Conjugated Polymers for Biological and Biomedical Applications

Edited by Bin Liu
Conjugated Polymers for Biological and Biomedical Applications
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Since the conferring of the Nobel Prize in Chemistry to conducting polymers in 2000, this versatile class of polymeric materials has generated tremendous interest from academia and industry. Conjugated polymers are organic macromolecules with π-conjugated backbone, which could be designed to display high electrical conductivity, outstanding photophysical properties, and excellent biocompatibility. They have been actively explored for a wide range of applications, spanning electronics, and energy harvesting to nanobiotechnology and nanomedicine. While the last 15 years have witnessed their rapid development in optoelectronic devices, the emerging field of conjugated polymers for biomedical applications has simultaneously attracted increasing attention recently. Specifically, they have found innovative applications in a variety of biotechnologies, ranging from biosensing that takes advantage of optical amplification, to cell imaging and image-guided therapy that fully utilizes the light-harvesting properties of conjugated polymers and their structure-dependent radiative and nonradiative pathways as well as their self-assembly properties with amphiphilic molecules. In fact, with their unique biophysicochemical attributes, conjugated polymer nanoparticles have been demonstrated to be even superior to other classes of nanomaterials, such as small organic dye-based nanoparticles, semiconducting quantum dots, and inorganic nanoparticles, in many biomedical applications. Remarkably, with the continual advancement in polymer design, synthesis, and processing strategies in the last few years, conjugated polymers have been increasingly reported to be highly promising for bioimaging, sensing, and for applications in disease therapy.

This book focuses on the fundamentals and biomedical applications of conjugated polymers and their nanoparticles for bioimaging, sensing, and disease therapy. It is organized into 13 chapters and has been written by well-recognized experts in the field. The first two chapters introduce the synthesis and optical properties of various conjugated polymers, with highlights on how to make organic soluble polymers compatible with the aqueous environment. Specifically, Chapter 1 provides an overview of the various strategies commonly employed to bring conjugated polymers into aqueous media for biological applications. Chapter 2 describes the different post-polymerization and direct-polymerization methods for the generation of conjugated polymer nanoparticles. The biological imaging and sensing applications of conjugated polymers
and their nanoparticles are covered from Chapters 3–7. Chapter 3 highlights the recent progress in the development of conjugated polymer nanoparticles for molecular sensing in vitro. The developments in the areas of conjugated-polymer-based fluorescent probes for in vivo fluorescence imaging of tumors, stimuli-responsive fluorescence imaging, in vivo fluorescence cell tracking, two-photon excited brain vascular imaging, and dual-modality in vivo imaging of tumors are summarized in Chapter 4. In Chapter 5, the mechanism of photoacoustic imaging as well as the preparation and applications of semiconducting polymer nanoparticles for in vivo photoacoustic imaging are discussed. Chapter 6 describes the application of conjugated polymer nanoparticles as contrast agents for two-photon live cell imaging. The imaging and sensing applications of water-soluble conjugated polymers are further demonstrated in Chapter 7.

In addition to imaging and sensing applications, conjugated polymers have also been widely explored for numerous therapeutic and functional biointerface applications. Some examples are highlighted in Chapters 8–12. Chapter 8 shows the fundamental properties of conjugated polymers as gene delivery vehicles and recent demonstrations of the utilizations of multifunctional conjugated polymers for the effective delivery of genetic materials, particularly pDNA and siRNA. A broad overview on the synthesis, functionalization, and applications of conductive-polymer-based functional structures for neural therapeutic applications, particularly for electro-stimulated drug delivery, neural cell and tissue scaffolds, and implantable biosensors and neural prostheses, is provided in Chapter 9. In Chapter 10, the design strategies as well as the applications of conjugated polymers for effective photodynamic therapy are discussed using anticancer and antimicrobial treatment as examples. Chapter 11 deals with the promising utilizations of conjugated polymers as near-infrared photothermal agents for image-guided cancer therapy and combination therapy. The potential applications of conjugated polymers and conjugated polymer nanoparticles for the detection of pathogens, cancer biomarker, miRNA, as well as for cancer and neurodegenerative disorder theranostics are discussed in Chapter 12. Finally, Chapter 13 focuses on the emerging field of polymer-grafted conjugated polymers for functional biointerface applications.

