mL of THF. The solution was cooled to0 °C, and a solution of ethyl chloroformate (6.86 mL,72.4 mmol) in 25 mL of THF was added dropwise to the reaction mixture. Then a solution of triethylamine (15.03 mL, 108.6 mmol) in 25 mL of THF was added dropwise (20 min). The white suspension was stirred for 2 h at 0 °C and subsequently at ambient temperature for overnight. The ammonium salt was filtered off and the solvent was removed under reduced pressure to give a bright liquid that was further purified by crystallization from dry THF to give white powder. Yield: 5.04 g (83%). ^{1}H NMR (500 MHz, CDCl$_3$, δ) 5.89 (m, 1H, CH$_2$=C*H*), 5.30 (m, 2H, C*H*$_2$=CH), 4.69 (d, 2H, CH$_2$=CHC*H*$_2$), 4.69 (d, 2H, CC*H*$_2$OC=O), 4.22 (d, 2H, CC*H*$_2$OC=O), 1.34 (s, 3H, C=OC(CH$_2$O)$_2$*CH*$_3$).

3.3.8 1-(3,5-bis(trifloromethyl)phenyl)-3-cyclohexylthiourea) (TU) (8)

Cyclohexylamine (1.85 g, 18.5 mmol) was added dropwise at room temperature to a stirring solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (5.0 g, 19 mmol) in THF (20 mL). After the solution was stirred for 4 h, the solvent was evaporated. The white residue was recrystallized from hexane to give TU as a white powder. Yield: 5.90 g (86%). Yield: 5.90 g (86%). ^{1}H NMR: δ = 7.52 (s, 1H, 5-ArH), 7.33 (s, 2H, 2,6-ArH), 6.50 (s, 1H, ArNH), 5.17 (s, 1H, CyNH), 4.40 (br 1H, NCyH), 2.03-0.86 (10H, CyH)

3.3.9 Synthesis of 4,10-Dioxatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (9)

Maleic anhydride (30 g, 0.30 mol) was suspended in 150 mL of toluene and the mixture warmed to 80 °C. Furan (33.4 mL, 0.45 mol) was added via syringe and the turbid solution stirred for 6 h. The mixture was then cooled to ambient temperature white solids formed during standing were collected by filtration and washed with 2 × 30 mL of petroleum ether and once with diethyl ether (50 mL) yielding **9** as white needless. (Yield= 44.4 g, 87%). Mp: 114-115 ^{o}C (DSC). ^{1}H NMR (CDCl$_3$, δ) 6.57 (s, 2H, C*H*=C*H*,bridge protons), 5.45 (s, 2H, -C*H*O, bridge-head protons), 3.17 (s, 2H,

C*H*-C*H*, bridge protons). ^{13}C NMR ($CDCl_3$, δ) 170.18, 137.29, 82.46, 48.88. Mass spectrometry (+EI) *m*/*z* (%): 167 [MH+] (50), 144 (35), 130 (20).

3.3.10 Synthesis of 4-(2-hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5- dione (10)

The adduct **9** (10 g, 60 mmol) was suspended in methanol (150 mL) and the mixture was cooled to 0 °C. A solution of ethanol amine (3.6 mL, 60 mmol) in 30 mL of methanol was addeddropwise (10 min) to the reaction mixture, and the resulting solution was stirred for 5 min at0 °C, then 30 min at ambient temperature, and finally refluxed for 8 h.After cooling the mixture to ambient temperature, solvent was removed under reduced pressure, and residue was dissolved in 150 mL of CH_2Cl_2 and washed with 3 × 100 mL of water. The organic layer was separated, dried over Na_2SO_4 and filtered. Removal of the solvent under reduced pressure gave white-off solid which was further purified by flash chromatography eluting with ethylacetate (EtOAc) to give the productas a white solid. (Yield= 4.9 g, 40%). Mp = 138-139 °C (DSC). ^{1}H NMR ($CDCl_3$, δ) 6.51 (s, 2H, C*H*=C*H*,bridge protons), 5.26 (s, 2H, -C*H*O, bridge-head protons), 3.74-3.68 (m, 4H, NCH_2CH_2OH), 2.88 (s, 2H, C*H*-C*H*, bridge protons). ^{13}C NMR ($CDCl_3$, δ) 177.03, 136.60, 81.09, 60.53, 47.74, 42.03. Mass spectrometry (+EI) *m*/*z* (%): 210 [MH+] (50), 145 (22), 142 (100), 124 (17).

3.3.11 Synthesis of 2-bromo-2-methyl propionic acid 2-(3,5-dioxo-10-oxa-4 azatricyclo [5.2.1.$0^{2,6}$] dec-8-en-4-yl) ethyl ester (11)

In a 250 mL of round bottom flask were added 10 (2.0 g, 9.55 mmol) and Et3N (1.44 mL, 10.54 mmol) in 100 mL of THF. The mixture was cooled to 0 °C, and a solution of 2-bromo isobutyryl bromide (2.34 g, 10.0 mmol) in 25 mL of THF was added dropwise (30 min) to the reaction mixture. The white suspension was stirred for 3 h at 0 °C and subsequently at ambient temperature for overnight. The ammonium salt was filtered off and the solvent was removed under reduced pressure to give a pale-yellow residue that was further purified by column chromatography over silica gel eluting with EtOAc/hexane (1/4) to give 11 as a white solid. (Yield= 1.86 g, 55%). Mp = 81-82 °C (DSC). ^{1}H NMR ($CDCl_3$, δ) 6.49 (s, 2H, CH=CH, bridge protons), 5.24 (s, 2H, -CHO, bridge-head protons), 4.31 (t, J = 5.2 Hz, 2H, NCH_2CH_2OC=O), 3.79 (t, J =5.2 Hz, 2H, NCH_2CH_2OC=O), 2.85 (s, 2H, CH-CH, bridge protons), 1.87

(s, 6H, C(CH_3)2-Br). 13C NMR ($CDCl_3$, δ) 176.12, 171.55, 136.83, 81.09, 62.36, 55.96, 47.74, 37.69, 30.83.

3.3.12 Synthesis of 4-(2-(1,3-dioxo-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindol-2(3H)-yl)ethoxy)-4-oxobutanoic acid (12)

10 (5 g, 23.9 mmol) was dissolved in 150 mL of 1,4-dioxane. To the reaction mixture were added Et_3N (16.58 mL, 119.6 mmol), DMAP (4.38 g, 35.8 mmol), and succinic anhydride (9.56 g, 95.6 mmol) in that order. The reaction mixture was stirred for overnight at 50 oC, then poured into ice-cold water and extracted with CH_2Cl_2. The organic phase was washed with 1 M HCl, dried over Na_2SO_4 and concentrated. The crude product was crystallized from ethanol to give 12 as white crystal. Yield: 5.9 g (80%). ^{1}H NMR ($CDCl_3$, δ) 6.50 (s, 2H, CH=CH, bridge protons), 5.25 (s, 2H, -CHO, bridge-head protons), 4.25 (t, J = 5.2 Hz, 2H, NCH_2CH_2OC=O), 3.74 (t, J =5.2 Hz, 2H, NCH_2CH_2OC=O), 2.87 (s, 2H, CH-CH, bridge protons), 2.66-2.53 (m, 4H, C=OCH_2CH_2C=OOH). 13C NMR($CDCl_3$, δ) 177.26, 176.35, 172.01, 136.83,81.09, 61.22, 47.74, 37.92, 29.24.

3.3.13 Preparation of furan-protected maleimide-end-functionalized PEG (PEG_{550}-MI) (13)

Me-PEG_{550} (Mn = 550) (2.0 g, 3.63 mmol) was dissolved in 50 mL of CH_2Cl_2. To the reaction mixture were added DMAP (0.044 g, 0.363 mmol) and 11 (2.24 g, 7.27 mmol) in that order. After stirring 5 min at room temperature, a solution of DCC (1.49 g, 7.27 mmol) in 10 mL of CH_2Cl_2 was added. Reaction mixture was stirred for overnight at room temperature. After filtration off the salt, the solution was concentrated and the viscous brown color product was purified by column chromatography over silica gel eluting with CH_2Cl_2/EtOAc mixture (1:1, v/v) and then with CH_2Cl_2/methanol (90:10, v/v) to obtain MI-PEG as viscous brown oil. Yield: 2.7 g (88%).^{1}H NMR ($CDCl_3$, δ) 6.50 (s, 2H, CH=CH as bridge protons), 5.25 (s, 2H, -CHO, bridge-head protons), 4.23 (m, 4H, CH_2OC=O), 3.75-3.51 (m, OCH_2CH_2 repeating unit of PEG, C=ONCH_2, and CH_2-PEG repeating unit), 3.36 (s, 3H, PEG-OCH_3), 2.87 (s, 2H, CH-CH, bridge protons) 2.61-2.56 (m, 4H, C=OCH_2CH_2C=O).

3.3.14 Preparation of pendant anthracene and allyl functionalized polycarbonate (PC-Anth/Allyl) (14)

PC-Anth/allyl was prepared by ROP of Ant-Carbonate (1,34 g, 3.83 mmol) and Allyl-Carbonate (0.76 g, 3.83 mmol) using both DBU (0.057 mL, 0.383 mmol) and **8** (0.14 g, 0.383 mmol) as catalyst and benzyl alcohol (0.034 mL, 0.383 mmol)as an initiator at room temperature for overnight. The degassed monomer in CH_2Cl_2 (9 mL), catalyst, and initiator were added to a 25 mL 2-neck round bottom flask that had been flame-dried under vacuum and purged with argon. The tube was degassed with three freeze-pump-thaw (FPT) and left invacumm.After the polymerization, the mixture was concentrated and precipitated into an excess amount of methanol at ambient temperature. Recovered polymer, redissolved in CH_2CL_2 and precipitated in methanol. It was isolated by filtration and dried at 40 ^oC in a vacuum oven for 6 h. ^1H NMR ($CDCl_3$, δ) 8.3 (br, Ar*H* of anthracene), 8.1 (br, Ar*H* of anthracene), 7.8 (bs, Ar*H* of anthracene), 7.4-7.2 (br, Ar*H* of anthracene and Ar*H* of Ph), 6.14 (bs, CH_2-anthracene), 5.85 (bs,C*H*=CH_2), 5.2-5.3 (br, CH_2=CH), 5.0 (s, 2H, OCH_2-Ph), 4.59 (br, OCH_2CH),4.2 (bs, CH_2OC=O of PC, 1.12 (bs, C=OC$(CH_2O)_2CH_3$).$M_{n,theo}$ = 7258; $M_{n,GPC}$ = 1908, $M_{n,NMR}$ = 5000, M_w/M_n = 1.58 (relative to PS standards).

