Chapter 1
Introduction

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Abstract This chapter provides introductory aspects to the readers so that they may understand readily and clearly the significance of the book edition. It is important for polymer chemists to know the present status of "enzymatic polymerization" and "green polymer chemistry." The former involves its historical background and characteristics including enzymatic reaction mechanism. The latter is related with several important "green" aspects, toward which the former is expected to contribute. Brief abstracts of all the chapters are also given for the easier understanding of the whole book.

Keywords Enzymatic polymerization · Green polymer chemistry · Enzymatic reaction mechanism · Reaction selectivity · Sustainable society · Bio-based materials · Polymer recycling

1.1 Introduction

This section deals with the generally important and introductory aspects for this book *Enzymatic Polymerization towards Green Polymer Chemistry*, for all the readers to recognize the significance of the book. The arguments are made based on the fundamental and application viewpoints.

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1.1.1 Historical Background of Enzymatic Polymerization

"Nature is our teacher." In fact, in chemistry field this saying reflects the situation of enzyme catalyst utilized for chemical reactions. Enzymes are natural catalysts, which catalyze all in vivo reactions indispensable for maintaining living systems. In vitro, on the other hand, they are able to catalyze various transformation reactions not only of natural substrates but of unnatural substrates, some of which are currently used for industrial productions like food, pharmacology, medicine, textile areas, etc.

The first enzyme discovered was diastase (amylase) extracted from malt solution by Payen and Persoz in 1833 [1]. Due to the mysterious and profound nature, enzymes and enzymatic functions have been attracted much attention as one of the most actively studied topics in science. In organic chemistry field, esterase catalysis was employed for the ester synthesis for the first time in the 1930s [2]. Then, in vitro enzymatic esterifications or transesterifications to produce esters have been studied since the 1980s in organic chemistry field [3–5].

In polymer chemistry field, "enzymatic polymerization" has been extensively studied and developed as a new method of polymer synthesis for almost these three decades. Enzymatic polymerization is a polymerization reaction using enzyme as catalyst, and it was defined as "chemical polymer synthesis in vitro (in test tubes) via nonbiosynthetic pathways catalyzed by an isolated enzyme" [6, 7]. Since the research advances related to the enzymatic polymerization have been so rapid and paid much attention, they have been reviewed and focused from time to time [6–30].

It is to be mentioned here that the progress of the polymer synthesis and related studies is given as follows with citing innovative works chronologically.

- Concept of macromolecules was established by H. Staudinger (1920s) [31, 32].
- Radical chain mechanism in organic chemistry was proposed (1930) [33].
- Nylon was disclosed via polycondensation (1930s) [34].
- Cationic ring-opening polymerization of tetrahydrofuran (1937) [35].
- Ionic chain mechanism was proposed (1940) [36].
- Discovery of Ziegler-Natta catalysts (1953 & 1955) [37–39].
- Living polymerization method was discovered (1956) [40].
- Solid-phase synthesis method of polypeptides was developed (1963) [41].
- Concept of supramolecular chemistry and supramolecular polymer (1960s) [42].
- Finding of conducting polymers (1977) [43].
- Metathesis catalysts have been developed (since 1950s) [44, 45].

Thus, from the viewpoint of polymerization reactions using catalyst (or initiator), the first period of the historically traditional methods is since the 1930s: radical, polycondensation, ring-opening, and ionic (cationic and anionic) polymerizations (from the 1930s to present); these polymerizations may be called as class 1, and the second period: transition-metal catalyzed polymerizations including Ziegler-Natta catalysts and metathesis catalysts (from the 1950s to present); these polymerizations

as class 2. Then, the enzymatic polymerization may be regarded as class 3, because the in vitro enzymatic catalysis is much different from the catalysis of classes 1 and 2, i.e., the enzymatic catalysis is really of bioorganic and supramolecular chemistry as argued below.

The above *definition of enzymatic polymerization* made at the early stage was strict, and therefore, sometimes became thought to be broader, i.e., enzymatic polymerization includes not only the above defined reactions but also reactions such as using acyltransferase enzyme as catalyst in microbial cells, using enzyme-model catalysts, and using enzyme as catalyst for polymer modifications. This book has been edited according to the broader definition.

