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Thiol- and Disulfide-containing Polymers: Structure Design and Synthetic Approaches

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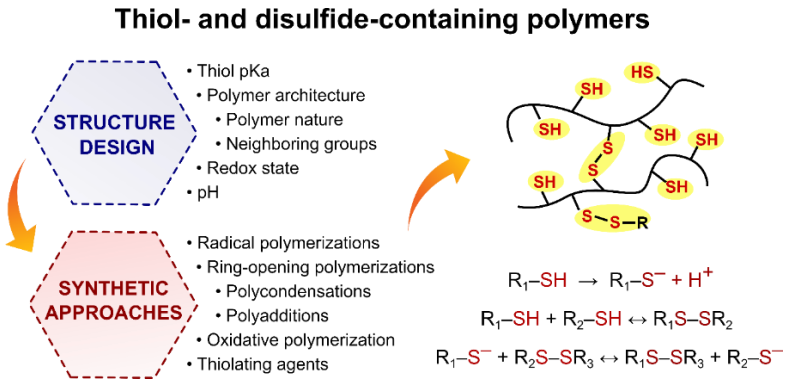
Graphical Abstract



Abstract. Thiol- and disulfide-containing polymers are an important class of functional polymers, also included in the so-called "dynamic covalent polymers", characterized by notable properties such as self-healing ability, redox response, high mucoadhesive nature, and relevant metal-ion complexation capability. Since the end of the last century, these polymers have been studied and applied extensively in different research areas, including the environmental and biomedical fields, so the current literature has several published works focused on their synthesis, characterization, and application. Structure design and preparation, control over thiol/disulfide reactivity, and evaluation of polymer properties and applicability are the main goals of works focused on thiol- and disulfide-containing polymers. In this sense, each of these aspects turns out to be related to the other and needs to be carefully reviewed and analyzed to carry out an adequate design, preparation, and utilization of these dynamic covalent polymers. Here, we present a review focused on the design and synthesis of the polymers. Initially, some generalities on thiol- and disulfide-containing polymers are provided, including important aspects associated with the reactive behavior of the polymers, especially, mediated by their thiol and disulfide groups. Next, the main polymerization protocols used for preparing the polymers are discussed, emphasizing radical polymerizations, ring-opening polymerizations, polycondensations, polyadditions, and oxidative polymerization of thiols. In addition, the structural modifications of preformed polymers, including those with natural and synthetic nature, using thiolating agents are approached and exemplified. Along the review, the advantages and disadvantages of each synthetic protocol are highlighted. Finally, some conclusions and perspectives about this research topic in polymer chemistry are provided.

Keywords: Thiolated polymers, thiomers, disulfide-containing polymers, synthesis, polymerization, thiolation.

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Content

1. Introduction

Nowadays, polymers represent a relevant class of functional materials with a wide range of applications, from the design of polymer-based products for daily use to intelligent stimuli-responsive macromolecular structures (Garcés et al., 2017; Otálora et al., 2019). One of the main reasons for the fast development of polymer science is the capability to modulate the physicochemical properties of polymers just by designing new monomers with suitable functional characteristics or by modifying the chemical structure of preformed polymers (Knoll et al., 2021; Parkatzidis et al., 2020; Penczek et al., 2021). Thus, a multitude of architectures (e.g., linear, ramified, cycled, and cross-linked structures), structures (e.g., natural, semi-synthetic, and synthetic), and functional groups (e.g., amine, carboxyl, aldehyde, amide, esters, among others) have been explored extensively in polymer research (Masoud et al., 2020; Palencia et al., 2021). In particular, a relatively recent class of polymers has attracted attention due to their unique properties: the so-called dynamic covalent polymers. These macromolecular structures possess covalent linkages capable of being formed and/or broken under controlled conditions but without high energy consumption, as in the case of breaking a common covalent bond. Some examples of dynamic covalent bonds are C=N (in imines or Schiff bases), C-N (in hindered ureas and amides), C-O (in esters), C-C (in Diels-Alder adducts), B-O (in boronic acids and boronate esters), Si-O (in siloxanes), and S-S (in disulfides) (Zheng et al., 2021). Depending on the intrinsic reactivity of each species, dynamic covalent bonds can be formed and broken through different stimuli, for example, pH and temperature changes, light irradiation, electric fields, redox potential, and particular molecules (Otálora et al., 2020). Taking into account this, polymeric structures based on dynamic covalent bonds have been extensively studied and applied in smart materials and systems, such as self-ordered systems, molecular switches and machines, self-healing materials, and stimuli-responsive cross-linked networks (García and Smulders, 2016).

In particular, thiol- and disulfide-containing polymers became relevant since the end of the last century among the different types of dynamic covalent polymers. As their name suggests, these polymers contain thiol (–S–H) and disulfide (–S–S–) linkages in their structure capable of suffering multiple reactions, such as thiol/disulfide interchanges, radical reactions, redox reactions, and metal ion complexations (Geven et al., 2021). Thiol and disulfide bonds provide polymers with unique and important properties: (i) biocompatibility due to structural similarity with proteins and other biological macromolecules, (ii) biodegradability due to redox processes, (iii) mucoadhesive properties due to thiol/disulfide interchange interactions with mucus layers, and (iv) interaction with metal ions by their sulfur atoms (Beaupre and Weiss, 2021). Likewise, thiol and disulfide groups can be further modified in polymer structures to generate macromolecules with more complex arrangements and functionalities (Kazybayeva et al., 2021; Summonte et al., 2021). In this respect, polymers bearing thiol and disulfide linkages have been used extensively in a multitude of applications, e.g., drug delivery, tissue engineering, sensors, removal of metal ions, self-healing materials, and multi-stimulus responsive polymeric systems (Chauan et al., 2015; Gou et al., 2021; Leichner et al., 2019a; Leonaviciute et al., 2016).

In literature, a wide range of methodologies with a focus on the preparation of thiol- and disulfide-containing polymers have been published. These can be classified as (i) methodologies based on the polymerization of thiol- or disulfide-containing monomers, and (ii) methodologies based on the structural modification of a preformed polymer using functionalizing (or thiolating) reagents (Becker and Wurm, 2018; Lakes et al., 2018; Macková et al., 2021; Perrone et al., 2018; Prüfert et al., 2017). In the first case, a great quantity of monomers with thiol and disulfide moieties have been designed to be used in step-growth (e.g., polycondensations, polyadditions, or oxidative polymerization) or chain-growth polymerizations (e.g., radical or ring-opening polymerizations), depending on the target molecular structure and properties of the dynamic polymer to be obtained (Feillée et al., 2016, 2017; Liu et al., 2019; Ussama and Shibata, 2021). In the second case, different reagents containing thiol or disulfide groups (e.g., cysteine, glutathione, thioglycolic acid, cystamine, etc.) are attached to a preformed polymer structure using a chemical reaction, such as amidation, amidination, ring opening, nucleophilic substitution, and reductive amination (Lerma et al., 2017; Menzel et al., 2016; Rohrer et al., 2017; Garcia-Quintero and Palencia, 2020). The control over resulting thiol contents is directly related to the synthetic approach used to obtain the polymer, being generally higher for polymerization-based protocols (Kim et al., 2020; Prasad et al., 2015). However, structural modification-based protocols provide the opportunity to use natural polymers as platforms for attaching sulfhydryl ligands, resulting in dynamic polymers with higher biocompatibility and biodegradability (Knoll et al., 2021; Perrone et al., 2018). On the other hand, the reactivity and further applications of the obtained polymers depend on intrinsic and extrinsic aspects, such as polymer

architecture, polymer nature, structure polarity, neighboring groups, pH, and redox state (Naga et al., 2019; Zeida et al., 2014). All these aspects can be taken into account in the design of thiol- and disulfide-containing polymers with the end of obtaining polymers with suitable properties for particular applications (Bermejo-Velasco et al., 2019; Leichner et al., 2019b).

Until now, the synthesis and applicability of thiol- and disulfide-containing polymers continue to be an important branch of research in polymer science. It is, therefore, necessary to review the most notable aspects of this class of dynamic covalent polymers, including their synthesis, reactivity, and applications. This review is the first part of a series of reviews on thiol- and disulfide-containing-polymers, in particular, focusing on the most relevant aspects to be taken into account in the design of these dynamic covalent polymers as well as on the synthetic protocols most commonly implemented to obtain them. First, a discussion on the general relationships between polymer structure, medium properties, and thiol/disulfide reactivity is provided. Second, different step-growth and chain-growth polymerization processes are exposed to illustrate their usage in the obtention of thiol- and disulfide-based polymers. Finally, is discussed an approach to the methodologies focused on the structural modifications of preformed polymers to generate sulfhydryl moieties in their structures. Throughout the review, the main characteristics, as well as the advantages and disadvantages of each synthetic protocol are highlighted.

2. Generalities on thiol- and disulfide-containing polymers

Polymers bearing thiol groups (-SH) as side-chain groups are denominated thiolated polymers or just "thiomers", a term introduced at the end of the last century to refer to a new class of mucoadhesive polymers (Bernkop-Schnürch et al., 1999; Bernkop-Schnürch, 2005). Due to their unique dynamic and response properties, thiomers have been extensively studied and applied in different research fields, e.g., the biomedical field (Gyarmati et al., 2013). With the arrival of thiomers to materials science, it was also unavoidable to focus on a similar class of polymers: those with disulfide groups (S–S) (Jia et al., 2019). These two types of polymers are intrinsically related, since disulfide groups possess a highly reversible character, producing thiol groups in different conditions. Likewise, thiols can be converted into disulfides using various oxidizing agents. Thus, reactive behavior and application of thiomers undoubtedly involve the consideration not only of the reactivity of thiols, but also of the reversible and dynamic character of disulfide formation, breakage, and/or exchange (Gyarmati et al., 2013).