3.3.15 Diels-Alder click reaction between PC-Anth/Allyl and furan-protected maleimide (MI-Br) (15)

PC-Anth/Allyl (0.5 g, 0.1 mmol, $M_{n,NMR}$ = 5000 g/mol, 1 equiv) and **11** (0.5 g, 1.45 mmol 15 equiv) were dissolved in 40 mL toluene. Next, the mixture was bubbled with nitrogen for 30 min and refluxed at 110 ^oC for 24 h in the dark. After this specified time, solution was evaporated to dryness and the residual solid was dissolved in THF, and subsequently precipitated in methanol. This dissolution-precipitation procedure was repeated two times and the obtained product was dried in a vacuum oven at 40 ºC for 24 h (Yield = 0.65 g). ^1H NMR (500 MHz, $CDCl_3$, δ) 7.38-7.18 (m, Ar*H* of benzyl and Diels-Alder adduct), 5.27 (bs, CH_2-Diels-Alder adduct),5.85 (m, 1H, CH_2=C*H*), 5.52 (m, 2H, CH_2=CH), 4.78 (bs, PhCH_2O of PC), 4.61 (d, 2H, CH_2=CHCH_2), 4.61 (d, 2H, CCH_2OC=O),4.30 (m, C*H*, bridge head proton), 4.22 (d, 2H, CCH_2OC=O), 3.58 (bs, CH_2OC=O of PC and C=OOCH_2CH_2), C=OOCH_2CH_2N, C=OOCH$_2$CH_2N, OCH_3,1.26 (s, 3H, C=OC$(CH_2O)_2CH_3$).

3.3.16 Thiol-ene click reaction of PC-*g*-MI with N-Acetyl-L-Cysteine Methyl-Ester (16)

15 (0.2 g, 0.026 mmol, $M_{n,theo}$=7800, 1 equiv.), N-acetyl-L-cysteine methyl-ester (0.16 g, 0.902 mmol 35 equiv, DMPA (0.05 g, 19.5 mmol, 0.7 equiv.) , 1,4 dioxane (1 mL) and toluene (5 mL) were put into a Schlenktube.The reaction mixture was degassed by three FPT cycles and left in vacuum. The mixture wasirradiated by a photoreactor (Rayonet) equipped with 10 lamp semitting light nominally at 365 nm at room temperature for 4 h. After that time, the polymerization mixture was diluted with THF and precipitated in methanol. This dissolution-precipitation (THF-MeOH)procedure was repeated two times. Thepolymer was dried for 24 h in a vacuum oven at 40 ^{o}C. (Yield: 0.11 g, 86 %). ^{1}H NMR ($CDCl_3$, δ) 7.38–7.17 (br, Ar*H* of cycloadduct), 5.52 (bs, 2H, C*H*$_2$-cycloadduct), 4.85-4.72 (br, C=OC*H*(CH_2)NH of cysteine, C*H* of cycloadduct), 3.75-3.34 (br, $SCH_2CH_2CH_2$,C=OOC*H*$_3$ of cysteine, C*H*-C*H*, bridge protons, NC*H*$_2$$CH_2OC$=O), 2.96 (m, 2H, NHCHC*H*$_2$S), 2.56-2.04 (m, 4H, OC=OC*H*$_2$C*H*$_2$C=OO), 2.56 (m, 2H, $NHCHCH_2SCH_2$),2.03 (m,3H,C=OC*H*$_3$ of cysteine), 1.25 (bs, C*H*$_3$ of PC).

3.3.17 Diels-Alder click reaction between PC-Anth/Allyl and PEG_{550}-MI (17)

PC-Anth/Allyl (0.5 g, 0.1 mmol, $M_{n,NMR}$ = 5000 g/mol, 1 equiv) and PEG_{550}-MI (1.27 g, 1.5 mmol, $M_{n,theo}$ = 840 g/mol, 15 equiv) were dissolved in 20 mLtoluene and 20 mL1,4-dioxane. Next, the mixture was bubbled with nitrogen for 30 min and refluxed at 110 ^{o}C for 27 h in the dark. After this specified time, solution was evaporated to dryness and the residual solid was dissolved in THF, and subsequently precipitated in methanol. This dissolution-precipitation procedure was repeated two times and the obtained product was dried in a vacuum oven at 40 ºC for 24 h (Yield= 0.7 g). ^{1}H NMR (500 MHz, $CDCl_3$, δ) 7.50-7.00 (m, Ar*H* of benzyl and Diels-Alder adduct), 5.81 (bs, C*H*=CH_2),5.49 (bs, C*H*$_2$-Diels-Alder adduct), 5.1-5.3 (br, C*H*$_2$=CH),5.0 (s, 2H, OC*H*$_2$-Ph),4.73 (m, C*H*, bridge head proton),4.56(br,OC*H*$_2$CH), 4.20 (bs, C*H*$_2$OC=O of PC and C=OOC*H*$_2$$CH_2$), 3.80-3.00 (m, OC*H*$_2$C*H*$_2$, PEG repeating unit, C=OOC*H*$_2$$CH_2N$, C=OO$CH_2$C*H*$_2$N, OC*H*$_3$end-group of PEG and C*H*-C*H* bridge protons), 2.57 and 2.48 (br, C=OC*H*$_2$C*H*$_2$C=O), 1.22 (bs, C*H*$_3$ of PC).

3.3.18 Thiol-ene click reaction of PC-*g*-PEG with N-Acetyl-L-Cysteine Methyl-Ester (18)

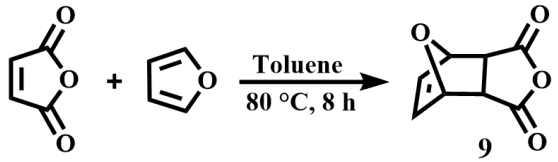
17 (0.1 g, 0.008 mmol, $M_{n,theo}$=12700, 1 equiv.), n-acetyl-L-cysteine methyl-ester (0.05 g, 0.282 mmol 35e quiv), DMPA (0.0014 g, 0.005 mmol, 0.7 equiv.) , 1,4-dioxane (1 mL) and toluene (5 mL) were put into a Schlenktube.The reaction mixture was degassed by three FPT cycles and left in vacuum. The mixture wasirradiated by a photoreactor (Rayonet) equipped with 10 lampsemitting light nominally at 365 nm at room temperature for 5 h. After that time, the polymerization mixture was diluted with THF and precipitated in methanol. This dissolution-precipitation (THF-MeOH)procedure was repeated two times. Thepolymer was dried for 24 h in a vacuum oven at 40 ^{o}C. (Yield: 0.11 g, 86 %). ^{1}H NMR (500 MHz,$CDCl_3$, δ) 7.38–7.17 (br, Ar*H* of cycloadduct), 5.52 (bs, 2H, CH_2-cycloadduct), 4.85-4.72 (br, C=OC*H*(CH_2)NH of cysteine, C*H* of cycloadduct), 3.75-3.34 (br, $SCH_2CH_2CH_2$,C=OOCH_3 of cysteine, C*H*-C*H*, bridge protons, NCH_2CH_2OC=O), 2.96 (m, 2H, NHCHCH_2S),2.56 and 2.48 (br, C=OCH_2CH_2C=O), 2.56-2.04 (m, 4H, OC=OCH_2CH_2C=OO), 2.56 (m, 2H, NHCHCH_2SCH_2)2.03 (m, 3H ,C=OCH_3 of cysteine), 1.25 (bs, CH_3 of PC).

4. RESULTS AND DISCUSSION

In this work, we studied Diels–Alder and Thiol-ene click reactions. Here, Diels-Alder reaction is usedas an alternative strategy for the preparation of PCs grafted with well-defined polymer and MI-Br, using the ‘‘grafting-onto’’ methodology. Thiol-ene click reaction is used to obtain cysteine funtional graft copolymer.Notably, it should be considered that Diels– Alder click reaction is a promising partner for the synthesis of a wide variety of biocompatible and biodegradable PCs, since it does not comprise toxic copper catalyst.

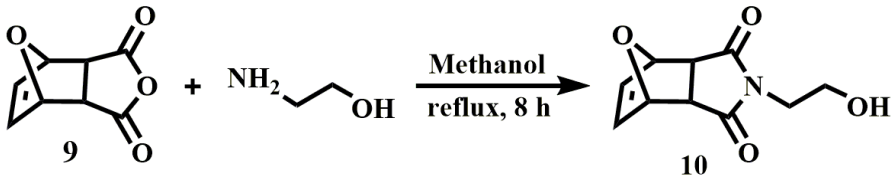
4.1 Synthesis of Maleimide Functional Structures

First of all, maleic anhydride and furan were reacted in toluene at reflux temperature for 8 h to give4,10-Dioxatricyclo[5.2.1.02,6]dec-8-ene-3,5-dione **(9)** (4.1). The anhydride **9** was obtained as small white needless.



(4.1)

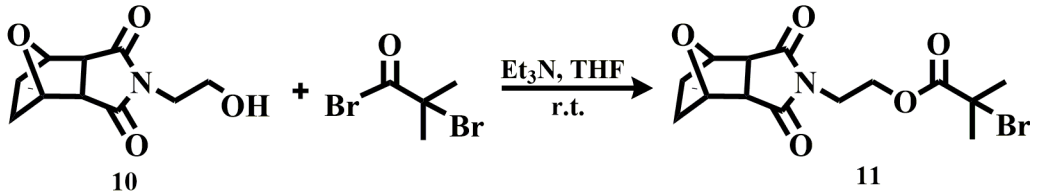
The reaction of the anhydride **9** was then carried out to give the 4-(2-Hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.02,6]dec-8-ene-3,5- dione **(10).** In this reaction, the anhydride **9** was suspended in MeOH and a solution of ethanolamine in MeOH was added at 0 ^{o} C, then the mixture refluxed for 8 h (4.2). Finally, compound **10** was obtained as a white solid.



