Chapter 2
Biomedical Polymers: Synthetic Strategies

2.1 Introduction

As discussed in Chap. 1, polymeric biomaterials of both natural and synthetic origin constitute an important class of biomedical materials that are used extensively in various applications ranging from drug delivery to tissue engineering. The use of natural polymers such as cellulose and collagen for various medical applications dates back to centuries. The very first reported synthetic polymer for medical use is poly(methyl methacrylate) (PMMA) by a British ophthalmologist, Sir Nicholas Harold, in 1949 for making intraocular lens [1]. Since then, several biostable and biodegradable synthetic polymers have been developed for various biomedical applications. However, complex nature of biomedical applications and the diverse biological responses at the material-biology interfaces, presents a challenge in developing a biomaterial with optimal biological, chemical, and physical characteristics. Following are some of the important criteria for selecting a polymeric material for biomedical uses [2]:

- Polymer, as well as its metabolites, should not evoke any adverse inflammatory or toxic responses in vivo.
- Polymer should be easy to process and sterilized.
- Polymer should have an acceptable shelf life and degradation time matching the application.
- Polymer should have mechanical properties to match the required application.

In this chapter, we discuss various synthetic strategies commonly used for preparing synthetic biomedical polymers by classifying them on the basis of the type of polymerization. A brief mechanistic description of each type of synthesis is illustrated with representative examples to provide a better understanding of the process and polymers prepared by the technique.

V.B. Damodaran et al., *Biomedical Polymers*,
SpringerBriefs in Applied Sciences and Technology,
DOI 10.1007/978-3-319-32053-3_2

2.2 Condensation Polymerization

Most natural polymers are condensation polymers. Condensation polymerization is a commonly used polymerization technique for preparing various biomedical polymers. The majority of these are *step-growth* polymerizations, which involve the stepwise condensation of bifunctional monomers with the elimination of small molecules such as water and HCl. A generalized equation for the linear polycondensation reaction involving two bifunctional monomers A and B can be given as:

$$nA + nB \rightarrow A(AB)_{n-1}B \tag{2.1}$$

For example, polyesters, an important class of biomedical polymers, are commonly prepared by condensation polymerization between a diol and a diacid with the elimination of water molecules (Fig. 2.1).

The polymerization proceeds in a step-wise manner with the initial formation of dimers, trimers, tetramers, etc. In equimolar concentrations of the diol and diacids and in the absence of any exogenous catalysts, the polymerization is found to catalyzed by the diacid itself. Under these conditions, the rate of polymerization can be given as [3, 4]:

$$-\frac{d[\mathrm{COOH}]}{dt} = k[\mathrm{COOH}]^2[\mathrm{OH}] \tag{2.2}$$

where [COOH] and [OH] represents the respective molar concentrations. Under equimolar concentrations Eq. (2.2) can be rearranged as:

$$-\frac{d[\mathrm{COOH}]}{dt} = k[\mathrm{COOH}]^3 \tag{2.3}$$

or

$$-\frac{d[\mathrm{COOH}]}{[\mathrm{COOH}]^3} = k\,dt \tag{2.4}$$

Integration of Eq. (2.4) within limits [COOH]=[COOH]$_0$ to [COOH]=[COOH]$_t$ and t =0 to t = t, the integrated rate equation can be given as:

$$2kt = \frac{1}{[\mathrm{COOH}]_t^2} + constant \tag{2.5}$$

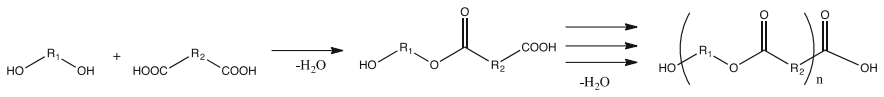

Fig. 2.1 Polycondensation between diol and diacid monomers

The extent of polymerization (p) at a given time t can be correlated to the monomer concentration as

$$p = \frac{Functional\ groups\ reacted}{Initial\ functional\ groups} = \frac{[\mathrm{COOH}]_0 - [\mathrm{COOH}]_t}{[\mathrm{COOH}]_0} \tag{2.6}$$

rearranging Eq. (2.6),

$$[\mathrm{COOH}]_t = [\mathrm{COOH}]_0(1-p) \tag{2.7}$$

By knowing the molar concentration, the average degree of polymerization at time t, $\overline{DP}$, can be defines as

$$\overline{DP} = \frac{[\mathrm{COOH}]_0}{[\mathrm{COOH}]_t} = \frac{[\mathrm{COOH}]_0}{[\mathrm{COOH}]_0(1-p)} = \frac{1}{(1-p)} \tag{2.8}$$

Equation (2.8) is known as Carothers equation [5, 6] and is extensively used to control the degree of polymerization and thereby achieve the desired polymer molecular weight.

Some representative biomedically relevant examples of condensation polymerization strategies will be illustrated in the following subsections.

2.2.1 Polyesters and Polyarylates

Polyesters constitute an important class of biomedical polymers by virtue of the ease of processibility and desirable degradation behavior and mechanical properties. In general, polyesters can be prepared by condensation polymerization as well as by ring opening polymerization (see Sect. 2.3.2). Polymerization reaction between either diols and dicarboxylic acids or between hydroxyl acids can be conveniently carried out in the presence of chemical or enzymatic catalysts. However, achieving a higher molecular weight through this method is challenging due to the reaction kinetics and changes in the stoichiometry of the reacting monomers. Additionally, in many cases, the by-products such as water can cause parallel hydrolysis of the polymer product. Continuous removal of such reaction by-products, using high vacuum for instance, to drive the polymerization to a reasonable molecular weight is a major bottleneck in polycondensation reactions.

Melt/solid-phase polycondensation reaction is a type of polycondensation reaction between diacids and diols, commonly carried out under high temperature and vacuum. A representative example is the synthesis of biodegradable aliphatic polyester poly(glycerol sebacate) (PGS) through a thermal polycondensation reaction between glycerol and sebacic acid at 120 °C under 30 m Torr vacuum [7]. The thermal condensation resulted in a colorless elastomer with the polyester backbone containing a small number of crosslinks and hydroxyl groups (Fig. 2.2).

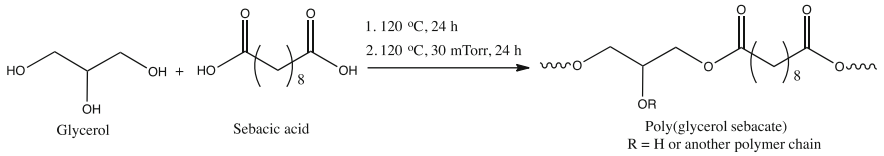

Fig. 2.2 Scheme illustrating the synthesis of poly(glycerol sebacate) through thermal polycondensation. Adapted from Ref. [7]

PGS is a bioresorbable elastomeric polymer and extensively evaluated for various biomedical applications such as soft and hard tissue engineering and controlled drug delivery [8]. In a similar way, a number of aliphatic polyester elastomers for various biomedical applications were prepared from diacid monomers such as citric acid and α-ketoglutaric acid with aliphatic diols and triols using thermal polycondensation reactions [9–12].

Thermal polycondensation reactions can also be performed in the presence of a catalyst to improve the specificity of the polymerization as well as to increase the molecular weight of the resulting polymer. Enzymatic catalysis using lipases and proteases were explored for improving the regioselectivity during the polycondensation without using any monomer activation and organic solvents. In one such attempt, Kumar et al. successfully prepared a terpolyester of sorbitol and glycerol with molecular weights up to 117 kDa using a lipase catalyst Novozyme-435 at 90 °C [13]. Various Lewis acids, metal salts and oxides, and organo-metallic compounds are also generally used as catalysts for polyester condensation reactions. Among these catalysts, titanium and zirconium alkoxides and dibutyltin oxide are found to be very effective in preparing polyesters with reproducible yields and high molecular weights [14].

Transesterification between hydroxyl-esters, carboxy-esters, or two ester groups is one of the most important polyesterification technique used for preparing various aliphatic, aliphatic-aromatic or aromatic polyesters (also known as arylates). Titanium alkoxides are very efficient catalysts for transesterification polymerizations, however in some cases it can cause undesirable discoloration to the resulting polymer [15]. A representative example is the synthesis of a polyester based on dimethyl terephthalate using titanium isopropoxide [16] (Fig. 2.3).

Various aliphatic and aromatic polyesters with controlled architecture and high molecular weights can be prepared using solution polyesterification techniques at atmospheric temperature and pressure. These reactions typically proceed through the activation of carboxyl groups with the use of activating agents such as carbodiimides, 1,1′-carbonyldiimidazole, and sulfonyl chlorides. Because of the use of mild reaction conditions, near neutral pH, process reproducibility, and ease of controlling the molecular weight of the resulting polymers, this technique is commonly used for the industrial scale manufacturing of many biomedical polyesters. For example, poly(lactic-*co*-glycolic acid) (PLGA), a widely used class of

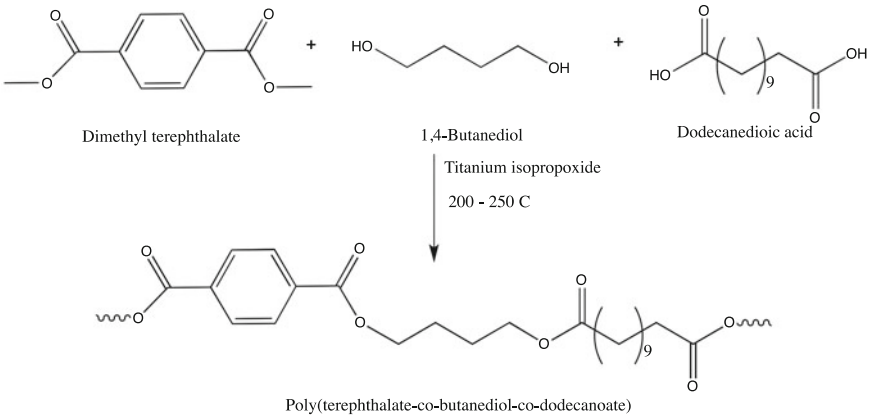

Fig. 2.3 Scheme illustrating the polycondensation through transesterification catalyzed by titanium isopropoxide

biomedical polyester, can be conveniently prepared with high degree of control over the monomer sequence and stereochemistry using a carbodiimide in presence of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) or 4-(dimethylamino)pyridinium 4-toluenesulfonate salt (DPTS) [17].

In general, use of a carbodiimide with DMAP alone produces polyesters with low molecular weights. However, under same reaction conditions, use of DPTS instead of DMAP produces polyesters with high molecular weights. Carbodiimide-mediated polyesterification proceeds through the formation of an *O*-acyl isourea intermediate (Fig. 2.4), which can successfully transfer into the formation of an ester derivative or the formation of *N*-acyl urea side product [Fig. 2.4, compound (**5**)]. Use of p-toluenesulfonic acid (PTSA) prevents the formation of *N*-acyl urea side product and substantially enhances the polyester conversion efficiencies, which ultimately leads to a high molecular weight for the resulting polyester [18].

2.2.2 Polyesteramides

Similar to polyesters, the polycondensation methods for preparing polyesteramides includes thermal as well as solution techniques. In general, thermal polycondensations are carried out in two steps with the preparation of a diamide-diester prepolymer at a low temperature followed by a high-temperature condensation under reduced pressure to achieve high molecular weights. Following this method, Asín et al. [19] reported the synthesis of a sequential polyesteramide derived from glycine (Fig. 2.5). However, thermal degradation of the amide bonds at high temperature can limit the molecular weight of the resulting polymer [20].