In general, thiol and disulfide groups can be part of a polymeric chain in different ways, and according to it, different tridimensional arrangements are obtained, e.g., linear, ramified, and completely cross-linked structures. For their part, thiols can be part of a polymer only as side-chain groups because of their characteristic molecular structure (**Figure 1A**). This establishes that each thiol group can be

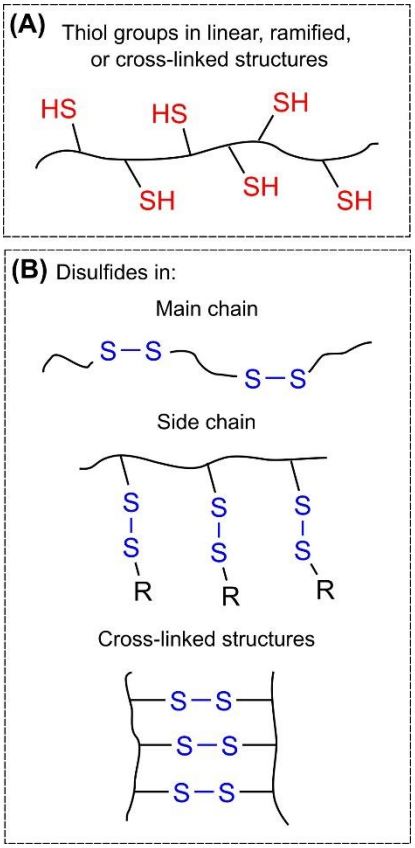

Figure 1. Participation of **(A)** thiol groups and **(B)** disulfide groups in polymer structures.

linked to one polymeric chain (or an organic fragment). Thus, the polymers based on thiols usually have a synthetic or semisynthetic origin obtained from the thiolation of the side chains of other precursor polymers (Cho et al., 2018). However, they can be also obtained in ramified or cross-linked structures, but the ramification or cross-linking mechanisms for their synthesis involve the participation of other types of functional groups (Qiu et al., 2003), as will be discussed in the next section.

In contrast, something different occurs with disulfide groups. These functional groups can be part of the side chain of a polymer, be part of a polymer backbone, or covalently interconnect two different polymeric chains since they can connect structurally two organic fragments, which can be equal or different (**Figure 1B**). In this way, disulfide groups are commonly used as structural bridges in 3D polymeric networks, e.g., hydrogels, which provide an interesting dynamic character in their behavior (Sun and Huang, 2016). In addition, linear and ramified polymers can be obtained with protected thiol groups in the form of disulfides, this is an important strategy to modulate their reactivity and avoid unwanted reactions before their target application (Dünnhaupt et al., 2012a).

Thiol and disulfide groups are included in polymer structures to provide them with dynamic properties, such as response to different types of stimuli (e.g., light, redox species, pH, and mechanical

force) and self-healing behavior (Altinbasak et al., 2020). In this sense, the type of polymer structure and the location of thiol or disulfide groups in it largely determine its properties and application. For example, linear thiomers are usually employed for mucoadhesive properties due to their flexibility and highly reactive thiol groups, which are capable of interacting with cysteamine residues of different proteins in mucus gel layers (Iqbal et al., 2012). On the other hand, thiolated and disulfide-containing cross-linked structures are used for tissue engineering or drug delivery, since they are able to suffer sol-gel transitions *situ* and be degraded by means of oxidation/reduction reactions, releasing drugs in target sites (Summonte et al., 2021).

2.1. Important considerations in the design of thiol- and disulfide-containing polymers

It is possible to observe a distinction in reactivity when considering two different types of thiol- and/or disulfide-containing polymers, e.g., those with application in drug delivery for any particular point of the human body and those with application in water treatment by metal ion complexation processes. In both examples, thiol or disulfide reactivity is influenced and, in this way, modulated by various aspects at the molecular level, such as tridimensional polymer architecture, polymer nature, structure polarity, neighboring groups, pH, and redox state (Naga et al., 2019; Roos et al., 2013; Wall et al., 2012; Zeida et al., 2014), being the most relevant ones. All these aspects need to be considered before the synthesis of the target polymer with the purpose of preparing the most suitable molecular structure for satisfying further applications. Thus, the polymer architecture determines to a great extent the reactivity of thiol and disulfide groups in any polymeric structure. Linear and ramified polymers possess chains with higher mobilities than tridimensional crosslinked polymers, such that thiol and disulfide groups in their structure need less time to interact with the target species (e.g., other thiol/disulfide groups in biological structures or metal ions), resulting in faster thiol/disulfide exchanges or higher complexation rates (Chauhan et al., 2015; Hintzen et al., 2012). To evaluate this, different amounts of cross-linking agents with respect to monomers are employed in polymerization processes, e.g., reprocessable cross-linked polyhydroxyurethanes were developed from the Polyaddition of bis(cyclic carbonate) with various ratios of cystamine and tris(2-aminoethylamine) as cross-linking agents, demonstrating the modulation in their reprocessing capacity, cross-linking density and recovery of mechanical properties (Fortman et al., 2018). Likewise, polymer nature and polarity play a fundamental role in thiol reactivity (Kafedjiiski et al., 2007). In some cases, natural polymers (e.g., cellulose, chitosan, pullulan, gelatin, among others) are preferred for biomedical applications, which require a high degree of biocompatibility and/or biodegradability (Federer et al., 2021). On the other hand, synthetic polymers (e.g., those obtained by the polymerization of vinyl monomers) are the best choice when good mechanical properties and physicochemical stability are required for a particular application, such as water treatment by adsorption processes (Waheed et al., 2021; Zhang et al., 2021a). In addition, polymers with highly polar chains are usually employed for applications in aqueous environments, e.g., hydrogels, due to their tendency to be wetted by water and acquire open chain conformations, which allow thiol groups to interact easily with the target species (Gajendiran et al., 2018).

Thiols are commonly described by their acidity, i.e., their pKa, which represents the facility to generate thiolate anions (RS–) in aqueous environments, it has been reported that aliphatic thiols show pKa values between 9 ~ 10 while aromatic thiols show pKa values between 5 ~ 7 (Hong et al., 2024). In this sense, it has been observed that thiol reactivity is influenced by the pH of the medium (Karimi et al., 2016; Yi and Khosla, 2016). Deprotonated thiols are commonly more reactive than protonated thiols due to their higher nucleophilic character. Thus, thiol/disulfide exchanges are faster when thiolate anions are the prevalent species in the medium, being determined by the pH value (Altinbasak et al., 2020; Fernandes and Ramos, 2004; Putzu et al., 2018). However, the nucleophilicity of thiols increases with their pKa so that sufficiently high pKa values tend to cause an opposite effect in the exchange rate. As a result, an optimal increase in the reaction rate is reached just right at the point where the thiolate anions become the dominant species (pH ~ pKa) (Nagy, 2013). Thiolate anions are also excellent species when dealing with applications on metal ion complexations (Gou et al., 2021; Zhang et al., 2020).

Besides their chemical structures, the pKa of thiols is influenced as well by their neighboring groups in the polymer chains. In general, electron-withdrawing groups (e.g., nitro, amino, and carbonyl groups) tend to lower the pKa of thiols; while electron-releasing groups (e.g., alkyl groups) tend to raise it (Bermejo-Velasco et al., 2019). This tendency also includes the presence of cationic and/or anionic moieties in the polymer. For instance, cationic groups stabilize thiolate anions, lowering their pKa. In contrast, anionic groups destabilize them, increasing their pKa (Beaupre and Weiss, 2021; Chu et al., 2017). In a similar way, hydrogen bonds have also been associated with the stabilization of thiolate anions (Roos et al., 2013). Taking into account this, the acidity of thiol groups in thiolated natural polymers has been successfully tuned to reach optimal mucoadhesive properties (Perrone et al., 2017; Summonte et al., 2021). In addition, charged neighboring groups influence the interaction between different polymeric chains and structures, such that oppositely charged fragments (e.g., positively charged amines and negatively charged carboxylate groups) ensure a sufficient approach of different thiol/disulfide groups, generating fast dynamic interchanges. On the contrary, similarly charged fragments generate repulsive electrostatic intermolecular interactions that avoid an efficient interaction between thiol/disulfide groups of different chains or structures (Leichner et al., 2019a).

Finally, thiol- and disulfide-containing polymers present different reactivity depending on their redox state, which is easily controlled by modifying the properties of the medium and/or the presence of particular chemical species. In their reduced state, thiols are able to interact with disulfide-containing structures and/or metal ions; however, in their oxidized state, thiols are in the form of disulfides,

which mainly interact with thiol-containing structures and may have limited interaction with metal ions (Beaupre and Weiss, 2021; Puri et al., 2020).

3. Synthetic approaches to obtain thiol- and disulfide-containing polymers

Thiol- or disulfide-containing polymers can be prepared by two main approaches: (i) by polymerizing a thiol- or disulfide-containing monomer (Qiu et al., 2003; Swindle-Reilly et al., 2009) or (ii) by functionalizing a pre-obtained polymer structure (Mao et al., 2019; Onbulak et al., 2012). The selected process will depend on different aspects, such as the molecular structure of the target polymer, the reactive behavior of the monomers and polymers, and their application. **Table 1** summarizes the main protocols to obtain thiol- and disulfide-containing polymers, including their respective advantages and disadvantages.

3.1. Polymerization reactions of thiol- and disulfide-containing monomers

Currently, there is a great variety of thiol- and disulfide-containing monomers used to obtain dynamic polymers. These can be used in step-growth or chain-growth polymerization reactions, depending on their structure and reactivity. Chain-growth polymerization reactions include radical and ring-opening polymerizations, while condensation and oxidative reactions are among the step-growth polymerizations used for obtaining thiol- and disulfide-containing polymers (Anumolu et al., 2011; Arslan, 2020a; Braslau et al., 2013).

3.1.1. Chain-growth polymerizations

3.1.1.1. Radical polymerization

As it is known from radical chemistry, thiol-based molecules are susceptible to radical reactions due to the direct participation of their sulfur atoms after relatively easy hydrogen abstraction, leading to retardation or chain transfer processes in this type of polymerization (Henríquez et al., 2003; Pfeifer et al., 2011). More specifically, chain transfer generates the inactivation of thiol groups through the formation of highly stable S-C bonds in the polymeric chains, which in various cases produces crosslinked structures with limited application as reversible or stimuli-responsive systems (Flynn et al., 2017; Thijssen and Vlierberghe, 2021). In the same way, thiols can react with alkenes, inactivating the monomers against radical polymerization and forming highly stable mercaptans (Sinha and Equbal, 2019). To overcome this, thiol-based molecules are usually *S*-protected before radical polymerization. Different types of derivative functional groups have been evaluated as *S*-protecting groups, including disulfides (Liu et al., 2013), thioesters or thiolactones (Espeel and Du Prez, 2015; Liras et al., 2013), dithioesters (Macková et al., 2021), thioethers and sylil-thioethers (Braslau et al., 2013), xanthates (Nicolaÿ, 2012), and trithiocarbonates (Zhuang et al., 2014), as can be seen in **Figure 2**. In particular, disulfide bonds are less susceptible to these undesired reactions, so this kind of sulfur functional group is widely employed in radical polymerizations (Solhi et al., 2012; Sui et al., 2019).

