CHEMICAL REVIEWS

Review

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Green Solvents in Carbohydrate Chemistry: From Raw Materials to Fine Chemicals

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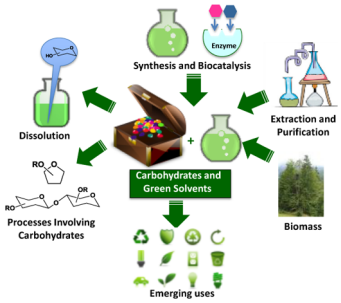

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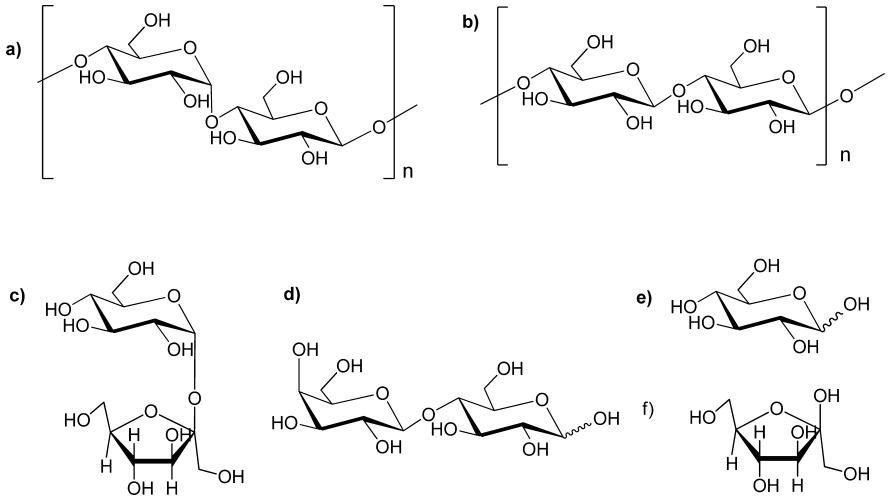
Scheme 1. Chemical Structures of Some Important Carbohydrates for Industrial Applications[a]



[a](a) Starch (α-amylose section), (b) cellulose, (c) sucrose, (d) lactose, (e) glucose, and (f) fructose.

1. INTRODUCTION

In recent decades, there has been an increasing effort to reduce the use of fossil fuels and oil derivatives, to decrease environmental pollution, and to counteract global warming. The use of biomass as raw material is becoming a major alternative to fossil fuels, since it is widely abundant and relatively inexpensive.[1] Carbohydrates, that is, cellulose, starch, and sucrose, are important raw materials in the chemical industry because they are produced from biomass that is readily available in large amounts, facilitating their large-scale application.[2] Carbohydrates display important functions in cell physiology and at the nanoscale in cell membranes, as part of glycoconjugates (glycoproteins, glycolipids, and polysaccharides) comprising the glycocalyx. Consequently, carbohydrates have important roles in many biological processes, including bacterial and viral infection, cancer metastasis, apoptosis, neuronal proliferation, and many other crucial intercellular recognition events.[3]

Carbohydrate-based compounds are also widely used in the pharmaceutical, cosmetic, detergent, and food industries. While these compounds are mainly produced by chemical methods, the use of enzymatic methods has been investigated over the past 20 years as a greener alternative to organic synthesis. Due to the low solubility of enzymes and carbohydrates in traditional organic solvents, research has focused on the chemical and enzymatic synthesis of carbohydrates in polar green solvents such as water, supercritical fluids (SCFs), and ionic liquids (ILs).[4]

It is necessary to define the concept of green chemistry, and the principles that govern it, in order to adapt the chemistry of carbohydrates to sustainable production and processing. A definition of green chemistry was proposed by Paul Anastas and John Warner[5] in 1998 as the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances. Green chemistry has 12 principles that may be summarized as follows:

1. Prevention: Chemistry must avoid the production of toxic and hazardous waste rather than removing these wastes after they are formed.
2. Atom economy: In a synthesis, all components used should be incorporated to the maximum extent possible into a final product.
3. Less hazardous chemical syntheses: Wherever possible, chemical synthesis should be designed to use and generate substances with low toxicity and low environmental impact.
4. Designing safer chemicals: Chemical products should be designed to exhibit their desired function with a minimum level of toxicity.
5. Safer solvents and auxiliaries: Auxiliary substances (for example, solvents) should be avoided if possible and should be innocuous when used.
6. Design for energy efficiency: Energy requirements of chemical processes should be minimized to reduce their environmental impact, and if possible, processes should be performed at ambient temperature and pressure.
7. Use of renewable feedstocks: Raw materials or feedstock should be renewable.
8. Reduce derivatives: Whenever possible, unnecessary derivatization (for example, protection/deprotection) should be reduced or avoided.
9. Catalysis: It is best to employ catalytic reagents (as selective as possible) rather than stoichiometric reagents.
10. Design for degradation: Chemical products should be designed so that at the end of their functional lifetime they undergo an innocuous degradation process and do not persist in the environment.
11. Real-time analysis for pollution prevention: Analytical methodologies should be developed to allow for real-time analysis without the formation of hazardous substances.
12. Inherently safer chemistry for accident prevention: Substances involved in a chemical process should be chosen to minimize the potential for chemical accidents.[5]

Traditional carbohydrate synthesis and modification frequently involves multiple protection and deprotection steps, the use of hazardous and harmful chemicals and solvents, and other harsh conditions that adversely impact the environment and human health.[6] There is a need to find new ways to produce carbohydrate-based products under more environmentally friendly conditions. Green chemistry offers the tools to build a sustainable industrial and research effort. Renewable feedstocks and biocatalyzed reactions carried out under mild conditions, at room temperature, in water or other green solvents, and with

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high atom efficiency are among the strategies employed to achieve such goals.[5,7]

In this review, the following two key points will be treated in depth: (1) carbohydrate feedstock for sustainable processes and products and (2) the role of green solvents in manufacturing of industrial carbohydrate-based products.

1.1. Types of Carbohydrates and Their Importance in the Chemical, Food, and Pharmaceutical Industries

Carbohydrates used as large-scale feedstock in industry include starch, cellulose, sucrose, glucose, and fructose (Scheme 1); they provide a number of advantages for widespread application. Other important saccharides with promising properties for small-scale processes include chitin, chitosan, and uronic acid-containing glycans. In this section, chemical, food, and pharmaceutical applications of these saccharides are reviewed.

