

Polymer Chemistry Series

# Redox Polymers for Energy and Nanomedicine

Edited by Nerea Casado and David Mecerreyes



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## Redox Polymers for Energy and Nanomedicine

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## CHAPTER 1

# *Introduction to Redox Polymers: Classification, Characterization Methods and Main Applications*

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## 1.1 Introduction

Redox polymers are those polymers that can undergo reversible oxidation (loss of electrons) and reduction (gain of electrons) processes, as defined by the International Union of Pure and Applied Chemistry (IUPAC). They contain electroactive sites or groups that sustain these redox processes, which can be located in the main polymer backbone, as in the case of electrically conducting polymers such as polypyrrole,<sup>1</sup> or in the polymer's side-chain, as in the case of a polymer bearing a ferrocene group.<sup>2</sup>

The redox reaction implies the variation of the oxidation state of the polymer, which provokes changes in the properties of the polymeric material. Therefore, depending on the oxidation state (oxidized or reduced), the polymer may exhibit different chemical, optical, electronic or mechanical properties. The reversibility and easy external control of redox processes

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have made redox polymers interesting for different applications and for the development of new electrochemical devices such as organic batteries, electrochromic devices, optoelectronic devices, biosensors or biofuel cells.<sup>3,4</sup>

Moreover, the applications of redox polymers in medicine have increased in the last 20 years, for example, on the development of new types of actuators and drug-delivery systems.<sup>5,6</sup> As already mentioned, redox polymers are also interesting for electrochromic and electroluminescence devices and organic solar cells, due to their optoelectronic properties.<sup>7,8</sup> However, the developments of optoelectronic polymers are not reviewed in this book, as they are commonly known as conducting, conjugated, electroluminescent or electrochromic polymers, rather than as redox polymers.

Thus, this book highlights current trends in the chemistry, characterization and application of redox polymers. In this chapter, we will introduce the topic by showing an overview of the different types of redox polymers, state-of-the-art characterization techniques and their applications. In this last part, the role of redox polymers in energy devices, such as batteries, supercapacitors, solar cells, biofuel cells, as well as in medical applications such as tissue engineering, drug delivery, actuators and bioelectronic devices, will be highlighted.

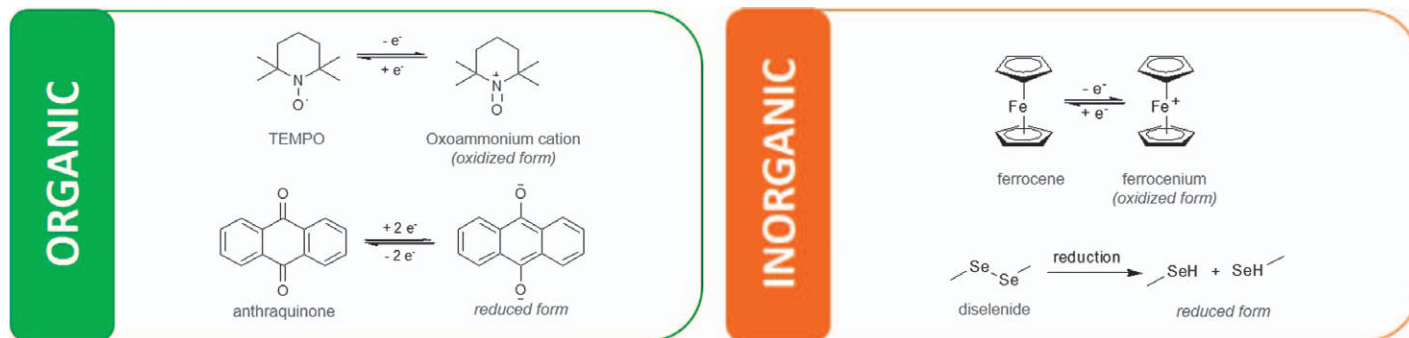
## 1.2 Classification of Redox Polymers

Redox polymers became popular in the early 1980s as a new class of electroactive polymer. The first examples were based on conducting polymer backbones such as polyacetylene<sup>1</sup> and polymers containing ferrocene groups. Nowadays, the redox polymer portfolio is formed by a wide variety of chemical structures, including various conjugated polymer backbones and/or electroactive moieties which can be organic or inorganic/organometallic species. Historically, redox polymers have been classified mainly using the following criteria:

- Location of the redox center: in the polymer backbone or as a pendant group,
- Nature of polymer backbone: conjugated/semiconducting or nonconjugated,
- Nature of redox center: organic or inorganic.

These classifications always include exceptions and hybrid forms due to the large variety of redox polymers that have been synthesized over the years.

In this chapter, we will show first examples of organic redox polymers (formed by C, H, N, O and S), where we distinguish between semiconducting polymers and nonconjugated redox polymers. Next, we describe redox polymers having organometallic or alternative atoms in their redox moiety. Then, we will explain state-of-the-art characterization techniques of redox polymers and their most important applications in energy and medicine (Figure 1.1).



**Figure 1.1** Oxidation and reduction processes of representative organic and inorganic moieties included in redox polymers.

## 1.2.1 Organic Redox Polymers

### 1.2.1.1 Conjugated/Semiconducting Polymers

Conjugated polymers (CPs) are composed of fully conjugated sequences of double bonds along the polymeric backbone. The extended conjugation and the additional doping provoke that conjugated polymers may exhibit bulk electric conductivity. Since the discovery of conductive polyacetylene by Shirakawa and co-workers in 1977,<sup>9</sup> conducting polymers have been widely investigated due to their interesting and tunable properties. In general, conducting polymers possess high electrical conductivity, easy processability, flexibility, low weight, low cost and the possibility of large-scale production.<sup>10–12</sup> Therefore, CPs have been employed in a wide range of applications including actuators, organic light-emitting diodes, batteries, supercapacitors, biosensors and drug-delivery systems.<sup>10–15</sup>

The most studied conducting polymers due to their high conductivity and easy synthesis are polypyrrole (Ppy), polyaniline (PANI), polythiophene (PT) and poly(3,4-ethylenedioxythiophene) (PEDOT). Among them, PEDOT is nowadays the most popular one due to its thermal and chemical stability, electro(chromic) properties and transparency, which are some of the reasons behind the success of its commercialization. Conducting polymers require partial oxidation or reduction processes to give rise to charged species, and thus, they can be considered as redox polymers. The generated charges are compensated by the appropriate counter ions, named dopants, to maintain the electroneutrality of the polymer.<sup>16</sup> The partial oxidation and reduction are known as p-doping and n-doping, respectively.<sup>17</sup> As a result of the doping process, charged defects such as *polarons* and *bipolarons* are created in the polymer chains, which are responsible for the electron conduction.

### 1.2.1.2 Nonconjugated Polymers

Organic redox-active groups, such as nitroxides, quinones, phenothiazines or viologens, have been incorporated in polymer structures either as pendant groups or in the main polymeric backbone. The synthesis of new redox polymers and copolymers has been actively pursued in recent years for their application in batteries, biofuel cells, sensors and drug-delivery systems, among others.

Nitroxide radicals are one family of redox-active organic groups. Nishide and co-workers pioneered the synthesis of polymers containing nitroxide radicals such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (see Figure 1.2, polymer 1).<sup>18,19</sup> This type of radical is very stable and possesses fast electron transfer kinetics, thus they have been of great interest for organic batteries and supercapacitors.<sup>20–22</sup> Block copolymers, containing nitroxide radicals in one of the blocks, have been developed to tune the properties and obtain responsive polymers,<sup>23</sup> organic cathodes<sup>24</sup> and polymers with resistive memory properties.<sup>25</sup> The TEMPO group has also been incorporated as a pendant group in conjugated polymers, such as polythiophene<sup>26</sup> and PEDOT



**Figure 1.2** Chemical structures of redox polymers containing electroactive organic moieties: as a pendant group (A, B) or in the polymer backbone (C, D), which can have at the same time conjugated (B, D) or aliphatic (nonconjugated) (A, C) backbones.

(polymer 4).<sup>27</sup> These polymers showed a synergetic effect between the redox properties of the conjugated backbone and the stable nitroxide radical, which are of great interest for battery applications.

Other types of stable radicals such as phenoxyl and verdazyl have been also incorporated in redox polymers with tuneable properties.<sup>28</sup> Phenoxyl radical polymers have found applications in energy storage.<sup>29</sup> For example, Schubert and co-workers synthesized phenoxyl-containing polymers with norbornene and methacrylate backbones<sup>30</sup> (polymer 2), which were applied as anode-active material in organic batteries due to the low redox potential. In a similar way, Price *et al.* reported the synthesis of 6-oxoverdazyl polymers with poly(phenyl methacrylate) backbone.<sup>31</sup>

Carbonyl-containing polymers are another relevant redox polymer family.<sup>32</sup> Carbonyls represent a common organic structural group, which can be found in a variety of redox moieties, such as anthraquinone, quinone, imide or anhydrides. Some examples in this area include polymers with anthraquinone derivatives<sup>33</sup> (polymer 5) or polyimides with naphthalene (polymer 6) or pyromellitic compounds.<sup>34</sup> Redox-active polyimides have been widely investigated as electrode materials for lithium,<sup>34,35</sup> sodium,<sup>36</sup> lithium-sulfur<sup>37</sup> and all-organic batteries,<sup>38</sup> as well as for applications in aerospace and electronics.<sup>39</sup> Quinone-containing polymers are very attractive for energy storage applications due to their high charge-storage capacity. Moreover, quinones are the principal redox center in natural organic materials, which makes them interesting in terms of sustainability.<sup>40</sup> Some examples include hybrid materials between conducting polymers, such as polypyrrole or PEDOT, and biopolymers like ligninsulfonates as electrode materials for batteries and supercapacitors.<sup>41–43</sup> Another interesting example is catechol-containing polymers,<sup>44</sup> which were applied as organic cathodes for lithium batteries,<sup>45</sup> while their ability to host various cations ( $H^+$ ,  $Li^+$ ,  $K^+$ ,  $Zn^{2+}$ ,  $Mg^{2+}$ ,  $Ca^{2+}$  and  $Al^{3+}$ ) in aqueous batteries has been recently demonstrated.<sup>46</sup> This kind of bioinspired catechol polymer has also been synthesized as nanoparticles, which could be used in a variety of battery technologies.<sup>47</sup>

Other organic functional groups such as viologen, triphenylamine and phenothiazine are known to possess redox properties. Viologen and triphenylamine moieties have been incorporated into different polymer backbones to obtain linear, cross-linked or porous polymers.<sup>48,49</sup> Polymers with viologen moieties (polymer 7) combine redox and electrochromic properties, which make them interesting for several fields, including electrochromism, energy storage, gas storage and separation, and biochemistry.<sup>50</sup> Polymers with carbazole and phenazine units (polymer 9) and its derivatives (phenothiazine, thianthrene) have been used for energy storage,<sup>51</sup> photovoltaic<sup>52</sup> and optoelectronic devices.<sup>53</sup> The application of phenothiazine-containing redox polymers (polymer 10) in energy storage devices has increased in the last decade due to their fast redox process and high redox potential (3.5 V vs.  $Li/Li^+$ ). Thus, they have been employed not only as electrode materials in Li/organic,<sup>54,55</sup> redox-flow<sup>56</sup> and all-organic<sup>57,58</sup> batteries but also as redox mediators in Li/O<sub>2</sub> batteries.<sup>59</sup>