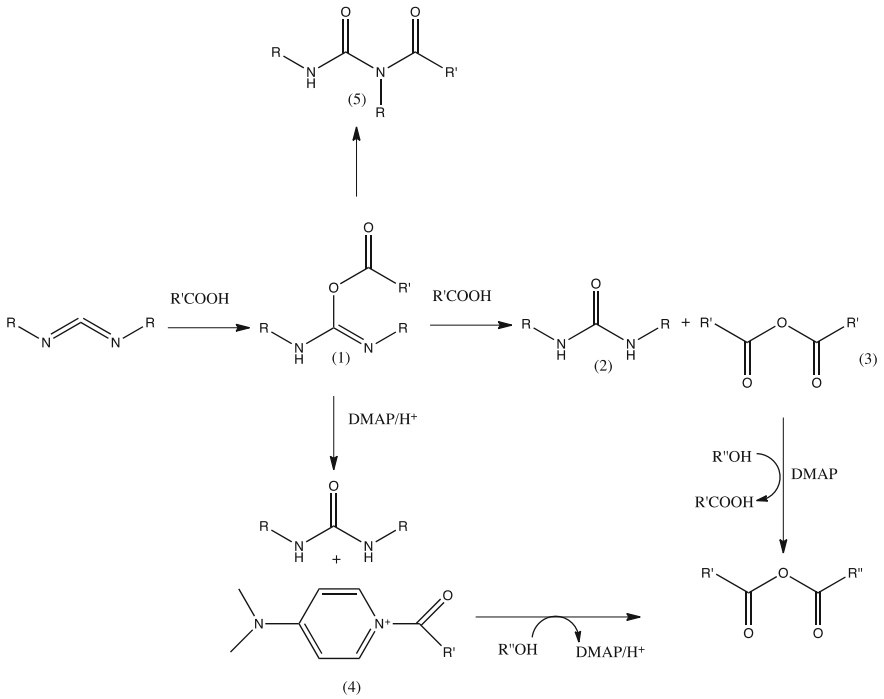

Fig. 2.4 Reaction pathways in carbodiimide mediated polyesterification. *1* *O*-acylisourea intermediate, *2* urea, *3* acid anhydride, *4* *N*-acylpyridinium intermediate, and *5* *N*-acyl urea side product. Adapted from Ref. [18]

Solution phase polycondensation is a convenient method of preparing a large variety of polyesteramides under ambient reaction conditions following the well-known peptide chemistries [21]. This method enables the synthesis of various biomedical polymers from non-toxic, naturally occurring building blocks such as α-amino acids and peptides [22, 23]. In many cases, the polymerization proceeds through the activation of carboxyl groups present in one of the monomers with the formation of an active ester similar to that mentioned in the case of polyesterification. Polyesteramides with high molecular weight and relatively low polydispersity can be prepared using this method by carefully controlling the reaction parameters, catalyst loading, and with the use of high purity monomers. A representative example is the synthesis of biodegradable polyesteramides containing peptide linkages Phe-Phe, Phe-Leu, Phe-Val, and Phe-Ala by Fan et al. using carbodiimide coupling chemistry from amino acids, adipoyl chloride, and 1,4-butanediol [24] (Fig. 2.6).

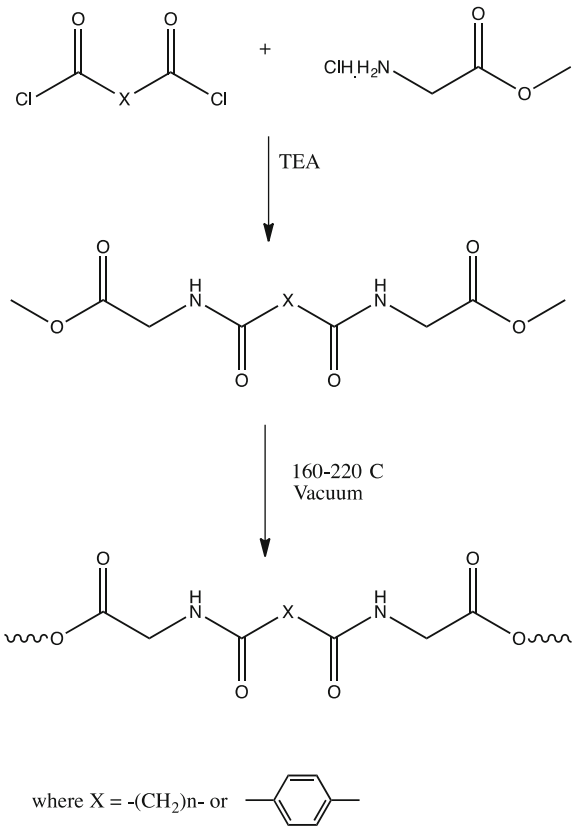

Fig. 2.5 Scheme illustrating the synthesis of polyesteramide following thermal polycondensation. Adapted from Ref. [19]

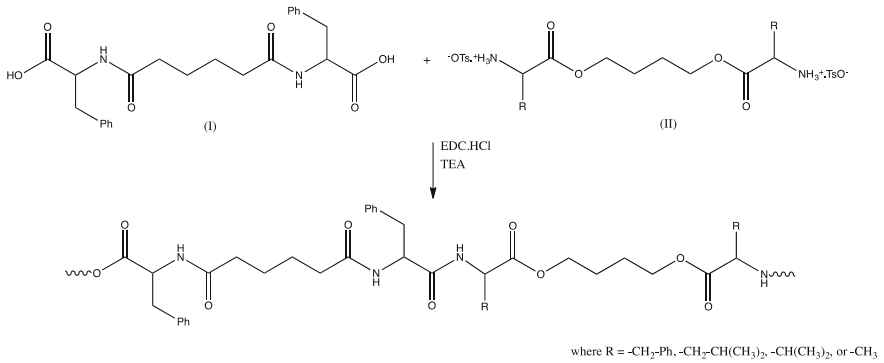

Fig. 2.6 Scheme illustrating the synthesis of polyesteramide following solution phase polycondensation. Monomer I: Di(phenylalanine) adipamide prepared from L-phenylalanine and adipoyl chloride under Schotten-Baumann condition. Monomer II: p-Toluenesulfonic acid salts of bis (amino acid)-1,4-butane diesters prepared by direct esterification of α-amino acids with 1,4-butanediol in presence of p-toluenesulfonic acid. Adapted from Ref. [24]

2.2.3 *Polycarbonates*

Similar to the synthesis of polyesters and polyarylates, polycarbonates can also be prepared via melt-phase transesterification condensation reactions [25, 26]. However, due to the requirement of high temperature and vacuum, poor control on the final molecular weight, and color formation during polymerization makes this process less attractive on a commercial scale and from a biomedical perspective [27]. Alternatively, polycarbonates with excellent control over their molecular profiles can be synthesized through phosgene chemistry from a variety of aliphatic and aromatic alcohols. Early stage development of polycarbonate following this chemistry was based on utilizing phosgene (carbonyl dichloride) as the reacting agent. However, due to the high toxicity and difficulty in handling phosgene gas, triphosgene (bis(trichloromethyl)carbonate) is currently used as a safer alternative to phosgene for polycondensation reactions. In the presence of initiators, triphosgene decomposes in situ into three molecules of phosgene enabling the formation of polycarbonates. The extreme reactivity of phosgene and triphosgene towards the formation of a carbonate linkage can be attributed to the formation of a carbonic acid derivative with the nucleophilic substitution of the alcohols or phenolic groups at the phosgene carbonyl carbon [28].

Representative examples of the use of phosgene chemistries for preparing biodegradable polycarbonates are illustrated in Figs. 2.7 and 2.8. Figure 2.7 presents the scheme illustrating a two-phase interfacial phosgene process used for making bisphenol-A polycarbonate with good control over molecular weight profile and reproducibility [29]. Figure 2.8 presents the use of triphosgene as the phosgenation reagent for the synthesis of poly(tyrosol-*co*-homovanillyl) carbonate from the naturally occurring phenolic monomers tyrosol and homovanillyl alcohol [30].

Through phosgenation chemistries, Kohn et al. have prepared a large variety of biomedically significant and bioresorbable polycarbonates from naturally occurring tyrosine-derived monomers (theoretically 'homologous' carbonate–amide copolymers) [23, 31]. Phenolic monomers prepared from tyrosine alkyl esters and desminotyrosine are polymerized using the phosgene chemistry to obtain polycarbonates with the required molecular weights. To improve the hydrophilicity of the polymer backbone, poly(ethylene glycol) (PEG) of a desired particular molecular weight and mole compositions are introduced during the polymerization. A library of tyrosine polycarbonates with predictable molecular weights, degradation rate, and mechanical properties have been prepared using this method and are currently extensively using for biomedical applications ranging from tissue engineering to drug delivery [32–34].

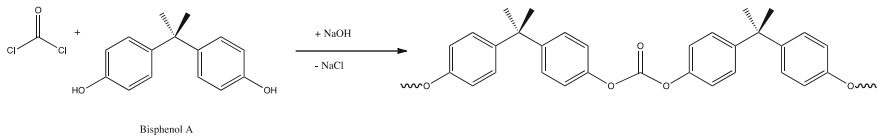

Fig. 2.7 Scheme illustrating the synthesis of polycarbonate following the interfacial phosgene chemistry. Adapted from Ref. [27]

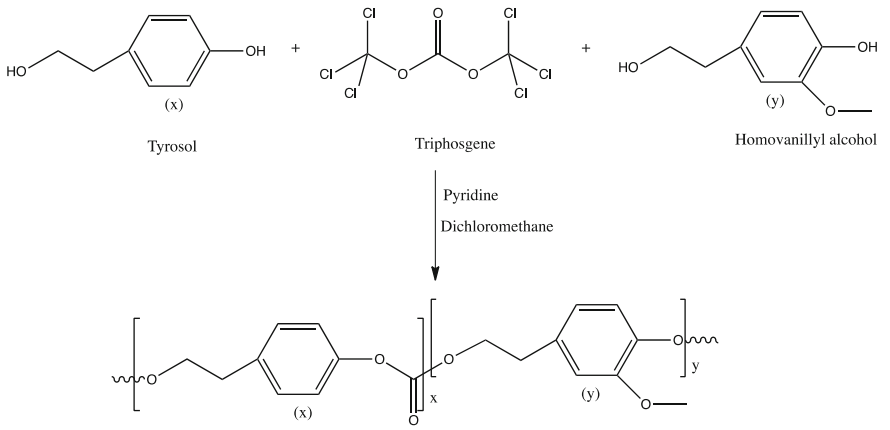

Fig. 2.8 Scheme illustrating the synthesis of polycarbonate using triphosgene

2.2.4 Polyurethanes

Polyurethanes (PUs), one of the most commonly used polymers for various blood-contacting biomedical applications, are generally prepared by the polycondensation reactions of diisocyanates with diols or amines [35, 36]. Reactions of diisocyanates with diols result in the formation of urethane linkages while diisocyanates reactions with amines result in urea linkages. Both aliphatic, as well as aromatic diisocyanate monomers, are commonly used for preparing polyurethane biomaterials. Examples include 1,4-butane diisocyanate (BDI), 1,6-hexamethylene diisocyanate (HDI), 4,4-dicyclohexylmethane diisocyanate (HMDI), and 4,4-diphenylmethane diisocyanate (MDI) [37]. Commonly used diols (or termed as polyols) for preparing polyurethanes includes polyethers, polycaprolactone, and polyesters with molecular weights up to 5000 Da.

