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Review

Chemical synthesis of polysaccharides and polysaccharide mimetics

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ABSTRACT

Polysaccharides are ubiquitous in nature, and play many critical roles in biology. As such, the synthesis of polysaccharides and of polymers mimicking the structure or function of polysaccharides is of keen interest in order to reveal structure-function relationships and to prepare biocompatible and biodegradable materials for research and commercial applications. Recent developments in polymerization methodologies are enabling the synthesis of polysaccharides and polysaccharide mimetics with a variety of structures and architectures. While there have been significant advances in overcoming the difficulties in controlling the regioselectivity and stereospecificity of glycosidic bond formation during polymerization, the development of efficient synthetic routes with general applicability to stereoregular and structurally complex polysaccharides remains a challenge. This review comprehensively describes the chemical polymerization methods to synthesize polysaccharides with different compositions and architectures (linear, branched, and hyperbranched) and the synthetic procedures to polysaccharide mimetics possessing, for example, amine linkages, amide linkages, and carbonate linkages. It begins with a discussion of the challenges and strategies for the synthesis of polysaccharides. We highlight the complexity observed in theses macromolecules due to the number and variety of stereo- and regio-types of glycosidic linkages present between monosaccharide residues. With regards to polysaccharide mimetics, we focus on polymers displaying important structural features present in natural polysaccharides, such as a rigid polymer backbone containing heterocyclic ring structures, short linkages with less than three atoms, as well as multiple hydroxyl groups. Both condensation polymerization and ring-opening polymerization are used to prepare linear polysaccharides, branched polysaccharides, hyperbranched polysaccharides, non-*O*-glycosidic linked polysaccharide mimetics, and pseudopolysaccharides. The review concludes with reflections and suggestions for future directions of investigation.

Contents

Abbreviations: DP, degree of polymerization; M_n, number-average molecular weight; M_w, weight-average molecular weight; LG, leaving group; NMR, nuclear magnetic resonance spectroscopy; GPC, gel permeation chromatography; TrNC, trityl isocyanide; TrCN, trityl cyanide; MeOTf, methyl triflate; TMSOTf, trimethylsilyl triflate; TBDMSOTf, *t*-butyldimethylsilyl triflate; Tf_2O, triflic anhydride; AgOTf, silver triflate; TfOH, triflic acid; TBABr, tetrabutylammonium bromide; TBAI, tetrabutylammonium iodide; $(i\text{-BuAlO})_n$, ECH isobutylaluminoxane-epichlorohydrin; CSA, 10-camphorsulfonic acid; CD, cyclodextrin; MeCD, *O*-permthylated cyclodextrin; MALDI-TOF MS, matrix assisted laser desorption ionization-time of flight mass spectrometry; ESI MS, electrospray ionisation mass spectrometry; FB, frequency of branching; TNF-α, tumor necrosis factor; DB, degrees of branching; Con A, Concanavalin A; DMAP, 4-(dimethylamino)pyridine; TPP, triphenylphosphine; DBU, 1,8-diazabicyclo[5.4.0]-7-undecene; DPPA, diphenylphosphoryl azide; CSI, chlorosulfonyl isocyanate; LiHMDS, bis(trimethylsilyl)amide; IR, infrared spectroscopy; Cbz;, carboxybenzyl; Pfp, pentafluorophenol; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; AIBN, azobisisobutyronitrile; DTBP, di-*tert*-butyl peroxide; BPO, benzoyl peroxide; *m*CPBA, *m*-chloroperbenzoic acid; ROMP, ring-opening metathesis polymerization.

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1. Introduction and scope

Polysaccharides, along with nucleic acids and proteins, are one of three classes of biopolymers that exist ubiquitously in nature, and play many critical roles in the biology of living systems including energy storage, structural support, lubrication, and cell signal transduction [1]. However, progress in polysaccharide research lags significantly behind that of proteins and nucleic acids in terms of synthesizing and manipulating these biopolymers, due to structural complexity and functional diversity [2,3]. Compared to proteins and nucleic acids whose primary structures are simply defined by types and consequences of monomers (amino acids and nucleotides correspondingly), the primary structures of polysaccharides vary in composition, sequence, regio- and stereo-types of linkages, branching, and molecular weight [4].

Structurally, polysaccharides are condensation polymers in which monosaccharide units are joined together by *O*-glycosidic linkages (Fig. 1). The *O*-glycosidic linkage is formed by the condensation or dehydration reaction of the hemiacetal hydroxyl group of one sugar (glycosyl donor) and a hydroxyl group of another sugar unit (glycosyl acceptor) [5]. In contrast to nucleic acids and proteins where monomers are joined together by a specific type of linkage (phosphodiester bond and peptide bond correspondingly), whose formation does not involve a stereocenter, a variety of stereo- and regio-types of glycosidic linkages exist between monosaccharide residues, including α-(1 → 2)-, α-(1 → 3)-, α-(1 → 4)-, α-(1 → 6)-, β-(1 → 2)-, β-(1 → 3)-, β-(1 → 4)-, and β-(1 → 6)-linkage (Fig. 2) [5,6]. Due to the presence of multiple hydroxyl groups, one residue of a glycosyl acceptor may connect to more than one glycosyl donor through different *O*-glycosidic linkages. Consequently, polysaccharides may be linear or branched, and the branches of various structures can occur at different positions of sugar units on the polysaccharide backbones with different branching densities [7]. Unlike proteins, polysaccharides generally exist as polydispersed polymers without defined molecular weights. The degree of polymerization (DP) usually varies from a hundred to a few hundred thousands [8]. The polydispersity of polysaccharides results from the fact that biosynthetic production is not under strict and direct genetic control: there is no template for the synthesis of polysaccharides. Instead, the program for polysaccharide synthesis is intrinsic to various enzymes (glycosidases and glycosyltransferases) that catalyze the polymerization of sugar units, and there is no specific stopping point in the synthetic process [8,9].

Permutations in these structural parameters consequently lead to an almost limitless array of polysaccharide chemical structures and compositions [4]. Sometimes a subtle variation in the monosaccharide unit, glycosidic linkage, or branching affords a dramatic change in polysaccharide structure, property, and/or function [5,9]. For example, both amylose and cellulose are natural homopolysaccharides consisting of (1 → 4)-linked glucose as repeating units, and the only difference in their primary structures lies in the stereochemistry of the glycosidic linkages: α-and β- for amylase and cellulose, respectively. This small difference in glycosidic linkage configuration affords completely different functions: amylose serves to store the chemical energy obtained from the process of photosynthesis, and cellulose acts as the structural materials of plants [9–11].

Owing to structural complexity and polydispersity of polysaccharides, it is challenging to understand the role they play in biological processes and elucidate the mechanism underneath