This is the first book that specifically focuses on conjugated polymers for biological and biomedical applications. This book has offered a comprehensive and balanced overview on the design, synthesis, and applications of conjugated polymers and their nanoparticles for biomedical imaging, sensing, and therapy. We believe that it is suitable for readers with diverse academic backgrounds and with different knowledge levels on conjugated polymers. It will guide new readers with minimum background to get started on conjugated polymers and also, offer experienced academics and researchers new outlooks and perspectives on this exciting field. Ultimately, we hope that our readers will find this book a pleasure to read and at the same time gain invaluable insights and ideas which will be beneficial to them. We believe that this is an excellent opportunity to highlight the remarkable basic science and technological potential of conjugated polymers, and to use the book to provide readers with a unique single source to understand the emerging applications in the exciting biomedical field.
To end this, we would like to extend our sincere gratitude to all parties who have contributed significantly to bring this book to fruition. Specifically, we thank all the authors for their precious contributions as well as the editorial team at Wiley-VCH for the dedicated and unceasing support.

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Strategies to Bring Conjugated Polymers into Aqueous Media

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1.1 Introduction

Conjugated polymers (CPs) are organic macromolecules with extended $\pi$-conjugation along the molecular backbone [1, 2]. Their unique optoelectronic properties that result from the highly delocalized $\pi$-electrons can be easily manipulated through modification of the conjugated backbones. As a result, CPs have been widely used in various research fields related to organic optoelectronic devices [3–5], chemo/biosensors [6, 7], and medical diagnosis and therapy [7–9]. For biology-related applications, the main obstacle is to render CPs water soluble or water dispersible. So far, mainly three strategies have been used to bring CPs into aqueous media, which include the design and synthesis of conjugated polyelectrolytes (CPEs) and neutral water-soluble conjugated polymers (WSCPs), as well as the fabrication of water-dispersible conjugated polymer nanoparticles (CPNPs) (Scheme 1.1).

CPEs are a kind of macromolecules characterized by $\pi$-conjugated backbones and ionic side chains [10]. Their solubility in aqueous media can be fine-tuned by modification of the ionic side chains. Although neutral WSCPs do not possess any charge, they have amphiphilic segments, for example, oligo(ethylene glycol) [11], that compensate for the hydrophobic nature of the conjugated backbones. These two strategies require the chemical modification of each polymer to bring them into water. A more general and straightforward method is to prepare for the CPNPs, which can in principle bring any organic soluble polymers into aqueous media [12]. To simplify our discussion, in this chapter, we only discuss CPNPs that are prepared from neutral CPs. The water solubility of CPNPs is largely determined by the polymer matrix used and the nanoparticle size, while their optical properties are associated with the neutral CP.

This chapter aims to provide readers with an overview of the strategies that can be used to bring CPs into aqueous media for potential biological applications. In this chapter, we will discuss the synthetic approaches for CPEs first, which is followed by the neutral WSCPs and CPNPs. The section on CPEs is organized
1 Strategies to Bring Conjugated Polymers into Aqueous Media

1.2 Synthesis of CPEs

In the past decades, a large number of CPEs have been successfully developed. According to their chemical structures, the synthesis of CPEs involves two aspects: construction of the conjugated backbones and incorporation of charged side chains. Many well-established polymerization methods have been employed to build the conjugated backbones (Scheme 1.2), which were typically catalyzed with organometallic complexes or bases, including Suzuki, Yamamoto, Stille coupling reaction and FeCl$_3$-catalyzed oxidative reaction for single bond formation; Heck, Witting, Knoevenagel, and Gilch coupling reactions for double bond formation; and Sonogashira coupling reaction for triple bond formation. In addition, CpCo(CO)$_2$-catalyzed homopolycyclotrimerization has also been used to synthesize hyperbranched CPEs [13]. Rational design of the conjugated backbones allows facile manipulation of their optical properties, such as absorption, emission, and quantum yield. The charges can be incorporated via direct polymerization of charged monomers or postfunctionalization of neutral CPs into CPEs (Scheme 1.3). According to the charge sign of the ionic side chains, CPEs can be categorized into three groups: anionic CPEs, cationic CPEs, and zwitterionic CPEs. The anionic groups generally include sulfonate [14], carboxylate [15], and phosphonate [16], while the cationic groups include quaternary ammonium [17], pyridinium [18], and phosphonium [19]. In the following section, we will use specific examples to show the synthetic approaches of CPEs with different charges. We start each section with polythiophenes, as they are commonly synthesized via electropolymerization and FeCl$_3$-catalyzed oxidative polymerization methods. The other CPEs are generally introduced following the sequence of single, double, and triple-bonded CPEs.
1.2 Synthesis of CPEs