In general, PUs can be prepared in single- or two-step polycondensation processes. In the single step synthesis, both diisocyanate and polyol monomers are treated together with a chain extender and catalyst at a higher temperature. However, poor control over the molecular weight profile and reproducibility are routinely encountered with this one-step polyurethane synthesis. A two-step process provides a commercially attractive method for preparing polyurethanes with very good control over the polymer properties and process reproducibility. In the two-step process, an NCO-terminated prepolymer is first prepared by reacting poyol with a slight excess of the diisocyante monomer (Fig. 2.9). In the subsequent step, the NCO-terminated prepolymer is allowed to react with a low molecular weight (less than 500 Da) diol or diamine chain extender. If the chain extender is a diol derivative, then additional urethane linkages will be generated, or if a diamine is used for the chain extension, then a urea linkage will be formed between the chain extenders. This two-stage prepolymer process provides polyurethanes with a uniform alternating block polymers with an orderly distribution of the soft segment

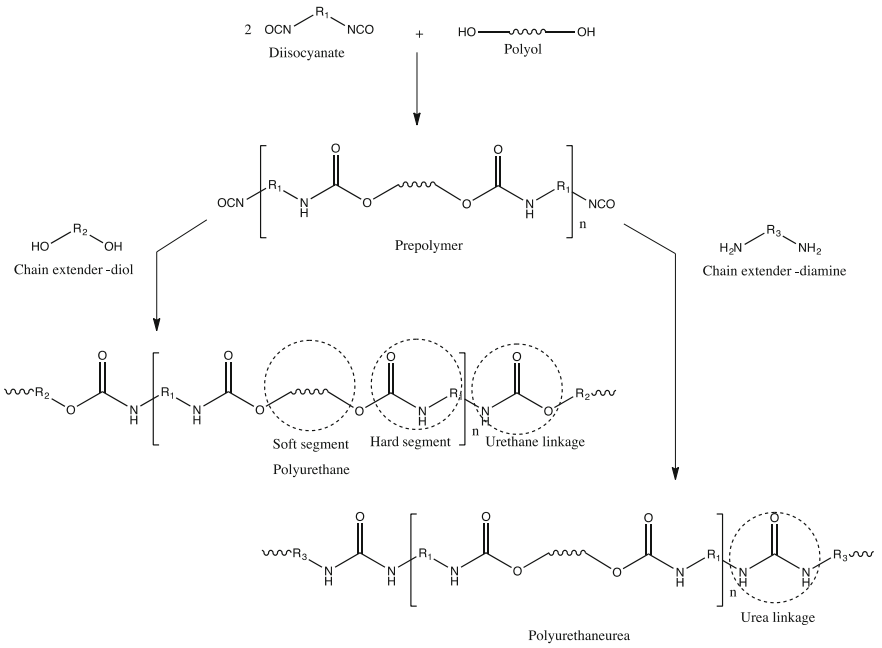

Fig. 2.9 Scheme illustrating the synthesis of polyurethane and polyurethaneurea using the two-step polycondensation process

(due to the diol monomer) and hard segment (due to diisocyanate and chain extender) compared to the single-step polycondensation process.

A representative example is the synthesis of amino acid based polyurethanes using L-tyrosine based chain extender, PEG and polycaprolactone diol as soft segments, and HDI and HMDI as diisocyanate components [38, 39]. By altering the soft and diisocyanate components, the researchers were able to prepare a number of polyurethanes with varying hydrophobicities and degradation behavior.

Because of the toxicity concerns associated with many diisocyanate monomers, researchers are currently exploring alternative environmentally benign non-isocyanate routes to synthesize polyurethanes, especially for biomedical applications. Reactions between carbamates with alcohols and chloroformates with amines have been investigated as alternative strategies [40–42]. Recently, Calle et al. reported an efficient non-isocyanate strategy for preparing a semi-crystalline and thermally stable polyurethane via a thiol-ene self-photopolymerization method [43]. In their approach, an aliphatic thiol–ene carbamate monomer (allyl(2-mercaptoethyl)carbamate, AMC) is first synthesized from cysteamine and allyl chloroformate using a one-step synthesis procedure (Fig. 2.10). In the subsequent step, AMC is then transformed into a thermoplastic polyurethane through thiol–ene photopolymerization by UV irradiation at 365 nm.

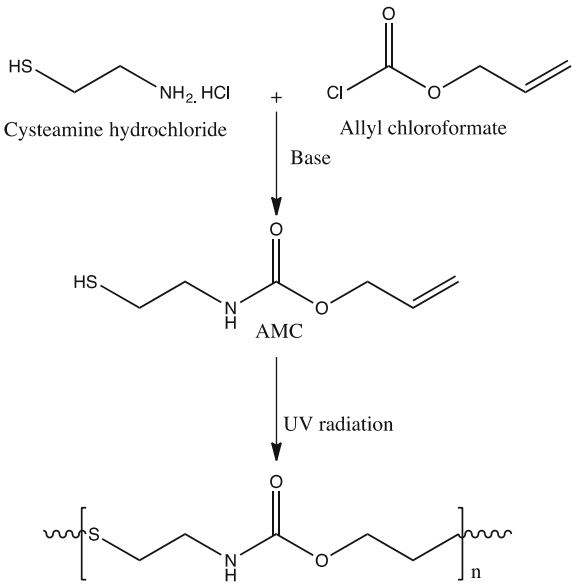

Fig. 2.10 Scheme illustrating the synthesis of a polyurethane polymer via non-isocyanate route

2.3 Addition Polymerization

Addition polymerization involves continuous propagation of a reactive species in a step-wise fashion. These polymerizations can be either chain terminated (*controlled addition polymerization*) or can be a living type polymerization without any chain termination (*living addition polymerization*). In the case of controlled addition polymerizations, the presence of the chain terminators can result in an early stage termination of the propagating chains. However, in the case of living polymerizations, the chain propagation continues with a uniform rate until all the monomers are consumed. Consequently, the resulting polymers will have very narrow molecular weight distributions with a linear increase in molecular weight with the monomer conversion and reaction time (Fig. 2.11).

In general, addition polymerization reactions can be considered as an aggregation process characterized by the following three types of equilibria:

i. equilibrium between monomeric species,
ii. equilibrium between polymeric species, and
iii. equilibrium between monomeric and polymeric species.

Because of these different types of equilibria, the polymerizability of a monomeric species is largely determined by various thermodynamic factors such as temperature, pressure, and monomer concentrations. Additionally the nature of the monomer species, such as amorphous or crystalline, substituents, and structure are found to have a significant influence on the polymerizability and selectivity of a

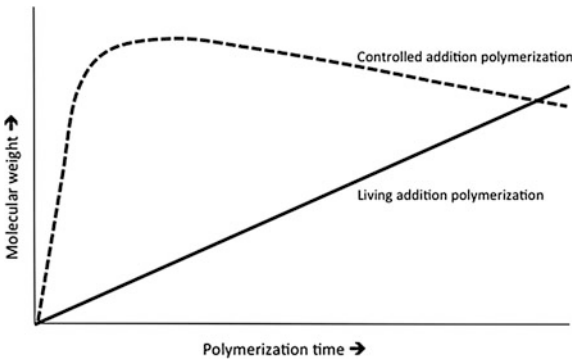

Fig. 2.11 Molecular weight profile of controlled and living addition polymerizations

particular polymerization mechanism. Depending on the nature of the chain initiator, addition polymerization can further be classified as ionic, free radical, or coordination polymerization. A brief overview of different types of addition polymerizations commonly used for preparing biomedical polymers is illustrated in the following sections.

2.3.1 Ionic Polymerization

In this type of addition polymerization, the active species possess ionic charges. Depending on the kind of the ionic species, these polymerizations can be further divided into anionic and cationic polymerization techniques.

2.3.1.1 Anionic Polymerization

In this type of polymerizations, the chain initiation is commonly achieved by the use of a strong nucleophile or through electron transfer, and the polymerization takes place by the nucleophilic attack of the negatively charged initiator. The propagating species in an anionic polymerization is negatively charged, and it is commonly balanced by positively charged counter-ions. Commonly used monomers include vinyl compounds with strong electron attracting or delocalization substituents or cyclic esters and ethers. In the absence of any chain termination (such as in the absence of any protic species), the number-average degree of polymerization at a given time t, $\overline{DP_n}$, can be given as:

$$\overline{DP_n} = \frac{[M]_0}{f[I]_0} x_p \tag{2.9}$$

where $[M]_0$ and $[I]_0$ are the initial concentrations of the monomer and the initiator, f is the initiator efficiency, and x_p is the monomer conversion [3, 44]. This equation

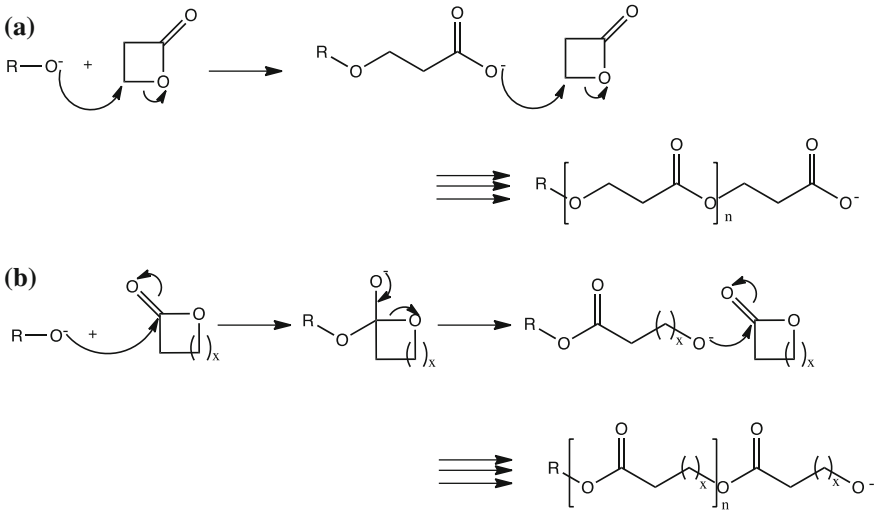

Fig. 2.12 Mechanism of anionic ring-opening polymerization of small cyclic (**a**) and larger cyclic (**b**) lactones (counter-ions omitted)

shows that both the degree of polymerization and the molecular weight of the resulting polymer are inversely related to the concentration of the anionic initiator.

Anionic ring-opening polymerization (AROP) of cyclic lactones are initiated by the nucleophilic addition of a metal alkoxide, followed by an alkyl-oxygen split for small cycles and acyl-oxygen scission for larger cycles [45] (Fig. 2.12). However, potential formation of cyclic oligomers and reduction in molecular weights caused by the deleterious intramolecular transesterification reactions are the serious drawbacks of AROP and make this technique less attractive for making polymers with well-defined and reproducible molecular weights.

AROP of β-lactams (cyclic amides) [46] have also been explored, in the same manner as lactones, by numerous biomaterial scientists for preparing various poly (β-peptides) with potential biomedical applications such as drug and gene delivery and tissue engineering. Recently a variety of biodegradable saccharide-derived polyamides were synthesized using AROP of β-lactam-sugar monomers. These polymers offer many advantages over other synthetic polymers used in biomedical applications due to their structural similarity with natural polysaccharides, rigid backbone, and hydrolytic and enzymatic degradability [47, 48]. A representative example is the synthesis of a chiral poly(amido-saccharide) (PAS) with well-defined molecular weight and narrow polydispersity by the AROP of a 1,2-linked glucose-based β-lactam using lithium bis(trimethylsilyl)amide (LiHMDS) as a co-initiator (Fig. 2.13) [47].