These carbohydrates are primarily obtained from renewable feedstocks made through photosynthetic pathways, that is, carbon fixation removing greenhouse gas from the environment. Furthermore, they do not contribute to fossil fuel consumption, therefore being greener than other raw materials. Cellulose and starch are among the most abundant polysaccharides in nature. The biological functions of cellulose and starch are very different, with starch acting as a reservoir of glucose storage for energy[8] and cellulose acting as a structural component in the cell.[9]

The starch polymer has a backbone chain of α-D-(1→4)-glucopyranose (amylose) with branches linked by α-D-(1→6)-glucopyranose (amylopectin) that can be conveniently obtained from many important crops such as wheat, rice, maize, tapioca, potato, and sweet potato.[10] Starch is an economically important carbohydrate because of its partial solubility in water, digestibility by animals, and ability to be converted into other higher-value compounds (i.e., ethanol or Kojic acid) through fermentation.[11] Oxidation, esterification, hydroxyalkylation, hydrolysis, and cross-linking are the most common modifications for preparation of starch derivatives.[12] As a consequence, these derivatives have important applications in food, chemical, and energy industries, such as the preparation of plasticized films and composites, thickeners, and stabilizers for food preparation, and as a source of dextrins and glucose, prepared through enzymatic hydrolysis, for biofuel production.[13]

Cellulose is a linear polymer composed entirely of β-D-(1→4)-glucopyranose. It is the most abundant biopolymer on earth and the most environmentally friendly and sustainable raw material. It has been widely used as the primary source of paper and other applications including textiles, hydrogels for medical uses, films and thickeners, and bioethanol production.[9a,14] Chemical modifications of cellulose include oxidation, hydrolysis, alkylation, and composite synthesis with addition of other polymers.[15]

Sucrose (β-D-fructofuranosyl-α-D-glucopyranoside) is a disaccharide widely found in plants and has been used as a sweetener for centuries.[16] Sucrose contains fructofuranose and glucopyranose that can be released by hydrolysis of its glycosidic bond. The enzymatic hydrolysis of sucrose produces a mixture of the two sugars, known as inverted sugars. Many research groups have put their efforts into optimizing new methods to obtain them.[17] These sugars are widely used in the food industry, for candy and sugared drink production, due to their sweeter taste compared to the original sucrose.[18] The content of monosaccharides and sucrose in invert syrups, honey, fruit juice concentrates, and other sugared solutions are an important subject in food technology. Consequently, adulteration of sugared syrups is a problem requiring analytical methods for quantification.[15b,18c,19]

Fructose is a ketohexose that normally exists in the furanose form. It is considered the sweetest natural sugar in the world and is sweeter than sucrose or glucose. Pure crystalline fructose has been available to the food industry since the late 1980s, even though today it is used in relatively minor amounts.[18c,20] Today, the main feedstock of fructose for food industry is corn flour (85%), but other sources include beet- or cane-derived sucrose and sweet potato starch by enzymatic processes.[10b,c,21] High-fructose syrup was developed in the 1950s but its appearance in the commercial food market took place in the 1960s. As a recent and successful sweetener in the food industry, high-fructose syrup is the most important manufactured source of fructose and is also a less expensive substitute for sucrose in industrial foods, such as soft drinks.[18b,c,20,22]

Glucose is a monosaccharide, present in all organisms and widely utilized by living cells for quick energy production as well as for synthesis of oligosaccharides and glycoconjugates involved in other physiological roles. In industrial microbiology, glucose is commonly used as a carbon source for culture growth and production of metabolites.[23]

Glucose is a fermentable sugar that is frequently obtained from lignocellulosic feedstocks by enzymatic hydrolysis and is also used for the production of bioethanol in processes that require rapid and complete utilization of biomass sugars.[24] Another industrial application of glucose is as a sweetener, although nowadays it has been largely replaced by high-fructose corn syrup because of its better sensory perception of aroma and flavor.[25]

Fermentation of appropriate microbes on feedstocks containing starch, lactose, glucose and other carbohydrates can result in production of lactic acid,[26] an α-hydroxycarboxylic acid with a broad range of applications that can be used as monomer for the production of poly(L-lactic acid) (PLA), a renewable biodegradable polymer.[27] PLA is normally produced in two steps: first, fermentative production of lactic acid, and second, chemical polymerization. PLA synthesis typically involves a fermentation process, often using metabolically engineered *Escherichia coli*.[28] PLA has been employed in tissue engineering for many years.[29] Composite films of PLA are also useful for antimicrobial packaging to reduce the risk of pathogen contamination in fruit and vegetable packages.[30]

Two important glucosamine-containing polysaccharides produced on a large scale are chitin and its derivative, chitosan. Chitin is a polymer with properties similar to cellulose except its monomeric unit, instead of being β-D-(1→4)-glucose, is β-D-(1→4)-*N*-acetylglucosamine. Chitosan is the deacetylated form of chitin that is usually prepared through its alkaline hydrolysis. Chitin is the structural polysaccharide present in crustacean and insect exoskeletons as well as fungal cell walls. Nowadays, chitin is obtained from the aquaculture industries, primarily from shrimp and prawns and other crustaceans, resulting in added value for material traditionally considered as waste.[31]

Chitin and chitosan are biodegradable, nontoxic, antibacterial, and biocompatible matrices. They are widely used in biomedical applications including wound healing, attenuation of the invasive activity of melanoma cells, antioxidant activity, and hydrogels for localized drug delivery.[32] Recently, production of chitin and chitosan nanofibers has been developed by electrospinning procedures.[32a,33] The stability of chitin and chitosan fibers decrease with increased de-*N*-acetylation.[34] Chitin and chitosan fibers have been prepared from many animal sources,[35−37] and composites of these polymers, such as chitin−methacrylic resins,

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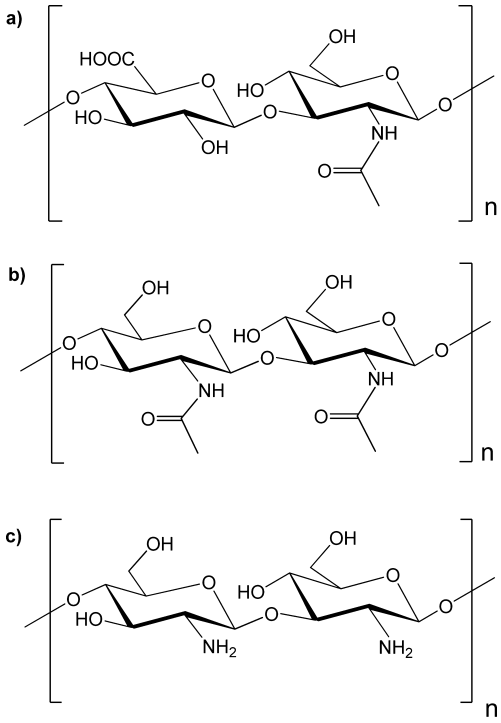
(carboxymethyl)chitin with poly(vinyl alcohol), glutaraldehyde cross-linked chitosan, and collagen−chitosan, are useful in designing fibers with specialized properties for tissue engineering applications.[37,38]

Uronic acids (oxidized monosaccharides, including glucuronic, mannuronic, guluronic, and galacturonic acids) are important components of polysaccharides widely used in the pharmaceutical, cosmetic, and food industries. For example, glucuronic acid is the major uronic acid extracted from *Aloe vera* and is mainly used for cosmetic applications for skin care.[39] Hyaluronic acid is a glycosaminoglycan polysaccharide composed of β-D-(1→4) glucuronic acid and β-D-(1→3)-*N*-acetyl glucosamine repeating units (Scheme 2) that is widely used for

Scheme 2. Glucosamine-Containing Polysaccharides with Broad Industrial Applications[a]



[a](a) Hyaluronic acid, (b) chitin, and (c) chitosan.

cosmetic regeneration and reconstruction of soft tissue.[40] Hyaluronic acid is used as a filler for soft-tissue augmentation. It results in lower immunogenic response and can be degraded in situ by hyaluronidase, although some medical complications in its use have been reported.[39b] It is also used as a dermal carrier for other active ingredients in cosmetic preparations (i.e., tocopherol).[39b] Those features of hyaluronic acid make it the most common of the temporary fillers.