An important example a of disulfide-based monomer employed in conventional free radical polymerization (CFRP) to obtain dynamic hydrogels is the commercially available N,N'-bis(acryloylcystamine) (BAC), which also serves as a cross-linking agent with disulfide bridges between different polymeric chains (Plunkett et al., 2003). In this sense, Aliyar et al. (2005) reported the preparation of reducible copolymeric hydrogels by CFRP using acrylamide and BAC. The polymerization process was performed in an aqueous ethanol solution at different molar ratios of disulfide cross-linking agent (2, 4, and 6 %). Approximately 15 hours of reaction time were needed to obtain the respective gels, which was confirmed by Raman and HPLC. The Raman spectrum of the gels showed characteristic absorption bands at 662 and 2580 cm^{-1} corresponding to the stretching vibration of the -C-S- and -S-H bonds, respectively. In addition, the resulting hydrogels showed redox responsiveness against D,L-dithiothreitol (DTT) and were completely solubilized in water in just 4 hours. Likewise, re-gelation of the resulting thiolated polymers was successfully carried out employing 3,3'-dithiodipropionic acid in less than 5 minutes, but importantly, the same behavior was observed using air as the oxidizing agent. In a similar work, Hiratani and co-workers (2001) reported the usage of BAC as a cross-linking agent in hydrogels based on N-isopropylacrylamide and lead methacrylate, which were obtained by CFRP in dioxane. In this case, DTT and $NaBrO_3$ were used as reducing and oxidizing agents, respectively, to probe the reversible behavior of disulfide bridges in the polymeric structure. Interestingly, the hydrogels presented a dual response: (i) against redox processes due to the presence of thiol/disulfide groups, and (ii) against the addition of salts (e.g., Ca^{2+}-based salts) due to their electrostatic interaction with carboxyl groups in the polymeric structure.

Other important examples of disulfide-containing monomers that have been used in CFRP are pyridyl disulfide derivatives (see **Figure 3**). This functional group possesses a relatively high stability against this type of polymerization, being ideal to obtain easily disulfide-containing polymers (Altinbasak et al., 2020). In addition, pyridyl disulfide groups may be easily removed from the polymer backbone through redox and exchange reactions mediated by thiol groups, producing the chemically inert pyridine-2-thione group (Boyer et al., 2008; Sui et al., 2019). In this sense, Solhi and co-workers (2012) reported the synthesis of a copolymer based on a pyridyl disulfide-containing monomer, i.e., 6-(2-amino ethyldisulfanyl) nicotinic acid, with acrylic acid by CFRP using azobisisobutyronitrile as the radical initiator and DMSO as the organic solvent at 80 °C in closed test tubes for 1 h. The characterization by FTIR, GPC, and MALDI-TOF-MS demonstrated the successful preparation of the polymers, which presented until 15 % of the pyridyl disulfide monomer in their structure and low polydispersity indexes (PDI) (1.07 – 1.2). However, the molecular weights of the synthesized polymers were

Table 1. The main synthetic routes implemented to obtain thiol- and disulfide-containing polymers.

Description	Advantages	Disadvantages	Ref.
Radical polymerization			
Chain-growth polymerization in which radicals are the propagating species. Mainly, vinyl monomers are employed for obtaining thiol- and disulfide-containing polymers. Living polymerization techniques, such as reversible addition-fragmentation chain-transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP), and nitroxide-mediated radical polymerization (NMRP), have also been used for this purpose.	- Relatively high molecular weights can be obtained. - High conversion values can be achieved in a short time. - High structural diversity on monomers and polymers. - Depending on the type of radical polymerization, low polydispersity indexes (PDIs) can be obtained.	- Rigorous reaction conditions are usually employed. - Side reactions, such as chain transfer, may be present. - Thiol protection is required. - Deprotection and/or modification of the polymeric structure after polymerization may be necessary.	Aliyar et al. (2005), Espeel and Du Prez (2015), Forsythe et al. (2021), Liu et al. (2013), Macková et al. (2021), Sui et al. (2019)
Ring-opening polymerization			
Chain-growth polymerization of cyclic monomers usually produces a polymer with linear repeating units. In this case, monomers with small ring structures (3 to 7 members) are commonly used.	- Relatively high molecular weights can be obtained. - Low PDIs can be obtained. - High structural diversity on monomers and polymers. - Disulfide bonds can be easily introduced into the polymer from the monomers. - Depending on the monomer, the control of polymer architecture can be achieved.	- High temperatures and toxic catalysts are needed in many cases. - Rigorous reaction conditions are usually employed. - Unwanted reactions may be present due to a lack of control in some polymerizations. - Low yields are often obtained.	Becker and Wurm (2018), Chen et al. (2013), Endo et al. (2004), Ishida et al. (2009), Kim et al. (2020), Liu et al. (2019), Penczek et al. (2021)
Polycondensation and polyaddition			
Polymerization reactions in which one or more monomers react to produce a polymer structure with or without subproduct generation (polycondensation and polyaddition, respectively). Their mechanism is based on the step growth of the polymer chains due to the reaction of their functional terminal groups.	- Relatively high molecular weights can be obtained. - High polymer purity can be reached. - Biodegradable linkages are usually obtained in the resulting polymer structure. - High structural diversity on monomers and polymers.	- Long reaction times are usually required. - High temperatures and catalysts are needed in many cases. - Limited yields are commonly obtained. - Obtained molecular weights are usually lower than in chain-growth polymerizations.	Ali et al. (2017), Arslan (2020a), Borska et al. (2021), Fuoco and Finne, Wistrand (2020), Lakes et al. (2018), Ussama and Shibata (2021), Martin et al. (2014), Prasad et al. (2015), Rekondo et al. (2014), Vader et al. (2011)
Oxidative polymerization of thiols			
Step-growth polymerization based on the oxidative coupling of thiols. It can be performed using various types of oxidizing agents (e.g., hydrogen peroxide, iodine, air, etc.), catalysts (e.g., iodide salts or enzymes), and reaction promoters (e.g., UV irradiation).	- Relatively high molecular weights can be obtained. - High structural diversity on monomers and polymers. - Control over polymer architecture can be achieved depending on the reaction conditions. - Mild reaction conditions are usually needed. - High yields can be obtained.	- Unwanted reactions, such as over-oxidation of the monomer and/or polymer structure, may be present. - The requirement of thiol groups in the monomer structure limits the presence of other types of functional groups (e.g., epoxides or alkenes). - Limited yields due to the presence of interfering species may be obtained.	Chemtob et al. (2018, 2019), Feillée et al. (2016, 2017), Ramadhan et al. (2020), Rosenthal-Kim and Puskas (2012)
Structural modifications of a preformed polymer			
Synthetic methodologies based on the structural modification of a preformed polymer through different types of chemical reactions with a functionalizing agent. As a result, a derivative polymer with sulfhydryl moieties is obtained. Various reactions are employed for this purpose: amidation, reductive amination, amidination, nucleophilic substitutions, etc.	- Control over the thiol content can be easily performed just by modification of reaction conditions. - Unwanted reactions can be avoided using click chemistry. - Control over the polymer architecture and the chemistry of side chain groups is performed separately. - Thiolated natural polymers can be obtained by this route.	- Drastic conditions or toxic reagents may be needed. - Thiol contents and reaction yields are limited by parameters like solubility, reactivity, and stability of the polymer and functionalizing agent.	Chauan et al. (2015), Knoll et al. (2021), Menzel et al. (2016), Palencia et al. (2016), Perrone et al. (2017), Rohrer et al. (2017)

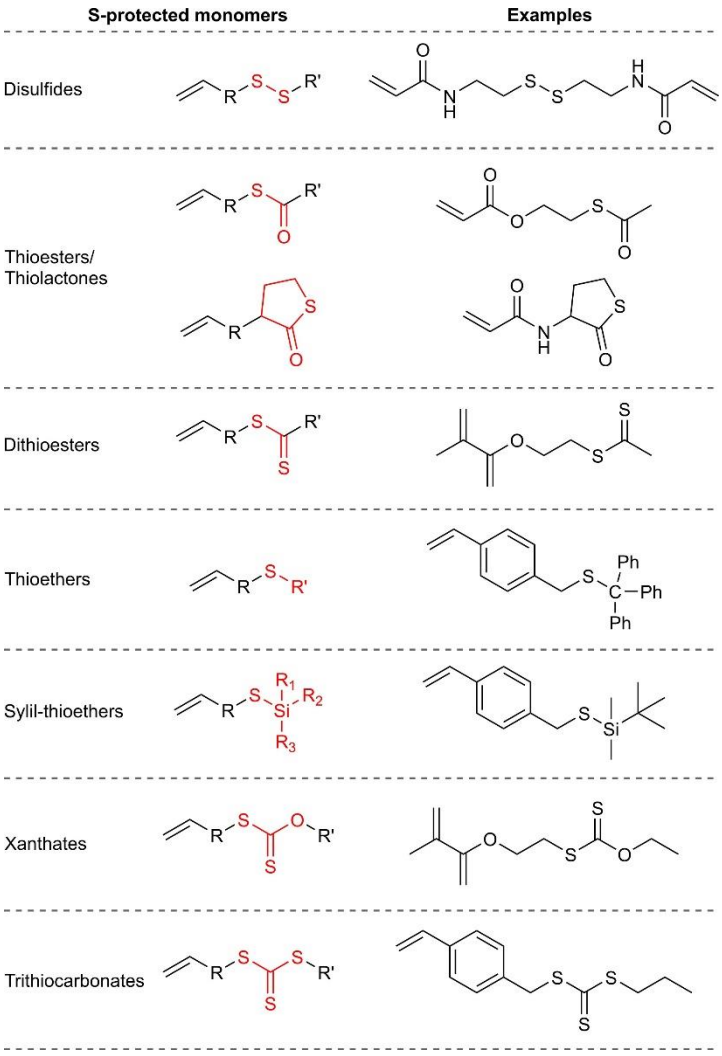

Figure 2. Different types and examples of S-protected monomers for radical polymerization (see the text for the references).

relatively low (2000 – 4000 Da), which were attributed to steric hindrance effects and low reactivity ratios between the nicotinic acid derivative and acrylic acid. In this point, higher molecular weights (> 36 kDa) have been obtained by copolymerizing *N*-[2-(2-pyridyldithio)]ethyl methacrylamide with *N*-(2-hydroxypropyl)methacrylamide under CFRP conditions (Wang et al., 1998).