(4.2)

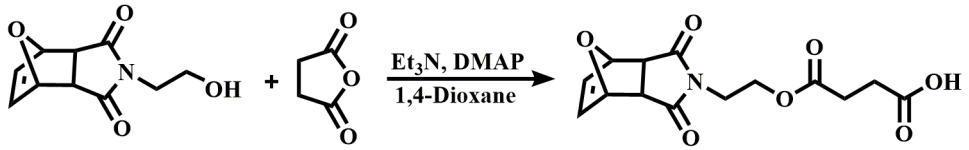
The synthesis of 2-bromo-2-methyl-propionic acid 2-(3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl) ethyl ester **(12)** was obtained via an

esterification reaction between **10** and 2-bromoisobutryl bromide in THF at room temperature (4.3). Thus, the initiators with proper functionalities for DA reaction were first prepared.



10 **11** **(4.3)**

The hydoxyl functionality of **10** was converted to carboxylic acid via a reaction with succinic anhydride in the presence of Et_3N/DMAP catalyst system and 1,4-dioxane as solvent in order to give the 4-(2-{[(3-acetyl-7-oxabicyclo[2.2.1]hept-yl)carbonyl]amino}ethoxy)-4-oxobutanoic acid **(12)** (4.4).



10 **12** **(4.4)**

From overlay ^{1}H NMR spectra Figure 4.1 of **12**, methylene protons next to the ester ($NCH_2CH_2OC{=}O$) and methylene protons adjacent to nitrogen ($NCH_2CH_2OC{=}O$) appeared at 4.25 ppm and 3.74 ppm respectively. Moreover, the multiplet peaks around 2.66-2.53 ppm confirmed successful conversion of hydroxyl group to carboxylic acid. From spectrum (c), it is clearly seen that the methyl protons next to Br were detected at 1.87 ppm and the methylene protons next to the ester unit at 4.31 ppm. Moreover, the characteristic protons of the adduct were also detected at 6.49 ppm (bridge vinyl protons), 5.24 ppm (bridge-head protons) and 2.85 ppm (bridge protons) respectively. These results confirmed that the synthesis of **12** was achived.

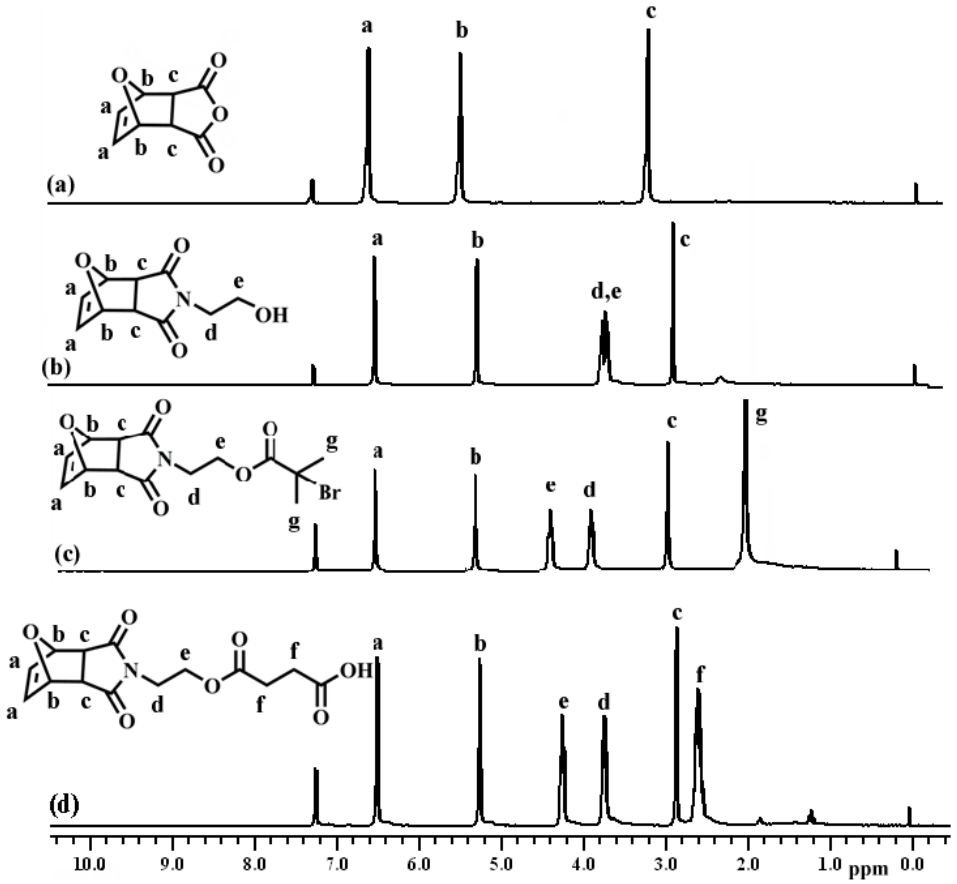
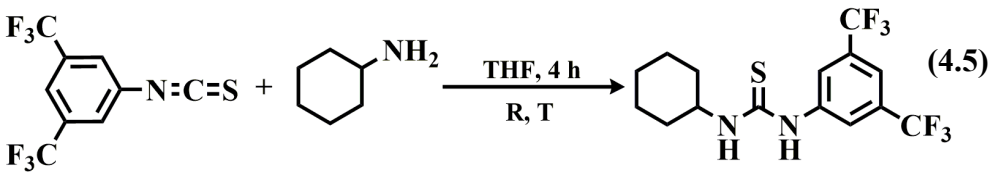


Figure 4.1: ^{1}H NMR spectra of: a) 4,10-Dioxatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5-dione (9); b) Synthesis of 4-(2-hydroxyethyl)-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene-3,5- dione (10);c) 2-bromo-2-methyl-propionic acid 2-(3,5-dioxo-10-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl) ethyl ester (11); d) 4-(2-{[(3-acetyl-7-oxabicyclo[2.2.1]hept-yl)carbonyl]amino}ethoxy)-4-oxobutanoic acid (12) in$CDCl_3$.

4.2 Synthesis of Co-catalyst TU

To synthesize first of all, maleic anhydride 1-(3,5-bis(trifloromethyl)phenyl)-3-cyclohexylthiourea) is in other world co-catalyst (TU), cyclohexylamine and 3,5-bis(trifluoromethyl)phenyl isothiocyanate were reacted in THF at room temperature for 4h (4.5). Finally, compound **8** was obtained as a white solid.



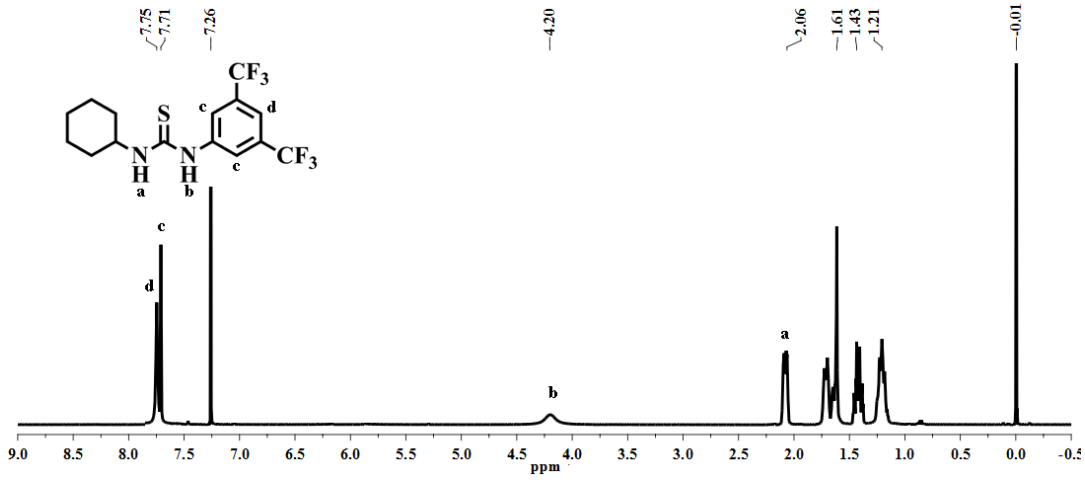
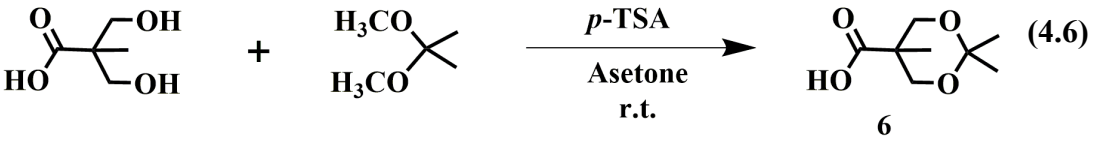


Figure 4.2: ^{1}H NMR spectrum of 1-(3,5-bis(trifloromethyl)phenyl)-3-cyclohexylthiourea) in CDCl3 (500 MHz).

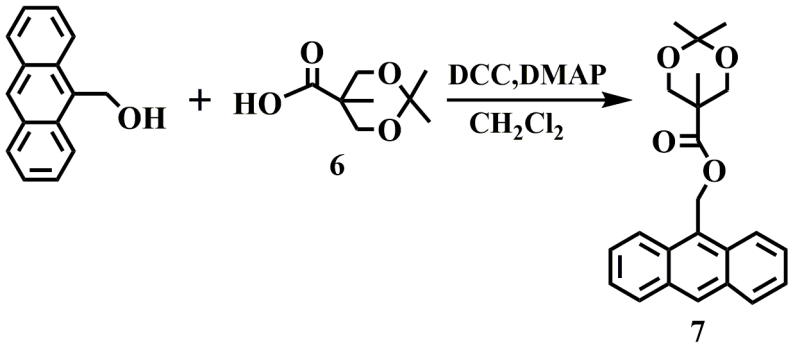
4.3 Preparation of Antracene and Allyl Functional Carbonate Monomers

First of all 2,2,5-trimethyl-[1,3]dioxane-5-carboxylic acid **(1)** was synthesized by this way; 2, 2-bis (hydroxymethyl)-propanoic acid was reacted with excess amount of dry acetone using *p*-toluene sulfonic acid as catalyst. Additionally, 2,2-dimethoxy-propane was deliberately used to provide acetone during the reaction. Process is given below schematically (4.6).