An important pharmacological application of glucose, galactose, and lactose as fine chemicals is their use for glycosylation of substrates to increase polarity and promote water solubility to enhance drug target delivery. The use of these saccharides is justified because of their low toxicity, low cost, high polarity, and specific recognition of cell surfaces. Consequently, there are reports of galactosylated nanodevices for delivering rivabirin, a prodrug that targets hepatic cells due to the carbohydrate affinity for hepatocytes;[41] glycosylation of polypropylene membrane for lectin adsorption;[42] conjugation of chitosan and lactobionic acid for galactosylation of chitosan for drug liver targeting;[42] and glycosylation of terpenoids with important pharmacological properties that may be used as prodrug substances.[43]

Oligosaccharides present on the cell surface play an important role in our immunological response to cancer: through this molecular interaction, the immune system can differentiate cancer cells from normal cells based on the presence of specific markers, called tumor-specific antigens.[44] Some important tumor markers include oligosaccharides from Lewis-y histoblood group,[45] T and Tn antigens,[46] CA 19-9 for pancreatic cancer,[47] and prostate-specific antigen,[48] among others. Today, the development of cancer vaccines, selective tumor cell targeting, and conjugates as specific cancer cell markers are major goals for synthetic carbohydrate chemists.[49] However, the main drawback in this research field is the rapid access to sufficient quantities of glycoconjugates or oligosaccharides for followup studies,[49d] which presents a bottleneck in developing carbohydrates with pharmaceutical applications.

1.2. Green Solvents in Chemical, Food, and Pharmaceutical Industries

The concept of green solvents is strongly related to the principles of green chemistry.[5] Strictly speaking, it is difficult to think of a truly green solvent beyond water. Water is nontoxic for living organisms and does not need to be manufactured, as it is readily available on most of the earth's surface. Carbohydrate chemistry is well suited to be developed in aqueous media, as hydrogen bonds that are formed between most carbohydrates and water facilitate their solubility. Some exceptions include polysaccharides of high molecular weight and highly crystalline polysaccharides that are often either slightly or completely insoluble in water.

In 2007 Capello et al.[50] developed a comprehensive framework for the environmental assessment of solvents by evaluating 26 organic solvents and quantifying their emissions and the resources used during their full life cycle. According to their results, alcohols such as methanol and ethanol and alkanes such as hexane and heptane are greener solvents than other traditional organic solvents such as dioxane, acetonitrile, acids, formaldehyde, and tetrahydrofuran (THF). Upon applying the green chemistry principles,[5] ethanol represents one of the most sustainable solvents due to its ready availability from renewable resources by fermentation of carbohydrate substrates.

Ethanol is the most well-known product of carbohydrate fermentation and has been used by mankind for millennia. It is the result of alcoholic fermentation normally achieved by the culture of *Saccharomyces cerevisiae*.[51] Classic ethanol fermentation is carried out with grapes and sweet fruits as raw material for production of wine and other alcoholic beverages, but modern technology allows the use of more complex feedstock, for instance, cellulose.[1b,10b,11a,52] Ethanol from biomass is normally called bioethanol, but when it is obtained from lignocellulosic materials (i.e., wood or fibrous plants) it is called a second-generation bioethanol.[53]

Bioethanol is not only a very useful highly polar organic solvent; it is also the focus of attention because of its potential to replace fossil fuels and has become the largest product of industrial biotechnology.[54] Several approaches are used to minimize the cost of every process step and maximize yeast efficiency and ethanol production. These include development of yeast strains with tolerance for physiological stress during alcohol production, yeast cell immobilization by flocculation, and use of membrane distillation for ethanol recovery.[12,51b,54b,55]

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Another renewable green solvent, ethyl lactate, is a nontoxic and biodegradable ester that can replace halogenated solvents in many industrial applications.[56] Since lactic acid and ethanol are products of carbohydrate fermentation, this solvent is an indirect product from biomass feedstock. Ethyl lactate is water-miscible because of its ability to develop intra- and intermolecular associations through hydrogen bonding.[57] Its properties have been theoretically and experimentally characterized over a wide range of pressure and temperature parameters, making ethyl lactate a green solvent of choice for process scale-up at the industrial level.[58]

Glycerol is a low-toxicity, biocompatible, and biodegradable solvent obtained from renewable sources such as oils and fats as a byproduct during saponification processes and also from the biodiesel industry.[59] For industrial purposes, glycerol has been traditionally used as a humectant in skin formulations because it has a moderate skin permeability coefficient (1.82×10^{-6} cm/s) and for its anti-irritant effect.[60] Due to recent overproduction of glycerol by the biodiesel industry, there is an active search for new applications for glycerol, leading to the development of new glycerol-derived solvents, including glycerol acetals, glycerol triacetate, glycerol carbonate, and alkyl glycerol ethers.[7b,61] Thus, in many ways glycerol competes with glucose as an inexpensive fermentation carbon source and in the area of green solvent production. Glycerol-based solvents have been widely used in biocatalysis research as new alternative media for enzyme-catalyzed reactions in disaccharide synthesis and can result in modified regioselectivity compared to reactions performed in aqueous medium, due to solvent−enzyme and solvent−substrate interactions.[7b,62]

Another biomass-derived solvent is 2-methyltetrahydrofuran (MeTHF), which is considered as a green solvent for its two main features: first, it can be produced from biomass feedstock like furfural or levulinic acid, and second, it is environmentally degraded by abiotic factors like air and sunlight.[63] Recently, the toxicological response in rats of MeTHF has been evaluated, resulting in a permitted daily exposure in humans of 6.2 mg/day, making it an appropriate green solvent for pharmaceutical and chemical purposes;[64] however, further study is needed for its wide-scale industrial application.[63,65]

Finally, neoteric solvents, for example, ILs, supercritical carbon dioxide ($scCO_2$), and fluorous solvents, have emerged as a green research area in recent decades with important application in biocatalysis.[7b,66] While ILs are not green solvents by definition,[67] careful selection of cations and anions, derived from renewable resources, and reduction of steps in their chemical synthesis can afford what is reasonably considered as an environmentally friendly solvent.[68] ILs have been used over the past decade as alternative solvents for enzyme-catalyzed reactions.[69] These solvents can affect enzyme conformational structure and afford different selectivity behavior due to these conformational effects.[70] Also, ILs have been used in preparation of solutions for carbohydrate substrates with low solubility in traditional solvents, for example, cellulose.[71]

2. TYPES OF GREEN SOLVENTS THAT CAN DISSOLVE CARBOHYDRATES: PROPERTIES AND DESCRIPTIONS

Green solvents are widely used nowadays in research and in industry.[72] The most important advantage for their use is their environmentally friendly nature. There is a great need of new green alternatives to traditional solvents[50] because they often account for most of the mass wasted in synthetic and industrial processes. Moreover, many common solvents utilized are toxic, flammable, and/or corrosive. Their volatility and solubility can contribute to air, water, and land pollution or be harmful to workers and very dangerous in case of an accident. Recovery and reuse, when possible, is often associated with energy-intensive distillation, and sometimes cross-contamination occurs. Chemists have searched for safer solutions to address all those shortcomings. The main solvent systems that are currently considered "green" are ILs,[73] SCFs,[74] fluorinated solvents,[75] deep eutectic solvents (DES),[76−78] biomass-derived solvents (BDS),[79] water,[80] and solventless systems.[81] In the field of carbohydrate chemistry, green solvents have targeted many applications[82] that will be discussed in this review, with special emphasis on enzymatic synthesis of carbohydrates under green conditions. In this section, the dissolving power of green solvents for carbohydrates and their role in chemical transformations will be addressed.