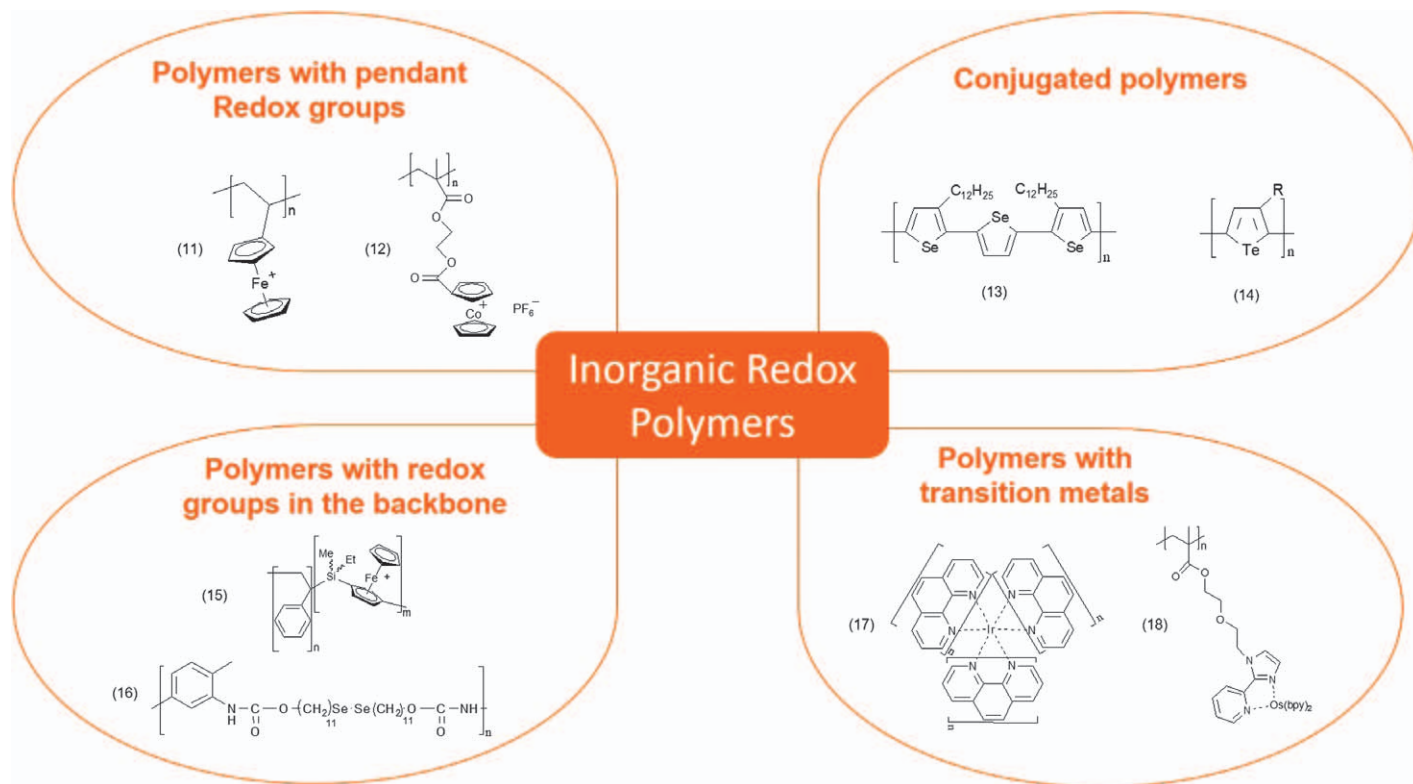
The last family of organic redox polymers consists of organosulfur compounds. Polymers with disulfide bonds and polysulfide moieties (polymer 8) have been investigated as electrode materials in batteries.<sup>60–62</sup> Specially, copolymers with high sulfur content synthesized by inverse vulcanization are interesting cathode materials to replace elemental sulfur in lithium/sulfur (Li/S) batteries with good cycling stability.<sup>63</sup> Disulfide bonds are also very interesting for drug-delivery applications, as they degrade under physiological reducing conditions.<sup>6</sup> Tetrathiafulvalene (TTF) is an important redox moiety with disulfide linkages, which can undergo two reversible redox processes to radical cation ( $\text{TTF}^+$ ) and dication ( $\text{TTF}^{2+}$ ). TTF-containing polymers (polymer 3) have been widely studied due to their interesting charge-transfer properties for organic electronics.<sup>64</sup>

### 1.2.2 Inorganic Redox Polymers

Inorganic redox moieties have also been incorporated into polymer materials either in the backbone or as pendant groups. Ferrocene is the gold-standard organometallic moiety due to its redox stability and reversibility. The ferrocene group has been integrated into several polymer backbones, from the simplest poly(vinylferrocene)<sup>60</sup> (Figure 1.3, polymer 11) to block copolymers with ferrocene in one of the blocks. In this manner, functional polymers with ferrocene units have been developed with interesting mechanical robustness, photo-physical, optoelectronic properties and stimuli-responsive properties.<sup>61,65</sup> Poly(vinylferrocene), for example, has been copolymerized with poly(methyl methacrylate) to form nanocapsules,<sup>63</sup> or with poly(ethylene oxide) to obtain water-soluble star polymers<sup>62</sup> for biomedical applications. Poly(ferrocenylsilane) polymers (polymer 15) are the most important polymers where the ferrocene group is located in the polymer backbone.<sup>66</sup> As an example, poly(ferrocenylsilane)-based gels and hydrogels were synthesized as redox-responsive materials.<sup>64</sup>

In contrast to ferrocene polymers, cobaltocene-containing polymers have been much less developed, probably due to the difficulty of preparing substituted derivatives. Cobaltocenium-containing polymers (polymer 12) have been used in electrochemistry, catalysis and biosensing.<sup>67,68</sup>

Conjugated polymers comprising inorganic elements in their structure such as selenium, tellurium or phosphorous have been investigated to modify their redox and optoelectronic properties. In the last decade, poly-selenophene conjugated polymers and copolymers (polymer 13) has been the most studied ones owing to their optical properties and their potential use in low-cost electronic devices.<sup>69,70</sup> As an example, Hollinger *et al.* synthesized selenophene–thiophene block copolymers, which phase-separate and exhibit interesting absorbance features for optoelectronic uses.<sup>70</sup> Moreover, the development of solution-processable poly(3-alkyltellurophene) polymers (polymer 14) proved their potential application for optoelectronic applications.<sup>71</sup> On the other hand, phosphole-containing polymers allow post-functionalization in the phosphorous center, as they



**Figure 1.3** Chemical structures of redox polymers containing electroactive inorganic moieties.



are able to tune the electronic properties. Phosphole-containing polymers have been applied in optoelectronic and sensing devices.<sup>72,73</sup>

Selenium is a nonmetal located in the chalcogen group of the periodic table between sulfur and tellurium elements. It possesses many similarities to the elements of its group, however, the bond energy of diselenide bond is smaller than the disulfide (Se–Se 172 kJ mol<sup>−1</sup> vs. S–S 226 kJ mol<sup>−1</sup>). Therefore, selenium-containing polymers are promising materials as redox-responsive drug carriers.<sup>74</sup> As an example, a polyurethane triblock copolymer with diselenide bonds was reported by Xu and Zhang's group (polymer 16). This block copolymer forms multiresponsive micellar aggregates, which are responsive to both oxidant and reductant conditions and suitable for controlled drug-delivery systems.<sup>75</sup>

Polymers with transition metals, such as zinc, copper, platinum and iridium, have been widely developed due to their intrinsic properties including redox, catalytic, magnetic, light absorption and emission properties (polymer 17).<sup>75–77</sup> Depending on the interaction of the metal with the polymeric chain and the nature of the chain, whether conjugated or not, the electronic and electrochemical properties may vary.<sup>78,79</sup> In this family, zinc-containing polymers have been the most studied ones due to the coordination ability of Zn(II) to develop a wide variety of structures.<sup>74</sup> Moreover, platinum-, osmium- and palladium-containing polymers have been also investigated in biomedical applications such as biosensors and drug delivery (polymer 18).<sup>80–82</sup>

### 1.3 Characterization of Redox Polymers

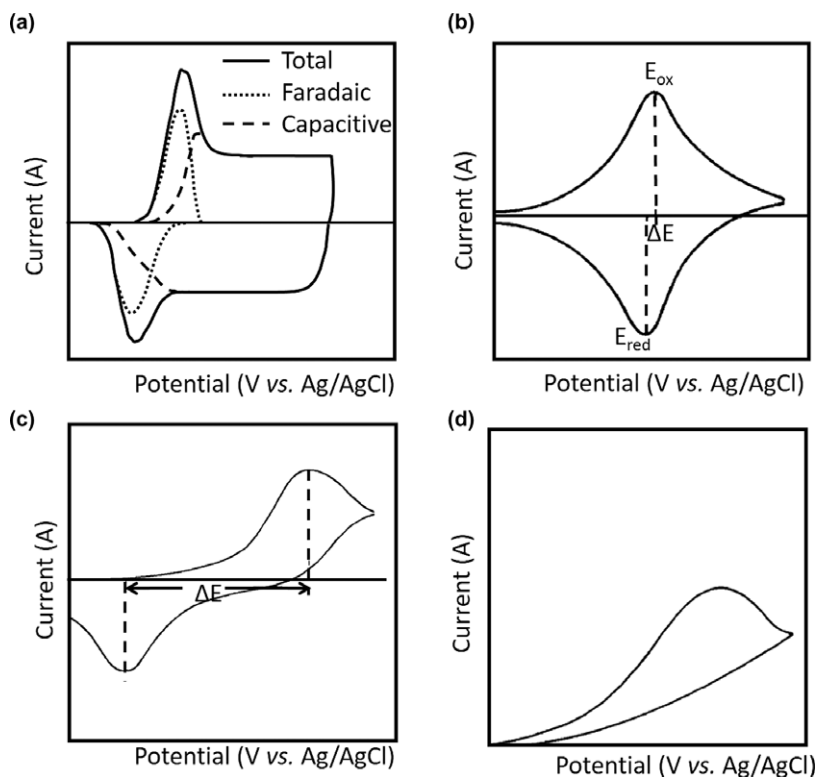
Apart from the conventional polymer characterization techniques for molecular weight distribution, glass transition, crystallization, physicochemical, thermal and mechanical properties, redox-active polymers are commonly analyzed by electrochemical techniques. Cyclic voltammetry (CV) is the most widespread characterization method, together with electrochemical impedance spectroscopy (EIS). Moreover, CV can be combined simultaneously with additional techniques such as UV–Vis–NIR, infrared spectroscopy, photoemission, electrochemical quartz microbalance (EQCM) and atomic force microscopy to study the changes taking place in the polymer during the redox processes. As electrochemical characterizations are very sensitive, besides the intrinsic factors defined by the polymer nature, external factors related to the sample preparation and electrochemical technique have to be taken into account during the characterization of redox polymers. The most important external factors affecting the electrochemical characterization are: sample preparation, dimensions of the sample (thickness, weight and area), kinetics of the redox process, nature of the electrolyte, type of set-up, temperature and formulation of the electrode when binders and conductive additive are included.



### 1.3.1 Cyclic Voltammetry (CV)

Cyclic voltammetry is a powerful and popular electrochemical method to study the oxidation and reduction processes of redox polymers. It provides information about the redox behavior of the material at different potentials and is a fast and reliable characterization technique.<sup>83</sup> In this experiment, a potential is applied to the working electrode (E), which is swept at a certain rate (scan rate) and the resulting current ( $i$ ) is measured. The obtained trace ( $i$  vs. E) is called a voltammogram or cyclic voltammogram, which is dependent on the type of process occurring at the electrode.

Redox polymers can present different voltammogram shapes depending on the redox behavior (see Figure 1.4). Conducting polymers present typically two types of currents: the faradaic current caused by the redox reaction and the capacitive current resulting from the electrical double layer generated on the surface of the electrode.<sup>3</sup> These two current responses can be observed in the voltammogram trace of Figure 1.4a. Redox polymers with localized redox moieties, either in the backbone or as a pendant group, show



**Figure 1.4** Cyclic voltammograms of (a) conducting polymer, (b) diffusion-controlled reversible redox process, (c) quasi-reversible process and (d) irreversible process.

only the faradaic current. The maximum current peak corresponds to the oxidation potential ( $E_{\text{ox}}$ ), while the minimum current peak to the reduction potential ( $E_{\text{red}}$ ) is shown in Figure 1.4b. The redox potential is usually determined by the average potential ( $E_{1/2}$ ) between the oxidation and reduction potentials, and is specific to the experimental conditions [ $E_{1/2} = \Delta E = (E_{\text{ox}} + E_{\text{red}})/2$ ], as the two peaks are separated due to the diffusion of the analyte to and from the electrode surface. The separation of oxidation and reduction peaks reveals the reversibility of the redox reaction. Reversible redox reactions present small  $\Delta E$  values ( $\Delta E < 57$  mV),<sup>84</sup> while in quasi-reversible processes  $\Delta E$  increases showing two separated and less sharp peaks in the cyclic voltammogram (Figure 1.4c). Moreover, if the process is completely irreversible, only one peak, oxidation or reduction, will be present in the cyclic voltammogram. Figure 1.4d shows a typical trace for a polymer with irreversible oxidation process.

The current response of redox polymers can be limited by two different processes. The first limiting process is related to the electron transfer kinetics between the electrode and the redox species, while the second one is due to the diffusion of the redox species to and from the electrode. Thus, diffusion is negligible for thin-layer electrodes, as the electroactive polymer deposited on the electrode surface is reacted very rapidly. On the contrary, electron transfer kinetics are not important for diluted solutions as the redox process will be affected only by the motion of the redox species. Most of redox polymers present an intermediate behavior between these two cases, which is called “finite diffusion.”<sup>3</sup>

The determination of the limiting process is usually carried out by cyclic voltammetry experiments at different scan rates. The scan rate determines how fast the applied potential is changed. Faster scan rates result in the decrease of the diffusion layer size, generating higher current responses. When the redox polymer is deposited on the electrode, a linear variation of the peak current with the scan rate shows that the process is not limited by diffusion. The current response is described by the following equation:

$$i_p = \frac{n^2 F^2}{4RT} \nu A \Gamma$$

where  $i_p$  is the peak current,  $n$  is the number of electrons,  $F$  is the Faraday constant,  $\nu$  is the scan rate,  $A$  is the electrode surface area,  $\Gamma$  is the amount of redox-active material deposited in the electrode surface,  $R$  is the gas constant and  $T$  is the temperature in Kelvin.