**Scheme 1.2** Polymerization methods most widely employed to construct conjugated backbones. Ar1 and Ar2 represent aromatic units.

**Scheme 1.3** Representative strategies for synthesis of CPEs through incorporation of charges via direct polymerization (a) and postpolymerization (b) method.
1.2.1 Anionic CPEs

1.2.1.1 Sulfonated CPEs

Sulfonated polythiophenes are generally synthesized through electropolymerization or FeCl₃-catalyzed oxidative polymerization methods. As shown in Scheme 1.4a, the first sulfonated polythiophene P2 was reported by Wudl’s group in 1987 [14]. 2-(Thiophen-3-yl)ethanol 1 reacting with methanesulfonyl chloride yielded methyl 2-(thiophene-3-yl)ethanesulfonate 2. Electropolymerization of 2 led to a neutral polythiophene P1, which was subsequently treated with NaI in acetone to give sulfonated P2. Using the same electropolymerization method, another sulfonated polythiophene P3 was developed by Zotti’s group (Scheme 1.4b) [20]. The key sulfonated monomer 4 was synthesized by alkylation of 4H-cyclopenta[2,1-b:3,4-b’]dithiophene 3 in the presence of 1,4-butanesultone and n-BuLi. The direct electropolymerization of 4 afforded P3. Unlike P2 prepared via postpolymerization strategy, the sulfonated groups of P3 are inherited from the key monomer 4. In addition, Leclerc’s group reported a sulfonated polythiophene P4 by oxidative polymerization method (Scheme 1.4c) [21]. Briefly, the alkoxylation of 3-bromo-4-methylthiophene 5 was performed in N-methyl-2-pyrrolidone in the presence of sodium methoxide and copper bromide, leading to 3-methoxy-4-methylthiophene 6, which reacted with 2-bromoethanol and sodium sulfite in toluene to yield 3-(2-bromoethoxy)-4-methylthiophene 7. Subsequent treatment of 7 with sodium

Scheme 1.4 Synthesis of sulfonated polythiophenes P2–P4.
sulfite in a mixture of water/acetone led to sodium 2-(4-methyl-3-thiophenyl-1-oxy) ethanesulfonate 8, which underwent FeCl$_3$-catalyzed oxidative polymerization to afford P4.

To synthesize CPEs with single bonded backbones, Suzuki polymerization was often used due to its high reaction yield and good selectivity toward various functional groups [22]. As shown in Scheme 1.5a, the first sulfonated poly($p$-phenylene) P6 was synthesized by Wegner’s group via the Suzuki polymerization method [23]. The key monomer 10 was prepared via the chlorosulphonation of 1,4-dibromobenzene 9 with chlorosulfonic acid in dichloromethane, followed by treatment with $p$-cresol in the presence of pyridine. Then, Pd-catalyzed Suzuki polymerization between 10 and 2,2’-(2-dodecyl-5-methyl-1,4-phenylene)bis(1,3,2-dioxaborinane) 11 in the presence of sodium carbonate yielded a neutral poly($p$-phenylene) P5. Subsequent solvolysis of P5 in a mixture of sodium butanolate/1-butanol followed by the addition of water, gave the sulfonated poly($p$-phenylene) P6 in quantitative yield. Only one of the two possible positional isomeric structures of the repeated unit is shown in P5 and P6 for the sake of simplicity in illustration.