2.1. Ionic Liquids

Ionic liquids (ILs) are low-temperature molten salts. Their nature, therefore, is ionic and most of them are organic compounds. The first report of an IL, $[Et_3N][NO_3]$, goes back 90 years, but its explosive nature precluded its widespread application. In the 1930s, an early patent application described cellulose dissolution by use of a molten pyridinium salt above 130 °C.[83] However, the use of ILs in chemical synthesis began in the 1990s,[84] affording first-generation ILs with unique physical−chemical properties, such as thermal and chemical stability, negligible volatility, flame retardancy, moderate viscosity, high polarity, low melting points, and high ionic conductivity. ILs that can dissolve many compounds without volatility and are thermally stable, and can be fine-tuned to show specific targeted behavior for an application, are referred to as second-generation ILs. Nowadays, third-generation ILs are being designed with the main goal of achieving specific desirable biological properties, such as enzymatic stability. Simultaneously, the number of studies on the toxicity, biodegradability, and environmental fate of ILs has increased.[50,85] Since ILs can often be fine-tuned to have desired properties for a particular application, they are referred to as designer solvents. Another green solvent characteristic of ILs is their reusability for the same chemical process repeatedly. Reaction products made in ILs can often be recovered by distillation from the nonvolatile IL or extracted with water or hydrocarbon solvents that are IL-immiscible. Most of the ILs are composed of a heterocycle (pyridine or imidazole) cation and a halide, organic acid, or isocyanate anion (Scheme 3). The most commonly used ILs, their abbreviated names, and their water solubilities are presented in Table 1.

Scheme 3. Chemical Structures of Common Ionic Liquids

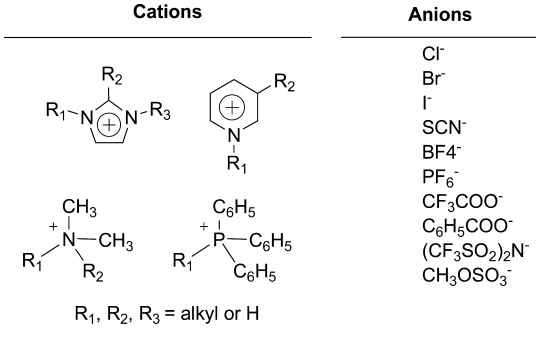

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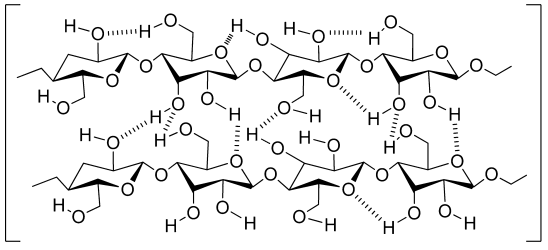
Table 1. Nomenclature of Commonly Used Ionic Liquids and Their Miscibility with Water[86]

cation	anion	common notation	water miscibility
1-butyl-3-methylimidazolium	tetrafluoroborate	[BMIM][BF_4]	yes
1-butyl-3-methylimidazolium	hexafluorophosphate	[BMIM][PF_6]	no
1-butyl-3-methylimidazolium	bis[(trifluoromethyl)sulfonyl]imide	[BMIM][Tf_2N]	
1-butyl-3-methylimidazolium	trifluoromethanesulfonate	[BMIM][Tfms]	yes
1-butyl-3-methylimidazolium	glycolate	[BMIM][$OHCH_2COO$]	
1-butyl-3-methylimidazolium	octylsulfate	[BMIM][$OctSO_4$]	yes
1-butyl-2,3-dimethylimidazolium	tetrafluoroborate	[BDMIM][BF_4]	yes
1-butyl-2,3-dimethylimidazolium	hexafluorophosphate	[BDMIM][PF_6]	no
1-butyl-2,3-dimethylimidazolium	trifluoromethanesulfonate	[BDIM][Tfms]	
1-butyl-4-methylpyridinium	tetrafluoroborate	[BMP][BF_4]	yes
1-ethyl-3-methylimidazolium	tetrafluoroborate	[EMIM][BF_4]	yes
1-ethyl-3-methylimidazolium	bis[(trifluoromethyl)sulfonyl]imide	[EMIM][Tf_2N]	no
1-ethyl-3-methylimidazolium	trifluoromethanesulfonate	[EMIM][Tfms]	yes
1-ethylpyridinium	tetrafluoroborate	[ETPY][BF_4]	
1-ethylpyridinium	trifluoroacetate	[ETPY][CF_3COO]	
1-butylpyridinium	bis[(trifluoromethyl)sulfonyl]imide	[BUPY][Tf_2N]	
1-butyl-1-methylpyrrolidinium	bis[(trifluoromethyl)sulfonyl]imide	[BMPY][Tf_2N]	partly
1-hexyl-2,3-dimethylimidazolium	tetrafluoroborate	[HDMIM][BF_4]	partly
1-hexyl-3-methylimidazolium	tetrafluoroborate	[HMIM][BF_4]	partly
1-hexyl-3-methylimidazolium	hexafluorophosphate	[HMIM][PF_6]	no
1-(3-hydroxypropyl)-3-methylimidazolium	hexafluorophosphate	[HPMIM][PF_6]	
1-(3-hydroxypropyl)-3-methylimidazolium	glycolate	[HPMIM][$OHCH_2COO$]	
1-(3-hydroxypropyl)-3-methylimidazolium	chloride	[HPMIM][Cl]	
1,3-dimethylimidazolium	methylsulfate	[MMIM][$MeSO_4$]	yes
3-methyl-3-nonylimidazolium	hexafluorophosphate	[MNIM][PF_6]	no
1-methoxyethyl-3-methylimidazolium	tetrafluoroborate	[MOEMIM][BF_4]	
1-methoxyethyl-3-methylimidazolium	hexafluorophosphate	[MOEMIM][PF_6]	
1-octyl-3-methylimidazolium	tetrafluoroborate	[OMIM][BF_4]	partly
1-octyl-3-methylimidazolium	hexafluorophosphate	[OMIM][PF_6]	no
1-octyl-3-nonylimidazolium	hexafluorophosphate	[ONIM][PF_6]	no
methyltrioctylammonium	bis[(trifluoromethyl)sulfonyl]imide	[MTOA][Tf_2N]	no
butyltrimethylammonium	bis[(trifluoromethyl)sulfonyl]imide	[BTMA][Tf_2N]	no
3-hydroxypropyl-trimethylammonium	bis[(trifluoromethyl)sulfonyl]imide	[HTMA][Tf_2N]	
3-cyanopropyl-trimethylammonium	bis[(trifluoromethyl)sulfonyl] imide	[CPRTMA][Tf_2N]	
butyltrimethylammonium	bis[(trifluoromethyl)sulfonyl] imide	[BTMA][Tf_2N]	
5-cyanopentyl-trimethylammonium	bis[(trifluoromethyl)sulfonyl] imide	[CPTMA][Tf_2N]	
hexyltrimethylammonium	bis[(trifluoromethyl)sulfonylimide	[HTMA][Tf_2N]	

Carbohydrates are highly polar molecules that are generally soluble in water, strong acids, or organic solvents capable of forming hydrogen bonds, such as dimethyl sulfoxide, dimethylformamide, pyridine, or 2-methylpropanol. With the exception of water, these solvents have many undesirable properties, and there is a need to find new, environmentally benign green solvents to dissolve them. A major advance occurred when ILs employed to dissolve carbohydrates were first used to dissolve a water-insoluble carbohydrate, cellulose. Cellulose forms a hydrogen-bonded supramolecular structure that makes it insoluble in water and most organic solvents (Schemes 1 and 4). Graenacher[83] showed that benzylpyridinium chloride or *N*-ethylpyridinium chloride had the ability to dissolve cellulose with the formation of solutions of various viscosities. However, alkylpyridinium salts usually have high melting points, thus limiting their applications as solvents.