When the redox polymer is dissolved in the electrolyte and involves freely diffusing redox species, the Randles–Sevcik equation describes how the peak current increases linearly with the square root of the scan rate.

$$i_p = 0.446 n F A C \left( \frac{n F \nu D}{RT} \right)^{1/2}$$

where  $C$  is the bulk concentration of the redox-active species and  $D$  is the diffusion coefficient of the redox-active species.<sup>83</sup>

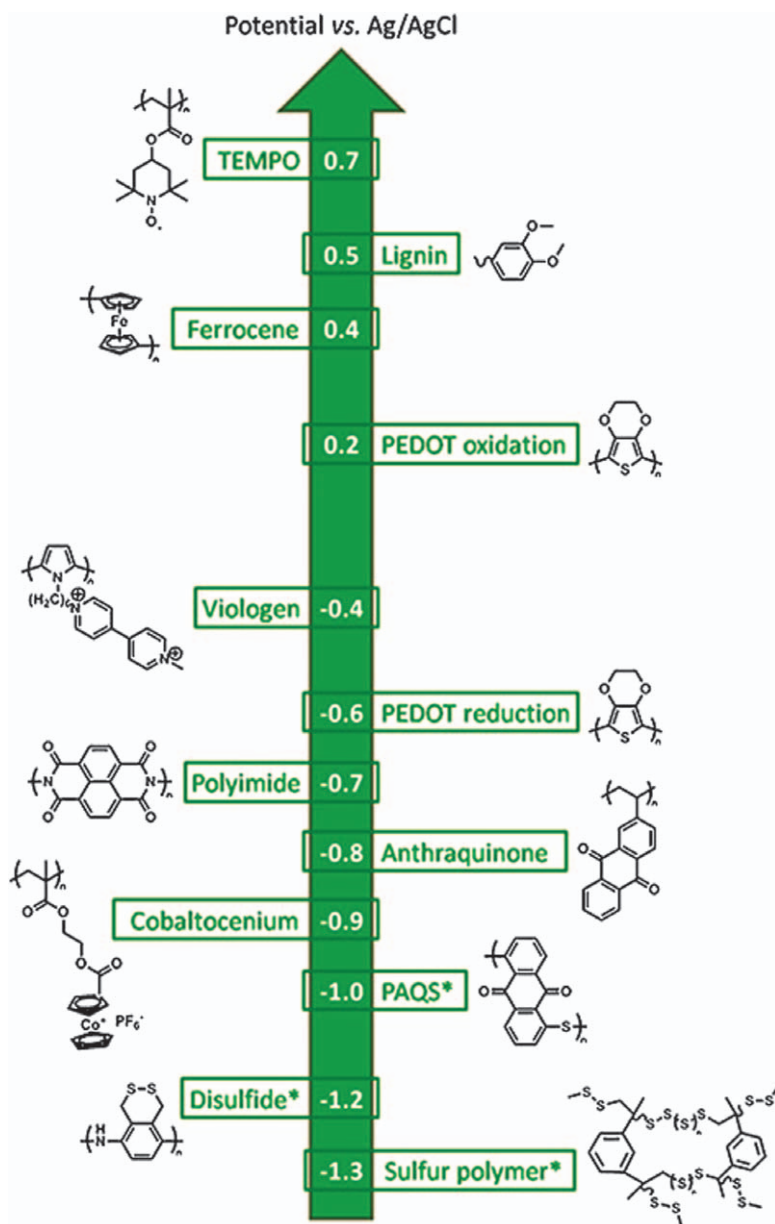
Moreover, the cyclic voltammetry can be used to obtain additional information. For example, if the relationship between the oxidation and reduction current peaks is equal to one, the process is reversible, meaning that all the oxidized species are reduced back. The charge related to the oxidation and reduction processes can be quantified by measuring the area under the curve and dividing it by the scan rate. Additionally, by dividing this charge by the mass of the redox-active species, the specific capacity of the polymer is obtained, while the capacitance is the relationship between the current and the scan rate.<sup>85</sup>

Cyclic voltammetry characterization can be done using a rotating disc electrode (RDE) hydrodynamic working electrode to analyze the mechanism and kinetics of the redox processes. When the RDE reaches a steady state, a constant laminar flow of the electrolyte solution is created at the electrode surface. In this way, the mass transport of the redox species is not a limiting factor and the kinetics of the redox reaction can be calculated. This technique has been employed for the determination of electrocatalytic behavior of redox polymers.<sup>86</sup>

In conclusion, cyclic voltammetry is a versatile and powerful electrochemical technique to analyze the redox potential of the electroactive polymers. This redox potential value is specific and crucial for each application of the redox polymers. Figure 1.5 shows the redox potential of most common electroactive moieties included in redox polymers, however, it is important to note that these values are dependent on the experimental conditions, such as the type of electrolyte, cell configuration or sample preparation. In energy storage applications like batteries, the redox potential of the polymer is important as it will determine its application, whether it is used as an anode or cathode material, together with the voltage of the device, which is given by the potential difference between the two electrodes. In supercapacitors, polymers with fast and wide redox processes are required to obtain high specific capacitances. On the other hand, for applications such as biosensors and biofuel cells, as the polymers are used as redox mediators, their redox potential should be similar to the enzyme or the reaction where they will be involved.

### 1.3.2 Electrochemical Impedance Spectroscopy (EIS)

Together with cyclic voltammetry, electrochemical impedance spectroscopy (EIS) is a powerful and complex technique to analyze the electrical characteristics of the polymer films. The electrochemical impedance is the response of a system (cell) to an applied potential. In this technique, the current is measured when a small-amplitude alternating current (AC) potential is applied to a cell in equilibrium. In order to have a pseudo-linear response, the excitation signal should be small ( $\sim 10$  mV). In this way, when the sinusoidal potential is applied, the current response at the same



**Figure 1.5** Redox potentials of common electroactive groups included in redox polymers. \*Potential values are taken from  $\text{Li/Li}^+$  reference electrode and changed to  $\text{Ag/AgCl}$  ( $\text{Li/Li}^+$  is  $-3.26$  V vs.  $\text{Ag/AgCl}$ ). Reproduced from ref. 3 with permission from Elsevier, Copyright 2016.

frequency is a phase-shifted sinusoid. The frequency dependence of this impedance can reveal complex chemical processes. EIS also provides information about the rate of charge transfer and transport processes.<sup>3</sup>

The response of the system is usually represented in Nyquist plots, where the imaginary impedance is plotted against the real impedance. The variation of the impedance with the frequency is characteristic of an electrical circuit. Therefore, an equivalent electrical circuit model, which describes the system, is generally used to interpret the obtained EIS data. Parameters such as the charge transfer resistance, Warburg diffusion coefficient or the capacitance can be obtained from the interpretation of the equivalent circuit. It is worth mentioning that each electrochemical system should be modeled with the best appropriate equivalent circuit. For example, a simple electrode reaction can be described by the Randle equivalent circuit, containing the solution resistance ( $R_s$ ), charge transfer resistance ( $R_{ct}$ ), Warburg impedance ( $Z_w$ ) and double-layer capacitance ( $C_{dl}$ ).<sup>87</sup> The main advantage of EIS is that both the diffusion coefficient and the redox capacitance can be obtained from the same experiment, while multiple experiments are required to analyze these two values with cyclic voltammetry.

Another electrochemical technique used in the characterization of redox polymers is the chronocoulometry. This involves the measurement of charge as a function of time when a potential step waveform is applied. Chronocoulometry is used to determine the electrode surface area, diffusion coefficients, adsorption of electroactive species, and the kinetics of electron transfer and mechanisms of chemical reactions.<sup>3</sup>

### 1.3.3 Coupling of Electrochemical Methods with Additional Characterization Techniques

The coupling of electrochemical techniques with other characterization methods, such as UV-Vis spectroscopy, is a very interesting approach to get a better understanding of the redox processes. These *in situ* analyses may also give information about the mechanism of the redox process. Next, the most widespread techniques that have been coupled with cyclic voltammetry will be explained.

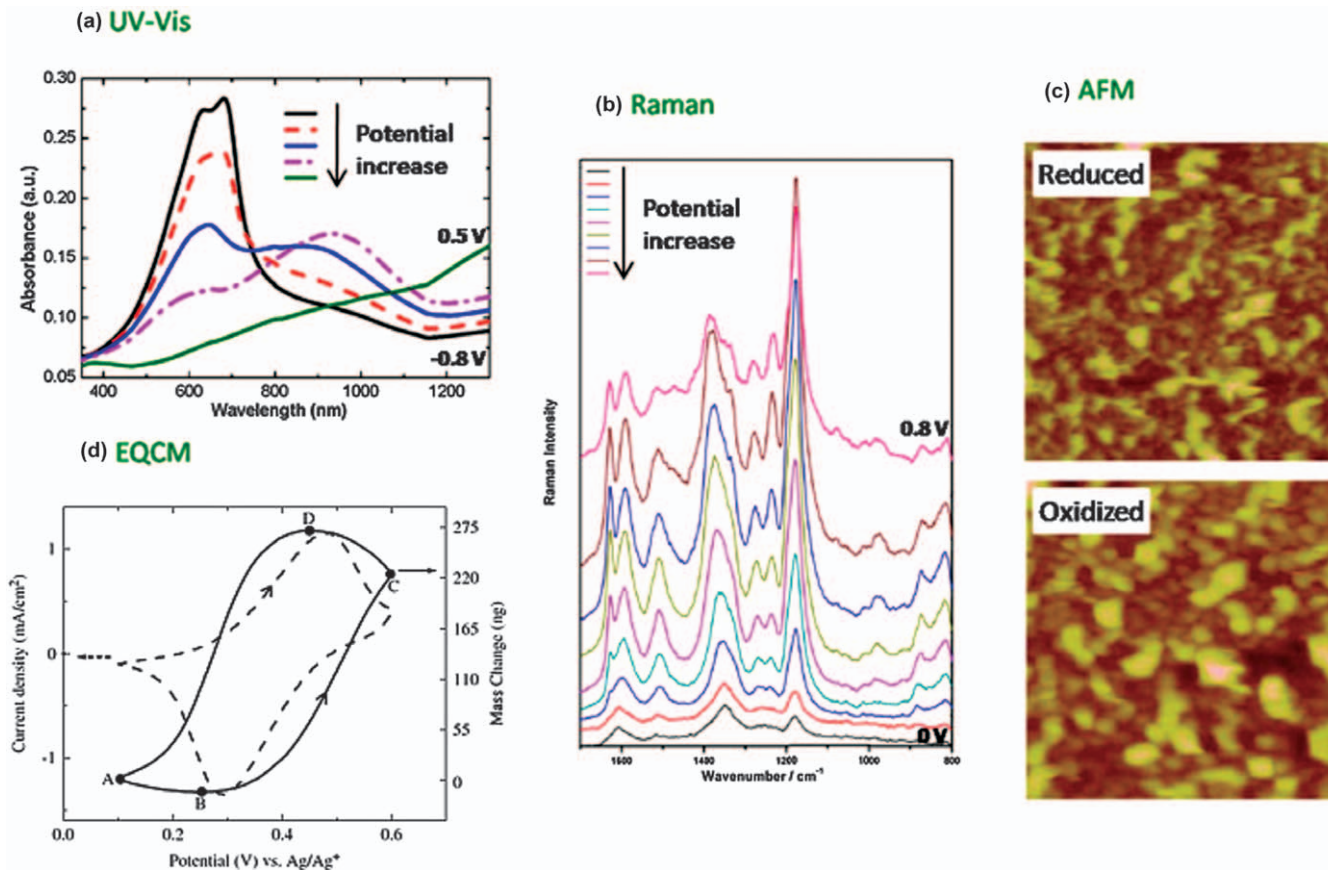
- Optical absorption characterization. UV-Vis-NIR spectroscopy provides information about absorption bands and the optical band gap of redox polymers. The coupling of this technique with electrochemistry is named spectroelectrochemistry.<sup>88,89</sup> It is also used to determine the stability of radical species,<sup>90</sup> polaron and bipolaron formation,<sup>91</sup> as well as color change during the redox reaction.<sup>92</sup> Therefore, spectroelectrochemistry is mostly used for the analysis of electrochromic materials and the development of photovoltaic and electrochromic devices. As an example, the UV-Vis-NIR spectrum of a PEDOT:PSS sample in Figure 1.6a at different potentials denotes the absorbance

changes, showing a polaron band at  $-0.2$  V vs. Ag/AgCl and increasing  $\pi-\pi^*$  transition band at higher potentials.