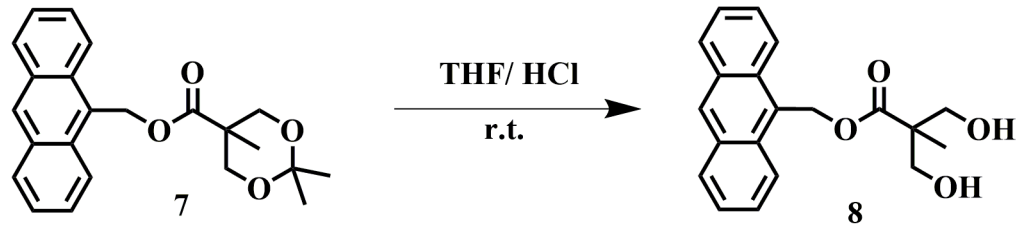
(4.6)

Initially, esterification reaction of anthracen-9-ylmethanol and 2,2,5-trimethyl-1,3-dioxane-5-carboxylic acid was prepared to synthesize **2** (anthracen-9-ylmethyl 2,2,5-trimethyl-1,3-dioxane-5-carboxylate) by catalyzing DCC and DMAP in CH_2Cl_2 at room temperature overnight (4.7).



(4.7)

Next, (anthracene-9-ylmethyl 2,2,5-trimethyl-1,3-dioxane-5-carboxylate) **3** was hydrolized in THF by adding HCl solution stirring for 2 hours at room temperature.

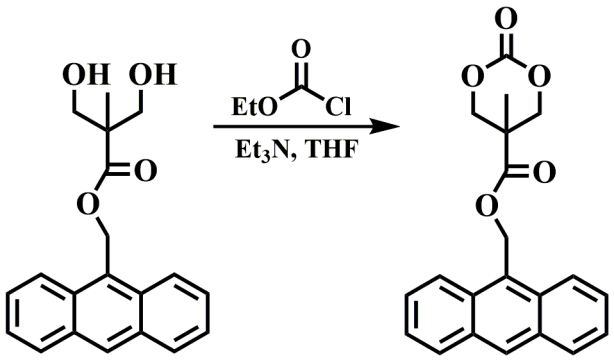


7 8 **(4.8)**

Thus, anthracen-9-ylmethyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate **3** was obtained. (4.8)

^{1}H NMR spectroscopy confirmed clearly the structure of 10 by appearance of characteristic signals of anthracene (δ 8.5 − 7.5) . It is obviously seen that the peak of methylene protons neighbouring to hydroxyl group is between 3.63 and 3.85 ppm.

In the following step, Anth-carbonate monomer (anthracen-9-ylmethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate) was synthesized (4.9). The cyclization was performed in the presence of ethyl chloroformate in dilute anhydrous THF solution via dropwise addition of triethylamine.



3 4 **(4.9)**

^{1}H NMR spectroscopy confirmed clearly the structure of **4** by appearance of characteristic signals of anthracene (δ8.5-7.5). The double doublets at δ 4.10/4.66 were attiributable to the methylene protons next to the carbonate. Importantly, no peak at δ 3.63-3.85 assignable to the methylene protons adjacent to the hydroxyl group was detected. The ^{1}H NMR and elemental analysis of Anth-carbonate showed similar outcome.

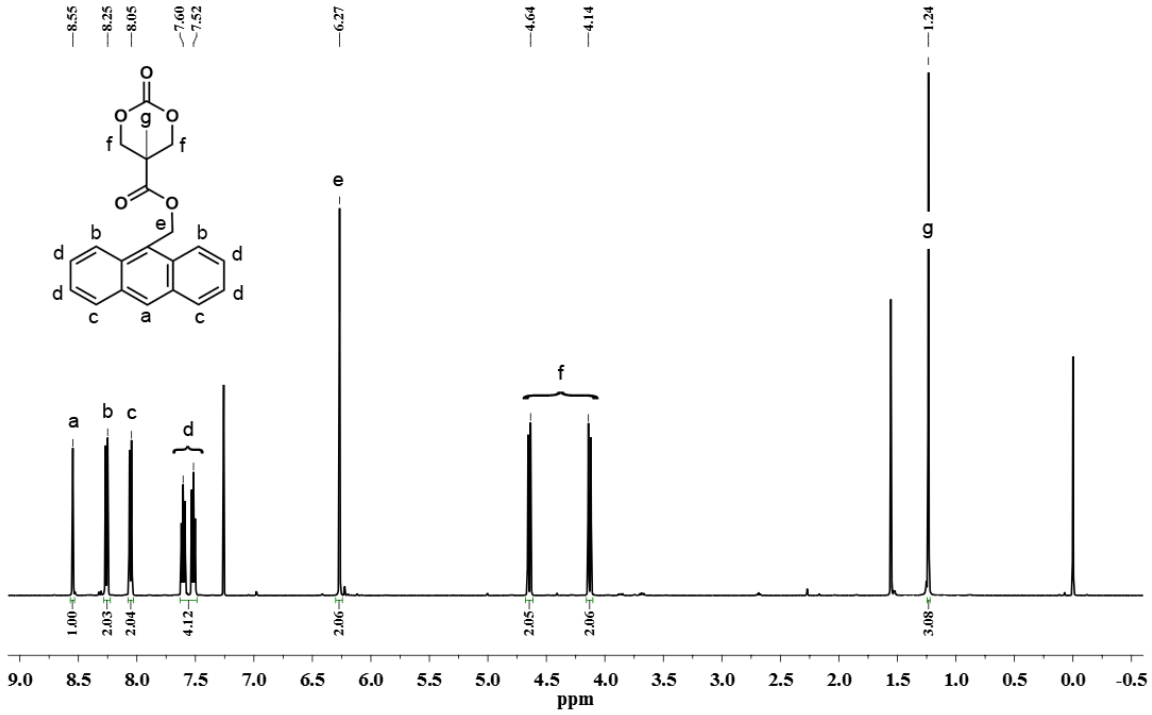


Figure 4.3: ^{1}H NMR spectrum of Anth-Carbonate in $CDCl_3$ (500 MHz).

In addition, ^{13}C NMR spectroscopy indicated a peak at 147.4 ppm that proved the cyclic carbonate formation.

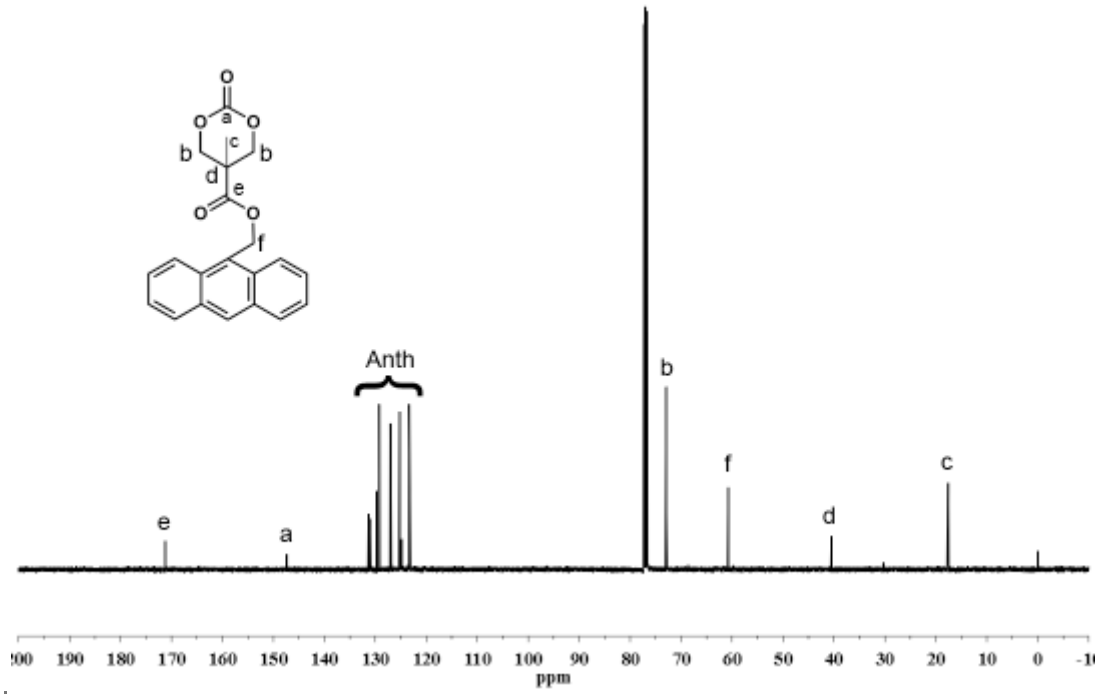
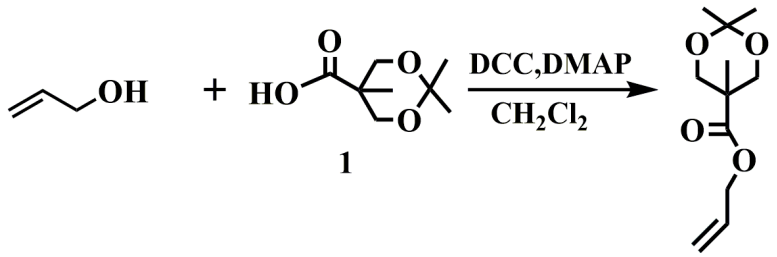


Figure 4.4: ^{13}C NMR spectrum of Anth-Carbonate in $CDCl_3$ (500 MHz).