AROP can be used in conjunction with other polymerization techniques to incorporate PEG or poly(ethylene oxide) (PEO) segments into the polymer backbone during the synthesis of various multi-block polymers to alter their water

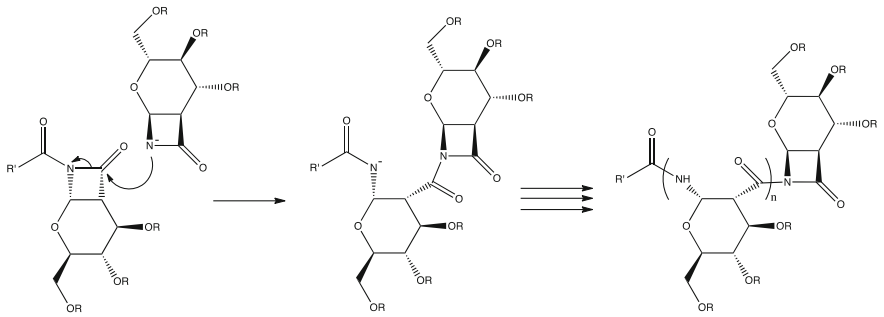

Fig. 2.13 An illustrative example for the synthesis of poly(amido-saccharide) using AROP

solubility and hydrophilicity [49]. Such "PEGylated" multi-block polymers are extensively used in various biomedical applications in the form of polymeric micelles for gene and drug delivery. A representative example is the synthesis of an amphiphilic ABC tri-block polymer, poly(ethylene-*alt*-propylene)-*block*-poly (ethylene oxide)-*block*-poly(hexyl methacrylate) (PEP-*b*-PEO-*b*-PHMA), with hydrophilic PEO as the middle block [50]. The PEP block was synthesized by anionic diene polymerization of isoprene followed by AROP to prepare the PEO block (PEP-*b*-PEO). Finally, PHMA is attached by atomic transfer radical polymerization (ATRP) to generate the tri-block polymer (Fig. 2.14).

2.3.1.2 Cationic Polymerization

Cationic polymerizations involve strong electron accepting agents, such as Lewis and Bronsted acids and Friedel-Crafts acylating and alkylating agents, and the active species are positively charged. In general, the initiation step is the formation of a cationic species, known as carbocation, followed by an SN_2-type nucleophilic attack of a second monomer in the propagation step [51] (Fig. 2.15). The rate of polymerization in a typical cationic polymerization is greatly dependent on the dielectric constant of the solvent, stability of the carbocation, and the electropositivity of the initiator. However, the molecular weight of a polymer synthesized by this method is totally independent of the concentration of the initiator used [3]. In the case of cationic ring-opening polymerization (CROP), the active species are cyclic "onium ions" and the ring-strain of these cyclic species act as the driving force for the propagation reactions. Other examples of the commonly used monomers for cationic polymerizations include vinyl ethers, α-vinyl and α-styrene derivatives [52].

CROP has been extensively used for preparing poly(2-oxazoline)s, an important biomedical polymer characterized by its structural similarities with the naturally occurring polypeptides. Commonly used initiators for this CROP include aliphatic

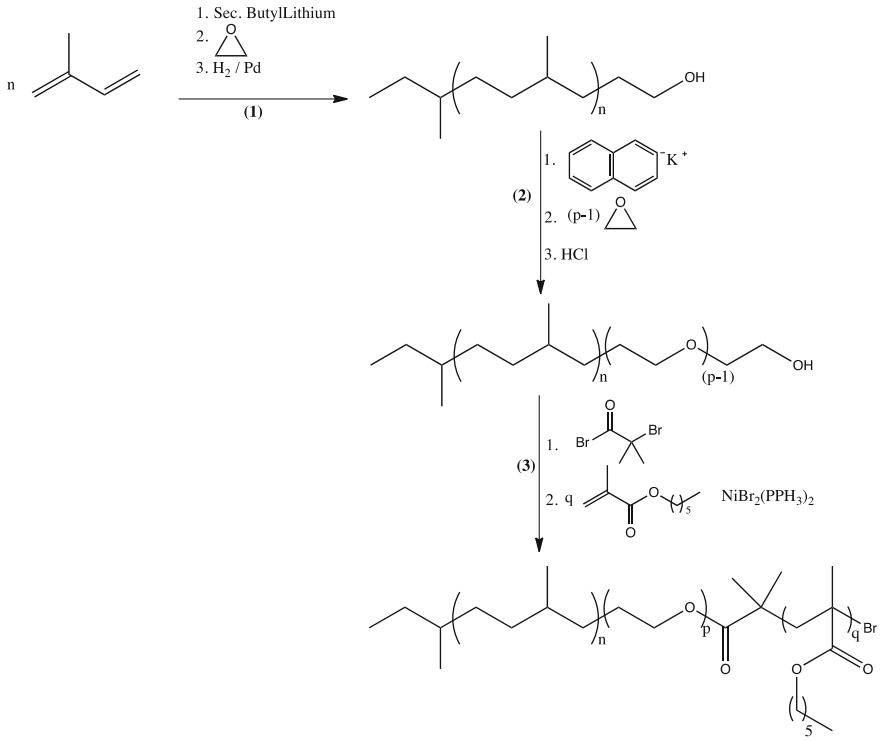

Fig. 2.14 Scheme illustrating the synthesis of ABC type tri-block polymer with hydrophilic PEO middle block using AROP. *1* Anionic polymerization followed by hydrogenation, *2* Anionic ring-opening polymerization, and *3* Chain end functionalization followed by atom transfer radical polymerization

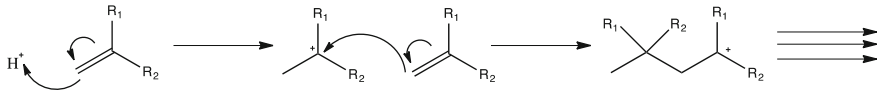

Fig. 2.15 Mechanism of cationic polymerization propagation (counter-ions omitted). Adapted from Ref. [4]

tosylates and triflates, but alkyl halides are also employed in some cases (Fig. 2.16). Because of the characteristic structural adaptability, biocompatibility, and stealth properties, poly(2-oxazoline) derivatives are currently gaining considerable interest for various biomedical applications, particularly as a potential alternative to PEG [53, 54].

Cationic polymerization of vinyl ethers is extensively used for preparing various biodegradable polymers containing acid-labile acetal linkages with potential

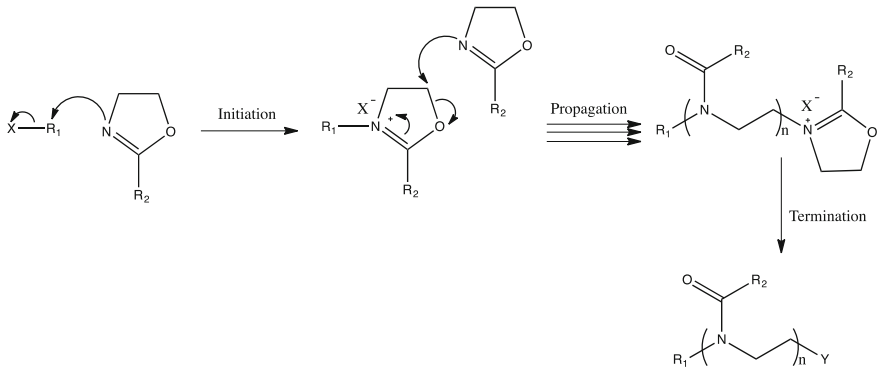

Fig. 2.16 Schematic illustration of the CROP for preparing poly(2-oxazoline)s

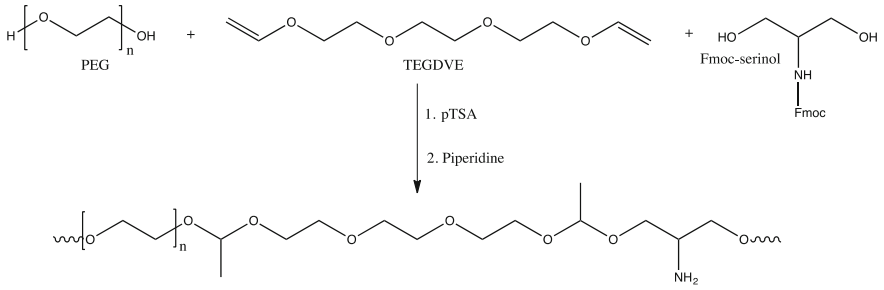

Fig. 2.17 Scheme illustrating the cationic polymerization of tri(ethylene glycol) divinyl ether (TEGDVE) with PEG and Fmoc-protected serinol using p-TSA

biomedical interests [55]. A representative example is the synthesis of an amino-functionalized polyacetal reported by Tomlinson et al. using a cationic polymerization of tri(ethylene glycol) divinyl ether with PEG and Fmoc-protected serinol using p-toluenesulfonic acid [56] (Fig. 2.17). Various polyacetals prepared in a similar way has been evaluated as potential polymer therapeutics for the controlled and site-specific lysosomotropic drug delivery [56–58]. However, one of the major drawbacks associated with the cationic polymerization of the vinyl ethers is the formation of undesired peculiar highly colored materials during the polymerization process. A detailed study by Aoshima and Higashimura [59] suggests that these coloration is due to the formation of certain oxonium ions. The oxonium ions are generated by the degradation of the polymer backbone as a result of the dealcoholation of the growing polymer chain in the presence of an acid catalyst initiator. This color formation can be prevented by using certain inhibitor additives such as cyclic aliphatic epoxides and unsaturated carboxylic acids and their esters [60].

2.3.2 *Coordination-Insertion Polymerization*

Coordination-insertion polymerization has been extensively used for preparing polymers such as polyesters and polyphosphoesters with well-defined molecular profiles. The most widely used polyesters such as polylactic acid (PLA) and poly (lactic-*co*-glycolic acid) (PLGA) are produced on industrial scale by following the coordination-insertion polymerization method catalyzed by tin(II)bis (2-ethylhexanoate) (Stannous octoate, $Sn(Oct)_2$). Other metal alkoxides containing free *p*-, *d*-, or *f*-orbitals such as Mg-, Ti-, Zr-, Fe-, Al-, Y-, Sm-, and Zn-alkoxides are also widely used as the catalyst for this type of polymerization [61].

Detailed mechanistic investigation of the coordination-insertion polymerization has been done by a number of researchers [62–65]. A generalized mechanism for the synthesis of PLGA catalyzed by stannous octoate is presented in Fig. 2.18, which involves the acyl-oxygen cleavage of the lactone with the insertion of the monomer into the metal-oxygen bond of the catalyst [66].

It is widely postulated that traces of impurities present in the reaction system such as water, alcohols, or acids can generate stannous alkoxides in situ from stannous octoate. Because the concentration of stannous alkoxide is significantly lower than that of the initial charged stannous octoate, it results in a higher degree of polymerization and high molecular weight. However, when additional alcohol is added to the reaction mixture, a higher concentration of the stannous alkoxide initiator will be produced in the system, which results in a faster rate of polymerization and low molecular weight polymers [67]. To illustrate this influence, it is worth to compare the ring opening co-polymerization of lactide and glycolide with and without adding any alcoholic monomers using stannous octoate as the catalyst. Under normal conditions the polymerization of lactide and glycolide initiated by stannous octoate proceeds with a steady polymerization rate, encouraging growing polymer chains and leading to higher molecular weights. When the same polymerization was performed in the presence of an alcoholic monomer, such as hydroxymethyl propionic acid (HMPA), a faster polymerization rate was observed with complete consumption of all the available monomers at the early polymerization stage (Fig. 2.19). The molecular weight of the polymer was found to increase to an extent at the early stage itself and then leveled off without any further chain growth. Consequently, the researchers obtained a relatively lower molecular weight polyester from the polymerization of lactide and glycolide, in the presence of HMPA [68, 69].