- Other spectroscopy techniques such as Raman and FTIR have also been coupled to electrochemistry to analyze the structural change in the polymer during the redox reaction. The appearance of new peaks, or the shifting or intensity changes in the peaks during the oxidation and reduction processes can provide information on the alteration in the bonding nature of the polymers (Figure 1.6b).<sup>89,93,94</sup>
- Surface characterization techniques can be also coupled with electrochemistry. Thus, surface morphology of redox polymers can be analyzed by scanning electron microscopy (SEM),<sup>95</sup> scanning tunneling microscopy (STM) or atomic force microscopy (AFM).<sup>96</sup> As an example, Figure 1.6c shows AFM images for PEDOT at reduced and oxidized states.
- Electrochemical quartz crystal microbalance (EQCM) is a powerful *in situ* technique to complement electrochemical experiments. It is able to detect mass changes in the deposited film during electrochemical experiments. Thus, it is used to analyze processes involving mass changes such as adsorption, electrodeposition, polymerization or doping.<sup>97</sup> For example, the *in situ* CV-EQCM spectrum of a poly(amine-imide) polymer is shown in Figure 1.6d. During its oxidation, the ions of the electrolyte are absorbed into the polymer film to compensate the ions formed and thus, increasing the total mass, while in the reduction the contrary process is observed, desorption of ions together with the decrease of the total mass.
- Electron spin resonance (ESR) spectroscopy is another interesting method to analyze the presence of polaron charge carriers, as they have spin, opposite to bipolaron charge carriers. This technique provides the concentration of polaronic species and charged species. Therefore, it is used to study the polymerization processes that occur *via* radical intermediates, the redox processes in radical polymers and doping levels in conducting polymers. For example, polyaniline and PEDOT conducting polymers have been intensely characterized by ESR spectroscopy.<sup>90</sup>

## 1.4 Applications of Redox Polymers

The growing interest in redox polymers is due to their versatility and wide range of applications. The most important fields where redox polymers have been employed are batteries and biosensors. However, the search for more sustainable and environmentally friendly materials in the last decade has increased the application of redox polymers in other energy devices such as supercapacitors, solar cells, biofuel cells or thermoelectric devices. Moreover, redox polymers are finding new opportunities in the development of medical systems such as actuators, drug-delivery systems, tissue engineering



**Figure 1.6** Examples of characterization techniques coupled with electrochemical methods. (a) UV-Vis spectrum of PEDOT:PSS film; (b) Raman spectrum of polyaniline oxidation; (c) AFM images of reduced and oxidized states of PEDOT; and (d) EQCM graph of a poly(amine-imide). Reproduced from ref. 3 with permission from Elsevier, Copyright 2016.



and bioelectronic devices. In the following sections, we will review the most important advances in the application of redox polymers in energy and medicine technologies.

### 1.4.1 Applications in Energy Conversion and Storage Devices

Energy has become one of the key issues of this century due to the growing population and the technological development. For this reason, the development of sustainable and green energy technologies has become of great importance in our society. New clean technologies which are able to create electricity from the natural abundant energy from the sun, waves or wind as well as to store that electricity are actively being searched. Redox polymers are playing an important role in the development of some of these technologies as will be highlighted in this section.

The most popular use of redox polymers nowadays is in electrochemical energy storage devices such as batteries, supercapacitors or flow cells. This will be extensively discussed in several chapters throughout this book, and due to its importance, we will dedicate a special subsection to this next. However, there are other technologies which are still in their infancy that are expected to have rapid development in the coming years. This is the case of the biofuel cells, where naturally occurring sugars are converted into electricity through an enzymatic process similar to the electrochemical biosensors using a redox polymer as the key ingredient.<sup>87</sup>

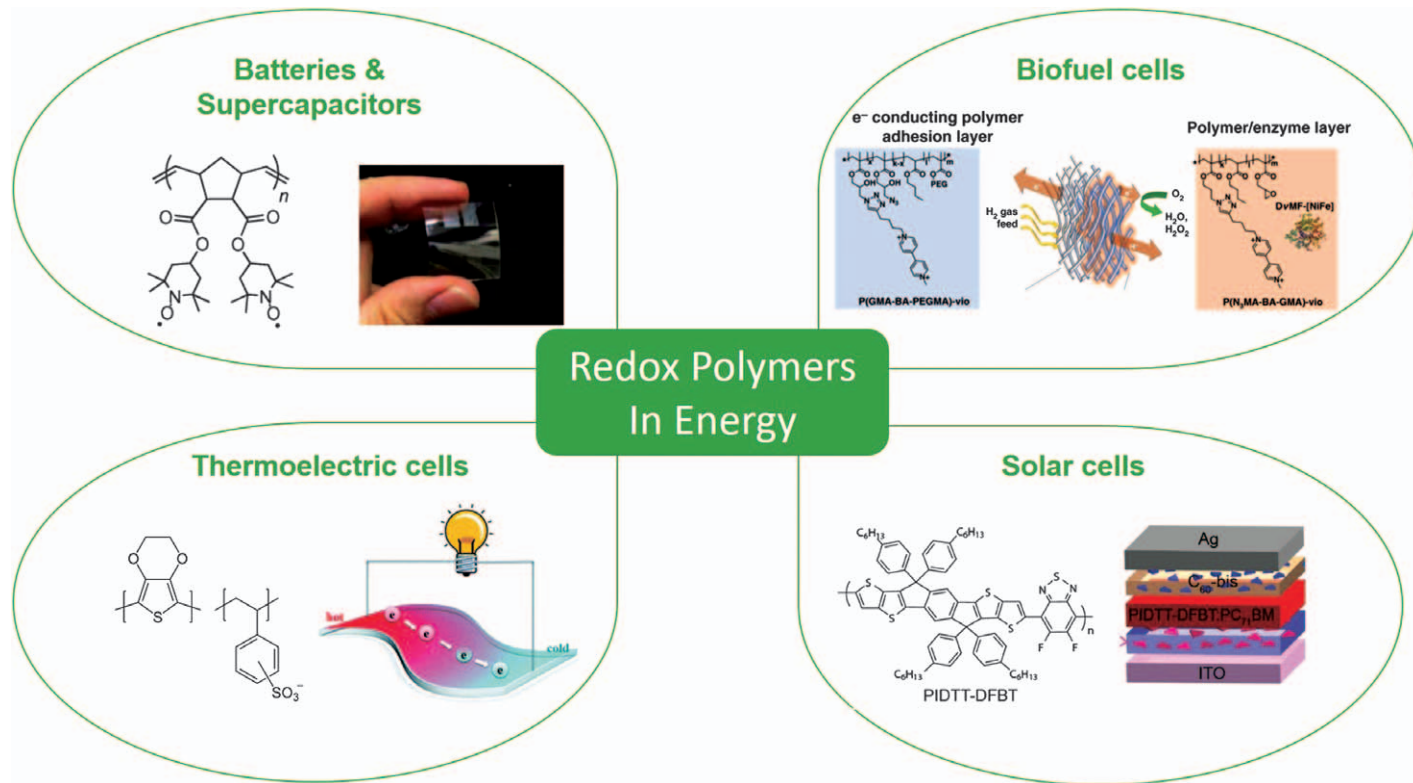
Two important types of devices that make use of similar redox polymers are thermoelectric cells and solar cells.<sup>98,99</sup> However, those devices that convert heat or light into electricity, respectively, are not discussed in this book. The reason behind this is that the polymers used in these cases, although they present redox type activity, are mostly known as (semi)-conducting, semiconjugated or optoelectronic polymers (Figure 1.7).

#### 1.4.1.1 Batteries and Supercapacitors

Redox polymers are actively being investigated in several electrochemical energy storage or battery technologies. Back in the 1980s there was a great deal of hype about the use of conducting polymers in batteries. However, the expectations did not become reality due to the stability issues of the batteries and supercapacitors based on most conducting polymers at that time. Nowadays there is renewed interest in the use of redox polymers in several emerging battery technologies, such as flexible thin batteries, fast-charging batteries, organic batteries, metal-air, redox-flow batteries or aqueous batteries. In these technologies, redox polymers can play a different role, for example, as active materials in the cathode or anode, as a redox-active binder or mediator, or as soluble catholyte or anolyte in aqueous redox flow batteries.

Through the chapters of this book, the authors will discuss the challenges and characteristics of the most important redox polymers in battery





**Figure 1.7** Examples of main applications of redox polymers in the energy field. (a) Batteries and supercapacitors. Adapted from ref. 22 with permission from the Royal Society of Chemistry. (b) Biofuel cells. Adapted from ref. 100 <https://doi.org/10.1038/s41467-018-07137-6>, under the terms of the CC BY 4.0 licence, <http://creativecommons.org/licenses/by/4.0/>. (c) Thermoelectric cells. Adapted from ref. 98 with permission from the Royal Society of Chemistry. (d) Solar cells. Adapted from ref. 99 with permission from John Wiley and Sons, © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.



technologies. In other words, how the different polymers families such as radical polymers, phenothiazine-type polymers, carbonyl polymers or catechol polymers are used in emerging battery technologies.<sup>44,101–104</sup> Chapter 8 is devoted to discussing the new battery configurations led by the use of redox polymers (Figure 1.8).

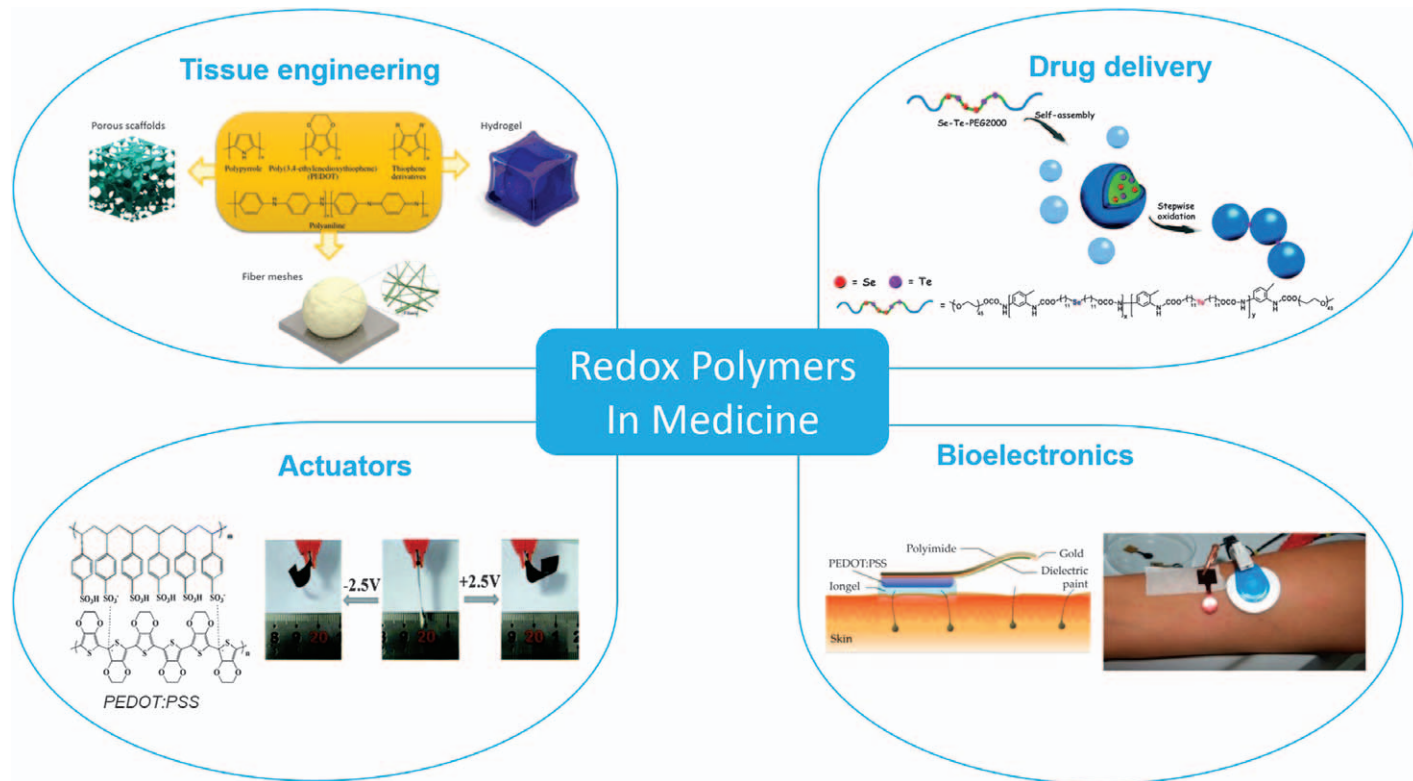
### 1.4.2 Applications in Medicine

Although energy is the most popular field of use of redox polymers, medicine is expected to be the most important one in the coming decades. Historically, the most important application of redox polymers has been in the area of electrochemical biosensors such as glucose or other types of bioactive compounds. However, as will be discussed in this book, there is a high demand for new materials such as redox polymers in emerging healthcare technologies which are specially important nowadays.