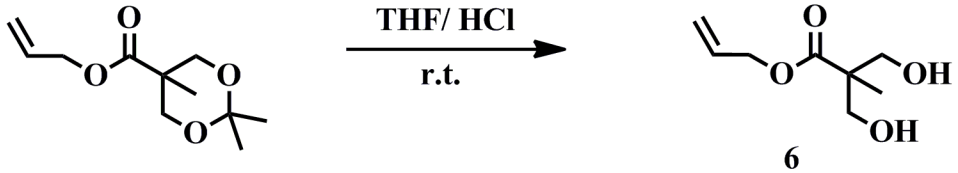
Then esterification reaction of allyl alcohol and 2,2,5-trimethyl-1,3-dioxane-5-carboxylic acid was prepared to synthesize **5** (allyl 2,2,5-trimethyl-1,3-dioxane-5-

carboxylate) by catalyzing DCC and DMAP in CH_2Cl_2 at room temperature overnight (4.10).



1 5 **(4.10)**

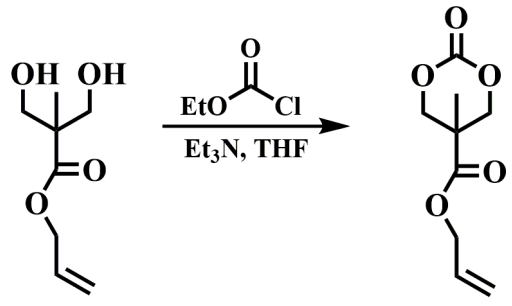
Next, (allyl 2,2,5-trimethyl-1,3-dioxane-5-carboxylate) **5** was hydrolized in THF by adding HCl solution stirring for 2 hours at room temperature.



5 6 **(4.11)**

Thus, allyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate **6** was obtained (4.11).

In the following step, allyl-carbonate monomer (allyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate) was synthesized (4.12). The cyclization was performed in the presence of ethyl chloroformate in dilute anhydrous THF solution via dropwise addition of triethylamine.



(4.12)

6 7

^{1}H NMR spectroscopy confirmed clearly the structure of **7** by appearance of characteristic signals of vinylic protons (δ 5.89-5.30). The double doublets at δ 4.69/4.22 were attiributable to the methylene protons next to the carbonate.

Importantly, no peak at δ 3.63-3.85 assignable to the methylene protons adjacent to the hydroxyl group was detected.

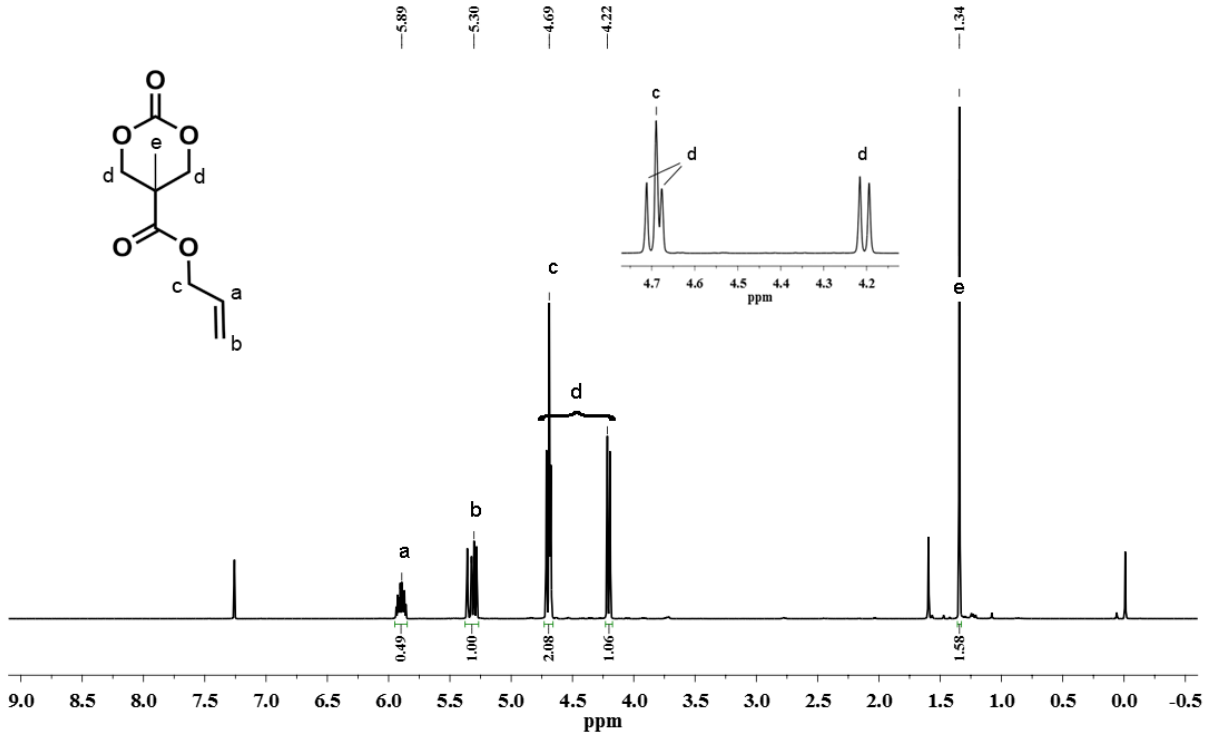


Figure 4.5: ^{1}H NMR spectrum of Allyl-Carbonate in $CDCl_3$ (500 MHz).

In addition, ^{13}C NMR spectroscopy indicated a peak at 148 ppm that proved the cyclic carbonate formation.

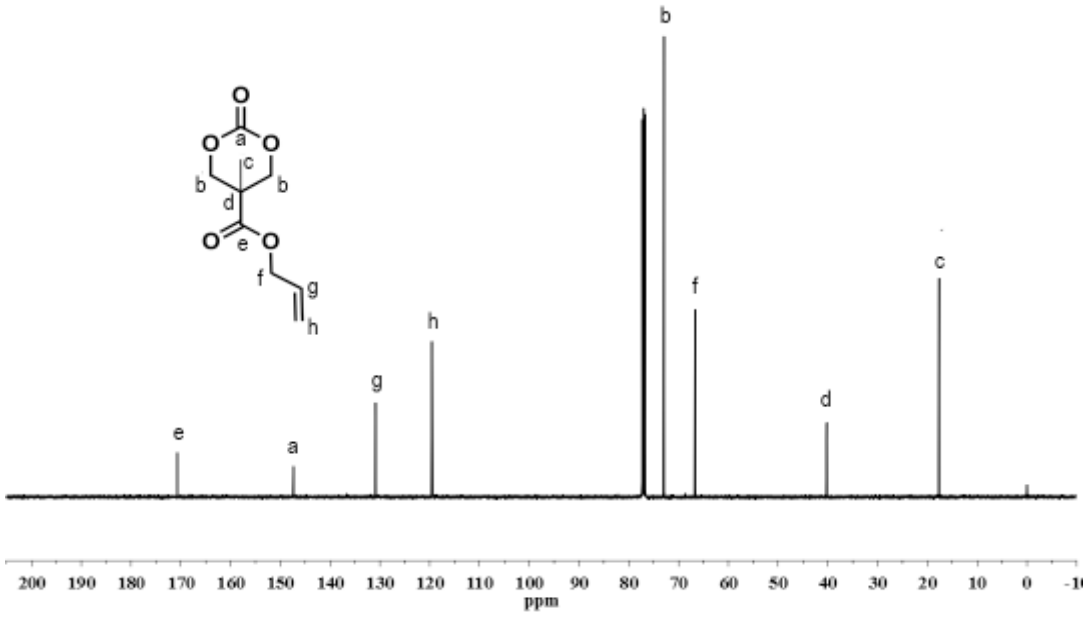


Figure 4.6: ^{13}C NMR spectroscopy of Allyl-Carbonate in $CDCl_3$ (500 MHz).

4.4 Preparation of anthracene and allyl functional polycarbonate (PC-Anth/Allyl)

The benzyl-terminated polycarbonate was prepared from the ROP of anthracene-9-ylmethyl 2,2,5-trimethyl-1,3-dioxane-5-carboxylate (**4**) and allyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate (**7**) using benzyl alcohol as initiator and TU/DBU as catalyst in CH_2Cl_2 at room temperature for 24 h. The structure of the PC was confirmed by ^{1}H NMR.

From ^{1}H NMR spectroscopy, two doublets (4.72 and 4.19 ppm) corresponding to the CH_2 adjacent to the carbonate group in 4 and **7** disappeared and a new broad singlet signal at 4.23 ppm that is assigned to the CH_2OC=O of PC appeared in association with the characteristic signals of the anthracene and CH_2 linked to the anthracene at 8.45-7.50 and 6.14 ppm, respectively. Also vinylic protons and CH_2 linked to the vinyl group are shown at 5.85, 5.21 and 4.59, respectively. (Figure 4.8).

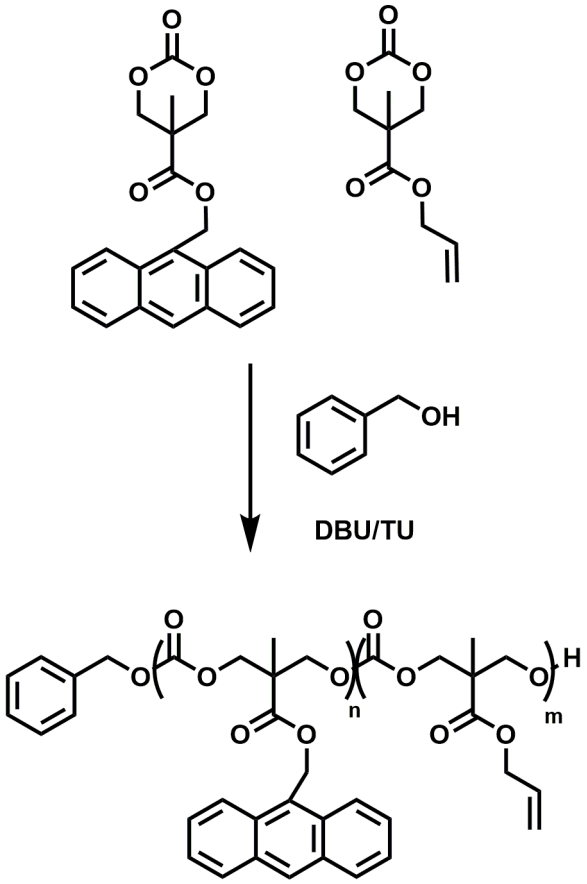


Figure 4.7: ROP of Antracene and Allyl Functional Carbonate Monomers

The number-average molecular weight ($M_{n,NMR}$ = 10 (DP_n) X 350 g/mol + 7(DP_n) X 200 g/mol MW of end-groups (108 g/mol) = 5008 g/mol) of the PC-anthracene/Allyl

could be calculated by comparing integrated signals of the main backbone. Next, the $M_{n,theo}$ was determined according to the following equation, $M_{n,theo}$ = ($[M]_0/[I]_0$) X MW of 20 (550 g/mol) X conv. % + MW of end-groups (108 g/mol) = 7258 g/mol and found to be consistent with the $M_{n,NMR.}$ The GPC analysis of PC-anthracene/allyl displayed a monomodal GPC trace with narrow polydispersity ($M_{n,GPC}$ = 1908 g/mol, M_w/M_n = 1.58 with respect to PS standards).