Since then, many reports on dissolution of cellulose in ILs[87,88] have shown that cellulose is more easily dissolved in ILs containing ammonium,[89] imidazolium[90] and pyridinium cations.[91] Also, ILs such as 1,3-dialkylimidazolium formates that are halogen-free have been used to dissolve cellulose, and various polysaccharides, including amylose,[92] have been dissolved at high concentrations under mild conditions. It is important to be able to dissolve cellulose, since it is a renewable resource and its current industrial processing is not a green process.[93] Upon acylation, it becomes soluble and can be used in many industrial applications, but that requires processing.

Scheme 4. Hydrogen-Bonded Supramolecular Structure of Cellulose



In situ viscosity measurements[94] have been used to measure the rate of cellulose dissolution in a number of ILs, and their performance as solvents has been assessed. [BMIM][95] dissolves cellulose faster than analogous ILs with chloride or dimethylphosphate anions. Analysis of the data highlights the influence of

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Table 2. Solubility of Different Carbohydrates in Different Ionic Liquids[98]

IL	carbohydrate	solubility
[BMIM][Cl]	cellulose	10 wt % (100 °C); 25 wt % (microwave, 3−5 s pulses); 10−18% (83 °C)
[BMIM][Cl]	wool keratin fibers	11 wt % (130 °C)
[BMIM][Cl]	eucalyptus pulp	≥13.6% (85 °C)
[BMIM][Cl]	Solucell 1175 cellulose	16 wt % (100 °C)
[EMIM][Cl]	eucalyptus pulp	≥15.8% (85 °C)
[AMIM][Cl]	cellulose	8−14.5 wt % (80 °C)
[AMIM][Cl]	Solucell 1175 cellulose	10 wt % (100 °C)
[AMIM][Cl]	KZO3 (1085) cellulose	12.5 wt % (100 °C)
[BDMIM][Cl]	eucalyptus pulp	≥12.8% (85 °C)
[BMPY][Cl]	cellulose	12−39% (105 °C)
[ADMIM][Br]	cellulose	4−12% (80 °C)
[BMIM][DCA]	D-glucose	145 $g{\cdot}L^{-1}$ (25 °C)
[BMIM][DCA]	sucrose	195 $g{\cdot}L^{-1}$ (25 °C), 282 $g{\cdot}L^{-1}$ (60 °C)
[BMIM][DCA]	lactose	225 $g{\cdot}L^{-1}$ (75 °C)
[BMIM][DCA]	β-cyclodextrin	750 $g{\cdot}L^{-1}$ (75 °C)
[BMIM][DCA]	amylose	4 $g{\cdot}L^{-1}$ (25 °C)
[MOEMIM][DCA]	D-glucose	91 $g{\cdot}L^{-1}$ (25 °C)
[MOEMIM][DCA]	sucrose	220 $g{\cdot}L^{-1}$ (25 °C)
[MOMMIM][DCA]	sucrose	249 $g{\cdot}L^{-1}$ (25 °C), 352 $g{\cdot}L^{-1}$ (60 °C)
[AMIM][HCOO]	cellulose	10−20 wt % (60−85 °C)
[EMIM][OAc]	eucalyptus pulp	≥13.5% (85 °C)
[BMIM][OAc]	eucalyptus pulp	≥13.2% (85 °C)
[EMIM][$(R)PO_2$]	microcrystalline cellulose (DP250)	10 wt % (45−65 °C)
[MOEMIM][BF_4]	D-glucose	5 $mg{\cdot}mL^{-1}$ (55 °C)

both anion basicity and relative concentration on the rate of dissolution. Molecular dynamics simulations have been performed to better understand the interaction between ILs and cellulose.[96] The two extreme states of cellulose dissolution include the crystalline microfibril state and a dissociated state in which all the chains of the microfibril are fully separated from one other by at least four solvation shells. Molecular dynamics simulations of the two states were carried out in water and in 1-butyl-3-methylimidazolium chloride, [BMIM][Cl], to provide a comprehensive analysis of solvent effects on cellulose dissolution. The results reveal two important molecular aspects of the mechanism of cellulose dissolution. The first is that perturbation of solvent structures by the dissolved cellulose chains can be a crucial factor in determining solubility, particularly the insolubility of cellulose in water at 300 K. Second, both the Cl anion and the BMIM cation of [BMIM][Cl] interact with the moieties of cellulose that form intersheet contacts, the most robust component of the interaction network of crystalline cellulose. The Cl anions can form hydrogen bonds with hydroxyl groups of the cellulose chains from either equatorial or axial directions. For BMIM cations, the calculated density profiles reveal that the contacts with cellulose chains along the axial directions are closer than those along the equatorial directions. An atomistic model of cellulose was simulated in a dissociated state and a microfibril state to represent dissolution. The calculated values of entropy and internal energy changes between the two states inform the interplay of energetic and entropic driving forces in cellulose dissolution. In both water and [BMIM][Cl], the entropy associated with solvent degrees of freedom decreases upon cellulose dissolution. However, solvent entropy reduction in [BMIM][Cl] is much smaller than that in water and counteracts the entropy gain from the solute degrees of freedom to a much lesser extent. Solvent entropy reduction in water also plays a major role in making the free energy change of cellulose dissolution unfavorable at room temperature. In [BMIM][Cl], interaction energies between solvent molecules and cellulose chains and the total entropy change both contribute favorably to the dissolution free energy of cellulose.

Highly effective solvents for the dissolution of cellulose at ambient temperature have been designed[97] by adding any aprotic polar solvent to 1-butyl-3-methylimidazolium acetate, [BMIM][AcO] (Table 2). The effects of molar ratio of aprotic polar solvents to [BMIM][AcO], anionic structure of ILs, and nature of the cosolvents on cellulose solubility have been studied in detail. The enhanced dissolution of cellulose is suggested to mainly result from preferential solvation of cations of the ILs by aprotic polar solvents, and this has been supported by conductivity measurements.

Other carbohydrate polymers, such as starch (Scheme 1),[99] were found to be soluble in ILs[100] such as [BMIM][Cl] and 1-butyl-3-methylimidazolium dicyanamide, [BMIM][DCA], in concentrations up to 10% (w/w) at 80 °C. Higher concentrations resulted in solutions with a viscosity too high for stirring. Upon acylation with anhydrides[101] in [BMIM][Cl], acetyl starch was obtained with various degrees of substitution. The acylation reaction did not proceed without pyridine. ^1H NMR and IR spectroscopy were used to determine the degree of substitution of starch. Viscosity studies indicated that the starch underwent a slight reduction in molecular weight during the course of acylation.