Thiol- and disulfide-containing polymers have also been obtained by means of more sophisticated radical polymerization techniques, such as RAFT polymerization, ATRP, and NMRP (Braslau et al., 2013; Fu et al., 2021; Macková et al., 2021; Tsarevsky and Matyjaszewski, 2005). In all these cases, there is a greater control on molecular weight, PDI, and polymer chemical structure, even after synthesis (Perrier et al., 2017; Truong et al., 2021). In addition, the applicability to a higher quantity of monomers and the tolerance

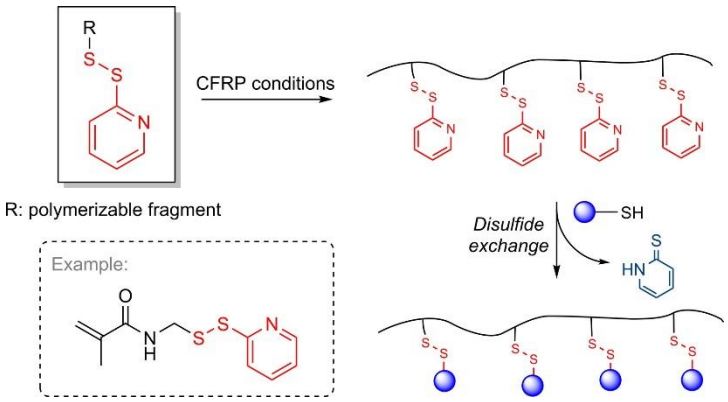

Figure 3. General scheme on the synthesis of disulfide-containing polymers using pyridyl disulfide-based monomers. As a side-chain group, pyridyl disulfide reacts with thiols through a disulfide exchange reaction, producing pyridine-2-thione (in blue) and a new disulfide group (Example was taken from Wang et al., 1998).

to a greater number of functional groups are important advantages of these sophisticated radical polymerizations, also called "living radical polymerizations" (Parkatzidis et al., 2020).

Among these, RAFT polymerization has been extensively applied to obtain thiol- and disulfide-based polymers due to two main reasons: (i) the most common protected thiol groups do not interfere with RAFT polymerization (Peng et al., 2016), and (ii) the best chain transfer agents used in this technique are based on sulfur functional groups, such as dithioesters, xanthates, and trithiocarbonates, which can be further modified to produce thiol and disulfide moieties (Hess et al., 2020). The above can be exemplified by the work published by Hrsic et al. (2013), in which they prepared amphiphilic block copolymers with pendant thiol groups by the RAFT polymerization of vinyl monomers with thioacetyl groups, as protected thiols, and 4-cyano-4-(thiobenzoylthio)pentanoic acid, as transfer agent. The resulting polymer presented pendant-protected thiol groups and terminal dithiobenzoate groups which were further modified by means of an alkyl amine to obtain free thiol groups. After that, thiol groups induced the self-assembly of the polymeric chains through the formation of disulfide bridges, producing nanometric micelles with a redox response. Similar works have been published but using pyridyl disulfide- (Peng et al., 2016; Wong et al., 2008), dithioester- (Macková et al., 2021), and thiosulfonate-based monomers (Arslan et al., 2020b).

On the other hand, ATRP and NMRP have also been implemented in the preparation protocols of disulfide-based polymers. In this case, the polymerization method has been focused on the usage of radical initiators containing disulfides or other types of protected thiol groups, such as sulfone or *tert*-butyl dimethyl silyl (TBDMS) groups (Forsythe et al., 2021; Hill et al., 2008). After the synthesis, the polymer is subjected to different conditions to generate free thiols, which can be terminal or pendant groups in the polymeric

chains depending on the type of monomers used in the polymerization (Tsarevsky and Matyjaszewski, 2005). For instance, Braslau and co-workers (2013) reported the synthesis of polymers with pendant and terminal thiol groups capable of suffering reversible crosslinking through disulfide/thiol redox chemistry. They used a series of nitroxide monomers containing thiols protected with different types of groups, including TBDMS, disulfide, and trityl group, as well as, containing different functionalities. The best results were achieved with the trityl group as the protecting agent of pendant and terminal thiol groups, resulting in polymers with molecular weights greater than 20 kDa and high redox response.

3.1.1.2. Ring-opening polymerizations

Ring-opening polymerization (ROP) is one of the most important polymerization techniques used to prepare polymers with biodegradable linkages, e.g., polyesters. As its name suggests, ROP is based on the ring-opening reaction of a cyclic monomer to produce propagating species capable of forming polymer chains with acyclic units. The driving force of this polymerization is the release of ring strain energy from the ring of the cyclic monomer (Penczek et al., 2021). Different types of cyclic monomers have been used in ROP, cyclic esters (or lactones) and epoxides are the main examples (Tschan et al., 2021). Likewise, catalysts and electrophilic or nucleophilic initiators are usually needed to carry out ROP (Song et al., 2020). Taking into account this, some works have been focused on the design of biodegradable disulfide-based polymers using ROP (Becker and Wurm, 2018; Chen et al., 2013; Kim et al., 2020; Liu et al., 2019). For example, Chen and co-workers (2013) reported the synthesis of poly(ε-caprolactone)s containing pendant disulfide groups by a ROP protocol using ε-caprolactone and a pyridyl disulfide-containing cyclic carbonate (**Figure 4A**). In this case, isopropanol and tin(II) octoate were used as ROP initiators and catalysts, respectively, obtaining the target polymers. Further modifications of the resulting polymeric structure were also possible through oxidation to form disulfides, or reduction to cleave the disulfides. The final polymers presented amphiphilic and dynamic character so that they formed micelles with excellent responses against thiol-reducing agents, e.g., DTT. In a similar work, Kim et al. (2020) recently reported the preparation of disulfide-based polymers by the ROP of 1,4,5-oxadithiepan-2-one, an analog of ε-caprolactone with a disulfide bridge in its structure (**Figure 4B**). To carry out this, the authors employed benzyl alcohol and diphenylphosphate as ROP initiator and catalyst, respectively. Low PDIs (<1.1), high conversion (>99 %), and relatively high molecular weights were the main characteristics of the developed ROP. Importantly, the polymers presented disulfide groups among their polymer backbones and, in this sense, they were able to respond to thiols and UV irradiation, resulting in their reversible de-

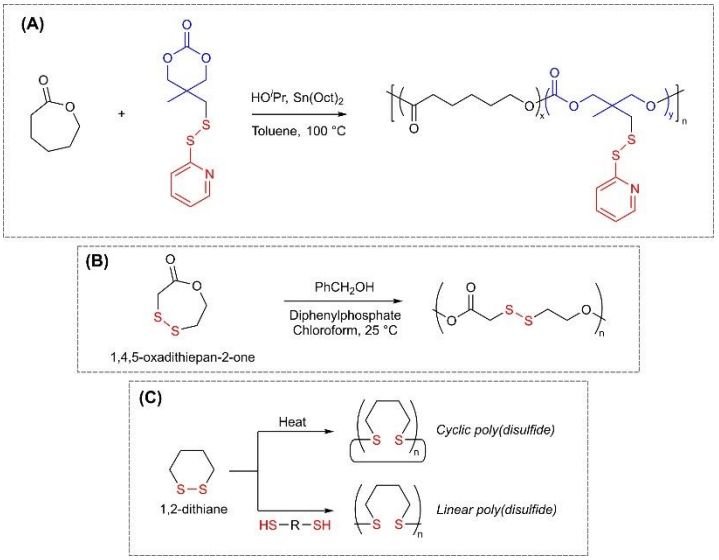

Figure 4. Some important examples of the preparation of poly(disulfide)s by ROP using **(A)** ε-caprolactone and a pyridyl disulfide-containing cyclic carbonate (Chen et al., 2013), **(B)** 1,4,5-oxadithiepan-2-one (Kim et al., 2020), and **(C)** 1,2-dithiane (Ishida et al., 2009).

gradation under controlled chemical and physical stimuli. Thus, this synthetic route represents an important alternative to obtaining dynamic disulfide-based polymers in which disulfide side reactions, low molecular weights, and high PDIs are avoided, as pointed out by the authors.

Interestingly, dynamic poly(disulfide)s can be obtained from cyclic disulfides or 1,2-dithianes (**Figure 4C**). This type of cyclic sulfur monomer is polymerized by ROP using either heating conditions or a thiol-reducing agent as an initiator, including dithiols (Endo et al., 2004; Ishida et al., 2009). It has been reported that temperature and the reactivity of the initiators are the main factors that influence the type of polymer obtained, which can be linear or cyclic. This means that it is possible to modulate not only the architecture of poly(disulfide)s, but also their reactive behavior, which is useful for regulating (bio)macromolecule conformations, mediating cellular redox homeostasis, controlling mechanical properties, drug delivery, and self-assembly (Liu et al., 2019). Relatively high molecular weights and highly redox response have been the most important properties of this type of dynamic disulfide polymers, which have been applied as smart responsive systems (Bang et al., 2012; Zhang et al., 2021b). Despite these important advances in the preparation of poly(disulfide)s by ROP, some aspects remain a challenge, for example, the usage of toxic catalysts and a lack of control in the polymerization process, resulting in unwanted chemical reactions that affect the structure of the resulting polymer (Bannin and Kiesewetter, 2015). For example, Hansen-Felby et al. (2022) reported the synthesis of a wide range of self-immolating poly(disulfides) of saturated aliphatic chains from 1,4-

butanedithiol, 1,5-pentanedithiol and 1,6-hexanedithiol monomers. The synthesis of poly(disulfides) was relatively simple and rapid, using an inert atmosphere, a temperature of 25 °C, the use of dichloromethane and acetic acid as a reaction medium, and lasting 4 hours. The polymers obtained presented polydispersity index values between 1.13 - 1.67 and high solubility in dichloromethane, chloroform, diethyl ether, and tetrahydrofuran. Furthermore, the synthesized poly(disulfides) showed a high degree of crystallinity and melting temperatures close to the physiological temperature that vary depending on the chain length of the precursor disulfide.

3.1.2. Step-growth polymerizations

3.1.2.1. Polycondensations and polyadditions

Thiol and disulfide-containing polymers can also be obtained using polycondensation- and polyaddition-based protocols. In these cases, common functional groups, such as amine, carboxyl, aldehyde, hydroxyl, and alkenes, among others, react to produce a polymeric structure (Shimoni et al., 2012). In addition, thiol and disulfide groups can participate in this type of polymerization but in special cases like thiol/disulfide exchange reactions (Bej and Ghosh, 2018). As a distinction, polycondensation refers to a polymerization process based on consecutive condensation reactions in which low-molecular-weight molecules are released as subproducts (e.g., the reaction between a carboxylic acid and an alcohol to produce a new ester linkage and water), while in polyaddition there is no any type of subproduct (e.g., the reaction between an isocyanate and an amine to produce a new urea linkage). However, both types of polymerizations have step-growth mechanisms, so they are usually considered in a single section. Transesterifications (Fuoco and Finne-Wistrand, 2020; Ussama and Shibata, 2021), amidations (Ali et al., 2017; Prasad et al., 2015), thiol/disulfide exchanges (Aluri et al., 2021; Bej and Ghosh, 2018; Zhuang et al., 2019), and condensations of silanols (Al Mahrooqi et al., 2018) are important examples of polycondensations used to obtain thiol- and disulfide-containing polymers. Likewise, Michael-type additions (Arslan, 2020a; Lakes et al., 2018; Vader et al., 2011), uretanization reactions (Borska et al., 2021; Martin et al., 2014; Rekondo et al., 2014), and epoxide ring-opening by various types of nucleophiles (De Luzuriaga et al., 2016; Li et al., 2021; Memon et al., 2022) are the most used polyadditions for this purpose.