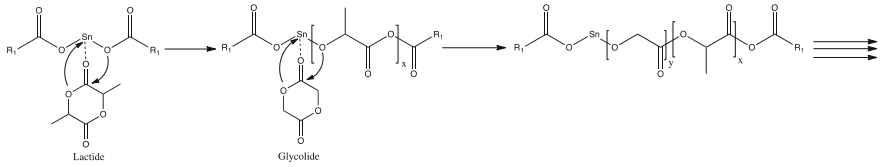

Fig. 2.18 Mechanism of PLGA polymerization catalyzed by stannous octoate

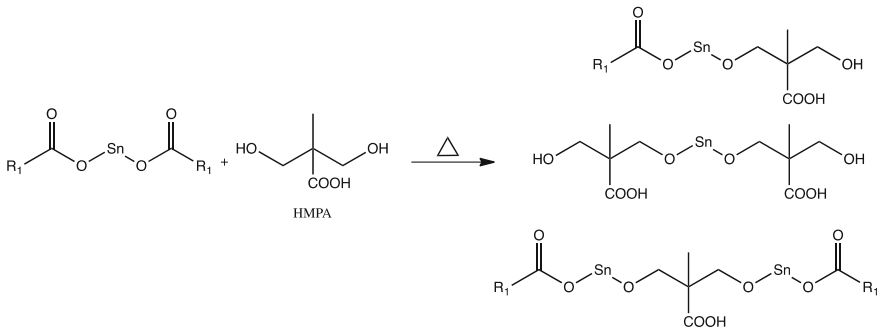

Fig. 2.19 Formation of various highly reactive and nucleophilic alkoxides from the reaction between stannous octoate and HMPA at higher temperatures. This process resulted in a change in polymerization mechanism due to complete conversion of all monomers at the early polymerization stage, resulting in low molecular weight polymerization products

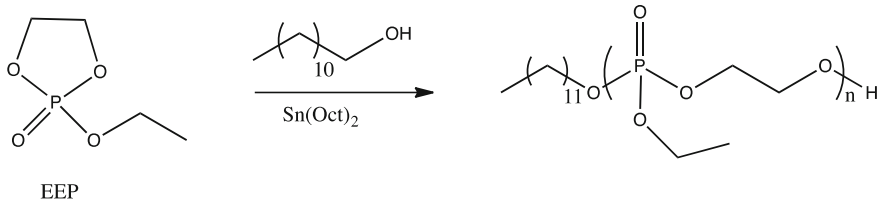

Fig. 2.20 Scheme illustrating the synthesis of PEEP through the polymerization of EEP catalyzed by stannous octoate

Polyphosphoesters (PPE) is another important class of biomedical polymers [70] that can be prepared by stannous octoate catalyzed coordination-insertion polymerization method. A representative example is the synthesis of poly(ethylene ethyl phosphate) (PEEP) as reported by Xiao et al. by the polymerization of the cyclic phosphoester 2-ethoxy-2-oxo-1,3,2-dioxaphospholane (EEP) using stannous octoate and dodecanol [71] (Fig. 2.20).

2.3.3 *Controlled/Living Radical Polymerization*

Because of the exceptional material design capabilities, including surface-tethering and bioconjugation, controlled/living radical polymerization (CRP) provides a very promising strategy for preparing various biomedical polymers with well-defined molecular structures [72, 73] (Fig. 2.21). Additional advantages of CRP include its tolerance to functional groups and its compatibility with different polymerization systems and solvents such as ionic liquids, supercritical CO_2, and aqueous systems [74–76]. The fundamental aspect of CRP involves a combination of a fast initiation

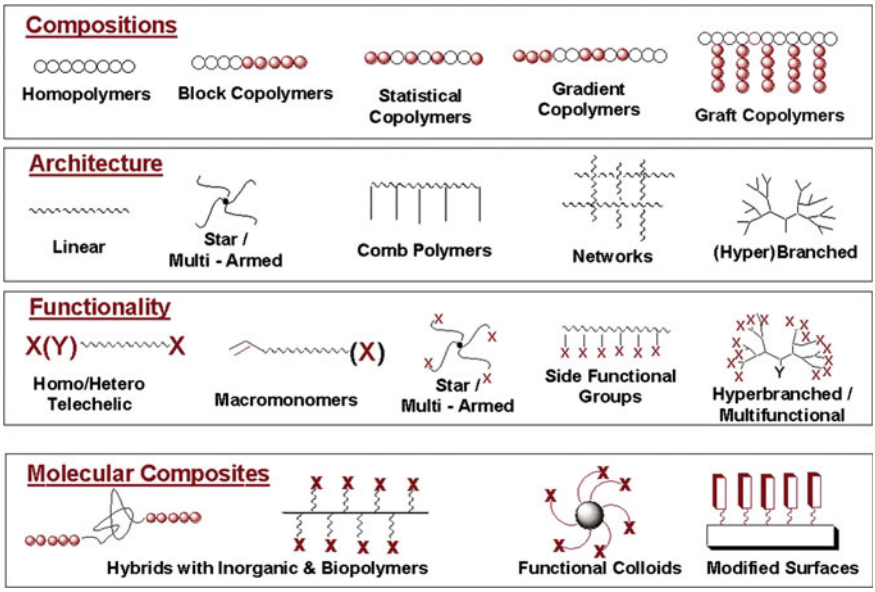

Fig. 2.21 Examples of molecular structures attained through CRP. Reproduced with permission from Ref. [72] © Elsevier

and the absence of termination, which results in an apparent simultaneous growth of all polymer chains. Following are the three major types of CRP polymerization:

i. Atom transfer radical polymerization (ATRP),
ii. Reversible addition/fragmentation chain transfer polymerization (RAFT), and
iii. Nitroxide-mediated polymerization (NMP).

2.3.3.1 Atom Transfer Radical Polymerization (ATRP)

ATRP technique provided one of the most efficient synthetic tools for preparing many polymer libraries with well-defined molecular profile and high degrees of functionalities. The unique capability of ATRP to synthesize polymers from inorganic/organic hybrid materials, surfaces, nanoparticles, and proteins makes this process well suited for preparing various polymeric materials for numerous biomedical applications [77, 78].

ATRP generally initiated with the formation of an alkyl free radicle by the hemolytic cleavage of an alkyl halide (R–X) by a catalyst (transition metal such as Cu with suitable ligands, M_t^n/L) (Fig. 2.22). The generated free radicle can either propagate with a suitable monomer, resulting in the formation of a polymer (rate constant k_p), or can terminate (k_t) or it can be reversibly deactivated with the metal-halide ligand complex (k_{deact}). The overall rate of polymerization depends on

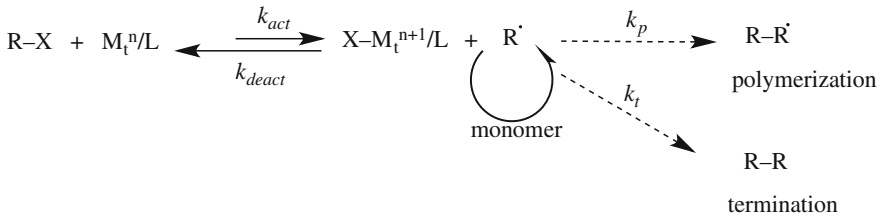

Fig. 2.22 Scheme illustrating the generalized mechanism of ATRP

the rate of equilibrium (k_{eq}) between the activation and deactivation steps as given by:

$$k_{eq} = \frac{k_{act}}{k_{deact}} \tag{2.10}$$

A higher value of k_{eq} indicates a high free radical concentration in the system, which can result in a higher degree of chain termination whereas a low k_{eq} indicates a low radical concentration that will slow down the rate of polymerization. Under optimized ATRP conditions, a relatively lower k_{eq} value will be normally maintained, which practically eliminates the undesired chain termination and results in the formation of polymers with narrow molecular weight distributions. A variety of functional monomers such as styrene, acrylates, acrylamides, vinyl acetate, vinyl pyridine, and vinyl pyrrolidone can be conveniently polymerized using this technique [79, 80].

ATRP is an exceptional tool for the synthesis of polymer-bioconjugates via *grafting from* technique from biomolecules such as proteins and peptides and even from high-value small molecule drug entities. These molecules can be conveniently modified to form suitable ATRP initiators to produce polymer-bioconjugates. Representative examples for polymer-bioconjugates prepared by ATRP using various functional biological initiators are illustrated in Fig. 2.23 [78].

Amphiphilic block copolymers with covalently linked hydrophilic and hydrophobic blocks capable of forming micelles can be conveniently prepared by ATRP techniques [86–88]. A representative example is the synthesis of polymethacrylate based pentablock copolymers (PBPs) via consecutive ATRP technique reported by Xu et al. [89] for non-viral gene delivery applications. In their approach, PBPs of poly(HEMA)-*b*-poly(DMAEMA)-*b*-PEG-*b*-poly(DMAEMA)-*b*-poly(HEMA) were prepared via consecutive ATRPs from di-2-bromoisobutyryl-terminated PEG (Br–PEG–Br) (Fig. 2.24). The very low in vitro cytotoxicity and excellent gene transfer efficacies exhibited by these PBPs demonstrated the versatility of the ATRP technique to tailor the polymer structural-property characteristics for such applications.

Functionalization of polymer surfaces using surface-initiated ATRP (SI-ATRP) is a convenient tool for making various functional materials, particularly for preparing anti-fouling and anti-bacterial surfaces, membranes, and for

(a)
GRGDS-poly(HEMA)
(b)
Streptavidin
Streptavidin macroinitiator
monomer, sacrificial initiator
CuBr/bipy
H2O
Streptavidin macroinitiator
Streptavidin-polymer conjugate
(c)
(d)
Myoglobin (Mb)
PLP
Myoglobin-CHO (Mb-CHO)
ABM
Myoglobin-Br (Mb-Br)
In situ ATRP
Myoglobin-N-Poly(oligo(ethylene glycol) methyl ether methacrylate) (Mb-N-Poly(OEGMA))
(e)
Genetic Incorporation
ATRP in PBS
polyMPEG-GFP

◀ **Fig. 2.23** Examples of polymer bioconjugates prepared by ATRP using functional initiators. **a** HEMA was polymerized by ATRP from an Initiator-S(tBu)D(tBu)GR(Pbf)G Wang Resin [81]. **b** A biotinylated ATRP initiator was used for the polymerization of PNIPAAm from streptavidin [82]. **c** Monomethoxy poly(ethylene glycol)-methacrylate was polymerized from 2-bromoisobutyramide derivatives of chymotrypsin as a protein-initiator, resulting in the conjugate containing a single, near-monodisperse polymer chain per protein molecule with polydispersity index 1.05 [83]. **d** POEGMA with low polydispersity and high yield, was grown solely from the *N*-terminus of the protein by in situ ATRP under aqueous conditions from myoglobin, to yield a site-specific (*N*-terminal) and stoichiometric conjugate (1:1) [84]. **e** A genetically encoded initiator (via the amino acid 4-(2′-bromoisobutyramido)phenylalanine) was used as an ATRP for the site-specific polymer growth of POEOMA from GFP [85]. Reproduced with permissions from Ref. [78] (©Elsevier), [82] (©American Chemical Society), [84] (©Proceedings of the National Academy of Sciences), and [85] (©American Chemical Society)

immobilization of biomolecules [90–92]. In general, SI-ATRP is performed by either attaching a suitable ATRP initiator on the polymer surface or by depositing a monolayer on the surface. A representative example is the SI-ATRP technique reported by Li et al. [93] for preparing IgG modified microdomains as potential biomarkers. In their approach, the researchers developed a α-bromine containing phenolic tether as the ATRP initiator for polymerization with 2-(dimethylamino) ethyl methacrylate (DMAEMA) and glycidyl methacrylate (GMA) to produce the corresponding polymer grafted films. The resulting DMAEMA and GMA grafted films were used for immobilizing IgG via electronic interactions and covalent coupling.