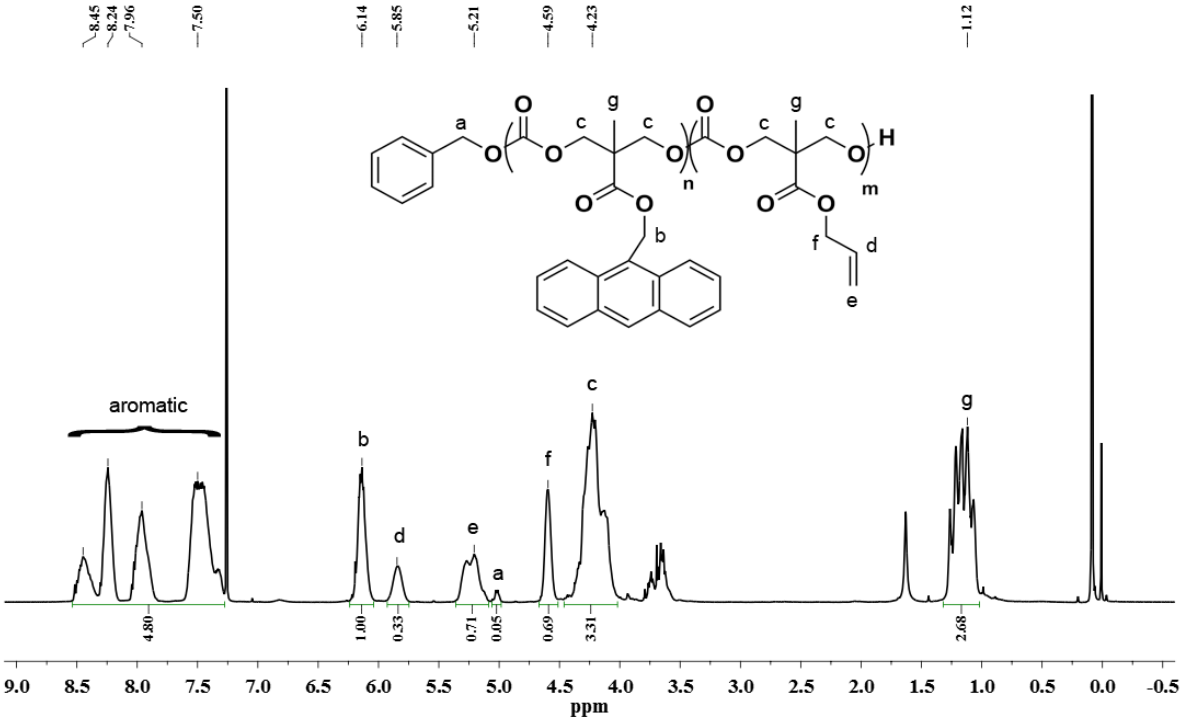


Figure 4.8: ^{1}H NMR spectrum of benzyl-terminated polycarbonate (PC-anthracene and allyl) and cyclic carbonate in $CDCl_3$ (500 MHz).

4.5 Diels-Alder click reaction between PC-Anth/Allyl with MI-Br (PC-*g*-MI)

Before the synthesis of graft copolymers a model reaction was carried out. In this case, PC-anth/allyl was clicked with **11**. After Diels-Alder click reaction, PC-*g*-Model was simply purified by precipitation in methanol and its structure was identified by GPC and ^{1}H NMR.The disappearance of anthracene aromatic protons in the range of 8.5 to 7.5 and the appearance of characteristic signals related with anthracene-maleimide cycloadducts at 5.52 (C*H*$_2$-anthracene-maleimide cycloadduct) and 4.78 (C*H*, bridge-head proton) were detected (Figure 4.9). The confirmed structure of PC-*g*-Model proves Diels-Alder click reaction having a potential in the preparation of graft copolymers.

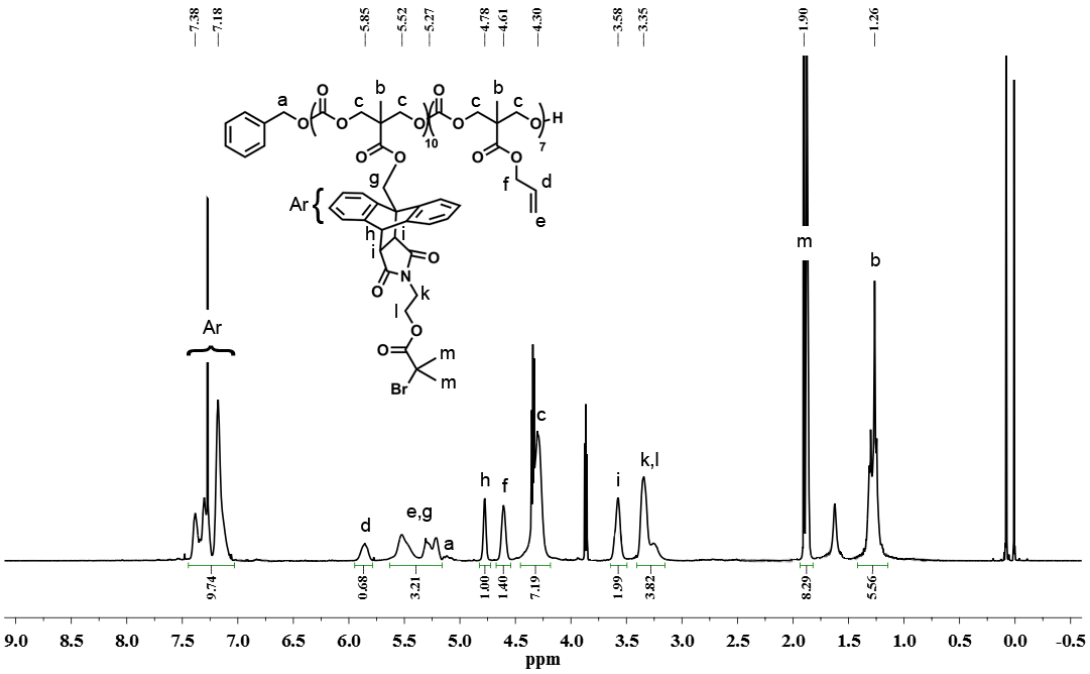


Figure 4.9: ^{1}H NMR spectrum of Diels-Alder click reaction between PC-Anth/Allyl with MI-Br (PC-*g*-MI 500 MHz).

The Diels-Alder adduct was monitored by UV spectroscopy by following the disappearance of the characteristic five-finger absorbance of the anthracene moiety at 300-400 nm and thereby, Diels-Alder efficiency (DA_{eff}) was calculated to be 98% by UV measurements with a ratio of final absorbance (A_t) at 24 h and initial absorbance (A_0); DA *eff* = (1-A_t/A_0) x 100 ($M_{n,GPC}$=3535 $M_{n,NMR}$=7800).

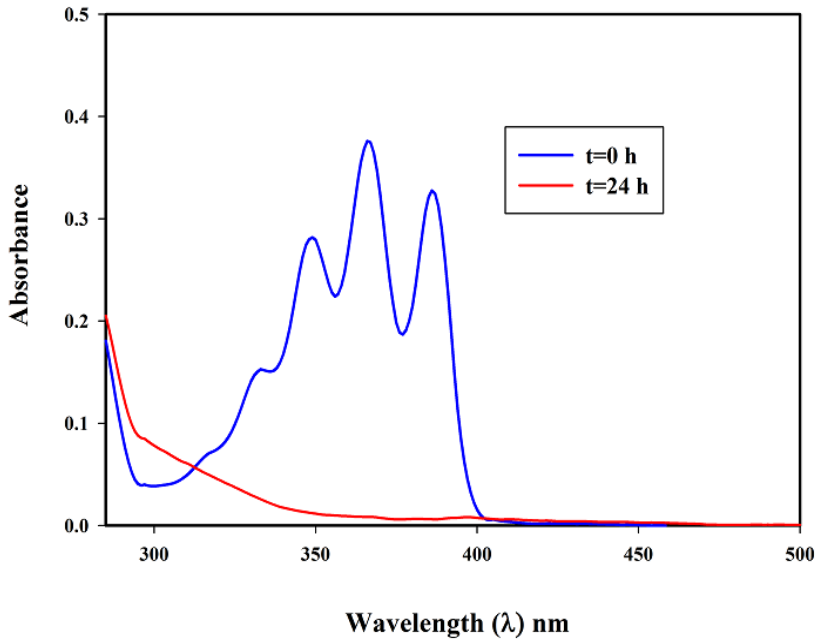


Figure 4.10: UV-Vis spectra of PC-*g*-MI (C_0 = 3.5 X 10^{-5} M in CH_2Cl_2).

4.6 Thiol-ene click reaction of PC-g-MI with N-Acetyl-L-Cysteine Methyl-Ester

The Thiol-ene reaction between PC-*g*-MI and N-Acetyl-L-Cysteine Methyl-Ester was occured by photo conditions. The reaction wasirradiated by a photoreactor (Rayonet) equipped with 10 lampsemitting light nominally at 365 nm at room temperature for 4 h. After that time, the polymerization mixture was diluted with THF and precipitated in methanol.