For instance, in tissue engineering redox polymers are very popular in the development of conducting scaffolds for the growth or sensing of tissues based on electrically sensitive cells such as neurons or cardiomyocytes.<sup>105</sup> In Chapter 10, the use of redox-sensitive polymers presenting mostly disulfide cleavable bonds in drug delivery will be discussed. These new redox-sensitive drug-delivery vectors are becoming very important nowadays due to their sensitiveness to reactive oxygen species (ROS). ROS are key intermediates in a number of biological mechanisms and their role and high concentration in different diseases are important factors. In Chapter 13, it will be discussed how through the use of redox polymers electric signals can be transformed in movement through devices such as electromechanical actuators.<sup>106</sup> Those devices are part of the global development of bioinspired devices known as artificial muscles of importance in a number of new technologies in the robotics or microelectronics areas. Last but not least, the use of redox polymers such as PEDOT in different bioelectronic devices such as biosensors or electrodes to interface with the biological signals will be discussed (Figure 1.9).

## 1.5 Conclusions

Through this chapter, the field of redox polymers and the topics that will be more deeply discussed in the different chapters of this book are introduced. First, the different types of redox polymers and their classification are presented based on the chemical nature and how the redox-active site is distributed within the polymer. Next, the main characterization methods used for assessing the properties of redox polymers are introduced. Finally, the main applications of redox polymers in energy and medicine are indicated as they will be discussed in depth through the different chapters of the book.



**Figure 1.9** Examples of the main applications of redox polymers in medicine and discussed in the chapters of this book. (a) Tissue engineering. Reproduced from ref. 105 with permission from the American Chemical Society, Copyright 2019. (b) Drug delivery. Reproduced from ref. 107 with permission from the Royal Society of Chemistry. (c) Actuators. Adapted from ref. 108 with permission from the Royal Society of Chemistry. (d) Bioelectronics. Adapted from ref. 109, <https://doi.org/10.3390/polym10090989>, under the terms of the CC BY 4.0 licence, <https://creativecommons.org/licenses/by/4.0/>.

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## CHAPTER 2

# *Synthetic Strategies and Methods for Redox Polymers*

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## 2.1 Introduction

One-electron oxidation and reduction reactions of organic compounds with closed-shell electron configuration generate highly reactive cation and anion radicals, respectively.<sup>1</sup> Such reactions on stable organic radicals also produce reactive cations or anions.<sup>2</sup> These redox reactions are very common in many chemically driven life processes, and can also be used to create new synthetic molecules and materials. Many different types of organic groups that can undergo reversible redox reactions have been classified into organic redox systems. Tuning the redox properties of organic compounds provides an opportunity to develop new organic materials designed for various applications, including transistors,<sup>3</sup> organic magnetics,<sup>4</sup> organic catalysts,<sup>5–7</sup> energy conversion,<sup>8–10</sup> energy storage,<sup>11–13</sup> biomedicine,<sup>14,15</sup> and many others.<sup>16</sup> This chapter aims to summarize a few of the most studied redox-active groups, the strategies and methodologies to synthesize and incorporate

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these chemical groups into polymers, and thus provide a comprehensive overview on application-directed design and synthesis of redox polymers. Their applications in biomedicine and energy storage will be discussed in the later chapters.

## 2.2 Design, Synthesis and Characterization of Redox Polymers

So far, organic redox-active groups mainly include open-shell organic radicals, closed-shell neutral or ionic compounds, and organometallics.<sup>1</sup> The very different (electro)chemical reactivities and redox behaviours dictate which synthetic method should be used in the synthesis of their polymer counterparts.<sup>12</sup> For instance, free-radical polymerization (FRP) techniques cannot be used to polymerize monomers consisting of persistent organic radicals due to their rapid radical termination reactions with other free-radicals. Different synthetic strategies are often required to design redox polymers with distinct chemical compositions and architectures to meet demands for diverse applications. The chemical structures and physical properties of redox polymers can be characterized by conventional polymer characterization techniques, including size exclusion chromatography (SEC), matrix-assisted laser desorption ionization–time of flight (MALDI-ToF) mass spectrometry, nuclear magnetic resonance (NMR), differential scanning calorimetry (DSC), and many more. Some redox groups and their further intermediates are radicals, which require further identification and quantification using electron spin resonance (ESR).

Redox polymers are functional polymers consisting of redox-active functionalities. Like many other functional polymers, redox polymers are mainly synthesized through the three following approaches: (i) direct polymerization of monomers consisting of redox-active groups; (ii) post-polymerization conversion of polymer precursors to redox polymers; and (iii) post-modification of reactive polymers with functional redox molecules.<sup>17</sup>

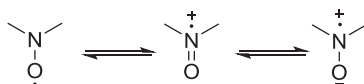
Techniques for direct polymerization of redox-active monomers include radical polymerization, ionic polymerization, step or condensation polymerization and metathesis polymerization, *etc.*<sup>18</sup> This direct monomer approach is versatile and straightforward, particularly for the synthesis of redox polymers with controlled molecular weight and architecture; this can be accomplished using living radical polymerization (LRP). When monomers are not compatible with these polymerization conditions, post-polymerization conversion or post-modification can be used. These latter approaches avoid the side reactions from the redox groups during polymerization, but still provide control over the chemical composition and architecture. Among the different polymerization techniques, LRP such as reversible addition–fragmentation chain transfer (RAFT) polymerization,<sup>19</sup> atom transfer radical polymerization (ATRP)<sup>20</sup> and single-electron transfer living radical polymerization (SET-LRP)<sup>21</sup> can control both the molecular

weight and polymer structure, affording polymers with diverse chemical compositions, physical properties, and the ability to be self-assembled into nanostructures and organic–inorganic hybrid materials with redox properties. Owing to their specific chemical properties, the content of this chapter is thus organized according to the type of redox groups. It should be noted that most of the synthetic work on redox polymers summarized in this chapter is for nonconjugated polymers. The synthesis of conjugated polymers consisting of redox groups is only briefly mentioned and reviewed more comprehensively elsewhere.<sup>11,22</sup> In addition, synthetic methods for some redox groups that have been well documented previously will be introduced here but will not be comprehensively covered.

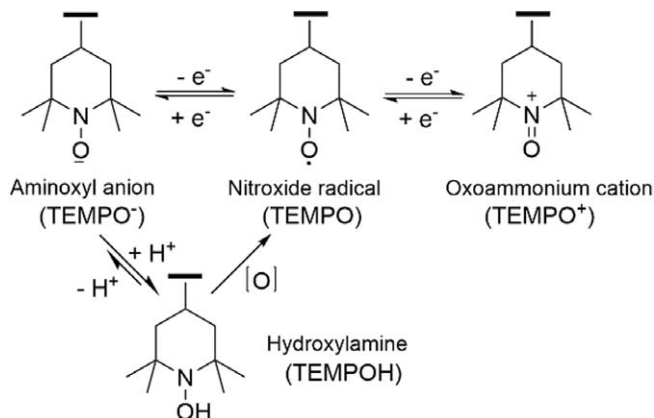
### 2.2.1 Redox Reaction of Nitroxide Radicals

Nitroxide radicals, first isolated in Russian in 1959,<sup>23</sup> are a class of stable radicals with an open-shell electron configuration. This type of radical possesses extremely high stability in oxygen and under heat. Also, the nitroxide radical is different from carbon-centred radicals as the nitroxide radical stability stems from the resonance delocalization of the unpaired electron across the N–O bond, as shown in Scheme 2.1.

In addition, the absence of an  $\alpha$ -H is also critical to prevent disproportionation and degradation of the nitroxide. A typical example of a nitroxide radical is 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). Theoretically, TEMPO and most of its derivatives or analogues can undergo an oxidation reaction to oxoammonium cations (TEMPO<sup>+</sup>) and a reduction reaction to aminoxy anions (TEMPO<sup>−</sup>). These redox reactions can, in principle, be carried out under chemical or electrochemical conditions, forming a reversible two-electron redox process. However, in many cases, the aminoxy anion can be rapidly protonated at the ambient condition to form a more stable hydroxylamine (*i.e.*, TEMPOH). TEMPOH is difficult to be electrochemically oxidized back to the TEMPO radical, but easily oxidized in the presence of weak oxidants such as oxygen or metal oxides (Scheme 2.2). The properties and applications of nitroxide radicals are determined by their single-electron spin and reversible redox properties. Since their discovery, a tremendous number of nitroxide radical derivatives have been reported, as summarized by Rozantsev.<sup>23</sup> The redox potential of nitroxide radicals is dictated by their inherent chemical structure, which has been well understood both theoretically and experimentally.<sup>24,25</sup> Recently, Jia and Coote<sup>26</sup> reported that both functional groups and heteroatom substitution on TEMPO have a great impact on the oxidation potentials, which range from 0.6 to 1.0 V *vs.* SHE (*i.e.*, standard hydrogen electrode).



**Scheme 2.1** Resonance structures of nitroxide radicals.



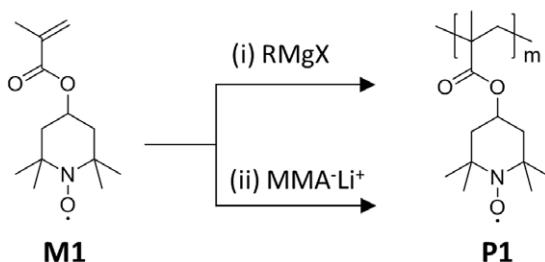
**Scheme 2.2** Proton-coupled two-electron redox reaction of TEMPO radical.

### 2.2.2 Redox Polymers Consisting of Nitroxide Radicals

Due to the potential widespread applications of nitroxide radical polymers (NRPs), they have been one of the most studied classes of redox polymers.<sup>27</sup> So far, most polymerization methods can be applied to produce NRPs, yielding abundant chemical compositions and physical architectures. Previous reviews have summarized the synthetic progress and applications for NRPs.<sup>17,28</sup> Therefore, we will provide a concise summary of the synthetic strategies and some recent progress.

In 1967, Griffith<sup>29</sup> first reported an anionic polymerization of TEMPO methacrylate M1 by using a Grignard reagent as initiator. Originally, the polymerization only produced oligomers, but later, Komaba<sup>30</sup> found this condition also led to gelation. Sukegawa<sup>31</sup> proposed that the carbanions in such aggressive organometallic initiators may attack the nitroxide radicals, resulting in cross-linking. To avoid this side reaction, the initiator was first capped with methyl methacrylate (MMA) and converted to a less reactive carbanion (MMA<sup>-</sup>Li<sup>+</sup>), which then allowed for the controlled polymerization of M1, producing the well-defined P1 with a number average molecular weight ( $M_n$ ) up to 20 kDa and with a low dispersity ( $D < 1.10$ ) (see Scheme 2.3).