Scheme 1.5 Synthesis of sulfonated CPEs P6 and P7 with single-bonded backbones through Suzuki polymerization method.
A direct polymerization method for synthesizing sulfonated poly(p-phenylene) P7 through Suzuki polymerization was reported by Reynolds’s group via three steps (Scheme 1.5b) [24]. 2,5-Dibromohydroquinone 13 was synthesized via bromination of 1,4-dimethoxybenzene 12 using bromine in tetrachloromethane, followed by the treatment with boron tribromide in anhydrous dichloromethane. Subsequent sulfonation of 13 with 1,3-propanesultone and sodium hydroxide in absolute ethanol led to the key sulfonated monomer 14, which directly reacted with 1,4-phenylenediboronic acid 15 through Suzuki polymerization to yield P7. Unlike P5 and P6, there is no isomeric structure for P7 due to its symmetric chemical structure.

To synthesize sulfonated CPEs with double-bonded backbones, various polymerization methods have been employed. Herein, we choose the widely studied poly(p-phenylenevinylene)s as the examples. The first sulfonated poly(p-phenylenevinylene) P10 was synthesized by Wudl’s group in 1990 [25], starting from the key monomer 16 (Scheme 1.6a). 16 was self-polymerized either in methanol or in water with the help of sodium methoxide or sodium hydroxide, respectively, yielding a reactive p-xylylene intermediate P8. Further hydrolysis followed by base-assisted elimination led to the sulfonated poly(phenylene vinylene) P10. The purity of 16 is very crucial to ensure that P10 can be obtained with narrow polydispersity and high molecular weight.

Another approach to synthesize P10 was reported by Gu et al. [26] As shown in Scheme 1.6b, potassium 3-(4-methoxyphenoxy)propanesulfonate 18 was prepared through the esterification of 4-methoxyphenol 17 with 1,3-propanesultone in anhydrous ethanol under basic conditions. Further chloromethylation of 18 with paraformaldehyde in acidic aqueous at 40 °C led to the key monomer 19. Gilch dehydrohalogenation polymerization of 19 was performed using t-BuOK as catalyst to give P10.

The same group also employed Witting polymerization to synthesize poly(p-phenylenevinylene) derivatives (Scheme 1.6c) [27]. A mixture of 19 and triphenylphosphine in anhydrous toluene was kept at reflux conditions leading to the monomer 20, which was copolymerized with terephthalaldehyde in tert-butyl alcohol through Witting condensation with potassium tert-butoxide as catalyst to yield alternating sulfonated poly(p-phenylenevinylene) P11.

Heck polymerization is also an important approach to synthesize sulfonated poly(p-phenylenevinylene) derivatives. As shown in Scheme 1.6d, the sulfonated diiodo-substituted monomer 22, which was synthesized with a similar approach as for 18, copolymerized with 1,4-dimethoxy-2,5-divinylbenzene 21 using palladium acetate and tri(o-tolyl)phosphine as cocatalysts in dimethyl sulfoxide under basic conditions affording the alternating sulfonated poly(p-phenylenevinylene) P12 [28].

In addition to the abovementioned approaches for synthesizing poly(p-phenylenevinylene), Knoevenagel polymerization has also been used to prepare cyano-substituted poly(p-phenylenevinylene) derivatives [29]. As shown in Scheme 1.6e, 4-methoxyphenol 17 subsequently underwent alkylation, chloromethylation, and cyanide exchange reactions to yield 23. Subsequently, the hydroxyl groups of 23 underwent sequential methanesulfonylation, iodination, and sulfonation, affording the key monomer 24. Knoevenagel condensation reaction between 24 and the neutral dialdehyde monomer 25 using t-BuONa as catalyst in a mixture of t-BuOH/DMF led to the sulfonated P13.
1.2 Synthesis of CPEs