^{1}H NMR spectroscopy clearly evidenced the structures of the targeted polymer. The disappearance of vinylic and CH_2 protons adjacent to the vinylic group coupled with the appearance of characteristic aliphatic peaks of cysteine indicating that thiol-ene reactions had successfully occurred.

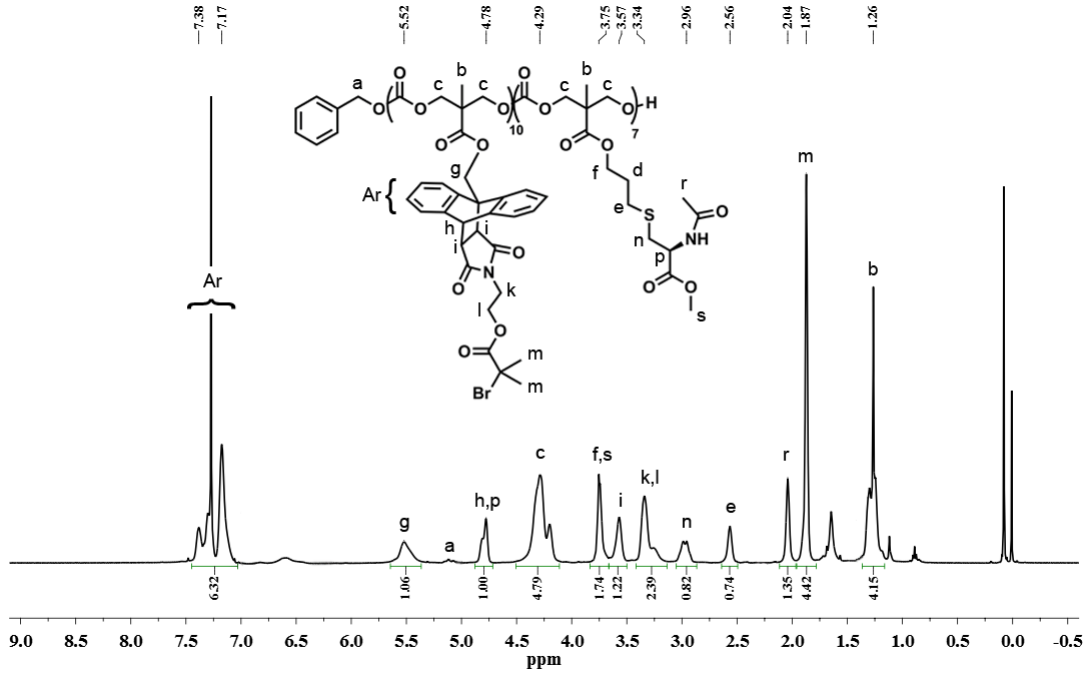


Figure 4.11: ^{1}H NMR spectrum of thiol-ene click reaction of PC-*g*-MI with N-Acetyl-L-Cysteine Methyl-Ester (500 MHz).

After purification the resulting polymer, a clear shift to the higher molecular weight region was detected from GPC measurements while maintaining narrow polydispersity index (M_w/M_n) and monomodal distribution ($M_{n,GPC}$=4125).

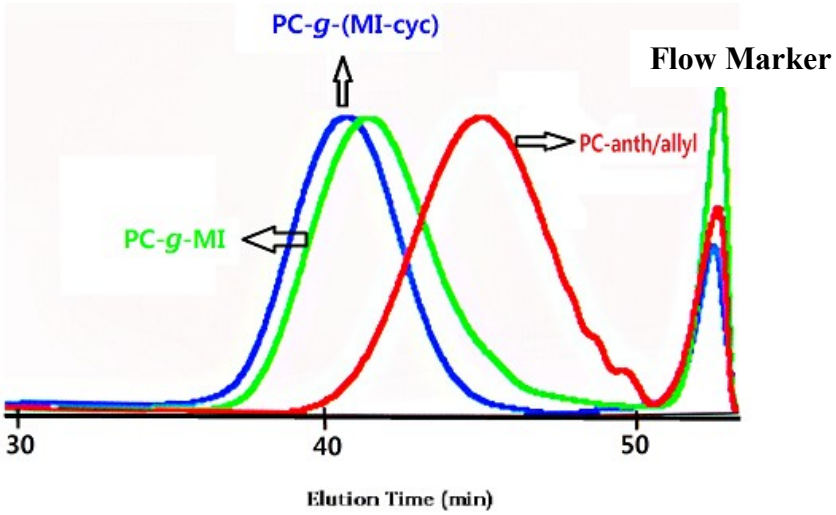
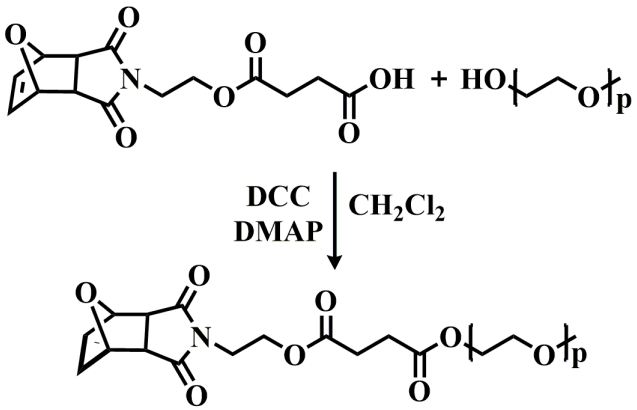


Figure 4.12: Overlay of GPC traces of PC-anth/allyl, PC-*g*-MI and PC-g-(MI-cyc) their block copolymers in THF at 30°C.

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 graft copolymers.

4.7 Diels-Alder click reaction between PC-Anth/Allyl and PEG_{550}-MI

First, PEG_{550}-MIwas obtained via an esterification reaction between Me-PEG (M_n=550) and excess amount of **12** in the presence of DCC as a coupling agent and DMAP as a catalyst (4.13).



(4.13)

From ^{1}H NMR spectrum of the polymer, the bridge and bridge-head protons were detected at 6.49, 5.24 and 2.86 ppm respectively. The $M_{n,NMR}$= 750 of MI-PEG was determined from a ratio of integrated peaks at 3.62 ppm (OCH_2CH_2 protons of PEG) to 6.49 ppm (vinyl end protons).

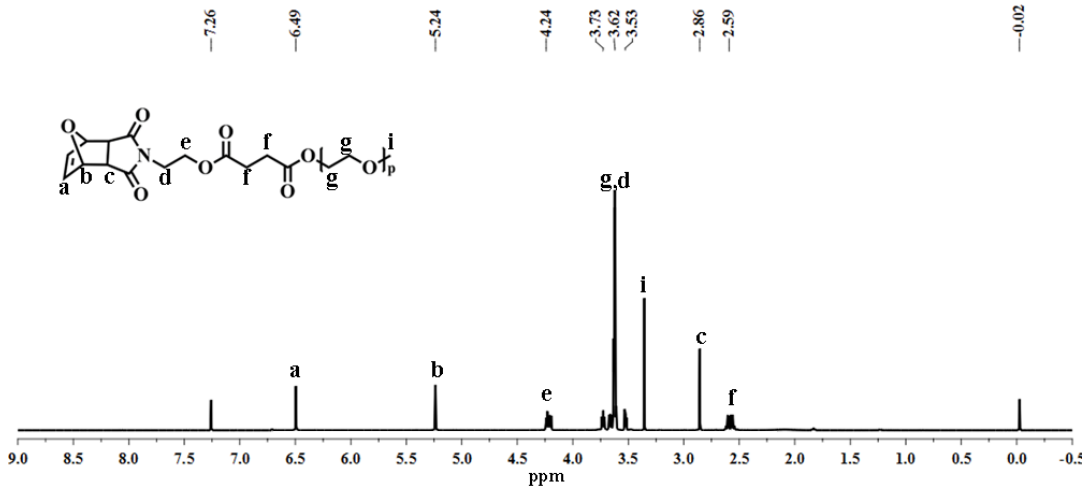


Figure 4.13: ^{1}H NMR spectrum of PEG550-MI in CDCl3(500 MHz).

The PC-anthracene/allyl polymer was subsequently ligated with well-defined α-furan-protected maleimide-terminated linear polymers, PEG_{550}-MI, in order to yield well defined PC graft copolymers under Diels-Alder reaction conditions. The 15 equiv of the α-furan protected maleimide-terminated homopolymers with respect to the PC-anthracene/allyl were deliberately chosen to ensure the reaction completion, as well as easy elimination from the reaction mixture. The Diels-Alder adduct was monitored by UV spectroscopy by following the disappearance of the characteristic five-finger absorbance of the anthracene moiety at 300-400 nm and thereby, Diels-Alder efficiency (DA_{eff}) was calculated to be 95% by UV measurements with a ratio of final absorbance (A_t)at 27 h and initial absorbance (A_0); DA *eff*= (1-A_t/A_0)x100 ($M_{n,NMR}$= 12700, $M_{n,GPC}$= 5153).

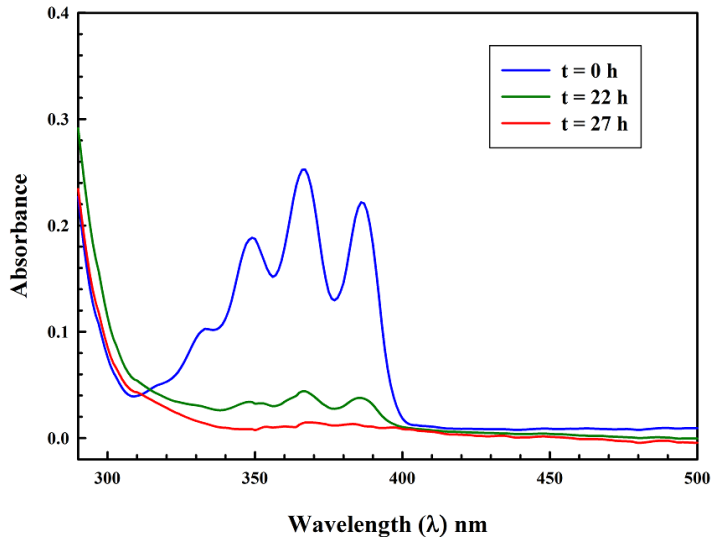


Figure 4.14: UV-Vis spectra of PC-*g*-PEG_{550} copolymer (C_0 = 2.66 X 10^{-5} M in CH_2Cl_2).