TEMPO and other nitroxide radicals have been converted to monomers with epoxide functionality, which can then be polymerized through an anionic ring-opening polymerization (AROP) by using an organic base. Compared to a carbanion, the alkoxide is a much weaker base and is therefore often used as an initiator in the synthesis of polyethers. 4-Glycidyl-TEMPO (GTEMPO) M2 was one of the most studied monomers due to its ease of both synthesis and purification.<sup>32,33</sup> Several different initiators have been used to initiate the polymerization of M2 to give a polyether-based NRP (see Scheme 2.4).<sup>34</sup> Attempts using AROP of GTEMPO initiated by diethyl zinc/water (Et<sub>2</sub>Zn/H<sub>2</sub>O) resulted in polymers with high dispersity ( $D \sim 1.7$ – $2.1$ ),

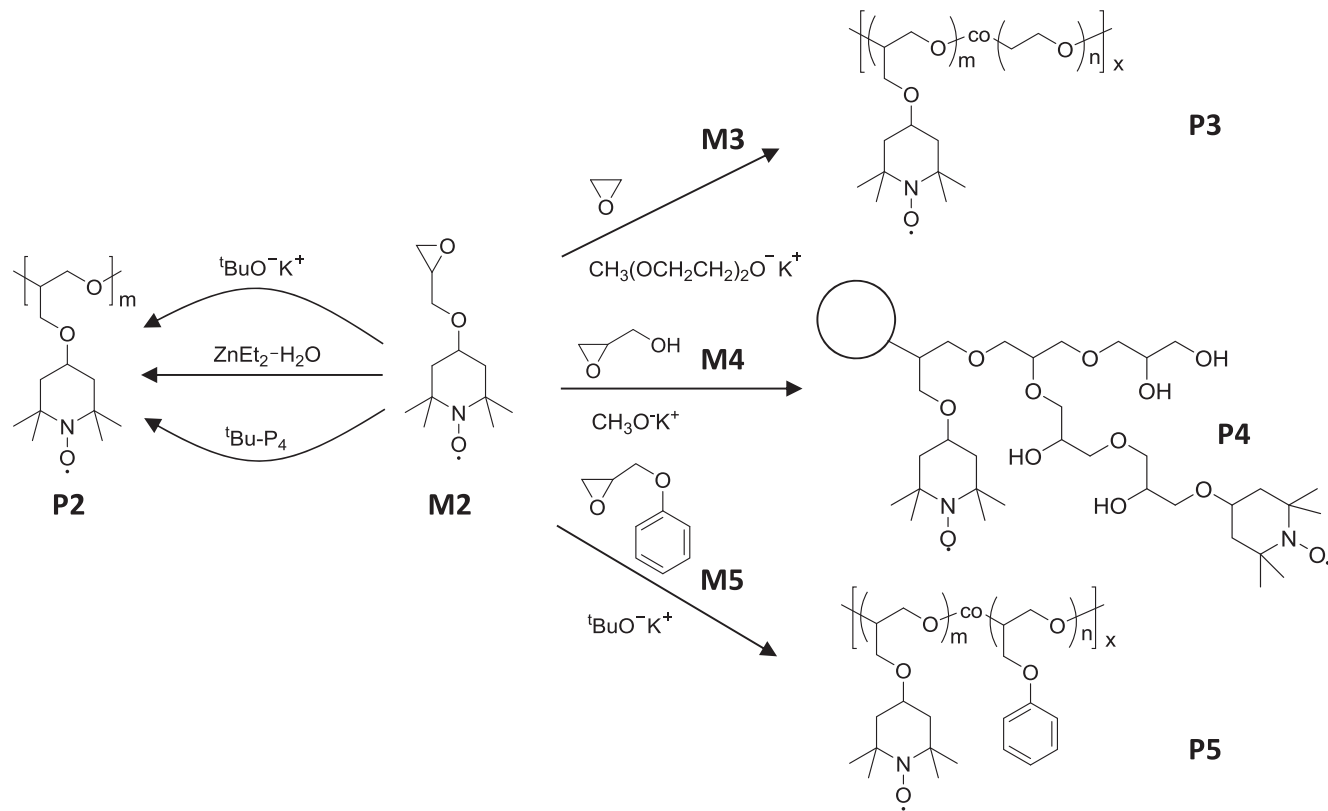


**Scheme 2.3** Synthesis of poly(TEMPO methacrylate) by anionic polymerization. Adapted from ref. 17 with permission from the Royal Society of Chemistry.

and in particular, it was found that there was a decrease in the radical number per repeating unit (*i.e.*, 0.62 spins/unit). Using a solid alkoxide, such as <sup>t</sup>BuOK as the initiator, the resulting polymers showed broad dispersity ( $\bar{D} \sim 1.3\text{--}1.7$ ) due to the heterogeneous initiation, but with nearly quantitative retention of radicals.<sup>35,36</sup> Recently, Nishide and Oyaizu<sup>37</sup> reported the AROP of M2 initiated by using a strong organic base (*i.e.*, <sup>t</sup>Bu-P<sub>4</sub>, a phosphazene) together with alcohol. This system successfully produced a polymer from M2 at room temperature with high retention of the radical groups, critical for applications. Huang<sup>32,33</sup> reported the anionic copolymerization of M2 with ethylene oxide M3 in THF, producing the copolymer P3 with a  $\bar{D}$  of 1.10. Similarly, Wang<sup>38</sup> synthesized hyperbranched nitroxide radical copolymers, P4, by using glycidol M4 as a comonomer. Endo<sup>36</sup> used <sup>t</sup>BuOK as an initiator for the copolymerization of M2 with M5, resulting in the copolymer P5. From this body of work, the density of nitroxide radicals in NRPs can be controlled by varying the molar ratio of M2 to the comonomers as found by electron paramagnetic resonance (EPR). Precise control over the radical density dictated whether they could be used as a macroinitiator to make highly dense bottlebrush polymers or directly applied in biomedicine and energy applications in which an appropriate nitroxide density gave better *in vivo* imaging and greater energy storage.<sup>32,33,39–41</sup>

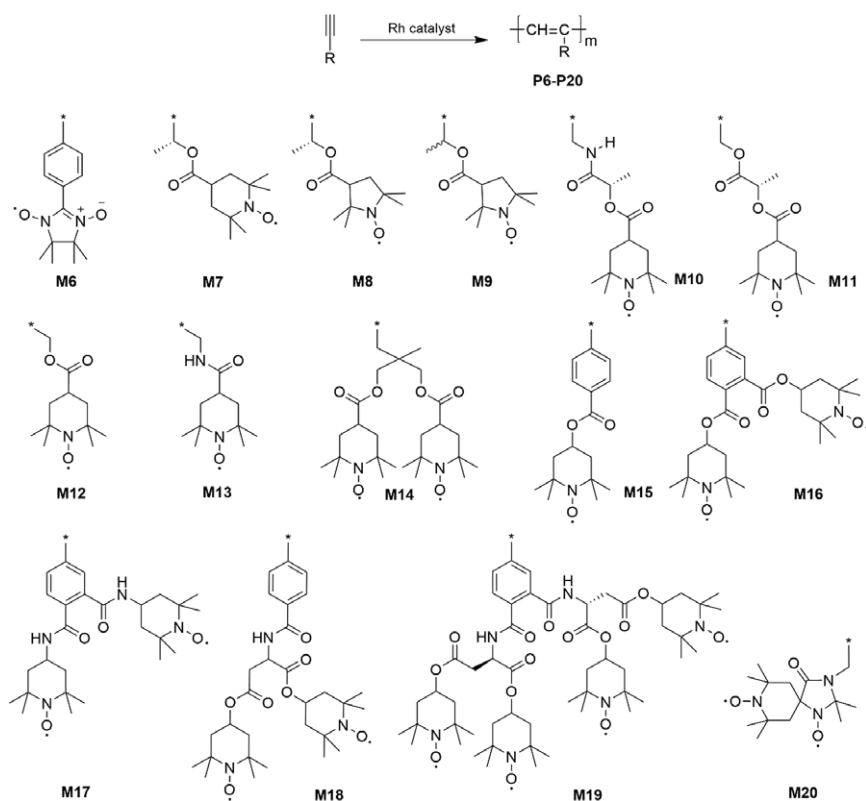
In addition, AROP of other nitroxide radicals such as 2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-oxy and 2,2,5,5-tetramethylpyrrolidin-1-oxy (PROXYL) with oxirane or oxetane were unsuccessful. Even the less studied cationic polymerization of these and other nitroxide radical monomers was also not successful since the nitroxide radicals were prone to degradation by the Lewis acid or tin catalyst complexes.<sup>36</sup> In an example, Nakahara<sup>42</sup> carried out a cationic polymerization of 4-vinyloxyl-TEMPO with BF<sub>3</sub>·Et<sub>2</sub>O as catalyst in DCM at  $-25\text{ }^{\circ}\text{C}$ . The polymerization yielded a TEMPO-containing poly(vinyl ether) gel, indicating an unavoidable side reaction with the nitroxide radicals.

Olefin metathesis polymerization using transition metals, especially rhodium (Rh) complexes, as a catalyst has been widely explored for the polymerization of radical-containing olefins such as alkene and acetylene.<sup>43,44</sup>



**Scheme 2.4** Anionic ring-opening (co)polymerization of GTEMPO to produce TEMPO-containing polyether. Reproduced from ref. 17 with permission from the Royal Society of Chemistry.

Fujii *et al.*<sup>45</sup> reported the synthesis of poly(phenylacetylene) consisting of nitronyl nitroxide radicals through an olefin polymerization of M6 with the rhodium catalyst, Rh(cod)(NH<sub>3</sub>)Cl (see Scheme 2.5). Nishide<sup>46</sup> used polymer P6 in applications such as organic magnetic materials and an electrochemical active component in the electrode. Based on the successful synthesis of such conjugated polymers, Masuda and co-workers<sup>47–49</sup> studied chiral effects on the electrochemical properties of NRPs through a series of acetylene functional nitroxide radical monomers (M7–M11) with different chiral centres. The polymerization was carried out at 30 °C using Rh catalysts (nbd)Rh<sup>+</sup>[η<sup>6</sup>-C<sub>6</sub>H<sub>5</sub>B-(C<sub>6</sub>H<sub>5</sub>)<sub>3</sub>] or [(nbd)RhCl]<sub>2</sub>-Et<sub>3</sub>N, resulting in polymers P7–P11 with *M<sub>n</sub>* greater than 10 KDa but high dispersity (*i.e.*, *D* ~ 1.5–11.5). To determine the effect of bulky or steric effects from the nitroxide radical on the electrochemical properties, they prepared a library of NRPs (P12–P19) with a polyacetylene backbone but with different densities of nitroxide side groups (M12–M19). Among these polymers (P10, P11 and P19), the side groups with chiral centres formed a helical conformation and enhanced the



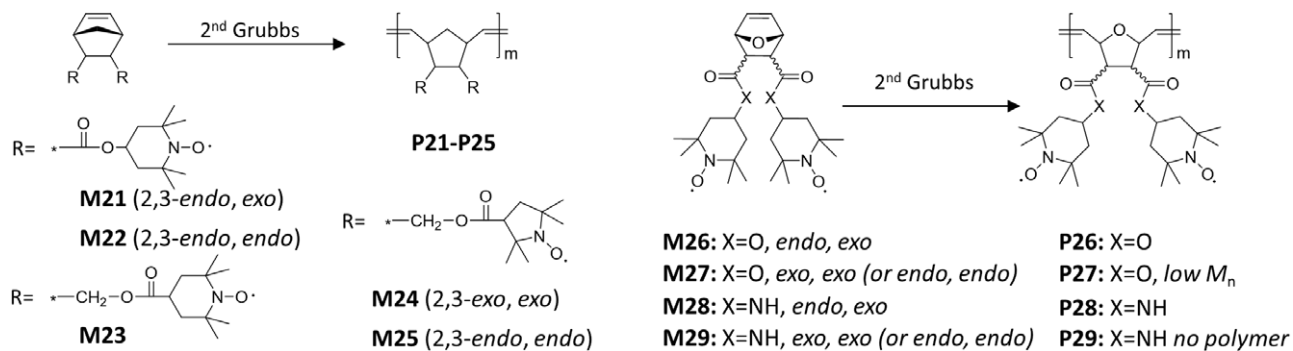
**Scheme 2.5** Olefin metathesis polymerization of acetylene functional nitroxide radical monomers to produce nitroxide-containing polyacetylenes. Reproduced from ref. 17 with permission from the Royal Society of Chemistry.



electrochemical properties.<sup>49</sup> For other NRPs, having multiple-radical side groups did not necessarily increase the electrochemical performance of polymers, and the underlying mechanism requires more research. Nesvadba<sup>50</sup> sought to increase the electrochemical performance through the polymerization of an acetylene functionalized spirobisnitroxide monomer, M20. Although the polymerization gave a polymer with an  $M_n$  up to 42 kDa, the anticipated unique architecture of the spironitroxide radical to provide a high energy density and voltage due to their double radicals and constrained ring structure did not eventuate. In fact, P20 formed a cross-linked gel upon polymerization and showed poor electrochemical redox stability, with side reactions stemming from the oxidation of the backbone, whereas bulky side groups prevent free rotation of the nitroxide radicals and inhibit the electron transfer efficiency.