To synthesize CPEs with triple-bonded backbones, Sonogashira coupling reaction is commonly employed. This reaction involves a palladium-catalyzed sp²–sp coupling reaction between aryl or alkenyl halides or triflates and terminal alkynes, with or without a copper(I) cocatalyst [30]. It can be performed under mild conditions, such as room temperature, in aqueous media. Several
monomers could also be synthesized with sulfonate functional groups. A direct polymerization approach to synthesize sulfonated polyfluorene P14 was reported by Liu’s group (Scheme 1.7a). It only requires one step to synthesize the key monomer 2,7-dibromo-9,9-bis(4-sulfonatobutyl)fluorene 27 via direct alkylation of 2,7-dibromofluorene 26 with 1,4-butane sultone and NaOH in DMSO [31]. The copolymerization of 27 and 4,7-diethynyl-2,1,3-benzothiadiazole 28 under Sonogashira coupling reaction conditions led to the sulfonated poly(fluorene vinylene) P14 [32]. In addition, as shown in Scheme 1.7b, the key sulfonated monomer 30 can be prepared using procedures similar to 18 and 22. Sonogashira reaction between 1,4-diethynylbenzene 29 and 30 in basic aqueous/DMF solution using tetrakis(triphenylphosphine)palladium and copper iodide as co-catalysts led to P15. In 2006, by utilizing the above mentioned strategy, Schanze’s group developed a series of sulfonated poly(phenylene ethynylene)s with variable band gaps based on the monomer 30 [33].

![Scheme 1.7 Synthesis of sulfonated CPEs P14 and P15 with triple-bonded backbones through Sonogashira reaction.](image)

### 1.2.1.2 Carboxylated CPEs

Carboxylated polythiophenes have been prepared through Yamamoto coupling polymerization, Stille coupling polymerization, and FeCl₃-catalyzed oxidative polymerization. As shown in Scheme 1.8a, the neutral poly(methyl thiophene-3-carboxylate) P16 was synthesized via the Yamamoto polymerization of methyl 2-(2,5-dichlorothiophen-3-yl)acetate 31 [15]. Subsequently, the hydrolysis of P16 in 2.0 M NaOH aqueous led to poly(sodium thiophene-3-carboxylate) P17. During the purification process, filtration was needed to remove the insoluble fraction. In addition, a CuO-mediated Stille coupling polymerization of 32 was carried out to give poly(4,5-dihydro-4,4-dimethyl-2-(2-thiophen-3-yl)ethyl)
1.2 Synthesis of CPEs

oxazole) \( P_{18} \) (Scheme 1.8b) \[34\], which was converted to \( P_{19} \) after acid-assisted hydrolysis and base treatment. Compared to \( P_{17} \) and \( P_{19} \), which only have one carboxylate group on each repeat unit, \( P_{20} \) reported by Wang’s group possesses two carboxylate groups on each repeat unit (Scheme 1.8c) \[35\]. The monomer \( 34 \) was synthesized by reacting 2-(3-thienyl)ethylamine hydrochloride \( 33 \) with methyl acrylate under basic conditions in the presence of boric acid. Oxidative polymerization of \( 34 \) in chloroform using \( \text{FeCl}_3 \) as oxidizing agent followed by hydrolysis in \( \text{NaOH} \) aqueous solution yielded \( P_{20} \).

Suzuki polymerization is generally used to synthesize carboxylated CPEs with single-bonded backbones. The first carboxylated poly(\( p \)-phenylene) \( P_{21} \) was reported by Wallow and Novak in 1991 \[36\]. As shown in Scheme 1.9a, \( \text{Pd}(0) \)-catalyzed Suzuki coupling reaction between 4,4′-dibromo-[1,1′-biphenyl]-2,2′-dicarboxylic acid \( 35 \) and 4,4′-di(1,3,2-dioxaborolan-2-yl)-1,1′-biphenyl followed by treatment with dilute hydrochloric acid yield \( P_{21} \) with free acid. \( P_{21} \) was completely insoluble in all common organic solvents, but was soluble in dilute aqueous base as its sodium, potassium, or triethylammonium salt.

A postfunctionalization approach to synthesize carboxylated poly(\( p \)-phenylene) was later reported by Rehahn’s group starting from the precursor polymer \( P_{22} \) (Scheme 1.9b) \[37\]. Owing to the high reactivity of bromide methylene group on \( P_{22} \), etherification of \( P_{22} \) with ethyl \( p \)-hydroxyl benzoate in a mixture of toluene/DMF in the presence of \( t \)-BuONa produced \( P_{23} \) in nearly quantitative yield. During the reaction process, the ester groups were kept intact. Almost all the ester groups of \( P_{23} \) was cleaved in a homogeneous solution of toluene in the presence of 10 equiv. of \( t \)-BuOK and only 2 equiv. of water, followed
by acidification with hydrochloric acid to yield \( \text{P24} \). However, unexpectedly, no hydrolysis of \( \text{P23} \) was observed in a two-phase system of water/toluene in the presence of NaOH.