Moreover, ^{1}H NMR spectroscopy clearly evidenced the structures of the target graft copolymer. A rough examination of the ^{1}H NMR spectra of graft copolymer proved the disappearance of the characteristic anthracene signals from 8.49 to 7.20 ppm coupled with the appearance of the C*H* (bridge-head proton) (*ca.* δ 4.75) and the CH_2-Diels-Alder adduct (*ca.* δ 5.64), indicating that the Diels-Alder reactions had successfully occurred. Also, the ^{1}H NMR spectroscopy analysis obviously showed the characteristic signals for the CH_2OC=O of the PC (4.27 ppm), the CH_2CH_2O of the PEG (3.64 ppm) segments in the corresponding graft copolymer.

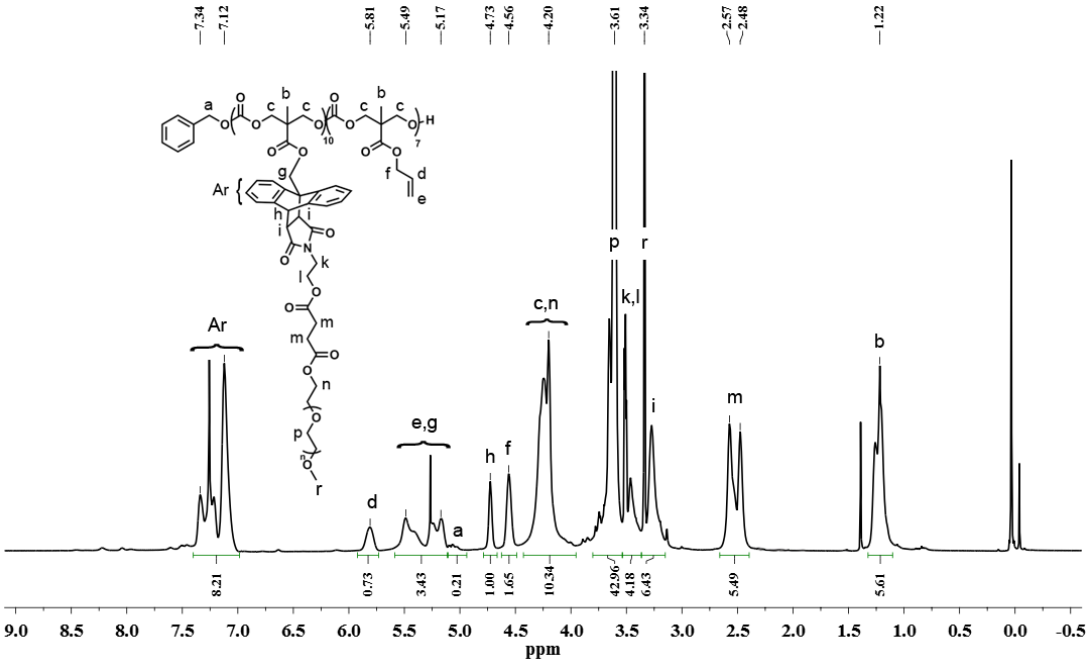


Figure 4.15: ^{1}H NMR spectrum of PC-*g*-PEG copolymer (from PC-anthracene/allyl and PEG_{550}-MI) in $CDCl_3$ (500 MHz).

4.8 Thiol-ene click reaction of PC-g-PEG with N-Acetyl-L-Cysteine Methyl-Ester

The Thiol-ene reaction between PC-*g*-PEG and N-Acetyl-L-Cysteine Methyl-Ester was occured by photo conditions. Thereaction was irradiated by a photoreactor (Rayonet) equipped with 10 lampsemitting light nominally at 365 nm at room temperature for 5 h. After that time, the polymerization mixture was diluted with THF and precipitated in methanol.^{1}H NMR spectroscopy clearly evidenced the structures of the targeted polymer. The disappearance of vinylic and CH_2 protons

adjacent to the vinylic group coupled with the appearance of characteristic aliphatic peaks of cysteine indicating that thiol-ene reactions had successfully occurred.

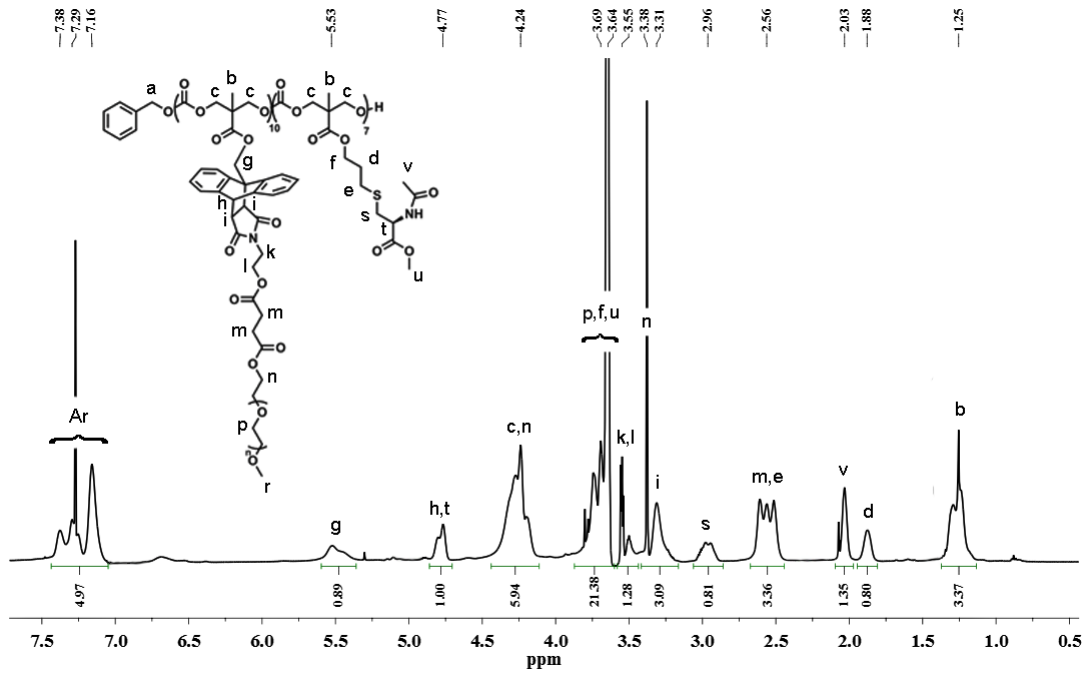


Figure 4.16: ^{1}H NMR spectrum of Diels-Alder click reaction between PC-Anth/Allyl with PEG_{550}-MI (PC-*g*-PEG) (500 MHz).

After purification the resulting polymer, a clear shift to the higher molecular weight region was detected from GPC measurements while maintaining narrow polydispersity index (M_w/M_n) and monomodal distribution ($M_{n,GPC}$=7696).

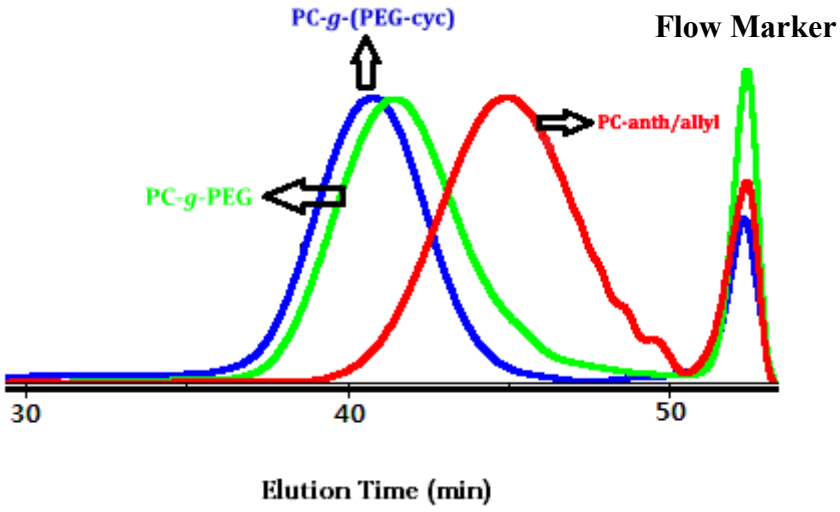


Figure 4.17: Overlay of GPC traces of PC-anth/allyl, PC-*g*-PEG, PC-*g*-(PEG-cyc) in THF at 30°C.

5. CONCLUSION

In this study, we described the synthesis of well-defined PC-based graft copolymers using the Diels-Alder click reactionof the PC-anthracene/allyl with α-furan protected maleimide and α-furan protected maleimide-terminated polymer (PEG_{550}-MI).Then we prepared Thiol-ene click reaction with N-Acetyl-L-Cysteine Methyl-Ester.UV spectroscopy indicated that DA efficiencies of the reactions were quantitative. Moreover, both GPC and ^{1}H NMR analysis confirmed a successful graft copolymer formation.Therefore, the Diels-Alder click reaction is found to be superior over the classical preparation of PC-graft copolymers via growing graft from the hydroxyl-terminated macroinitiator using only ROP. Notably, Diels-Alder reaction becomes a more prominent particularly for the preparation of a variety of biocompatible polymers (such as PC), because it does not use any toxic copper catalyst compared to the CuAAC.

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CURRICULUM VITAE

Name Surname: Binnaz CANOL

Place and date of birth: İstanbul, 14/02/1988

Address: Boğaziçi Cad. Çeşmibülbül Sok. Şişecam Şimşek Sitesi B:16/D:6 Beykoz/Istanbul, Turkey

E-Mail: bcanol@itu.edu.tr

B.Sc.: Yildiz Technical University (Chemistry) Davutpasa, Istanbul, Turkey.

M.Sc.: Istanbul Technical University (Polymer Science and Technology) Maslak, Istanbul, Turkey.

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