1.1.2 Characteristics of Enzymatic Polymerization

Catalyst Enzymes Since so many studies have been accumulated on enzymatic functions, over several thousand kinds of enzymes are known nowadays. According to the Enzyme Commission, all the enzymes are classified into six main groups [46]. Of the six, oxidoreductases, transferases, and hydrolases have been actually employed for various polymerization reactions, since these enzymes are proved highly active catalysts for many purposes and areas in fundamental studies as well as practical applications (Table 1.1) [30]. Epimerases are rarely used for polysaccharide modification as mentioned in Chap. 12. In addition, ligases have been entitled to catalyze a polymerization reaction [47].

Catalysis Mechanism Concerning the reaction mechanism of enzymatic reactions, the following two are important fundamental issues.

First, Fischer proposed "key and lock" theory in 1894, which mentioned the specific relationships between the enzyme and the substrate [48], where the substrate is a "key" and the enzyme plays the role of "lock." This interactive relationship is nowadays known as the molecular recognition; in an in vivo reaction (cycle A, Fig. 1.1), natural substrate is recognized specifically by the enzyme to form the enzyme-substrate complex. With forming the complex, the substrate is activated via transition state by supramolecular interaction to form a new bond to give the product with perfect regio- and/or stereoselectivity control. It is essential, therefore, that the substrate is recognized by the enzyme for proceeding of the reaction. In an in vitro reaction (cycle B, Fig. 1.1), on the other hand, an artificial substrate must be recognized by the enzyme to form the enzyme-artificial substrate complex; then the artificial substrate is activated via transition-state to form a new bond with controlling all the reaction selectivity perfectly, ending up with the product formation.
Second, Pauling suggested in 1946 the specific reason why enzymes cause the catalysis under mild reaction conditions like in living cells [49, 50]. Enzymatic reaction pathway and its energy diagram are shown as Scheme 1.1 and Fig. 1.2, respectively [30]. An enzyme (E) and a substrate (S) form a complex (ES) through a key and lock

Table 1.1 Classification of enzymes, typical example enzymes, macromolecule examples synthesized by enzymatic polymerization as well as modified by enzymatic reaction [30, 47]

Class	Enzymes	Example enzymes	Macromolecules synthesized	Macromolecules modified
1	Oxidoreductases	Peroxidase, laccase, tyrosinase, glucose oxidase	Polyphenols, polyanilines, polythiophenes, vinyl polymers	Polysaccharides, polypeptides, lignins (proteins)
2	Transferases	Phosphorylase glycosyltransferase, acyltransferase	Polysaccharides, cyclic oligosaccharides, polyesters	Polysaccharides, polypeptides (proteins)
3	Hydrolases	Glycosidase (cellulase, amylase, xylanase, chitinase, hyaluronidase), lipase, protease, peptidase	Polysaccharides, polyesters, polycarbonates, polyamides, poly(amino acid)s, polyphosphates, polythioesters	Polysaccharides, polypeptides (proteins)
4	Lyases	Decarboxylase, aldolase, dehydratase		
5	Isomerases	Epimerase, racemase, isomerase		Polysaccharides
6	Ligases	Ligase, synthase, acyl CoA synthase, cyanophycin synthetase	Cyanophycin	

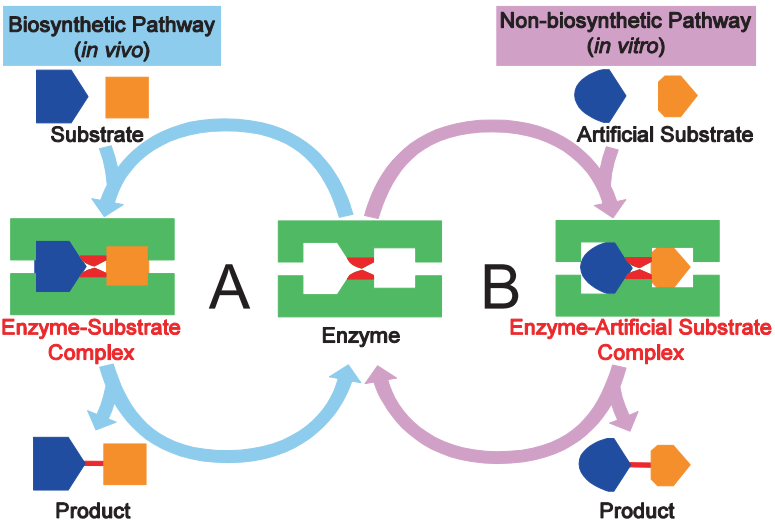

Fig. 1.1 Schematic expression for "key and lock" theory for in vivo enzymatic reactions via biosynthetic pathway (cycle A) and for in vitro enzymatic reactions via nonbiosynthetic pathway (cycle B). (Reproduced with permission from [30]. Copyright 2016 American Chemical Society)