Step-growth polymerizations have shown to be a good synthetic approach to obtaining redox-responsive polymers based on disulfide and thiol groups. In particular, high structural diversity, architecture control, yields, and molecular weights can be achieved through the above-mentioned step-growth polymerizations. In particular, polyadditions have gained recognition due to their "click chemistry" nature which makes these polymerizations highly selective with minimal or no presence of unwanted reactions (Billiet et al., 2009). Likewise, in polyadditions there is no need to remove any by-products from the reaction, resulting in simpler, greener, and more efficient polymerization protocols (Otálora et al., 2019; Durham and Shipp, 2021). For instance, Lakes and co-workers (2018) reported the synthesis of tridimensional polymer networks with disulfide linkages by an aza-Michael type polyaddition, as can be seen in **Figure 5**. This polymerization was based on the nucleophilic addition of the amine groups of cystamine to the electrophilic C=C bonds of diethylene glycol diacrylate.

The polymerization was successfully performed at 60 °C for 24 h as was corroborated by FTIR measurements, obtaining disulfide-containing hydrogels with a yield of 93 %. In this sense, this type of polymerization is a good representation of polyadditions capable of producing a polymeric structure without subproduct generation, i.e., the monomers (e.g., nA + nB) react to produce an adduct-type repeating unit ([AB]n). In a similar work, Vader and co-workers (2011) effectively copolymerized N,N′-cystaminebisacrylamide with two classes of amines: 4-amino-1-butanol and ethylenediamine, through an aza-Michael type polyaddition at 45 °C in a methanol/water mixture. The resulting polymers reached molecular weights ranging between 1.6 and 11.7 kDa with PDIs between 1.4 and 2.4 and were further used to form redox-sensitive polyplexes with RNA fragments.

Another example of polyaddition is provided by Rekondo and colleagues (2014). In their work, they obtained self-healing elastomers based on aromatic disulfide metathesis. To do this, a polyaddition based on the click reaction between nucleophilic groups, such as hydroxyl and amine groups, and a highly electrophilic group, such as an organic isocyanate, was performed. Specifically, they employed poly(propylene glycol)-based polyols, an aliphatic diisocyanate, and a disulfide-containing aromatic diamine, obtaining elastomeric polymeric networks based on the formation of urethane, urea, and disulfide linkages. This synthetic protocol was carried out at 60 °C for 16 h and was easily monitored by FTIR until reaction completion through the variation of band intensities corresponding to the carbonyl group of urethane moiety at 1720 cm^{-1} and amide II at 1534 cm^{-1}.

Interestingly, two or more types of condensation/addition reactions can be used in a single polymerization protocol to obtain thiol- and disulfide-containing polymers. This is the case of the work reported by Zhuang et al. (2019), which was focused on the step-growth polymerization of different substituted thiolactones with pyridinyl disulfide ethylamine (PDS-NH_2) to form disulfide-containing polyamides. Initially, it can be expected that thiolactone forms poly(thioester)s by ROP in the presence of a nucleophilic initiator, e.g., an amine, as has been reported previously (Bannin and Kiesewetter, 2015; Suzuki et al., 2016).

However, the inclusion of PDS-NH_2 in the ROP of thiolactone allows disulfide-containing polyamides to be formed, as theauthors highlighted. They established that the polymerization occurs throu-

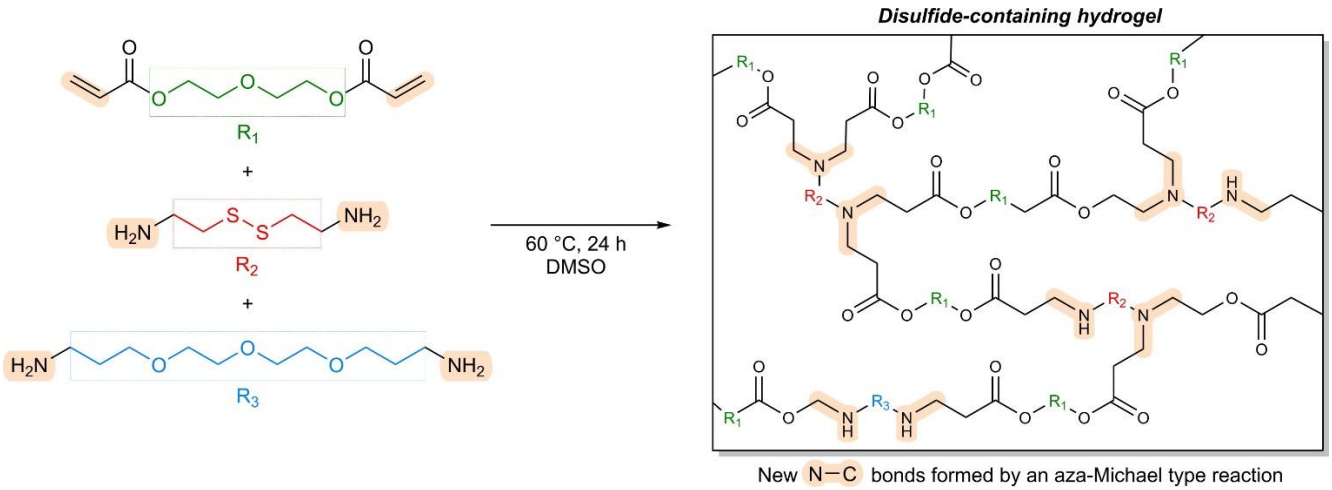

Figure 5. Preparation of redox sensitive hydrogels by an aza-Michael type polyaddition between cystamine, 4,7,10-trioxa-1,13-tridecanediamine and diethyleneglycol diacrylate (Lakes et al., 2018).

gh a cascade-type mechanism based on the combination of an amine-thiolactone ring-opening reaction with a disulfide metathesis, as illustrated in **Figure 6**. In total, seven different substituted thiolactones were successfully co-polymerized with PDS-NH_2 through this synthetic route, obtaining disulfide-based polyamides with molecular weights higher than 8 kDa in almost 3 hours. Likewise, various copolymers were also obtained through this step-growth polymerization. In this sense, Bej and Ghosh (2018) also used thiol/disulfide exchange to obtain telechelic poly(disulfide)s. Here, the polymerization was carried out using pyridyl disulfide and a dithiol, which react through a step-growth mechanism based on the nucleophilic exchange of thiol and disulfides under mild conditions (25 °C, 2 – 6 h, and CH_2Cl_2 as solvent) at relatively high yields (68–84 %).

3.1.2.2. Oxidative polymerization of thiols

Thiols can form disulfides through oxidative processes mediated by different agents, among which are chemical oxidizing agents (e.g., oxygen, hydrogen peroxide, and iodine) or biological catalysts like, for example, several oxidoreductases (Ramadhan et al., 2020; Rosenthal-Kim and Puskas, 2012). Likewise, thiol oxidation can be assisted by physical agents, like UV irradiation, in conjunction with particular organic molecules (e.g., triazabyciclodecene and phenylglyoxylic acid) that serve as the initiators of the process in the presence of air as the oxidizing component (Feillée et al., 2016; Spiliopoulou and Kokotos, 2021). Various salts have also been reported as efficient catalysts for thiol oxidation, e.g., iodide salts (Fairbanks et al., 2011; Kirihara et al., 2007). In this sense, thiol oxidation has a high diversity of reaction conditions and the possibility of being carried out under mild conditions at high yields. Therefore, some protocols focused on the preparation of poly(disulfide)s have been based on the step-growth polymerization of thiols by oxidative couplings (Chemtob et al., 2018, 2019; Mohanty et al., 2018; Tran et al., 2020).

Specifically, disulfide-containing polymers have been prepared by means of oxidative couplings using organic molecules with two or more thiol groups in their structures. These can have other types of functional groups (e.g., carboxylic acids, amines, ethers, and esters) that do not interfere with the step-growth polymerization of thiols. An example of this is the work published by Tran and co-workers (2020), which was based on the preparation of multifunctional poly(disulfide)-based hydrogels with fast self-healing and degradability due to the metathesis and redox chemistry of their disulfide linkages. To do this, the authors copolymerized 2,3-dimercapto-1-propanol with meso-2,3-dimercaptosuccinic acid through oxidative couplings of their thiol groups (see **Figure 7**). The polymerization was carried out in DMSO at 30 °C for 6 days using HBr as the oxidizing agent. Only a small amount of HBr (5 % mol with respect to the total monomer quantity) was needed to successfully complete the reaction and obtain a gel system. In addition, further cross-linking and the increase of hydrophilic nature was achieved through electrostatic interactions between the carboxylic groups of the polymeric structure and Ca^{2+} ions in an aqueous medium, obtaining finally hydrogels with dynamic disulfide linkages, as was confirmed by FTIR monitoring of the spectral band associated with -SH groups, mechanical tensile tests, and degradation experiments. In a similar work, Yang et al. (2020) prepared functional hydrogels using a two-step process, involving various cross-linking reactions by means of thiol oxidative couplings, thiol-catechol Michael addition, and thiol-yne click reac tions. Particularly, they performed an oxidative polymerization of a