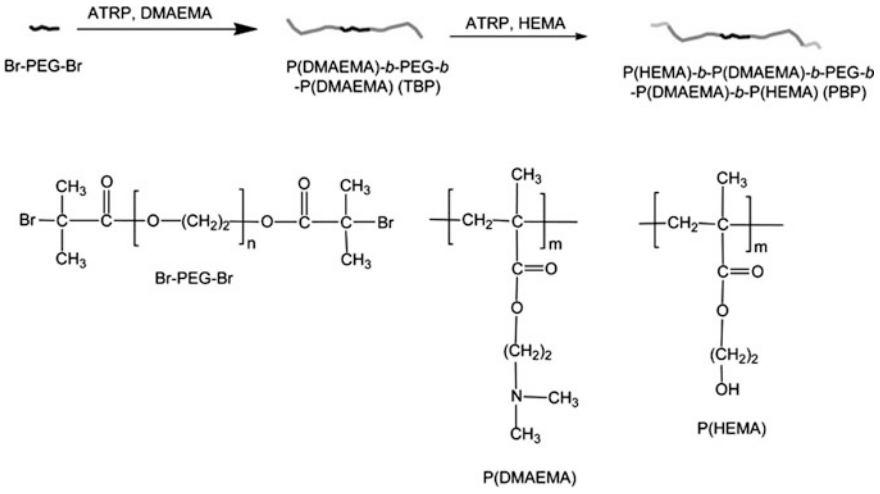

Fig. 2.24 Schematic diagram illustrating the preparation of P(HEMA)-*b*-P(DMAEMA)-*b*-PEG-*b*-P(DMAEMA)-*b*-P(HEMA) pentablock copolymer (PBP) via consecutive ATRPs from di-2-bromoisobutyryl-terminated PEG (Br–PEG–Br) (EG = ethylene glycol, DMAEMA = (2-dimethyl amino)ethyl methacrylate, HEMA = 2-hydroxyethyl methacrylate). Reproduced with permission from Ref. [89] © Elsevier

2.3.3.2 Reversible Addition/Fragmentation Chain Transfer Polymerization (RAFT)

RAFT polymerization, which involves reversible deactivation by degenerate chain transfer, is an efficient CRP technique to produce a wide variety of functional biomedical polymers with well-defined molecular profile. The generalized mechanism of the RAFT polymerization (Fig. 2.25) [94] involves the addition of a propagating radicle ($P_n^{\cdot}$) to an addition-fragmentation transfer agent (**1**, also known as the RAFT agent). The intermediate **2**, can either generate a polymeric macro-RAFT agent (**3**) by releasing a radicle (R·) or lose the propagating radicle, $P_n^{\cdot}$, to regenerate the starting materials. The effectiveness of the RAFT polymerization depends significantly on the RAFT agent, in which the functional substituent Z determines the reactivity of the RAFT agent to form the intermediate **2** by shifting the RAFT equilibria to the right. Commonly used RAFT agents include dithiocarbamate [95, 96], dithioester [97, 98], trithiocabonate [99, 100], and xanthane [101, 102]. Various monomers such as acrylates, methacrylates, acrylamides, styrene, and many vinyl derivatives can be conveniently polymerized following this technique [94].

Utilizing the RAFT polymerization technique, Du et al. [103] successfully prepared pH-sensitive degradable polymersomes for the tumor-targeted delivery of doxorubicin. A pH-sensitive biodegradable tri-block polymer, poly(ethylene glycol)-*b*-poly (2,4,6-trimethoxybenzylidene-1,1,1-tris(hydroxymethyl)ethane methacrylate)-*b*-poly (acrylic acid) (PEG-PTTMA-PAA), was prepared by RAFT copolymerization of 2,4,6-trimethoxybenzylidene-1,1,1-tris(hydroxymethyl)ethane methacrylate (TTMA) and acrylic acid (AA) using PEG- 4-cyanopentanoic acid dithionaphthalenoate (PEG-CPADN) as the macro-RAFT agent. Similar RAFT polymerization approaches are reported by a number of researchers for preparing biodegradable multi-block polymers for anti-fouling [104, 105], biomedical imaging [106], drug delivery [107, 108], and tissue engineering [109] applications.

One of the key features of the RAFT polymerization is the potential functionalization capability by carefully selecting the functional substituent Z of the RAFT agent (see Fig. 2.25). Quémener et al. [110] developed a clickable (1,3-dipolar cycloaddition) azide and alkyne functionalized RAFT agents and well-defined block polymers of vinyl acetate and styrene were prepared by combining RAFT polymerization and click chemistry. A similar combination of RAFT and click chemistry has been successfully evaluated to generate various block polymers for polymer- protein and drug conjugations [111].

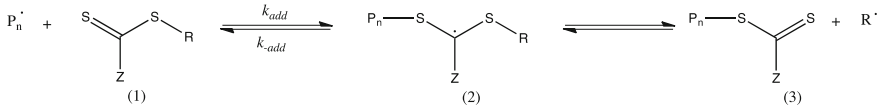

Fig. 2.25 Mechanism of RAFT polymerization

2.3.3.3 Nitroxide-Mediated Polymerization (NMP)

Similar to other CRP methods, NMP is also a versatile technique for preparing polymers with well-defined molecular structures. The simplified mechanism (Fig. 2.26) [112] involves the hemolytic decomposition of an alkoxamine bond of an NMP initiator (see intermediate **1**, Fig. 2.26) to generate a propogating alkyl radicle $R_n^{\cdot}$. Because of the very low equilibrium constant [rate of dissociation (k_d) to the rate of association (k_a)], only a very limited concentration of the propagating radicle will be available at a given time limiting the reverse termination process. This results in an uninterrupted growth of the polymer chain until all the monomers are completely consumed, which results in a very narrow molecular weight distribution for the resulting polymer.

NMP technique provides a convenient tool to prepare polymeric bioconjugates as a potential building block for numerous nanotechnology and biomedical applications. The very first such attempt was reported by Chenal et al. [113] by preparing a fluorescent α-functional polymethacrylates with PEG side chains using *N*-hydroxysuccinimidyl (NHS) ester-containing alkoxyamines. Recently, Harrison et al. reported the development of a new class of anticancer nanocarriers derived from gemcitabine–polyisoprene conjugated nanoparticles prepared by NMP of a gemcitabine-functionalized alkoxamine initiator (**3**, see Fig. 2.27) [114].

Many researchers have successfully combined NMP with other polymerization techniques, such as *N*-carboxyanhydride (NCA) polymerization, for preparing polymer-bioconjugates. A representative example is the synthesis of PEO and poly (*N*-vinyl pyrrolidone) (PNVP) polymer/polypeptide hybrids (macromolecular *chimeras*) reported by Karatzas et al. [115] by combining NMP and NCA polymerization techniques. In this approach, block copolymers of PNVP and polypeptides (PVNP-*b*-poly(γ-benzyl-l-glutamate) (PNVP-*b*-PBLG), PNVP-*b*-poly(*tert*-butyloxycarbonyl-l-lysine (PNVP-*b*-PBLL), and PNVP-*b*-PBLG-*b*-PBLL) were synthesized using the stable radicle-4-NH_2-TEMPO and NMP technology (Fig. 2.28). The amino groups were used as the initiator for NCA polymerization to prepare macroradicals, which were then subsequently polymerized by NMP in the presence of AIBN and acetic anhydride.

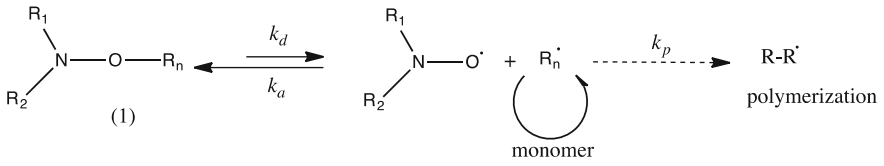

Fig. 2.26 Mechanism of NMP polymerization, where the intermediate *1* represents the general NMP initiator with a labile alkoxyamine bond

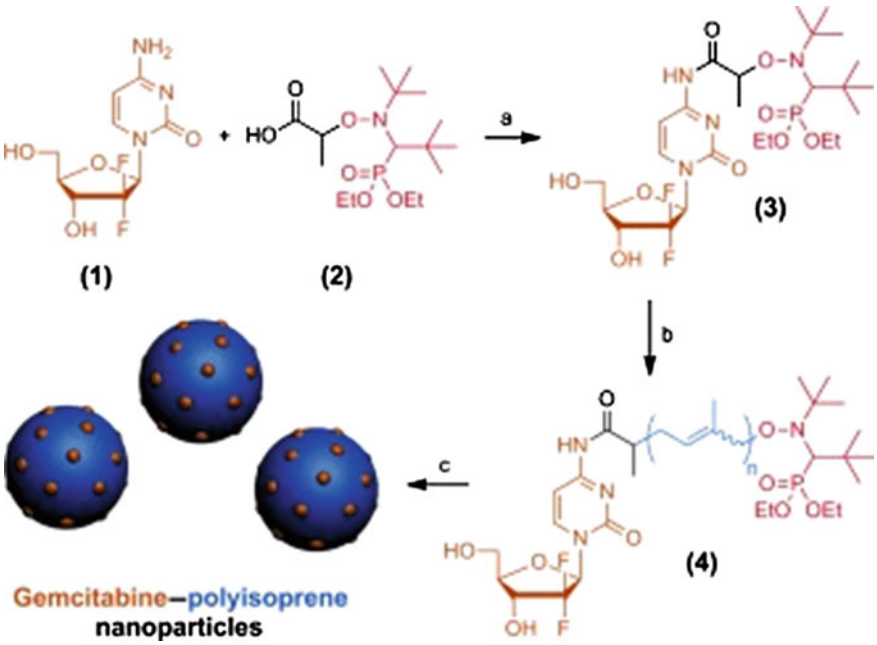

Fig. 2.27 Design of gemcitabine–polyisoprene conjugate nanoparticles. Reaction conditions: **a** PyBOP, DIPEA, DMF, 25 °C, 24 h. **b** Isoprene, pyridine, 115 °C, 2–16 h. **c** Nanoprecipitation (THF/H_2O, 1:2). DIPEA = diisopropylethylamine, PyBOP = benzotriazol-1-yloxytripyrrolidino phosphonium hexafluorophosphate. Reproduced with permission from Ref. [114] © WILEY-VCH Verlag GmbH & Co.

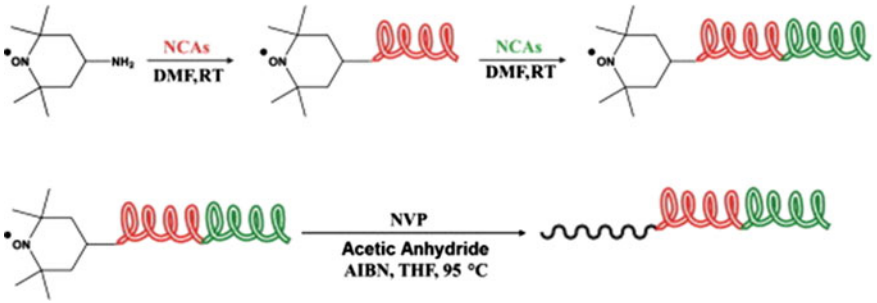

Fig. 2.28 Scheme illustrating the synthesis of well-defined functional macromolecular *chimeras* by combination of NMP and NCA polymerization techniques. Reproduced with permission from Ref. [115] © Elsevier

2.4 Conclusion

Synthesis of biomedical polymers requires a complex combination of carefully selected polymerization methods, monomers, catalysts, and other parameters to obtain the polymer with the desired properties. With the advancements in the polymerization techniques and technologies, and stringent control over the monomer structure and catalyst, well-defined polymers with tailored properties can be conveniently prepared to match the requirements of a desired biomedical application.