Scheme 1.1 Fundamental reaction pathway with enzymatic catalysis

$$E + S \rightleftharpoons ES \rightleftharpoons [ES]^{\ddagger} \rightleftharpoons EP \rightleftharpoons E + P$$

E: enzyme, S: substrate, P: product

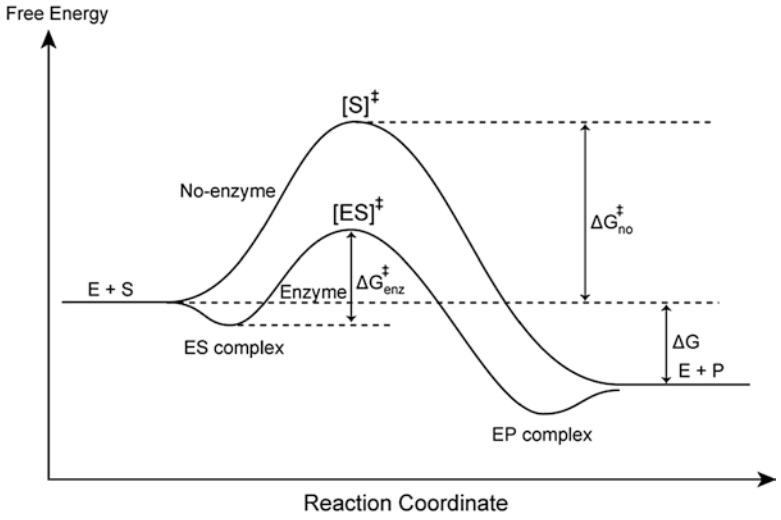

Fig. 1.2 Energy diagram for a chemical reaction: Comparison between an enzyme-catalyzed reaction and a reaction without enzyme. (Reproduced with permission from [18]. Copyright 2009 American Chemical Society)

interaction, which activates the substrate to lead to a transition-state ($[ES]^{\ddagger}$) for the reaction to proceed readily, where the activation energy ($\triangle G_{enz}^{\ddagger}$) is greatly lowered by the stabilization effect of the enzyme, in comparison with that ($\triangle G_{no}^{\ddagger}$) of a reaction without enzyme via a transition-state $[S]^{\ddagger}$, i.e., the enzyme stabilizes the transition-state via complex formation to lower the activation energy.

The enzymatic catalysis normally brings about the rate acceleration of 10^6–10^{12}-fold; however, a specific case reached even 10^{20}-fold [51]. The mechanism of in vivo enzymatic reaction shown in Scheme 1.1 and Fig. 1.1 is generally well accepted [52]. It is also noted that the concept of "catalytic antibody" brought about a new way for reaction selectivity, which is different from that of enzymatic reaction [53]. The difference in mechanistic aspect to cause the selectivity between the enzymatic reaction and the antibody-related reaction is that the former selectively binds the transition state and the latter binds the ground state.

The above key and lock theory does not necessarily mean that the enzyme and substrate relationship requires an absolutely strict combination, but the relationship involves flexibility to some extent. This is the fundamental reason why enzymes are able to catalyze in vitro reactions. So far as the substrate is recognized by the enzyme to form an ES complex, the enzyme-catalyzed reaction is realized in vitro. It is to be paid attention that supramolecular chemistry operates very importantly during the course of reaction, in particular, in the transition-states. These arguments are the cases for all the enzyme-catalyzed synthesis of macromolecules.

As to an important aspect of the enzyme-substrate interactions, monomer of the polymerization must be recognized by the enzyme. It was speculated, therefore, that if the monomer possesses a close structure to that of the transition-state, the monomer is easily recognized by the enzyme, to lead to complex formation and to bring about a transition-state. Then, the polymerization reaction shall proceed smoothly. Based on the speculation, a monomer was newly designed to have the transition-state analogue substrate (TSAS) monomer and was polymerized successfully to produce artificial (synthetic) chitin. The concept of TSAS monomer was proposed for the first time [54] and serves for designing a novel polymerization reaction.