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There are a number of review articles that discuss different aspects of the use of ILs in carbohydrate chemistry, in particular, dissolution[88,102] and functionalization of simple sugars,[103] cyclodextrins,[104] cellulose,[87,88] chitin/chitosan[105] and starch,[106] Liu et al.,[107] have reported the solubilities of common monosaccharides, disaccharides, and polysaccharides in weakly coordinating ILs such as 1-butyl-3-methylimidazolium tetrafluoroborate, [BMIM][BF_4], and 1-butyl-3-methylimidazolium hexafluorophosphate, [BMIM][PF_6], as well as other synthesized ILs such as 1-methoxyethyl-3-methylimidazolium tetrafluoroborate, [MOEMIM][BF_4]. For example, D-glucose dissolves at much higher concentrations in [MOEMIM][BF_4] than in *tert*-butyl alcohol. The solubility of glucose is influenced much more by the nature of the anion than that of the cation. ILs containing the DCA anion dissolve glucose more than an order of magnitude better than their tetrafluoroborate counterparts. The behavior of the 1-(2-methoxyethyl)-2,3-dimethylimidazolium chloride and hexafluorophosphate salts were compared[108] with that of the analogous BMIM salts to examine the influence of the ether oxygen on salt thermal properties for a typical constituent cation used in the preparation of ILs. Tan and Macfarlane[109] have shown that the high solubility of carbohydrates can be attributed to the H-bond acceptor properties of the DCA anion,[107] which was recently recognized as a prerequisite for dissolving complex molecules. Their density and solubility was assayed in different ILs—1-ethyl-3-methylimidazolium dicyanamide, [EMIM][DCA]; [BMIM][DCA]; Aliquat dicyanamide or trihexyltetradecylphosphonium dicyanamide, [Aliquat][DCA]; and 1-ethyl-3-methylimidazolium trifluoroacetate, [EMIM][CF_3COO]—between 288 and 339 K. ILs based on Cl, DCA, formate (HCOO), and acetate (OAc) anions[110] could dissolve up to 10−20% (wt) cellulose, and >100 g·L^{-1} other carbohydrates such as D-glucose, sucrose, lactose, and cyclodextrin (Table 3).

Table 3. Solubility of Glucose in Ionic Liquids at 25 °C[88,111]

solvent	solubility (g/L)
[BMIM][BF_4]	1.1
[BMIM][DCA]	145
[BMIM][PF_6]	0.5
[MOMMIM][Tf_2N]	0.5
[MOMMIM][BF_4]	4.4
[MOMMIM][TfO]	4.3
[MOEMIM][Tf_2N]	0.5
[MOEMIM][PF_6]	2.5
[MOEMIM][BF_4]	2.8
[MOEMIM][TfO]	3.2
[EOEMIM][Tf_2N]	0.5
[EOEMIM][PF_6]	0.7
[EOEMIM][BF_4]	2.8
[MOMMIM][DCA]	66
[MOEMIM][DCA]	91
[EOEMIM][DCA]	70

Also, sugar alcohols, such as xylitol and sorbitol,[112] represent a class of compounds that could play an important role in biorefining. More recently, ILs have been used in dissolving and processing biomass.[109] For example, [BMIM][Cl] could dissolve considerable amounts of cellulosic materials and lignin from different wood samples over 24 h at 100 °C. The solubilization of carbohydrates in ILs has enabled a number of chemical derivatizations of these natural products in homogeneous systems, as well as cellulose regeneration for a variety of applications (such as enzymatic hydrolysis, blending with wool keratin, and producing enzyme-encapsulated films). Unfortunately, since carbohydrate-dissolving ILs are typically composed of Cl, DCA, HCOO, and OAc anions, these anions form strong hydrogen bonds with carbohydrates for dissolving them. For this reason, these ILs are more likely to denature enzymes,[113] preventing a further enzymatic modification of dissolved carbohydrates in ILs. Zhao et al.[98] reported newly designed ILs that are capable of dissolving carbohydrates without considerably inactivating enzymes. Since the high molar concentration of anions in ILs is responsible for enzyme denaturation, perhaps a lower anion concentration could reduce the enzyme-inactivating nature of ILs. Therefore, a longer substituent on the cation would increase the molecular weight and thus decrease the anion concentration of an IL. However, a longer alkyl chain on the cation dramatically increases the melting point and viscosity of the resulting IL. In contrast, glycols and their derivatives are known to have low melting points and low viscosities. Therefore, poly(ethylene oxide)s could be incorporated into cationic or anionic units to produce the liquid state of ion-conductive polymers. In particular, various ILs have been synthesized by grafting alkyloxy substituents (ether or alcohol groups) onto the imidazolium ring or pyridinium ring. The inclusion of alkyloxy or alkyloxyalkyl groups can lower the melting points of the resulting organic salts, yielding room-temperature ILs in most cases. In addition, the oxygen atoms embedded in the glycol chain may act as hydrogen-bond acceptors, interacting with carbohydrates to dissolve them. Following this rationale, a series of imidazolium and tetraalkylammonium ILs carrying glycol substituents in the side chain were prepared, and then the solubilities of sugars and cellulose in these new solvents were determined.

Carbohydrates are among the most abundant, low-cost natural sources of chiral materials. These considerations prompted the design, synthesis, and characterization of carbohydrate-based ILs as new chiral solvents.[114] Owing to the presence of many hydroxyl groups, these carbohydrate-based ILs provide high coordination ability that can be tuned by varying the electronic density of their oxygen atoms through a proper protecting-group pattern. Therefore, carbohydrate-based ILs could be used as coordinating solvents in stereoselective and/or metal-catalyzed reactions. Also, most carbohydrate-based ILs can be obtained from renewable sources.[115,109]

Water is one of the major impurities of IL and has a strong impact on the solubility of carbohydrates in ILs because it modifies the solvation ability of ILs.[116] Therefore, it is very important to report that the real ability of IL to dissolve carbohydrates as water efficiently masks the solubility behavior and is one of the major hindrances in dissolution of carbohydrates in ILs. Interactions of 1-butyl-3-methylimidazolium carboxylate ionic liquids ([BMIM][HCOO], [BMIM][AcO], and [BMIM][EtO]) with glucose in water were studied by use of their volumetric properties, viscosity, and conductivity as well as NMR spectroscopy.[110] Volumetric interaction parameters were also obtained from the transfer volumes of the ILs. The contributions of the solvent properties and the IL−solvent interactions were extracted, together with molar activation energies (of the ILs for viscous flow of the aqueous glucose plus IL solution). In addition, ^{13}C and ^{1}H NMR spectra of methyl β-D-glucopyranoside and β-D-glucopyranoside with ILs and D_2O were studied. The NMR results did not show any strong interactions between glucopyranosides and ILs. The

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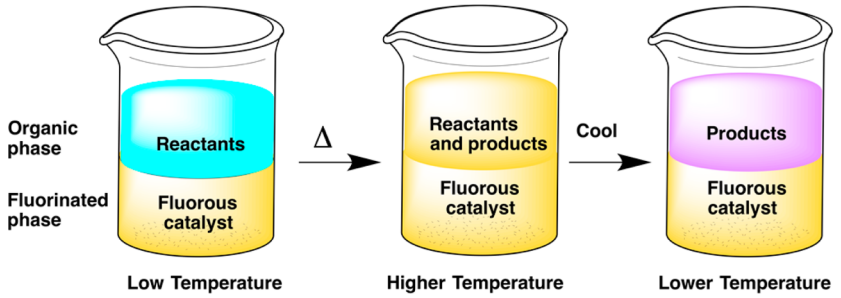

Figure 1. Fluorous biphasic system. Adapted from ref 130. Reproduced with permission form ref 130. Copyright 2012 Elsevier.

properties and their changes were also discussed in terms of size, structure, and solvation of the ILs and glucose.