References

1. Damodaran, V.B., J. Joslin, and M.M. Reynolds. 2012. Preparing biocompatible materials for non-permanent medical devices. *European Pharmaceutical Review* 17(5): 71–77.
2. Middleton, J.C., and A.J. Tipton. 2000. Synthetic biodegradable polymers as orthopedic devices. *Biomaterials* 21(23): 2335–2346.
3. Seymour, B.R., and C.E. Carraher. 1992. *Polymer chemistry an introduction* (3rd Edition). New York: Marcel Dekker, Inc.
4. Allock, H.R., and F.W. Lampe. 1990. *Contemporary polymer chemistry* (2nd Edition). Englewood Cliffs: Prentice Hall.
5. Carothers, W.H. 1929. Studies on polymerization and ring formation. I. An introduction to the general theory of condensation polymers. *Journal of the American Chemical Society* 51 (8): 2548–2559.
6. Carothers, W.H. 1936. Polymers and polyfunctionality. *Transactions of the Faraday Society* 32: 39–49.
7. Wang, Y., et al. 2002. A tough biodegradable elastomer. *Nature Biotechnology* 20(6): 602–606.
8. Rai, R., et al. 2012. Synthesis, properties and biomedical applications of poly(glycerol sebacate) (PGS): A review. *Progress in Polymer Science* 37(8): 1051–1078.
9. Yang, J., A.R. Webb, and G.A. Ameer. 2004. Novel citric acid-based biodegradable elastomers for tissue engineering. *Advanced Materials* 16(6): 511–516.
10. Yang, J., et al. 2006. Synthesis and evaluation of poly(diol citrate) biodegradable elastomers. *Biomaterials* 27(9): 1889–1898.
11. Barrett, D.G., and M.N. Yousaf. 2008. Poly(triol α-ketoglutarate) as biodegradable, chemoselective, and mechanically tunable elastomers. *Macromolecules* 41(17): 6347–6352.
12. Yapor, J.P., et al. 2015. Biodegradable citrate-based polyesters with S-nitrosothiol functional groups for nitric oxide release. *Journal of Materials Chemistry B* 3(48): 9233–9241.
13. Kumar, A., et al. 2003. Versatile route to polyol polyesters by lipase catalysis. *Macromolecules* 36(22): 8219–8221.
14. Fradet, A., and E. Maréchal. 1982. *Kinetics and mechanisms of polyesterifications*, in *Polymerizations and Polymer Properties*, 51–142. Berlin, Heidelberg: Springer.
15. Finelli, L., et al. 2004. Comparison between titanium tetrabutoxide and a new commercial titanium dioxide based catalyst used for the synthesis of poly(ethylene terephthalate). *Journal of Applied Polymer Science* 92(3): 1887–1892.
16. Trotter, J.R., F.B. Joyner, and R.L. McConnell. 1984. *Polyester waxes based on 1,12-dodecanedioic acid*, US.
17. Li, J., R.M. Stayshich, and T.Y. Meyer. 2011. Exploiting sequence to control the hydrolysis behavior of biodegradable PLGA copolymers. *Journal of the American Chemical Society* 133(18): 6910–6913.

18. Moore, J.S., and S.I. Stupp. 1990. Room temperature polyesterification. *Macromolecules* 23 (1): 65–70.
19. Asín, L., et al. 2001. Sequential poly(ester amide)s based on glycine, diols, and dicarboxylic acids: thermal polyesterification versus interfacial polyamidation. Characterization of polymers containing stiff units. *Journal of Polymer Science Part A: Polymer Chemistry* 39 (24): 4283–4293.
20. Rodriguez-Galan, A., L. Franco, and J. Puiggali. 2010. Degradable poly(ester amide)s for biomedical applications. *Polymers* 3(1): 65.
21. Katsarava, R. 2003. Active polycondensation: from pep tide chemistry to amino acid based biodegradable polymers. *Macromolecular Symposia* 199(1): 419–430.
22. Sun, H., et al. 2011. α-Amino acid containing degradable polymers as functional biomaterials: rational design, synthetic pathway, and biomedical applications. *Biomacromolecules* 12(6): 1937–1955.
23. Bourke, S.L., and J. Kohn. 2003. Polymers derived from the amino acid l-tyrosine: polycarbonates, polyarylates and copolymers with poly(ethylene glycol). *Advanced Drug Delivery Reviews* 55(4): 447–466.
24. Fan, Y., M. Kobayashi, and H. Kise. 2000. Synthesis and biodegradability of new polyesteramides containing peptide linkages. *Polymer Journal* 32(10): 817–822.
25. Ueda, M., and K. Mizoguchi. 1997. Synthesis of polycarbonate by melt self-polycondensation of 4,4′-isopropylidenedi(p-phenylene)bis(2,2,2-trichloroethyl) carbonate. *Polymer* 38(13): 3369–3372.
26. Zhu, W., et al. 2011. High-molecular-weight aliphatic polycarbonates by melt polycondensation of dimethyl carbonate and aliphatic diols: synthesis and characterization. *Polymer International* 60(7): 1060–1067.
27. Fukuoka, S., et al. 2007. Green and sustainable chemistry in practice: development and industrialization of a novel process for polycarbonate production from CO_2 without using phosgene. *Polymer Journal* 39(2): 91–114.
28. Cotarca, L., and H. Eckert. 2004. *Phosgenations—A Handbbok*. Weinheim, Germany: Wiley-VCH.
29. King, J.A.J. 2000. Synthesis of polycarbonates. In *Handbook of polycarbonate science and technology*, ed. D.G. Legrand and J.T. Bendler. NY: Marcel Dekker.
30. Sommerfeld, S.D., et al. 2014. Enzymatic surface erosion of high tensile strength polycarbonates based on natural phenols. *Biomacromolecules* 15(3): 830–836.
31. Pulapura, S., and J. Kohn. 1992. Tyrosine-derived polycarbonates: backbone-modified "pseudo"-poly(amino acids) designed for biomedical applications. *Biopolymers* 32(4): 411–417.
32. Lo, M.-C., et al. 2015. Coating flexible probes with an ultra fast degrading polymer to aid in tissue insertion. *Biomedical Microdevices* 17(2): 1–11.
33. Lewitus, D., et al. 2011. Ultrafast resorbing polymers for use as carriers for cortical neural probes. *Acta Biomaterialia* 7(6): 2483–2491.
34. Abramson, S., et al., 2002. Characterization of degradable polymers for orthopedic application. In *Polymer based systems on tissue engineering, replacement and regeneration*, ed. R. Reis and D. Cohn, 125–138. Netherlands: Springer.
35. Burke, A., and N. Hasirci. 2004. Polyurethanes in biomedical applications. In *Biomaterials*, ed. N. Hasirci and V. Hasirci, 83–101. USA: Springer.
36. Szycher, M. 2012. *Szycher's handbook of polyurethanes, second edition*. Boca Raton, FL: CRC Press.
37. Gabriel, L.P., et al. 2014. Isocyanates as precursors to biomedical polyurethanes. *Chemical Engineering Transactions* 38: 253–258.
38. Yang, J., et al. 2014. Synthesis and characterization of biocompatible polyurethanes for controlled release of hydrophobic and hydrophilic drugs. *Frontiers of Chemical Science and Engineering* 8(4): 498–510.
39. Sarkar, D., et al. 2009. Synthesis and characterization of L-tyrosine based polyurethanes for biomaterial applications. *Journal of Biomedical Materials Research, Part A* 90A(1): 263–271.

40. Zahn, V.H., and M. Dominik. 1961. Lineare oligomere aus hexamethylendiisocyanat und butandiol-(1,4). *Die Makromolekulare Chemie* 44(1): 290–311.
41. Morgan, P.W., and S.L. Kwolek. 1964. Low temperature solution polycondensation of piperazine polyamides. *Journal of Polymer Science Part A: General Papers* 2(1): 181–208.
42. Figovsky, O., L. Shapovalov, and F. Buslov. 2005. Ultraviolet and thermostable non-isocyanate polyurethane coatings. *Surface Coatings International Part B: Coatings Transactions* 88(1): 67–71.
43. Calle, M., et al. 2014. An efficient nonisocyanate route to polyurethanes via thiol-ene self-addition. *Journal of Polymer Science Part A: Polymer Chemistry* 52(21): 3017–3025.
44. Baskaran, D., and A.H.E. 2010. Müller, Anionic vinyl polymerization. In *Controlled and living polymerizations*, 1–56. Weinheim: Wiley-VCH Verlag GmbH & Co. KGaA.
45. Lecomte, P., and C. Jérôme. 2012. Recent developments in ring-opening polymerization of lactones. In *Synthetic biodegradable polymers*, ed. B. Rieger, et al., 173–217. Berlin, Heidelberg: Springer.
46. Hashimoto, K. 2000. Ring-opening polymerization of lactams. Living anionic polymerization and its applications. *Progress in Polymer Science* 25(10): 1411–1462.
47. Dane, E.L., and M.W. Grinstaff. 2012. Poly-amido-saccharides: synthesis via anionic polymerization of a β-lactam sugar monomer. *Journal of the American Chemical Society* 134 (39): 16255–16264.
48. Zhang, J., et al. 2009. Access to poly-β-peptides with functionalized side chains and end groups via controlled ring-opening polymerization of β-lactams. *Journal of the American Chemical Society* 131(4): 1589–1597.
49. Grubbs, R.B. 2005. Multiblock copolymers: PEO stuck in the middle. *Macromolecular Chemistry and Physics* 206(6): 625–627.
50. Mahajan, S., et al. 2004. Synthesis of amphiphilic ABC triblock copolymers with PEO as the middle block. *Macromolecular Rapid Communications* 25(22): 1889–1894.
51. Goethals, E.J., et al. 1994. Tailored polymers by cationic ring-opening polymerization. *Die Angewandte Makromolekulare Chemie* 223(1): 1–11.
52. Aoshima, S., and S. Kanaoka. 2009. A renaissance in living cationic polymerization. *Chemical Reviews* 109(11): 5245–5287.
53. Adams, N., and U.S. Schubert. 2007. Poly(2-oxazolines) in biological and biomedical application contexts. *Advanced Drug Delivery Reviews* 59(15): 1504–1520.
54. Lava, K., B. Verbraeken, and R. Hoogenboom. 2015. Poly(2-oxazoline)s and click chemistry: a versatile toolbox toward multi-functional polymers. *European Polymer Journal* 65: 98–111.
55. Goethals, E.J., and F. Du Prez. 2007. Carbocationic polymerizations. *Progress in Polymer Science* 32(2): 220–246.
56. Tomlinson, R., et al. 2002. Pendent chain functionalized polyacetals that display pH-dependent degradation: a platform for the development of novel polymer therapeutics. *Macromolecules* 35(2): 473–480.
57. England, R.M., et al. 2012. Polyacetal-stilbene conjugates—the first examples of polymer therapeutics for the inhibition of HIF-1 in the treatment of solid tumours. *Journal of Controlled Release* 164(3): 314–322.
58. Garripelli, V.K., et al. 2010. A novel thermosensitive polymer with pH-dependent degradation for drug delivery. *Acta Biomaterialia* 6(2): 477–485.
59. Aoshima, S., and T. Higashimura. 1984. Vinyl ether oligomers with conjugated-polyene and acetal terminals: a new chain-transfer mechanism for cationic polymerization of vinyl ethers. *Polymer Journal* 16(3): 249–258.
60. Dougherty, J.A., and F.J. Vara. 1993. *Cationic polymerization of vinyl ethers without color formation (WO1993002119 A1)*.
61. Mecerreyes, D., R. Jérôme, and P. Dubois. 1999. Novel macromolecular architectures based on aliphatic polyesters: relevance of the "coordination-insertion" ring-opening polymerization. In *Macromolecular architectures*, ed. J. Hilborn, et al., 1–59, Berlin, Heidelberg: Springer.