1.1.3 Green Polymer Chemistry

Recently, "green" is a keyword everywhere in the world, due to the importance of the earth environment. A book "green chemistry" was published in 1998; it pointed out the future direction of chemistry research and chemical industry [55]. The book showed 12 philosophical principles to chemists for mitigating the environmental problems yet maintaining the sustainable society. In the polymer chemistry area, "green polymer chemistry" was first noted in 1999 [56]. Among the 12, enzymatic polymerization for green polymer chemistry is concerned with the following issues: reaction conversion must be high (atom economy); starting materials and product polymers are to be of low toxicity or nontoxicity; reaction processes must be designed to lower the toxicity; solvents or other supports are to be minimized in quantity; energy consumption must be minimized to perform the reaction; starting materials are to be renewable rather than depleting resources; using protection and/or deprotection steps for reactions is to be minimized; reactions are hoped to be a catalytic process rather than a mol/mol reaction; product polymers are desirably biodegradable; and chemical disasters are to be prevented. In this context the green character of enzymatic polymerization has often been argued [7, 12, 15, 18–20, 23–30, 47, 56–60].

Owing to the research importance of the area, a new journal *Green Chemistry* was launched in 1999 from The Royal Society of Chemistry. Then, other new journals have been launched like *ACS Sustainable Chemistry & Engineering* (2013) and *Environmental Science & Technology Letters* (2014). Further, the followings are some examples currently published: *Trends in Green Chemistry*, *Green Chemistry Letters and Reviews*, *International Journal of Green Chemistry and Bioprocesses*, *ChemSusChem*, *Environmental Chemistry Letters*, *Current Green Chemistry*, *Green and Sustainable Chemistry*, and so forth.

The appearance of these journals clearly indicates the future direction to which our society should go with taking seriously the environmental and sustainable issues as the most important. Enzymatic polymerization is addressed as a powerful polymer synthesis method for conducting the green polymer chemistry. It involves many advantageous green aspects concerning clean-processes, reaction selectivity, energy savings, natural and renewable resource problems, carbon dioxide emission, etc. These advantageous aspects are described more concretely below [30, 60].

Characteristics of Enzyme Catalyst Enzyme is a nontoxic, renewable natural catalyst, which is free from a metal in most cases. The catalytic activity is very high even in vitro. In some cases, enzyme is robust enough to be used in combination with other chemical catalysts, allowing a new chemo-enzymatic process. An immobilized enzyme can be recovered and repeatedly used. Moreover, enzyme catalyzes a very complicated reaction, when the substrate monomer is adequately designed, as seen particularly in the polysaccharide synthesis; the products like cellulose, hyaluronic acid, chondroitin, etc. are the macromolecules having the most complicated structure ever synthesized in vitro.

The above characteristics are to be noted in particular from the viewpoint that "nature is our teacher." Enzyme-catalyzed reactions often provide us with ideas for biomimetic chemistry, and then, the approach will lead to develop new efficient reaction processes.

It is fortunate that nowadays various enzymes become widely available and the reaction mechanism has increasingly been elucidated due to extensive studies on the area, including X-ray structure analysis, and hence, the enzymatic method will be extended more readily in the future.

Clean Reactions under Mild Conditions with High Selectivity Enzyme-catalyzed reactions normally proceed under mild conditions: at a lower temperature, at around neutral pH, under ordinary pressure, etc. The rate of these reactions is very large in terms of the turnover number. Moreover, the reactions are highly selective in all respects such as enantio-, regio-, chemo- and choro-selectivities [59–63], and hence, they give a clean reaction system with producing no- or minimal by-products. These advantages contribute to energy savings by all means and are normally hard to be achieved by conventional catalytic reactions.

Starting Raw Materials Enzymatic polymerizations are able to use many renewable bio-based materials as starting substrates in place of fossil-based raw materials. They include important platform materials such as cellulose, amylose, lignin, plant-oils, lactic acid, itaconic acid and anhydride, succinic acid and anhydride, sebacic acid, several fatty acids, 1,4-butanediol, sorbitol, glycerol, cardanol, tuliparin, chitin, etc. which shall appear in this book. All of these chemicals are derived from bio-based corn, wheat, sugar cane, cassava, switch grass, some animals, etc. via fermentation and/or chemical/physical treatments. Using the renewable starting materials accords with the concept of "carbon neutral" not to increase the carbon dioxide emission. In addition, environmentally benign reagents can be employed; water, oxygen from air, hydrogen peroxide, carbon dioxide, etc. are applicable.