Another postpolymerization approach to synthesize carboxylated polyfluorene was reported by Liu’s group (Scheme 1.9c) [38]. Direct alkylation of \( \text{26} \) via Michael addition of the 9-position carbon with tert-butylacrylate afforded fluorene ester \( \text{36} \), which was converted to the corresponding diboronate ester \( \text{37} \) under Suzuki–Miyaura reaction conditions in the presence of bis(pinacolato) diborane, \( \text{Pd(dppf)}_2\text{Cl}_2 \), and KOAc with anhydrous DMF as the solvent. In the next step, Suzuki polymerization between \( \text{36} \) and \( \text{37} \) led to the neutral precursor polymer \( \text{P25} \). Contrary to the preparation of \( \text{P24} \) where the hydrolysis was performed under basic condition, \( \text{P26} \) was obtained by the hydrolysis of \( \text{P25} \) in acid condition followed by the neutralization with aqueous \( \text{Na}_2\text{CO}_3 \).

Carboxylated CPEs with double-bonded backbones have been synthesized through Heck and Gilch polymerization methods. As shown in Scheme 1.10a, Heck coupling polymerization between \( \text{38} \) and the diiodo-substituted monomer \( \text{39} \) in DMF using \( \text{Pd(OAc)}_2 \) and \( \text{P(o-Tolyl)}_3 \) as cocatalysts yielded the precursor polymer \( \text{P27} \), which was hydrolyzed into carboxylated \( \text{P28} \) in THF with \( t\)-BuOK.
as the base [39]. \textbf{P28} is only soluble in DMSO and dilute aqueous bases such as NaOH and NH₄OH but is insoluble in CHCl₃. Similarly, Gilch dehydrochlorination polymerization was also used to synthesize carboxylated poly(phenylene vinylene) \textbf{P29} (Scheme 1.10b) [40]. The key monomer 40 was prepared by etherification of 4-methoxyphenol 17 with 1-bromohexanoic acid ethyl ester and MeONa, followed by chloromethylation with formaldehyde and hydrochloric acid. In the next step, Gilch dehydrochlorination polymerization of 40 in the presence of \textit{t}-BuOK yielded the carboxylated \textbf{P29}.

\textbf{P28}

\textbf{P29}

\textbf{P30}

\textbf{P32}

\textbf{P31}

\textbf{P33}

\textbf{P34}

Scheme 1.10 Synthesis of carboxylated CPEs \textbf{P28} and \textbf{P29} with double-bonded backbones.

Sonogashira coupling reaction is the most commonly used method to synthesize carboxylated CPEs with triple-bonded backbones. As shown in Scheme 1.11a, \textbf{P30} was directly obtained by polymerization of 3,5-diiodo benzoic acid 41 with acetylene gas in water in the presence of a water-soluble Pd(0) catalyst, CuI co-catalyst, 1 equiv. of NaOH and 3 equiv. of Et₃N [41].

Bunz’s group synthesized \textbf{P32} by a postpolymerization method (Scheme 1.11b) [42]. Starting from 2,5-diiodohydroquinone 42, reaction with 2-bromoethyl acetate in butanone in the presence of K₂CO₃ yielded the ester-protected diiodo-monomer 43. Subsequent alkylation utilizing trimethylsilylacetylene and the catalysts of Pd(PPh₃)₂Cl₂/CuI with trimethylamine as the solvent
furnished 44 after desilylation with tetrabutylammonium fluoride in THF. It is important to note that the ester groups were not cleaved under such basic conditions. Copolymerization between 43 and 44 under Sonogashira reaction conditions yielded the neutral P31, which was converted to P32 through hydrolysis with NaOH in methanol [42].