Ring-opening metathesis polymerization (ROMP) is the most used metathesis polymerization technique specifically suitable for cyclic alkene monomers. Using the Grubbs catalyst, control over the molecular weights and structures of norbornene polymers could be obtained, demonstrating its living polymerization behavior.<sup>44</sup> Masuda<sup>47,51,52</sup> pioneered the synthesis of a series of TEMPO-containing norbornene or oxanorbornene monomers M21–M29, and their corresponding polymers using the 2nd-generation Grubbs catalyst (see Scheme 2.6). Compared to the metathesis polymerization of acetylene-based monomers as discussed before, ROMP usually had much shorter polymerization times even under mild conditions (*e.g.* completed in 45 min in  $\text{CH}_2\text{Cl}_2$ , at 30 °C). However, the polymers reported by Masuda had high dispersity ( $D > 3.5$ ) and in many cases formed gels with no explanation for their observation.<sup>47,51</sup> It was noted that these NRPs were thermally stable at temperatures up to 220 °C due to the stable polynorbornene backbone, a distinct advantage for high-temperature applications over other polymer types. In addition, the radical–radical distance obtained by X-ray crystallographic data showed that the endo/endo (P22) or exo/exo (P23) orientation was 10 Å, a value smaller than endo/exo (P21)-orientation. Although these isomers possess the same radical density, P21 demonstrated a much higher charge/discharge capacity than P22 and P23, suggesting the importance of the spatial configuration of TEMPO moieties.<sup>51</sup>

Nishide<sup>53</sup> subsequently synthesized a densely grafted NRP brush through a combination of AROP and ROMP. A nitroxide radical macromonomer with a norbornene chain-end was prepared *via* AROP and further polymerized using 2nd- or 3rd-generation Grubbs catalyst, producing P1 bottlebrushes with molecular weights from 32 to 230 kDa and the lowest dispersity of 1.17. Atomic force microscopy (AFM) characterization revealed the size of the rod-like polymer brushes was 5–6 nm in width and 30–40 nm in length. This was consistent with the theoretical size of fully stretched bottlebrush polymers. A thin-film electrode fabricated of the P1 bottlebrush demonstrated quantitative redox of all TEMPO radicals, indicating excellent electron hopping between the interchain radicals on the polymer side chains as supported by molecular dynamic simulation.<sup>54</sup> Johnson<sup>55</sup> further reported the synthesis of



**Scheme 2.6** ROMP of norbornene and oxonorbornene functional nitroxides to produce nitroxide-containing polymers. Reproduced from ref. 17 with permission from the Royal Society of Chemistry.

norbornene-based macromonomer consisting of nitroxide radical and poly(ethylene glycol) (PEG) (M30) after copolymerization, resulting in a PEG bottlebrush (P30) with both nitroxide radicals and fluorescent probes (see Scheme 2.7). This polymer was then used as a redox-responsive dual-imaging agent.

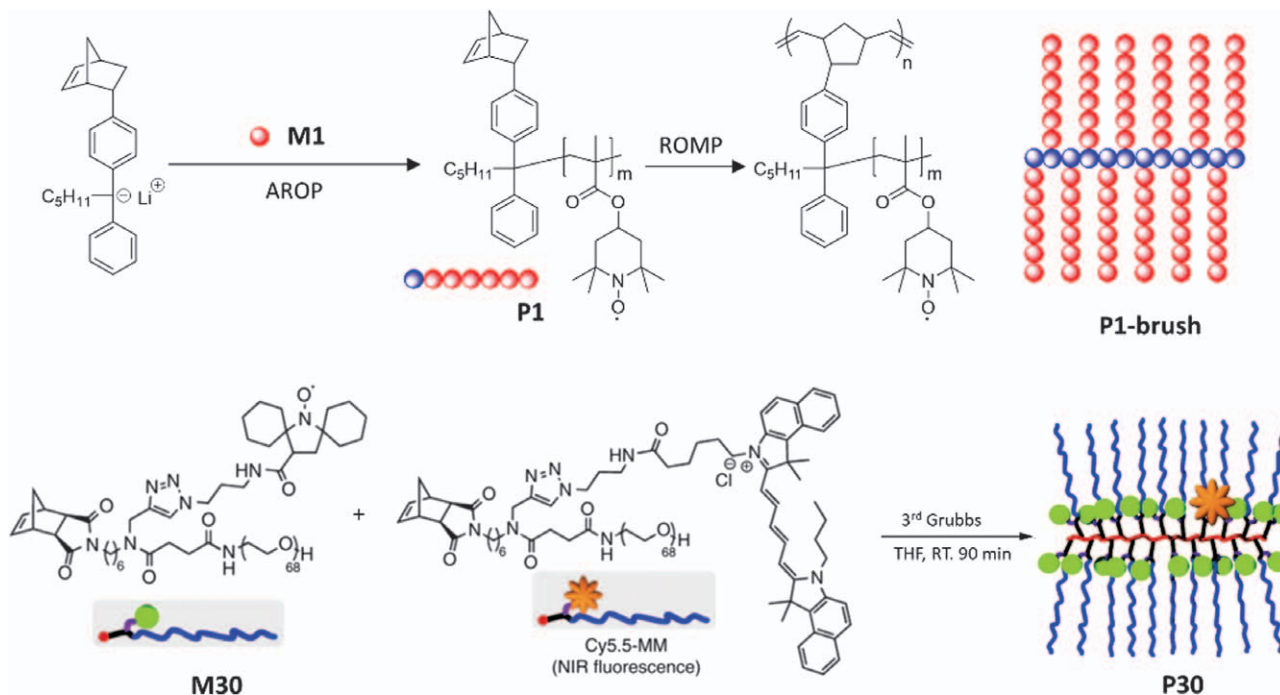
Recently, Delaittre<sup>56</sup> reported a ROMP-induced self-assembly (ROMPISA) technique to synthesize NRP nanoparticles with a core-shell structure. By changing the solvent from THF in the first step to the EtOH/THF mixture in the second, a linear poly(norbornene) block P31 self-assembled into core-shell nanostructures. Such NRP self-assembled nanoparticles could oxidize alcohols when used as a polymer-supported catalyst and with excellent recycling capability (see Scheme 2.8).

During the last decade, the Grubbs 3rd-generation catalyst has been used for the cyclopolymerization of 1,6-heptydiyne and its derivatives.<sup>57</sup> Utilizing this key feature, Jia<sup>58</sup> recently designed a 1,6-heptadiyne functional TEMPO M32 and successfully converted it to a conjugated NRP, P32 (see Scheme 2.9). The polymerization reached a near quantitative monomer conversion within a few minutes at  $-15^{\circ}\text{C}$ . The resultant polymer P32 had an  $M_n$  up to 27 kDa and a dispersity of 1.13. This is a new method to prepare conjugated NRPs. P32 showed great film-formation properties, potentially useful for film-based energy storage devices.

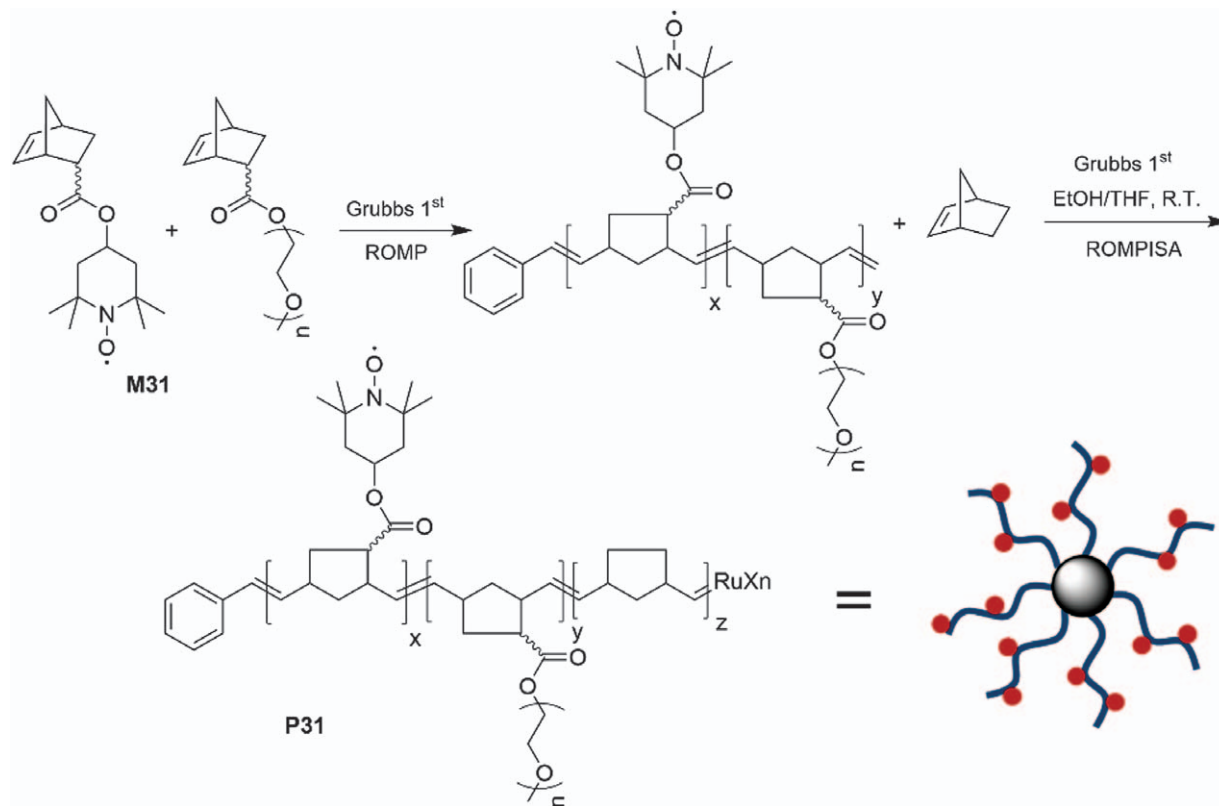
Turning our attention to the formation of NRP film, Nishide<sup>59</sup> reported the first NRP network with a polyester backbone using stepwise Michael polyaddition. An acetylacetone-functionalized TEMPO M33 was reacted with a multiacrylate cross-linker using 1,8-diazabicyclo undec-7-ene (DBU) as a catalyst, producing a cross-linked poly( $\beta$ -ketoester) film P33 (see Scheme 2.10). This work provided a straightforward strategy to prepare thin-film electrodes *in situ* with good mechanical properties and thermal stability.

Seeking a well-defined NRP polyester, Barner-Kowollik and Fairfull-Smith<sup>60</sup> recently reported the preparation and ring-opening polymerization of a nitroxide containing carbonate M34. Using DBU and thiourea as the catalyst system, they found that radicals have no influence on the ring-opening copolymerization with D/L-lactide in a wide range of compositions between 10% and 80% of M34. This work demonstrates the synthesis of biocompatible and biodegradable NRPs, which is of great interest in biological applications (see Scheme 2.11).

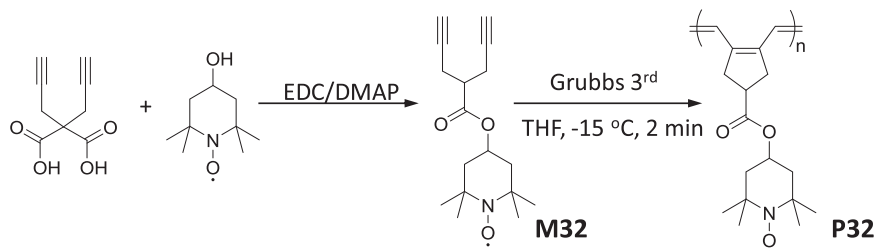
Some other methods, such as an oxidation polymerization, have also been applied for the synthesis of NRPs. The most common monomer is thiophene, to which nitroxide radicals couple through different linkages. TEMPO functional thiophene M35 was synthesized *via* esterification or etherification. Chemical oxidation of this type of monomers by  $\text{FeCl}_3$  formed polymers along with some side reactions.<sup>61</sup> Lutkenhaus<sup>62–64</sup> reported the electrochemical oxidation polymerization and directly coated the corresponding NRPs on the electrode surface for further electrochemical studies (see Scheme 2.12).



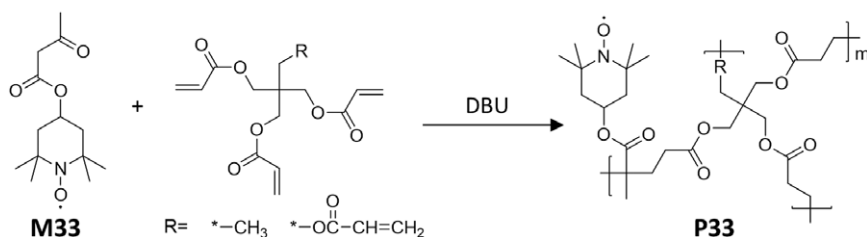
**Scheme 2.7** ROMP of norbornene-functional macromonomers to produce nitroxide-containing bottlebrush polymers. Reproduced from ref. 17 with permission from the Royal Society of Chemistry, from ref. 53 with permission from the American Chemical Society, Copyright 2014, and from ref. 55 with permission from Springer Nature, Copyright 2014.