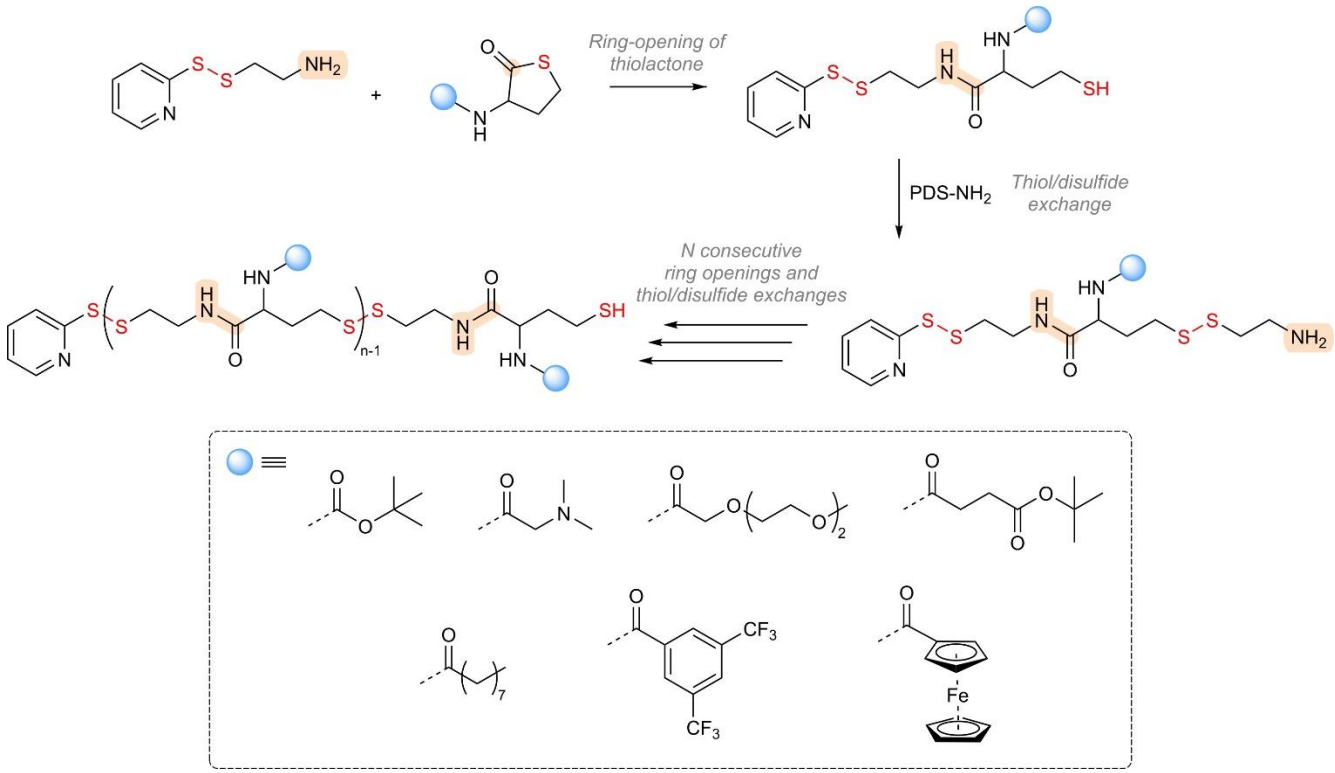

Figure 6. Step-growth polymerization of substituted thiolactones with PDS-NH_2 for preparing redox sensitive polyamides through a "cascade-type" mechanism.

thiol-terminated four-arm poly(ethylene glycol) using NaIO4 as an oxidizing agent under mild conditions in an aqueous medium. Several minutes were sufficient to induce oxidative coupling be tween thiol groups, resulting in the formation of various hydrogel systems even at different concentrations of the thiol-containing monomer.

On the other hand, disulfide-containing polymers can be obtained by oxidative coupling of thiols using UV irradiation as a reaction promoter. The advantage of this methodology is the possibility to carry out the polymerization in situ in a short time, which is highly important in various applications, for example, coatings and electronic materials (Chemtob et al., 2018). In addition, it can be performed without the use of any other chemical additive, diminishing or avoiding post-polymerization purification protocols. Also, it has been reported that the architecture of poly(disulfide)s can be controlled by UV irradiation, e.g., from linear to cyclic structures depending on the monomer structure (Chemtob et al., 2019). However, as a disadvantage, photopolymerization of thiols may lead to various unwanted side reactions, e.g., bond breakage or over-oxidation, and low yields due to the presence of non-target absorbing species. To overcome this, some authors have proposed the employment of UV irradiation in conjunction with organic molecules capable of adsorbing and modulating the irradiation that is "felt" by the reaction medium, avoiding any kind of unwanted reactions that may negatively affect the resulting polymeric structure and promoting effectively the polymerization reaction (Feillée et al., 2016, 2017).

3.2. Structural modifications of a preformed polymer

Thiol or disulfide groups can be introduced by the direct modification of the structure of a pre-formed polymer. In this case, different classes of chemical reactions are performed between the functional groups of the native polymer and a functionalizing agent, also called a "thiolating agent", in order to generate moieties with sulfhydryl groups along the polymeric structure (Armengol and Laffleur, 2021; Milloti et al., 2009; Prüfert et al., 2017). Through this synthetic approach, control over the thiol content of the polymer structure can be easily performed just by modification of reaction conditions, e.g., the amount of functionalizing agent, concentration, and temperature, among other parameters (Bonegel and Bernkop-Schnürch, 2014; Kumar and Sinha, 2013). However, some drawbacks are related to the solubility, reactivity, and stability of the polymer to be modified and the functionalizing agent employed for that purpose (Geven et al., 2021; Gyarmati et al., 2013). **Figure 8** illustrates some examples of the functionalizing agents most used for introducing thiol groups in polymeric structures, while **Table 2** summarizes the most representative reactions using these functionalizing agents.

Natural, semi-synthetic, and synthetic polymers have been used as platforms to covalently attach sulfhydryl moieties. To perform this,

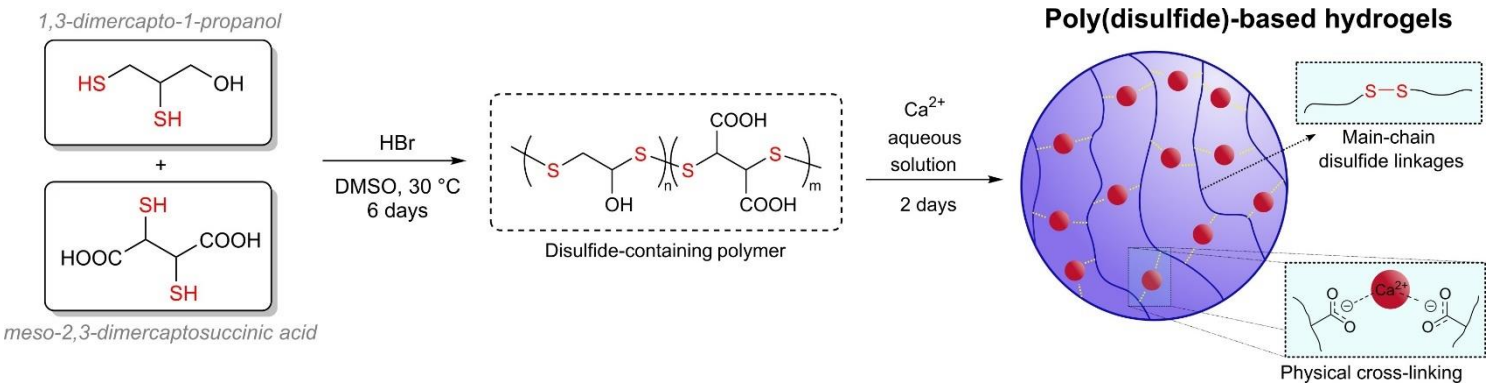

Figure 7. Preparation of self-healing and degradable hydrogels by the oxidative polymerization of 2,3-dimercapto-1-propanol with *meso*-2,3-dimercaptosuccinic acid using HBr as oxidizing agent.

it is necessary that the target polymer possess functional groups capable of reacting with the employed functionalizing agent. For instance, chitosan has been modified with different functionalizing agents (e.g. *N*-acetyl-L-cysteine, thioglycolic acid, 6-MNA, etc.) through amidation reactions, in which the amino groups of chitosan form new amide linkages by reacting with carboxylic acid groups of the functionalizing agent (Dünnhaupt et al., 2012b; Menzel et al., 2016; Perrone et al., 2018; Prüfert et al., 2017). These reactions are easily performed in the presence of EDAC or DIC, two different carbodiimides capable of activating carboxylic acids against nucleophilic substitution reactions by *N*- or *O*-nucleophilic reagents (see **Path A** in **Figure 9**) (Gokhale and Lee, 2012; Kasprzak et al., 2018). This results to be a better synthetic option than reactions with drastic conditions, for example, esterification reactions catalyzed by acids, since thermolabile groups can be present in the polymer structure or unwanted side reactions can be induced at higher temperatures or acidic environments. In addition, when the concentration of the nucleophilic reagent is low and/or the nucleophilic substitution is slow even in the presence of the carbodiimide, some additives can be used, for example, NHS. In this sense, it is possible to increase the reaction rate and the yield of the substitution forming an intermediate with greater stability and susceptibility to react with the nucleophile (**Path B** in **Figure 9**) (Laurano et al., 2020; Wang et al., 2011). Using EDAC/NHS-mediated amidation, other natural (e.g., gelatin, gellan gum, and pectin) and synthetic polymers (e.g., PAAc, Fixomer™ A-30, PEO-PPO-PEO-based polyurethane, and CG4500) have been successfully functionalized with thiol ligands, reaching contents of approximately 755 µmol free thiol groups attached per gram polymer (Jalil et al., 2019; Knoll et al., 2021; Laurano et al., 2020; Prüfert et al., 2020; Rohrer et al., 2017).

Amidation reactions can be performed using thiol- or disulfide- containing functionalizing agents. Among these, disulfide-containing functionalizing agents are preferred over those containing free thiols since the former produce *S*-protected thiols in polymer structures, which have a higher dynamic covalent character in mucoadhesive applications, for example; furthermore, *S*-protected ligands prevent possible side reaction with the participation of thiol groups, being further inactivated (Dünnhaupt et al., 2012a). This is the case of the usage of 6-MNA dimer as a functionalizing agent for obtaining thiolated chitosan with increased mucoadhesive properties of great significance in drug delivery applications (Menzel et al., 2016). An important advantage of using MNA-*S*-protected polymers in biomedical applications lies in that, once they suffer thiol/disulfide interchanges with thiolated platforms or structures, they release 6-MNA molecules, which do not present any kind of harmful effect against living cells (Maria et al., 2020). Based on this strategy, 6-MNA derivatives like AMENA and Cys-MNA have been used to functionalize gellan gum and pectin, respectively, obtaining disulfide-containing semi-synthetic polymers with high mucoadhesion, biodegradability, and compatibility (Jalil et al., 2019; Knoll et al., 2021).