To increase the number of carboxylate groups on each repeat unit, Wang’s group reported P33 from the key monomer 46 (Scheme 1.11c). Starting from the alkylation of 2,7-dibromofluorene 26 with ethyl bromoacetate under basic conditions followed by treatment with HCl solution, the obtained intermediate further reacted with L-aspartic acid dimethyl ester hydrochloride via N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) hydrochloride-catalyzed coupling reaction at room temperature to yield 45 [43]. The key monomer 46 can be easily obtained by reaction between 45 and trimethylsilylacetylene using Pd(PPh₃)₂Cl₂/CuI as catalyst.
followed by desilylation with tetrabutylammonium fluoride in THF. Subsequently, Sonogashira coupling reaction between 46 and Pt(PMe₃)₂Cl₂ 47 followed by hydrolysis of the ester groups using 2M KOH solution as the base yielded the desired carboxylated P33 with four carboxylate groups on each repeat unit [44].

1.2.1.3 Phosphonated CPEs

As compared to sulfonated and carboxylated CPEs, the studies concerning phosphonated CPEs are less reported [16, 45, 46]. As shown in Scheme 1.12a, 3-(3-bromopropoxy)thiophene 49 was synthesized from 3-methoxythiophen 48...
and 3-bromopropanol in toluene in the presence of NaHSO₄. Treatment of 49 with triethyl phosphite yielded the phosphonic acid diethyl ester 50. Direct electropolymerization of 50 led to the precursor polymer P34, which was hydrolyzed into phosphonated P35 using bromotrimethylsilane [16].

A phosphonated polyfluorene P36 was also synthesized by Wang’s group via direct Suzuki polymerization method (Scheme 1.12b) [46]. Starting from 2,7-dibromo-fluorene 26, reaction with 1,3-dibromopropane in aqueous NaOH yielded 2,7-dibromo-9,9-bis(3-bromopropyl)fluorene 51, which reacted with triethylphosphite to afford 52 in a quantitative yield. Treatment of 52 with trimethylsilyl bromide and subsequently water yielded 2,7-dibromo-9,9-bis(3-diethoxylphosphorylpropyl)fluorene 53. Direct Suzuki polymerization between 53 and 1,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene using Pd(dppf)Cl₂ as catalyst in DMF and Na₂CO₃ aqueous solution gave P36 with molecular weight higher than 15 kDa.

Phosphonated CPE P38 with triple-bonded backbones was also synthesized. As shown in Scheme 1.12c, bromination of 54 in acetonitrile using carbon tetrabromide and triphenylphosphine yielded 55, which underwent iodination to give the compound 56. The key monomer 57 was synthesized from 56 using a similar procedure to 50 and 52. P38 was then prepared via Sonogashira reaction between 57 and 1,4-diethynybenzene to yield P37, which was followed by trimethylsilyl bromide treatment to promote the hydrolysis of the butylphosphonate ester groups (Scheme 1.12c) [45]. However, Sonogashira reaction between the hydrolysis product of 57 and 1,4-diethynybenzene could not afford high molecular weight for P38, presumably because the ionic phosphonate groups can coordinate with and deactivate the catalysts during the polymerization.

### 1.2.2 Cationic CPEs

#### 1.2.2.1 Ammonium CPEs

Ammonium polythiophene P39 was reported by Leclerc’s group through direct oxidation of cationic thiophene monomer 59 (Scheme 1.13a) [47]. The key monomer 59 was prepared from the Williamson reaction between 3-bromo-4-methylthiophene 5 and 3-(diethylamino)propanol to yield 58, which was followed by quaternization with bromoethane. Oxidative polymerization of 59 in chloroform using FeCl₃ as the oxidizing agent yielded P39. Alternatively, a postpolymerization method to synthesize ammonium polythiophene was also reported by McCullough’s group [48]. As shown in Scheme 1.13b, a neutral polythiophene P40 was synthesized from 2-bromo-3-hexylbromothiophene 60 via Ni(dppp)Cl₂ catalyzed coupling reaction. Quaternization of P40 with methylamine in a mixture of THF/methanol yielded the cationic P41. It should be pointed out that the chemical structure of P40 should be written as P42 with a bromide on the conjugated backbone terminal, according to the reaction. Using P42 as a macromonomer and 2-bromo-(9,9-diocetylfluorene)-7-pinacolato boronate 61 as AB-type monomer under Suzuki cross-coupling conditions, Scherf’s group has successfully synthesized all-conjugated cationic diblock copolythiophenes P44 through a “grafting from” approach (Scheme 1.13c) [49].