For reference, during 2011 the sum of 3.5 million tons of bio-based polymers were globally produced, which represents a share of 1.5% of the global polymer production of 235 million tons. The bio-based polymers are expected to be about 12 million tons by 2020, which is compared with the global production of about 400 million tons, the bio-based share being increased to 3%. Thus, the bio-based production capacity will grow faster than the global production [47]. This trend shall contribute to mitigate the global environmental problems with reducing the consumption of fossil resources as well as with contributing to the carbon neutral concept.

Product Polymers Enzymatic polymerization creates new polymers which do not produce via conventional methods due to a very complicated structure. Product polymers from biomasses are nontoxic, and almost all are biodegradable, which are benign to nature. Functionalized polyesters and polysaccharides often provide with value-added products, which are applicable to biomedical and pharmaceutical areas.

Reaction Solvents In vivo enzymatic reactions usually take place in a water solvent system. However, in vitro enzymatic reactions are sometimes robust enough to be carried out not only in an organic solvent but also in a green solvent, like water, supercritical carbon dioxide, and ionic liquids, or in other green solvents.

Polymer Recycling and Degradation First, the case is concerned with the lipase catalysis for polyesters. The ester group is relatively easy for bond-forming and bond-breaking, which is a reversible process. A new method of chemical recycling of polyesters using lipase catalysis was proposed [64–66]. The principle lies in that the ring-opening polymerization system of lactones by lipase catalysis is reversible between linear polymers and cyclic oligomers, which can be controlled by changing the reaction conditions. A continuous flow method combining degradation-repolymerization must be a good way of chemical recycling [67]. Polyester degradation through lipase catalyst is specific to the stereochemistry of polyester backbone as well as branches [68]. Cutinase is also a polyester hydrolase, showing a capability to hydrolyze polyethylene terephthalate (PET, a polyester) to its monomeric units. Cutinase was decorated in strategic positions with sugars to improve a plastic-degrading ability, making it more effective at breaking down PET for the better recycling [69].

Second, enzymatic degradation behaviors of polysaccharides like cellulose by cellulase [70] and chitin by chitinase [71], as well as various nylon polymers and copolymers by nylon hydrodase [72], are well studied by using high-speed atomic force microscopy [70, 71] and gas cluster secondly ion mass spectrometry [72]. These results involve possible application of enzymatic biomass degradation to biofuel developments, fabrication of fibers, and recycling of polyesters.

1.2 Chapter Relations

According to the issues discussed above, we editors made the chapter formation composed of 12 chapters and asked the expert polymer chemists to write the chapter manuscript. The authors of the respective chapter have been very active in the field worldwide and comprehensively wrote/reviewed on the chapter subject including the up-to-date status.

In Chap. 1, the editors described the significance and importance of “enzymatic polymerization” and “green polymer chemistry,” including their historical background. A general scheme of enzymatic polymerization is discussed, and character-

istics of green polymer chemistry are stressed. In addition, a brief description on the contents of 12 chapters is presented. The editors hope that the readers make this book utilized for their further activities.

In Chap. 2, Shoda et al. reviewed the glycoside hydrolase-catalyzed polycondensation of activated glycosyl monomers such as glycosyl fluorides and ring-opening polyaddition of sugar oxazoline monomers, all of which were newly developed reactions. Thus, various kinds of natural polysaccharides were produced for the first time, e.g., cellulose (particularly stressed by the first in vitro synthesis in 1991) and xylan via polycondensation and chitin, hyaluronic acid, and chondroitin via ring-opening polyaddition. Further, these new polymerizations enabled to create various nonnatural polysaccharides. A new concept of "transition state analogue substrate" (TSAS) was also explained.

In Chap. 3, Loos and Kadokawa wrote on the phosphorylase-catalyzed polymerizations to produce polysaccharides. Phosphorylases are rather tolerant with respect to utilizing modified donors and acceptor substrates; they are used for preparation of natural oligo- and polysaccharides, glycoconjugates and their analogues, and for diversification of natural products. Their strict primer-dependence nature allows synthesis of various hybrid materials such as amylose supramolecules of amylose-polymer inclusion complexes.