An analogous reaction to amidation is amidination. In this case, new amidine linkages are produced through the reaction between the side amino groups of a polymer backbone and thiolated imidates, such as ISATC or 2-iminothiolane (also known as Traut's reagent), as can be seen in **Figure 10** (Bernkop-Schnürch et al., 2003; Palmberger et al., 2008). Using this synthetic route, polymers like PAA, chitosan, and gelatin have been thiolated in high yields, obtaining derivative polymers susceptible to redox reactions and thiol/disulfide exchanges (Ibie et al., 2015; Rohrer et al., 2015). Among the most used thiolated imidates, ISACT is preferred over 2-iminothiolane since chemically-unstable 4-thiobutylamidine structures are formed using the latter, diminishing the resulting thiol contents (Bonegel and Bernkop-Schnürch, 2014). However, ISATC-based functionalization requires treatment with hydroxylamine to deprotect the thiol groups (Kafedjiiski et al., 2005b, 2006), which increases the number of steps, costs, and environmental impacts of the synthetic protocol. It has been highlighted that thiol contents higher than 250 µmol per gram of po-

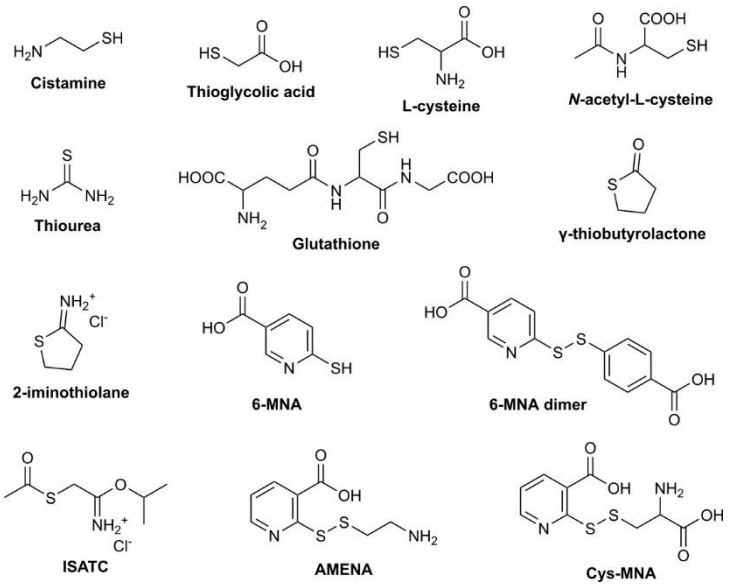

Figure 8. Chemical structures of the most representative functionalizing agents used to obtain thiol- and disulfide-containing polymers. Here, ISATC: isopropyl-S-acetylthioacetimidate; 6-MNA: 6-mercaptonicotinic acid; AMENA: 2-(2-amino ethyldisulfanyl) nicotinic acid; Cys-MNA: 2-((2-amino-2-carboxyethyl)disulfanyl)nicotinic acid.

mer can be easily obtained using amidination reactions, which results to be competitive values with some amidation protocols (Le-Vinh et al., 2023; Krauland et al., 2006).

Other types of chemical reactions can be used for thiolating polymers, for example, reductive aminations, nucleophilic substitutions, and ring opening reactions (Leonaviciute et al., 2016; Maleki et al., 2015; Perrone et al., 2017). In some cases, it is necessary to previously modify the native structure of a polymer to generate functional groups capable of being coupled with the functionalizing agent. For instance, natural polymers like pullulan, glycogen, and HEC are treated with $NaIO_4$, as an oxidizing agent, to introduce aldehyde groups in their structures. After that, cysteamine is introduced through a reductive amination employing $NaBH_3CN$ as the reducing agent, resulting in new C–N bonds (see **Figure 11**) (Perrone et al., 2017; Rahmat et al., 2011). Here, high thiol contents (up to 280 μmol/g) are correlated with high oxidation degrees and relatively long reaction times (Leonaviciute et al., 2016).

Similarly, hydroxyl-containing natural polymers, e.g., pullulan and HEC, can be treated with N-bromosuccinimide and triphenylphosphine to generate bromine atoms in their polymeric structure. Then, these halogen atoms are substituted by specific nucleophilic reagents, such as thiourea, to obtain thiol groups (see **Figure 12A**) (Sarti et al., 2010). Moderate thiol contents (130–958 μmol/g) are obtained through this type of reaction; however, relatively high temperatures and long reaction times are required

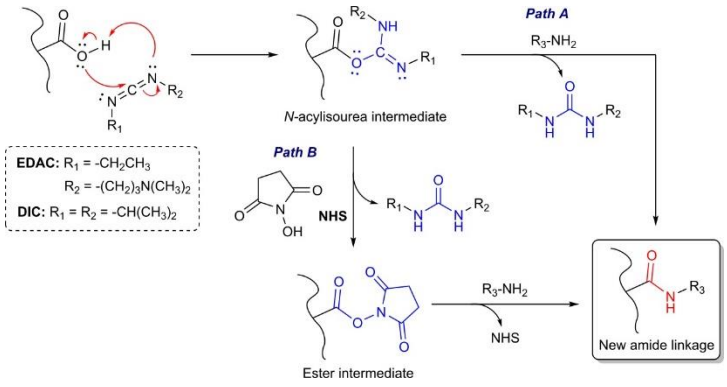

Figure 9. (**Path A**) Mechanism of amidations mediated by EDAC or DIC, in which an O-acylisourea is formed as an intermediate. (**Path B**) Participation of NHS in EDAC- or DIC-mediated amidations. Here, a more stable and reactive ester intermediate is produced in the course of the reaction.

(Leonaviciute et al., 2016; Suchaoin et al., 2016). A greener, faster, and more efficient approach to this reaction has been proposed using microwave irradiation, without a previous substitution of hydroxyl groups by halogen atoms (see **Figure 12B**) (Chauhan et al., 2015). On the other hand, functionalizing agents with higher nucleophilic character can be used to obtain thiolated polymeric networks under moderate reaction conditions, as has been proposed by Lerma et al. (2017) on the thiolation of PVA using cysteamine and L-cysteine.

Finally, ring-opening reactions have been proposed as a kind of click methodology to obtain thiomers. In these cases, ring opening can occur either in the main chain of polymers with cyclic repeating units, such as polyaspartamide, or in the molecular structure of the functionalizing agent, such as γ-thiobutyrolactone. In the former case, nucleophilic reagents, like cysteamine, are used to perform the ring opening and generate sulfhydryl moieties. This methodology requires long reaction times (up to 90 h) and generates moderate yields (~5–22 %) and low thiol contents (~7–46 μmol/g) (Barbarić et al., 2007). In the latter case, the functional groups of the polymer structure can induce a ring opening of the cyclic functionalizing agent. For instance, hemicellulose was thiolated using γ-thiobutyrolactone by a one-pot ring-opening reaction based on: (i) hydroxyl deprotonation by NaH, (ii) ring opening of γ-thiobutyrolactone, and (iii) protonation of thiol groups. Moderate thiol contents (~130 μmol/g) have been obtained using this synthetic approach (Maleki et al., 2015).

5. Conclusions and perspectives

Various aspects are of importance for the successful preparation and application of thiol- and disulfide-containing polymers. Previous any synthetic protocol, it is necessary to design properly a polymer structure that, besides containing thiol and/or disulfide groups, possesses physical and chemical properties suitable for the target

Table 2. The most used functionalizing agents and their respective reactions to obtain thiol- and disulfide-containing polymers.

Functionalizing agent	Reaction type	Modified polymer	Conditions	Ref.
Cysteamine	(A–B, E) Reductive amination (C) Amidation (D) Ring opening reaction (F) Nucleophilic substitution.	(A) Oxidized glycogen (B) Oxidized HEC (C) Gelatin (D) Polyaspartamide (E) Oxidized pullulan (F) PVC	(A–B) $NaBH_3CN$, diluted HCl, 25 °C, 72 h. (C) EDAC, NHS, H_2O, 25 °C, 24 h. (D) DMF, 25 °C, 18 h. (E) H2O, $NaBH_3CN$, 25 °C, 72 h. (F) DMSO/0.1 M NaOH, 35 °C, 4 h.	(A) Perrone et al. (2017) (B) Rahmat et al. (2011) (C) Rohrer et al. (2017) (D) Barbarić et al. (2007) (E) Leonaviciute et al. (2016) (F) Lerma et al. (2017)
Thioglycolic acid	(A, C) Amidation (B) Esterification	(A) Chitosan (B) *Moringa oleifera* gum (C) PEO-PPO-PEO-based polyurethane	(A) EDAC, H_2O, 25 °C, 3 h. (B) (i) 7 N HCl, 80 °C, 150 min; (ii) Acetone. (C) EDAC, NHS, H_2O, 4 °C, 1 h.	(A) Dünnhaupt et al. (2012b) (B) Grewal et al. (2019) (C) Laurano et al. (2020)
L-cysteine	(A–F) Amidation (G) Nucleophilic substitution	(A–B) PAAc (C) Fixomer™ A-30 (D) CG4500 (E–F) Polycarbophil (G) PVC	(A, E–F) EDAC, diluted HCl, 25 °C, 3 h. (B) DIC, DMF, 25 °C, 18 h. (C–D) EDAC, NHS, H_2O, 25 °C, 1.5 h. (G) DMSO/0.1 M NaOH, 35 °C, 4 h.	(A) Iqbal et al. (2012) (B) Leichner et al. (2019b) (C) Prüfert et al. (2017) (D) Prüfert et al. (2020) (E) Lam et al. (2017) (F) Vetter et al. (2010) (G) Lerma et al. (2017)
N-acetyl-L-cysteine	Amidation	(A) Chitosan (B) Glycol chitosan	(A–B) EDAC, diluted acidic solution, 25 °C, 6 h.	(A) Schmitz et al. (2008) (B) Perrone et al. (2018)
Glutathione	Amidation	(A) PAA (B) Glycol chitosan	(A–B) EDAC, diluted acidic solution, 25 °C, 3 h.	(A) Kafedjiiski et al. (2005a) (B) Perrone et al. (2018)
Thiourea	Nucleophilic substitution	(A) Chitosan (B) Brominated pullulan (C) PVA	(A) (i) diluted acetic acid, MW 640 W, 2 min; (ii) 0.2 M NaOH, MW 640 W, 90 s. (B) (i) DMSO/NMP, 80 °C, 16 h. (ii) 3 M NaOH, 5 min. (iii) 3 M H_2SO_4. (C) (i) 10.13 M HCl, 60 °C, 24 h. (ii) 9.29 M NaOH, 12 h. (iii) 3 M H_2SO_4, 12 h.	(A) Chauan et al. (2015) (B) Leonaviciute et al. (2016) (C) Suchaoin et al. (2016)
γ-thiobutyrolactone	Ring opening	O-Acetyl-galactoglucomannan	(i) NaH, 25 °C; (ii) functionalizing agent; RT; (iii) NH_4Cl.	Maleki et al. (2015)
2-iminothiolane	Amidination	(A, D–E) Chitosan (B) PAA and quaternized PAA (C) Gelatin	(A, D–E) Diluted acetic acid, 25 °C, 5–14 h. (B) Diluted HCl, 25 °C, N_2, 14 h. (C) H_2O, 25 °C, 4 h.	(A) Bernkop-Schnürch et al. (2003) (B) Ibie et al. (2015) (C) Rohrer et al. (2015) (D) Palmberger et al. (2008) (E) Krauland et al. (2006)
ISATC	Amidination	(A–C) Chitosan	(A–C) (i) Diluted acetic acid, 25 °C, 2.5 h; (ii) NH_2OH, 30 min.	(A) Kafedjiiski et al. (2005b) (B) Krauland et al. (2005) (C) Kafedjiiski et al. (2006)
6-MNA	Amidation	Chitosan	EDAC, Dioxane/H_2O, 25 °C, 7 h.	Milloti et al. (2009)
6-MNA dimer	Amidation	Chitosan	EDAC, diluted acid solution, 25 °C, 3 h.	Menzel et al. (2016)
AMENA	Amidation	Gellan gum	Diluted acidic solution, EDAC, NHS, 25 °C, 4 h.	Jalil et al. (2019)
Cys-MNA	Amidation	Pectin	EDAC, NHS, H_2O, 25 °C, 7 h.	Hintzen et al. (2013) Knoll et al. (2021)