A water-stable IL,[117] 1-butyl-3-methylimidazolium trifluoromethanesulfonate, [BMIM][CF_3SO_3], has been used in aqueous biphasic systems with a large range of monosaccharides and disaccharides and polyols. Binodal curves, tie-lines, densities, and viscosities of the coexisting aqueous phases were determined for each ternary system. The proposed systems are low-viscosity, offering enhanced features over conventional polymer-based aqueous biphasic systems. In addition, the partitioning of model biomolecules, such as L-tryptophan, caffeine, and β-carotene, was also investigated to examine the applicability of such aqueous biphasic systems. These systems are particularly interesting in the recovery of bioactive products from natural sources, while the availability of carbon-based compounds to cells constitutes a major advantage in separations from fermentative media. Moreover, the use of carbohydrates in ionic-liquid-based aqueous biphasic systems constitutes a step forward along the biorefinery concept, envisaging sustainable conversions of biomass into a broad spectrum of biobased products.

A new generation of IL structures based upon conjugation of the organic superbase 1,1,3,3-tetramethylguanidine with carboxylic acids such as formic, acetic, and propionic acids has been reported.[118] This method produces ionic liquids that both rapidly dissolve cellulose to high concentration and are recyclable by distillation with recoveries and purities over 99%.

More recently, Ruß and König[119] have proposed alternatives to ionic liquids (sugar melts, deep eutectic solvents) since their impact on the environment is still under debate. The components of a green solvent should exhibit low acute toxicity and be rapidly degraded in the environment. The current consensus is that ILs cannot be generalized as either green or toxic because their environmental impact is strongly dependent on the species of cation and anion used within the IL. The best alternative proposed is deep eutectic solvents (DES), which will be discussed later in this review.

2.2. Supercritical Fluids

Supercritical fluids (SCFs)[74,120] are compounds that, above a critical temperature and pressure, show both gas- and liquid-like properties near the critical point. SCFs have been extensively developed as solvents in various kinds of applications such as dry cleaning and polymer impregnation and extraction of chemicals and foods. Supercritical CO_2 ($scCO_2$) is the most widely used SCF because of its nontoxic and nonflammable characteristics. $scCO_2$ has low critical temperature and pressure and it is inexpensive. However, an important factor that limits its use is its poor solvent properties relative to those of organic liquids. This hurdle has led to the investigation of CO_2-philic groups that enhance the solubility of $scCO_2$-insoluble derivatives. Nevertheless, $scCO_2$ is one of the most popular green solvents because of its favorable physical and chemical properties. Recyclability, ease of solvent removal, and readily tunable solvent parameters make $scCO_2$ a desirable alternative over conventional solvents. Among potential uses of $scCO_2$, synthesis and extraction of biologically active molecules[121] as well as separation of natural products such as proteins and carbohydrates have immense application prospects.

Carbohydrates substituted with carbonyl groups have been proposed as economical, environmentally benign CO_2-philes, circumventing the low solubility of underivatized carbohydrates in $scCO_2$.[122] The high solubility of these carbonyl systems in $scCO_2$ is attributable to Lewis acid−Lewis base interactions between CO_2 and CO_2-philic Lewis base functionalities such as carbonyl groups. Acetylated sugar derivatives exhibit high solubility in liquid and $scCO_2$.[123] Peracetylated sorbitol and β-D-galactose are soluble under mild conditions in $scCO_2$, high pressures are required to dissolve peracetylated β-cyclodextrin, and peracetoxyalkyl chains impart CO_2 solubility to amides.

The use of cosolvents, such as ethanol and water, has been reported[124] to solubilize tagatose and lactulose. ^{1}H NMR spectroscopy under high pressure and at high resolution was used[125] for the first time to investigate the solution structure of a carbohydrate-based system, sucrose octaacetate, in $scCO_2$. These studies indicated that the average solution-state conformation of the β-D-glucopyranosyl ring of sucrose octaacetate in $scCO_2$ medium is consistent with the $^4C_1$ chair form, while the β-D-fructofuranosyl ring adopts an envelope conformation. This investigation also suggests that $scCO_2$ is a promising medium to study the solution structure and conformation of acetylated sugar systems. Spectral manifestations of a specific interaction between the acetate methyl protons and CO_2 molecules were also presented.

Supercritical water (scH_2O) is a high-temperature and -pressure fluid that has many applications in extraction and processing of chemicals in industry. The advantages of scH_2O include no toxicity, fast diffusion of dissolved compounds, low viscosity, low surface tension, reduced hydrogen bonding and improved solubility of less polar compounds. Faster reaction rates and increased extraction rates are also observed in scH_2O. In contrast, corrosion-based degradation is maximal close to critical temperature, which limits many of its applications. One way to circumvent this problem is to use pressurized water near its critical temperature.[126]

The combined effect of pretreatment with scH_2O[127] and mechanochemical grinding in a ball mill on the physicochemical properties of chitin and its enzymatic degradation was examined. Chitin showed reduced mean molecular weight, lower crystallinity index, lower crystallite size, greater d-spacing, weaker hydrogen bonds, and the amide group was more exposed compared with untreated chitin. These properties increased the

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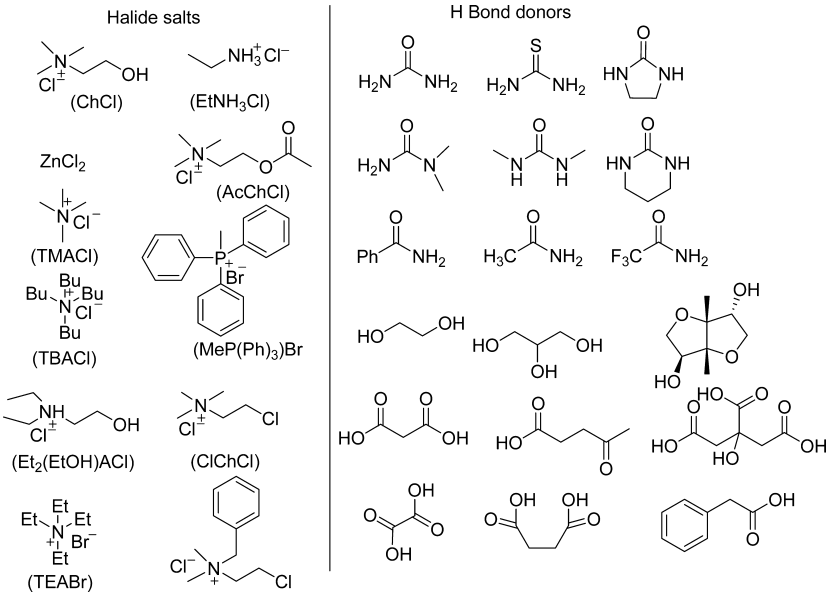
Scheme 5. Most Common Deep Eutectic Solvents



hydrophilicity of the chitin and enhanced its enzymatic degradation. The *N*,*N*′-diacetylchitobiose yield after enzymatic degradation of chitin following pretreatment with scH_2O (400 °C, 1 min) and grinding (800 rpm, 10 min) was 93%, compared with 5% without any treatment, 37% with scH_2O pretreatment alone (400 °C, 1 min), and 60% with grinding alone (800 rpm, 30 min).