**Scheme 2.8** ROMPIISA technique for the preparation of NRP nanoparticles.  
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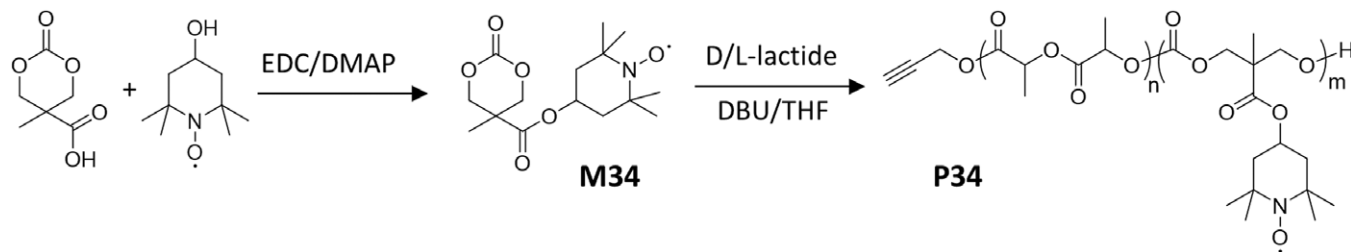
**Scheme 2.9** Ring-closure olefin metathesis polymerization of 1,6-heptadiyne functional TEMPO to produce TEMPO-containing conjugated polyacetylene. Adapted from ref. 58 with permission from the American Chemical Society, Copyright 2019.



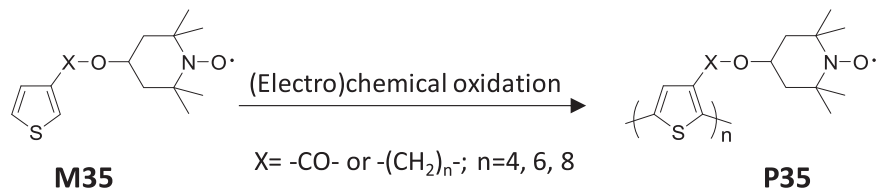
**Scheme 2.10** Michael polyaddition polymerization to synthesize a NRP network with polyester backbone. Reproduced from ref. 59 with permission from the Royal Society of Chemistry.

Inspired by the adhesive mussel and taking advantage of the auto-oxidation polymerization of dopamine, Barner-Kowollik and Fairfull-Smith<sup>65</sup> recently designed a dopamine functional TEMPO derivative M36. In a basic buffer solution, the dopamine moiety in M36 polymerized to a polydopamine (P36) film coating on the substrate. The hydroxylamine salt was converted to nitroxide radicals through aerobic oxidation under basic condition (see Scheme 2.13). This polydopamine-coated surface with nitroxide radicals has potential antibacterial applications and in preventing initial biofilm formation.<sup>66</sup>

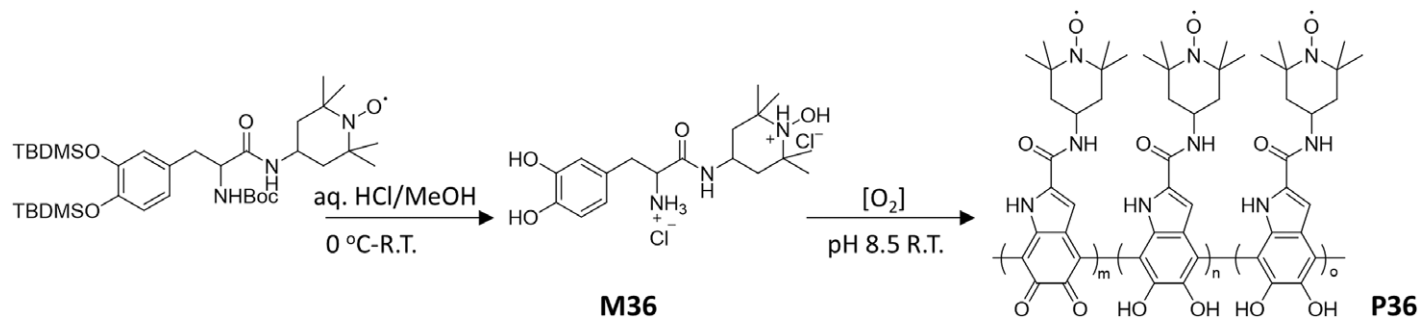
Many NRPs can be prepared through the post-polymerization conversion of precursor polymers to NRPs. This strategy allows the design of a variety of nitroxide radical precursor monomers [*i.e.*, (meth)acrylate, (meth)acrylamide and styrene] and the polymerization by both FRP and LRP techniques<sup>17</sup> (see Scheme 2.14). However, due to the basic secondary amine, aminolysis of the RAFT agent occurred during polymerization and required acidic conditions to obtain controlled molecular weight distributions.<sup>67</sup> ATRP of these monomers produced polymers with molecular weights only up to 30 kDa.<sup>67</sup> To overcome these limits, Gohy<sup>68</sup> reported the synthesis of NRP P37 through a SET-LRP process followed by oxidation, in which M37 was polymerized with copper (0)/PMDETA (*N,N,N',N'',N''*-pentamethyldiethylenetriamine) as a



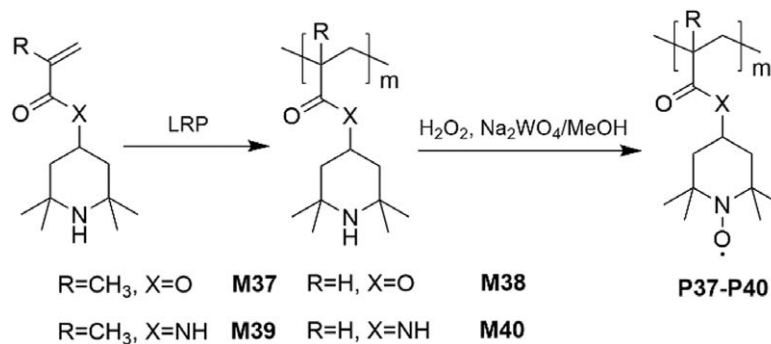
**Scheme 2.11** Ring-opening polymerization of cyclic carbonate to prepare NRP with polycarbonate backbone. Reproduced from ref. 60 with permission from the Royal Society of Chemistry.



**Scheme 2.12** (Electro)chemical oxidation polymerization of thiophene functional TEMPO to prepare NRP with conjugated polythiophene backbone.

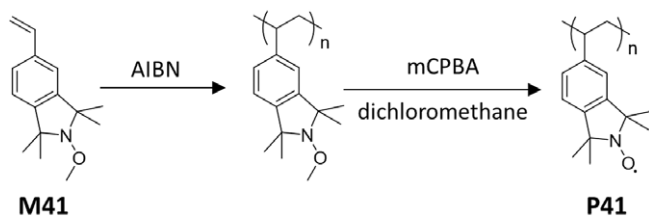


**Scheme 2.13** Oxidation polymerization of dopamine functional TEMPO to prepare surface-immobilized NRP. Reproduced from ref. 65 with permission from the American Chemical Society, Copyright 2018.



**Scheme 2.14** Synthesis of NRPs through LRP of 2,2,6,6-tetramethylpiperidine functional (meth)acrylate or (meth)acrylamide followed by oxidation. Reproduced from ref. 17 with permission from the Royal Society of Chemistry.





**Scheme 2.15** Synthesis of TMIO polymer through FRP followed by oxidation deprotection.

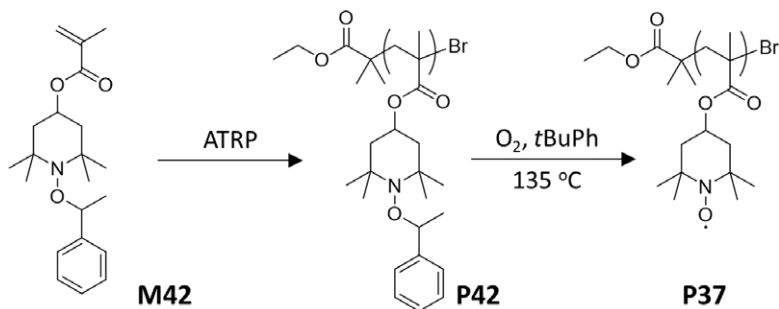
Reproduced from ref. 74 with permission from the American Chemical Society, Copyright 2018.

catalyst at 40 °C with an apparent propagation rate constant  $k_{p,app}$  of  $1.557 \times 10^{-4} \text{ s}^{-1}$  and  $M_n$  up to 11 kDa. Jia<sup>69</sup> further modified the polymerization condition by replacing PMDETA with Me<sub>6</sub>TREN (tris[2-(dimethylamino)ethyl]amine), a ligand more efficient for SET-LRP. The polymerization was much faster with a  $k_{p,app}$  of  $8.1 \times 10^{-4} \text{ s}^{-1}$  at 25 °C. More importantly, this condition produced NRPs (P37) with an  $M_n$  up to 169 kDa, which possessed very low solubility in commonly used organic electrolytes and showed a more stable electrochemical performance when used as cathode materials. LRP can also grow NRPs (P37–P40) from functional surfaces through surface-initiated ATRP followed by oxidation, producing patterned films that can be used for transparent devices.<sup>70–72</sup>

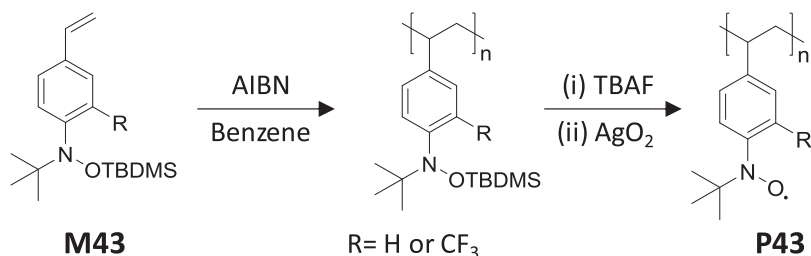
1,1,3,3-Tetramethylisoin-2-yl-oxyl (TMIO) is another nitroxide structure which has been well-studied by Bottle.<sup>73</sup> The redox potential of TMIO was higher than TEMPO derivatives. Recently, Blinco<sup>74</sup> designed a methyl-protected TMIO with a vinyl group M41. After FRP, the polymer was deprotected by *meta*-chloroperbenzoic acid (*m*CPBA) to convert it to a TMIO radical polymer P41 (see Scheme 2.15). P41 showed a redox potential of about 1.2 V vs. SHE, having great potential in a high-voltage polymer battery.

Another approach to protect nitroxide radicals is through a nitroxide radical coupling (NRC) reaction.<sup>75,76</sup> Ecker and co-workers<sup>77</sup> reported the ATRP of an alkoxyamine methacrylate M42, producing protected NRP P42. Comparing with monomer M37, ATRP of M42 produced the precursor polymer P42 with a much narrower dispersity ( $\mathcal{D} = 1.1$ ) due to no interference from the secondary amine. The alkoxyamine moieties on P42 can be decomposed upon heating in the presence of oxygen, regenerating nitroxide radicals with an efficiency of 93% (see Scheme 2.16).

Apart from cyclic nitroxide radicals, Suga *et al.*<sup>78</sup> designed noncyclic nitroxide radicals such as 4-(*N*-tert-butyl-*N*-doxylamine)benzene and its derivatives. To make polymer counterparts using FRP, this nitroxylstyrene was protected by tert-butyldimethylsilyl (TBDMS) to form monomers M43 with different substitutions. Polymer P43 was obtained through FRP followed by the successive deprotection of TBDMS groups and the oxidation of hydroxylamine. Redox potentials of this type of radicals were greatly influenced by R substituents (see Scheme 2.17). Where there was no substitution on the



**Scheme 2.16** Synthesis of poly(TEMPO methacrylate) through ATRP of alkoxyamine functional monomer followed by thermal deprotection. Reproduced from ref. 77 with permission from the American Chemical Society, Copyright 2013.



**Scheme 2.17** Synthesis of phenyl nitroxide polymer through FRP followed by successive deprotection and oxidation. Reproduced from ref. 78 with permission from the American Chemical Society, Copyright 2007.

phenyl ring (*i.e.*,  $R=H$ ), the radical showed a reversible oxidation reaction (*i.e.*,  $NO^\bullet/NO^+$ ) with potential of 0.83 V (*vs.* Ag/AgCl). When R was switched to  $CF_3$ , the oxidation reaction was no longer reversible, but a reversible reduction couple (*i.e.*,  $NO^-/NO^\bullet$ ) was observed with a potential of  $-0.92$  V. This work suggests redox potentials of phenyl nitroxide radicals can be easily altered through the electronic inductive effect on the phenyl ring.

When NRPs were used as redox-active materials for biological applications or organic catalysts, they may not require having very high radical densities. In these cases, post-modification would be a simple way to make redox-active NRPs. Poly(*N*-acryloxysuccinimide) (PNAS) as one of the most used functional polymers has been employed to prepare functional NRPs. Bergbreiter<sup>79</sup> reported the post-modification of PNAS with both 2-propanamine and small-molecule nitroxide radical M44, which produced a random copolymer comprised of thermal-responsive poly(*N*-isopropyl acrylamide) segments and pendent nitroxide radicals (see Scheme 2.18). Upon the redox reaction of nitroxide radicals, the lower critical solution temperature (LCST) of P44 changed accordingly, demonstrating both redox- and