*HEC: Hydroxyethylcellulose; EDAC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride; DIC: N,N'-diisopropylcarbodiimide; PAAc: Poly(acrylic acid); NHS: N-hydroxysuccinimide; MW: Microwave; CG4500: Acrylic acid/acrylamide-methyl propane sulfonic acid copolymer; Fixomer™ A-30: poly(methacrylic acid-co-sodium acrylamidomethyl propane sulfonate); PVA: Poly(vinyl alcohol); PEO-PPO-PEO: poly(ethylene glycol)-poly(propylene glycol)-poly(ethylene glycol) triblock copolymer; PAA: Poly(allyl amine); PVC: Poly(vinyl chloride).

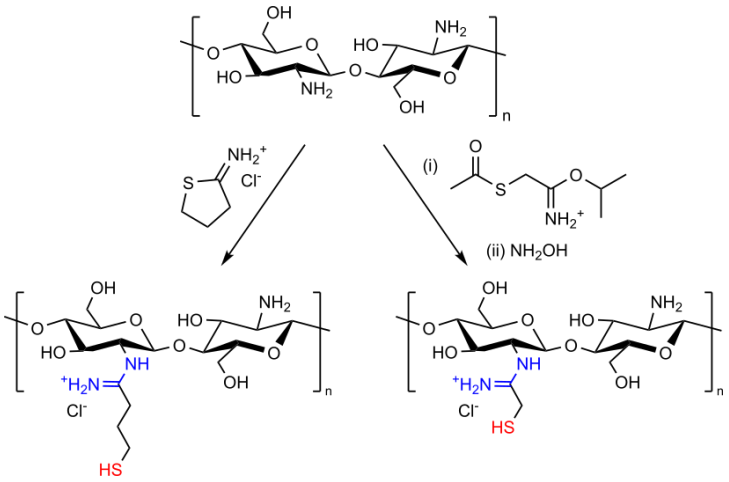

Figure 10. Thiolation of chitosan using 2-iminothiolane (Palmberger et al., 2008) and ISATC (Kafedjiiski et al., 2006).

application(s), e.g., drug delivery or metal ion removal. In this sense, it comprises taking into account thiol pKa, polymer nature, polymer architecture, pH, and redox state, just to mention the most important aspects that affect polymer reactivity. After that, it is necessary to define a proper synthetic protocol that allows us to prepare efficiently the designed polymer. Here, there is a great variety of methodologies that can accomplish the purpose, which is divided into (i) polymerization-based protocols and (ii) structural modifications of a preformed polymer. On the first hand, chain-growth polymerizations, such as via radicals or ring-opening, or step-growth polymerizations, such as polycondensations, polyadditions, or oxidative coupling of thiols, are suitable options. On the other hand, different chemical reactions can be performed to attach sulfhydryl or disulfide moieties in a polymer structure already formed, including amidations, amidinations, nucleophilic substitutions, and reductive aminations, among others. The selected synthetic protocol will depend on factors like polymer structure, polarity, stability, solubility, biocompatibility, and degradability. Likewise, aspects associated with the reactivity of monomers and thiolating agents need to be taken into account. In general, polymerization reactions produce higher thiol and disulfide contents in the resulting polymer. However, functionalization reactions allow us to consider the usage of natural and semi-synthetic macromolecular structures, which make the resulting thiol- or disulfide-based polymer suitable for biomedical applications and related. Besides, thiol content can be modulated to obtain adequate dynamic character based on thiol/disulfide exchange for satisfying a multitude of requirements.

Dynamic covalent polymers based on thiol and disulfide chemistry continue to be an important topic in polymer chemistry and science. The necessity to advance in the design and preparation of smart po-

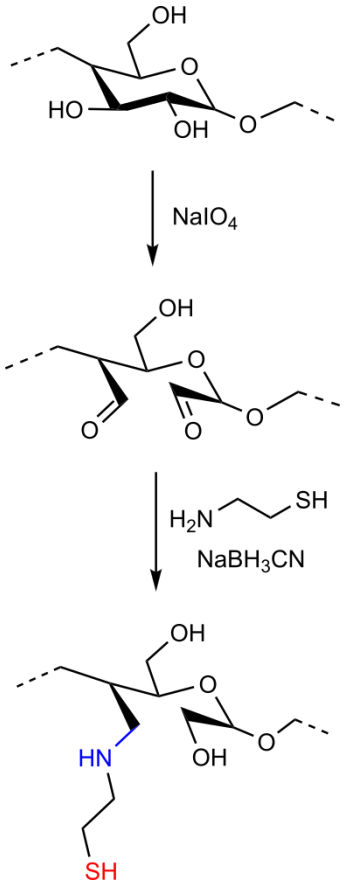

Figure 11. Thiolation of oxidized glycogen by reductive amination using cysteamine (Perrone et al., 2017).

lymeric systems that can be applied in relevant and, in some cases, complex applications, is one of the main reasons incentivizing to research of thiol- and disulfide-based polymers. According to this, it is expected that literature associated with these polymers increases its numbers in terms of relevant and useful works. In particular, some aspects would be approached for advancing in the study of thiol- and disulfide-containing polymers and, especially, their synthesis: (i) designing thiol- and disulfide-based monomers that can be easily used in polymerization reactions, but with limited or null unwanted reactions, (ii) implementing in higher extent living polymerizations, so that their relevant properties as polymerization protocols can be exploded for preparing thiol- and disulfide-containing polymers, (iii) studying in depth the ability of thiolating agents to modify preformed polymers, especially, using click chemistry as a green and efficient methodology, (iv) designing, obtaining, and using new types of thiolating reagents with better efficiencies, and finally (v) investigating in depth the intrinsic and extrinsic aspects that affect the reactivity of thiol- and disulfide-based polymers.

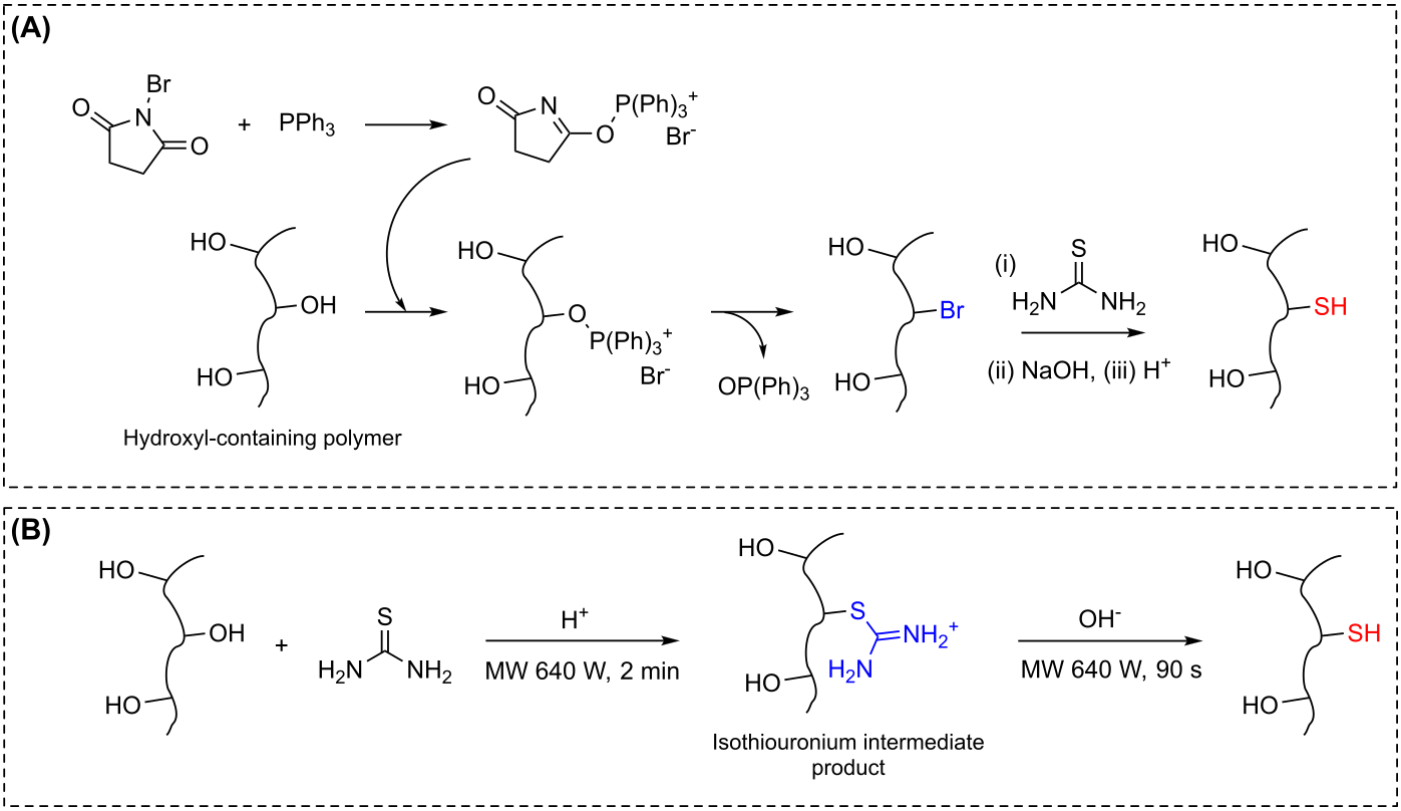

Figure 12. **(A)** Bromination of a hydroxyl-containing polymer by N-bromosuccinimide and triphenylphosphine and its subsequent thiolation using thiourea. **(B)** Microwave-assisted thiolation of a hydroxyl-containing polymer using thiourea.

Conflict interest. The authors declare that there is no conflict of interest.

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