62. Duda, A., and S. Penczek. 1995. On the difference of reactivities of various aggregated forms of aluminium triisopropoxide in initiating ring-opening polymerizations. *Macromolecular Rapid Communications* 16(1): 67–76.
63. Kowalski, A., A. Duda, and S. Penczek. 2000. Mechanism of cyclic ester polymerization initiated with Tin(II) Octoate. 2. Macromolecules fitted with Tin(II) alkoxide species observed directly in MALDI-TOF spectra. *Macromolecules* 33(3): 689–695.
64. Ricca, A., and J.C.W. Bauschlicher. 1994. *Journal of Physical Chemistry* 98: 12899.
65. Kricheldorf, H.R., I. Kreiser-Saunders, and A. Stricker. 2000. Polylactones 48. SnOct2-initiated polymerizations of lactide: a mechanistic study. *Macromolecules* 33(3): 702–709.
66. Albertsson, A.-C., and I.K. Varma. 2003. Recent developments in ring opening polymerization of lactones for biomedical applications. *Biomacromolecules* 4(6): 1466–1486.
67. Zhang, X., et al. 1994. Mechanism of lactide polymerization in the presence of stannous octoate: the effect of hydroxy and carboxylic acid substances. *Journal of Polymer Science Part A: Polymer Chemistry* 32(15): 2965–2970.
68. Damodaran, V.B., et al. 2012. S-Nitrosated biodegradable polymers for biomedical applications: synthesis, characterization and impact of thiol structure on the physicochemical properties. *Journal of Materials Chemistry* 22(13): 5990–6001.
69. Damodaran, V.B., and M.M. Reynolds. 2011. Biodegradable S-nitrosothiol tethered multiblock polymer for nitric oxide delivery. *Journal of Materials Chemistry* 21(16): 5870–5872.
70. Zhao, Z., et al. 2003. Polyphosphoesters in drug and gene delivery. *Advanced Drug Delivery Reviews* 55(4): 483–499.
71. Xiao, C.-S., et al. 2006. Kinetics and mechanism of 2-ethoxy-2-oxo-1,3,2-dioxaphospholane polymerization initiated by stannous octoate. *Macromolecules* 39(20): 6825–6831.
72. Matyjaszewski, K., and J. Spanswick. 2005. Controlled/living radical polymerization. *Materials Today* 8(3): 26–33.
73. Braunecker, W.A., and K. Matyjaszewski. 2007. Controlled/living radical polymerization: features, developments, and perspectives. *Progress in Polymer Science* 32(1): 93–146.
74. Qiu, J., B. Charleux, and K. Matyjaszewski. 2001. Controlled/living radical polymerization in aqueous media: homogeneous and heterogeneous systems. *Progress in Polymer Science* 26(10): 2083–2134.
75. Xia, J., et al. 1999. Atom transfer radical polymerization in supercritical carbon dioxide. *Macromolecules* 32(15): 4802–4805.
76. Carmichael, A.J., et al. 2000. Copper() mediated living radical polymerisation in an ionic liquid. *Chemical Communications* 14: 1237–1238.
77. Pyun, J., and K. Matyjaszewski. 2001. Synthesis of nanocomposite organic/inorganic hybrid materials using controlled/"living" radical polymerization. *Chemistry of Materials* 13(10): 3436–3448.
78. Siegwart, D.J., J.K. Oh, and K. Matyjaszewski. 2012. ATRP in the design of functional materials for biomedical applications. *Progress in Polymer Science* 37(1): 18–37.
79. Matyjaszewski, K. 2014. From cationic ring-opening polymerization to atom transfer radical polymerization. *Polimery* 59(1): 24–37.
80. Matyjaszewski, K., and J. Xia. 2001. Atom transfer radical polymerization. *Chemical Reviews* 101(9): 2921–2990.
81. Mei, Y., et al. 2004. Solid-phase ATRP synthesis of peptide—polymer hybrids. *Journal of the American Chemical Society* 126(11): 3472–3476.
82. Bontempo, D., and H.D. Maynard. 2005. Streptavidin as a macroinitiator for polymerization: in situ protein—polymer conjugate formation. *Journal of the American Chemical Society* 127 (18): 6508–6509.
83. Lele, B.S., et al. 2005. Synthesis of uniform protein—polymer conjugates. *Biomacromolecules* 6(6): 3380–3387.

84. Gao, W., et al. 2009. In situ growth of a stoichiometric PEG-like conjugate at a protein's N-terminus with significantly improved pharmacokinetics. *Proceedings of the National Academy of Sciences* 106(36): 15231–15236.
85. Peeler, J.C., et al. 2010. Genetically encoded initiator for polymer growth from proteins. *Journal of the American Chemical Society* 132(39): 13575–13577.
86. Mühlebach, A., S.G. Gaynor, and K. Matyjaszewski. 1998. Synthesis of amphiphilic block copolymers by atom transfer radical polymerization (ATRP). *Macromolecules* 31(18): 6046–6052.
87. Hua, M., et al. 2005. Successful ATRP syntheses of amphiphilic block copolymers poly (styrene-block-N, N-dimethylacrylamide) and their self-assembly. *Polymer Journal* 37(2): 59–64.
88. Sun, H., et al., 2015. Synthesis of well-defined amphiphilic block copolymers via AGET ATRP used for hydrophilic modification of PVDF membrane. Journal of Applied Polymer Science. 132(24): n/a-n/a.
89. Xu, F.-J., et al. 2008. Pentablock copolymers of poly(ethylene glycol), poly((2-dimethyl amino)ethyl methacrylate) and poly(2-hydroxyethyl methacrylate) from consecutive atom transfer radical polymerizations for non-viral gene delivery. *Biomaterials* 29(20): 3023–3033.
90. Fristrup, C.J., K. Jankova, and S. Hvilsted. 2009. Surface-initiated atom transfer radical polymerization-a technique to develop biofunctional coatings. *Soft Matter* 5(23): 4623–4634.
91. Singh, N., et al. 2008. Surface-initiated atom transfer radical polymerization: a new method for preparation of polymeric membrane adsorbers. *Journal of Membrane Science* 309(1–2): 64–72.
92. Ma, H., et al. 2006. Surface-initiated atom transfer radical polymerization of oligo(ethylene glycol) methyl methacrylate from a mixed self-assembled monolayer on gold. *Advanced Functional Materials* 16(5): 640–648.
93. Li, C.Y., F.J. Xu, and W.T. Yang. 2013. Simple strategy to functionalize polymeric substrates via surface-initiated ATRP for biomedical applications. *Langmuir* 29(5): 1541–1550.
94. Moad, G., E. Rizzardo, and S.H. Thang. 2013. *Fundamentals of RAFT Polymerization*, in *Fundamentals of Controlled/Living Radical Polymerization*., The Royal Society of Chemistry. p. 205–249.
95. Schilli, C., M.G. Lanzendörfer, and A.H.E. Müller. 2002. Benzyl and cumyl dithiocarbamates as chain transfer agents in the raft polymerization of N-isopropylacrylamide. In situ FT-NIR and MALDI—TOF MS investigation. *Macromolecules* 35(18): 6819–6827.
96. Keddie, D.J., et al. 2012. Chain transfer kinetics of acid/base switchable N-aryl-N-pyridyl dithiocarbamate RAFT agents in methyl acrylate. *N-Vinylcarbazole and Vinyl Acetate Polymerization. Macromolecules* 45(10): 4205–4215.
97. Thomas, D.B., et al. 2004. Hydrolytic susceptibility of dithioester chain transfer agents and implications in aqueous RAFT polymerizations. *Macromolecules* 37(5): 1735–1741.
98. Li, C., and B.C. Benicewicz. 2005. α-Cyanobenzyl dithioester reversible addition–fragmentation chain-transfer agents for controlled radical polymerizations. *Journal of Polymer Science Part A: Polymer Chemistry* 43(7): 1535–1543.
99. Kang, H.U., et al. 2013. One-step synthesis of block copolymers using a hydroxyl-functionalized trithiocarbonate RAFT agent as a dual initiator for RAFT polymerization and ROP. *Journal of Polymer Science Part A: Polymer Chemistry* 51(4): 774–779.
100. Mayadunne, R.T.A., et al. 2000. Living polymers by the use of trithiocarbonates as reversible addition—fragmentation chain transfer (RAFT) agents: ABA triblock copolymers by radical polymerization in two steps. *Macromolecules* 33(2): 243–245.
101. Bernard, J., et al. 2008. Preparation of a xanthate-terminated dextran by click chemistry: application to the synthesis of polysaccharide-coated nanoparticles via surfactant-free ab initio emulsion polymerization of vinyl acetate. *Journal of Polymer Science Part A: Polymer Chemistry* 46(8): 2845–2857.

102. Destarac, M., et al. 2002. Xanthates as chain-transfer agents in controlled radical polymerization (MADIX): structural effect of the O-alkyl group. *Macromolecular Rapid Communications* 23(17): 1049–1054.
103. Du, Y., et al. 2012. pH-sensitive degradable chimaeric polymersomes for the intracellular release of doxorubicin hydrochloride. *Biomaterials* 33(29): 7291–7299.
104. Zheng, X., et al. 2015. Antifouling property of monothiol-terminated bottle-brush poly (methylacrylic acid)-graft-poly(2-methyl-2-oxazoline) copolymer on gold surfaces. *Journal of Materials Chemistry B* 3(9): 1921–1930.
105. Zhan, X., et al., 2014. Preparation, surface wetting properties, and protein adsorption resistance of well-defined amphiphilic fluorinated diblock copolymers. *Journal of Applied Polymer Science* 131(23): n/a-n/a.
106. Huang, Z., et al. 2015. *Synthesis of amphiphilic fluorescent PEGylated AIE nanoparticles via RAFT polymerization and their cell imaging applications*. *RSC Advances* 5(109): 89472–89477.
107. Tang, M., et al. 2015. *Influence of 2-(diisopropylamino)ethyl methacrylate on acid-triggered hydrolysis of cyclic benzylidene acetals and their importance in efficient drug delivery*. *Polymer Chemistry* 6(37): 6671–6679.
108. Kuo, C.-Y., et al., *Thermo- and pH-induced self-assembly of P(AA-b-NIPAAm-b-AA) triblock copolymers synthesized via RAFT polymerization.* Journal of Polymer Science Part A: Polymer Chemistry, 2015: n/a-n/a.
109. Keen, I., et al. 2010. Degradable hydrogels for tissue engineering—Part II: responses of fibroblasts and macrophages to linear PHEMA. *Journal of Biomimetics, Biomaterials and Tissue Engineering* 8: 89–102.
110. Quemener, D., et al. 2006. RAFT and click chemistry: a versatile approach to well-defined block copolymers. *Chemical Communications* 48: 5051–5053.
111. Li, M., et al. 2008. Responsive polymer-protein bioconjugates prepared by RAFT polymerization and copper-catalyzed azide-alkyne click chemistry. *Macromolecular Rapid Communications* 29(12–13): 1172–1176.
112. Nicolas, J., et al. 2013. Nitroxide-mediated polymerization. *Progress in Polymer Science* 38 (1): 63–235.
113. Chenal, M., et al. 2011. First peptide/protein PEGylation with functional polymers designed by nitroxide-mediated polymerization. *Polymer Chemistry* 2(7): 1523–1530.
114. Harrisson, S., et al. 2013. Nanoparticles with in vivo anticancer activity from polymer prodrug amphiphiles prepared by living radical polymerization. *Angewandte Chemie International Edition* 52(6): 1678–1682.
115. Karatzas, A., et al. 2009. Synthesis of well-defined functional macromolecular chimeras based on poly(ethylene oxide) or poly(N-vinyl pyrrolidone). *Reactive and Functional Polymers* 69(7): 435–440.

http://www.springer.com/978-3-319-32051-9

Biomedical Polymers
Synthesis and Processing
Damodaran, V.B.; Bhatnagar, D.; Murthy, N.S.
2016, VIII, 71 p. 52 illus., 17 illus. in color., Softcover
ISBN: 978-3-319-32051-9