In Chap. 4, Kimura and Iwata summarized the developments on enzymatic synthesis of polysaccharides by using sucrase (glucansucrase or fructansucrase) as catalyst. Sucrose as monomer is polymerized catalyzed by the former or the latter to produce glucans or fructans, respectively. Product polymers properties, possibility on application of the products as new bio-based materials, and the polymerization mechanism are also discussed.

In Chap. 5, Kobayashi and Uyama described the polyester synthesis via polycondensation reaction with hydrolases as catalyst. Characteristics of lipase catalysis are mentioned from fundamental aspects as well as practical applications. Polycondensation reactions were those of oxyacids or their esters, and of dicarboxylic acids or their esters with alcohols, via dehydration and/or transesterification. Ring-opening addition-condensation polymerization produced unique functional polyesters. Lipase was mainly used as catalyst and also with some protease catalyst.

In Chap. 6, Uyama and Kobayashi dealt with the polyester synthesis via ring-opening polymerizations (ROPs) with catalyst of hydrolases, mainly using lipase. Various cyclic esters, lactones, produced polyesters via lipase-catalyzed ROP, often giving terminal functional polyesters. Lipase catalysis showed unique polymerization behaviors of lactones with different ring-size, which was discussed from ROP mechanistic viewpoint. Lipase catalysis induced enantio-, regio-, and chemo-selective ROPs, which could hardly be achieved by conventional chemical catalysts. ROP of lactones in a variety of media is mentioned for green synthesis of polyesters.

In Chap. 7, Taguchi et al. stated that the natural polyester polyhydroxyalkanoate (PHA) is synthesized via thioester exchange reaction in microbial cells. PHA synthase is the key for producing the various structure-regulated, functional polyesters. In reflecting the importance of bio-based plastics, Kaneka Company built a pilot-scale plant for PHA production in 2011, which is an important news.

In Chap. 8, Numata et al. reviewed the synthesis of polypeptides using proteases enzymes as catalyst. Polypeptides synthesized are of α-peptide linkage structure, and enzymes used are various proteases such as papain, bromelain, α-chymotrypsin, protease K, trypsin, and thermolysin. Starting monomers were mainly natural amino acids and some unnatural amino acids.

In Chap. 9, Uyama reviewed comprehensively the enzymatic oxidative polymerization to aromatic polymers. Phenols, anilines, and thiophenes are mainly used as monomers. As catalyst enzyme, peroxidase containing Fe as active center, laccase, tyrosinase, and bilirubin oxidase (the last three containing Cu as active center) are employed for the polymerization. With using hydrogen peroxide as oxidant, the polymerization of phenols efficiently produce phenolic polymers, most of which are hardly obtained by conventional chemical catalysts. Many product polymers are useful as various functional materials.

In Chap. 10, Higashimura dealt with oxidative polymerization of aromatic monomers catalyzed by enzyme model complexes to produce poly(aromatic)s. The enzyme model complexes used are Fe-containing peroxidase models and Cu-containing monooxygenase and oxidase models, in which H_2O_2 or O_2 is employed as oxidant. The poly(aromatic)s obtained like polyphenols, poly(phenylene oxide)s, polyanilines, and polypyrroles possess excellent physical and chemical properties, as exemplified by "artificial urushi" prepared from cardanol.

In Chap. 11, Zhang and Hollmann presented the synthesis of vinyl polymers via enzymatic oxidative polymerization. The initiating species for the radical polymerization are generated via Fe-containing peroxidase- or Cu-containing laccase-catalyzed radical formations, where H_2O_2 or O_2 are employed as oxidant, with using normally a β-diketone compound together. Parameters to control the polymer properties are introduced and discussed.

In Chap. 12, Cheng covered enzymatic modification of polymers, with focusing literatures for the period 2012–2018 among huge number of studies conducted for research and development and potential industrial applications. The enzymes include mostly hydrolases, oxidoreductases, transferases, and isomerases. The substrates used were polysaccharides, proteins, fats, oils, and lignins, all of which occur abundantly in nature. The types of reaction are polymer hydrolysis and degradation, polymerization, oxidation, glycosylation, crosslinking, and transformation of functional groups. The combination of the biopolymers and enzymes represents opportunities for new product developments and green polymer chemistry.

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