2.3. Fluorous Solvents

The term fluorous solvent was first popularized by Horvath[128] to describe highly fluorinated alkanes, ethers, and tertiary amines that possess some special features for use in biphasic systems.[129] Fluorous solvents are highly fluorinated or perfluorinated solvents that are immiscible with both organic and aqueous solvents; thus hexane and perfluorohexane, also known as FC-72, are immiscible. Unlike water, however, the miscibility of fluorous solvents with organic ones is temperature-dependent. At room temperature, perfluorohexane forms two distinct layers with most organic solvents. This bilayer (Figure 1) becomes completely miscible at 24.8 °C; with other solvent systems, there is greater variation in the temperature of complete miscibility, for example, a biphasic mixture of 3 mL of hexane and 1 mL of toluene with 3 mL of perfluorinated solvent.

Fluorous biphasic systems have been used in extractions and in biocatalytic reactions.[131] In the field of biocatalysis,[132] the first report of a lipase-catalyzed reaction in a fluorous solvent involved the formation of poly(ethylene glycol)−lipase complex that enhanced lipase activity more than 16-fold over the native lipase powder. The poly(ethylene glycol)−lipase complex exhibited markedly higher alcoholysis activities in fluorous solvents than in conventional organic solvents. The optimum reaction temperature in the fluorous solvent perfluorooctane was 55 °C and the optimum pH for preparation of the poly(ethylene glycol)−lipase complex was 9.0, similar to the conditions for lipase-catalyzed reaction in aqueous solution. The alcoholysis reaction in fluorous solvent requires the addition of an organic solvent (isooctane) that is miscible with the fluorous solvent in order to dissolve nonfluorinated substrates. Lipase activity in the fluorous solvent is significantly influenced by the volume ratio of isooctane in the reaction medium. Fluorous ILs have been used in the dissolution and hydrolysis of cellulose to achieve good recovery of glucose.[133]

2.4. Deep Eutectic Solvents

A deep eutectic solvent (DES) is a fluid that is generally composed of two or three inexpensive and safe components that are capable of self-association, often through hydrogen-bond interactions, to form a eutectic mixture with a melting point lower than that of each individual component. DES were first discovered[134] by mixing metal salts such as zinc, aluminum, tin, and iron chlorides with quaternary ammonium salts. Although both salts have very high melting points, their appropriate mixing leads to the formation of a liquid phase, the so-called eutectic phase.[135]

DESs are generally liquid at temperatures below 100 °C. The principle of creating ILs and DES was demonstrated for mixtures of quaternary ammonium salts (Scheme 5) with a range of amides and carboxylic acids and was later extended to choline chloride with alcohols and to urea with sugars or organic acids. Some features of these DESs make them have an advantage over ILs because they are easier to prepare in high purity at low cost. The higher melting points of many DESs, however, can hamper their application as a green solvent at room temperature. These DESs exhibit similar physicochemical properties to the traditionally used ILs, while being much cheaper and potentially environmentally friendlier. DESs can be formed between a variety of quaternary ammonium salts (H-bond acceptors) and carboxylic acids (H-bond donors) as shown in Scheme 5. One advantage of DESs is that their synthesis is 100% atom-economic and their purity is high. Abbott et al.[134] have reported a series of DESs based on choline chloride and carboxylic acids. Highly crystalline cellulose acetate dissolves in a DES,[136] which is less expensive than an IL. In addition, DESs can be easily prepared via purification process or reaction medium and most formulations are nontoxic and biodegradable. A DES exhibits its unusual solvent properties owing to its high chloride ion concentration and its specific activity, allowing it to break H-bonding networks between the oxygen and hydrogen atoms in acetate functional groups. This bond disruption causes the oxygen atom to be unoccupied, thus givinging the Li^+ ions mobility by forming a

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temporary coordination.[137] Moreover, the incorporation of DES also displays high ionic conductivity as a result of its high mobility and high concentration of carrier ions.[134]

Monosaccharides, mainly glucose, fructose, or both, easily obtained from most fruits, have been used to synthesize sugar-based DESs. Hayyan et al.[138] have reported a novel fructose-based DES of choline chloride (2-hydroxyethyltrimethylammonium), which has been synthesized at different molar ratios. Physical properties such as density, viscosity, surface tension, refractive index, and pH were measured and analyzed as a function of various temperatures (25−85 °C). The analysis of these physical properties revealed that these new DESs have the potential to be utilized in future industrial applications involving processing and separation of food constituents. Meanwhile, a glucose-based DES[139] of choline chloride (2-hydroxyethyltrimethylammonium chloride) was synthesized at different molar ratios. The physical properties of density, viscosity, surface tension, refractive index, and pH were investigated as a function of temperature in a practical range of 298.15−358.15 K. Analysis of these physical properties revealed that these novel DESs have the potential to be utilized for widely industrial applications involving processing and separation of food constituents and pharmaceutical applications, as well as media for chemical reactions.[134,77]

A series of polymer electrolytes composed of corn starch,[140] lithium bis(trifluoromethanesulfonyl)imide (LiTFSI), and DES were fabricated by solution-casting technique. This DES was synthesized from a mixture of choline chloride and urea at a molar ratio of 1:2. The addition of DES was crucial in enhancing the room-temperature ionic conductivity by increasing the amorphous elastomeric phase in corn starch/LiTFSI matrix. The ionic transport mechanism is improved, and an appreciable amount of ion-conducting polymer electrolytes is produced. The highest ionic conductivity achieved for the polymer electrolyte composition corn starch/LiTFSI/DES (14:6:80 wt %) is 1.04×10^{-3} S·cm^{-1}. The anomalies that were observed with the addition of DES upon formation of neutral ion multiples were visually revealed by scanning electron microscope (SEM) micrographs. The possible dipole−dipole interaction between the constituents was visualized by Fourier transform infrared (FTIR) spectroscopy upon change in cage peaks.

Dai et al.[135] have reported that certain abundant plant primary metabolites changed their state from solid to liquid when they were mixed in proper ratio. This finding leads one to think that natural DESs play a role as an alternative medium to water in living organisms, and a wide range of natural products was tested, which resulted in discovery of over 100 natural DESs from nature. The interaction between the molecules was investigated by NMR spectroscopy to elucidate these deep eutectic features. All the tested natural DESs show clear hydrogen bonding between components. In the next step, physical properties of natural DESs such as water activity, density, viscosity, polarity, and thermal properties were measured as well as the effect of water on the physical properties. In the last stage, the novel natural DESs were applied to solubilization of a wide range of biomolecules such as non-water-soluble bioactive natural products, gluten, starch, and DNA. In most cases the solubility of the biomolecules evaluated in that study was much higher than in water. On the basis of those results, novel natural DESs may be anticipated as potential green solvents at room temperature in diverse fields of chemistry. The use of choline-derived ionic solvents for the rapid decrystallization of cellulose has also been reported.[141] The effect of additives on the decrystallization of cellulose is presented as well as the recycling of these neoteric ionic fluids. The decrystallization rate of cellulose in sustainable choline-derived ILs is greatly enhanced compared to that in imidazolium chloride-based ILs.

2.5. Biomass-Derived Solvents

Nowadays, biomass is an alternative source of raw materials to obtain green solvents.[142] Biorefining is becoming a sustainable way to obtain a variety of renewable chemicals that have been proposed by many research groups.[143] In order to be competitive with petrochemicals, biomass-derived products should have advantageous chemical properties that can be profitably exploited and/or their production should offer cost-effective benefits. Sustainable processes such as fermentation, enzymatic hydrolysis, or esterification are involved in their production. The main sources of biomass (Table 4) can be classified into four groups according to their nature: (1) carbohydrates (starch, cellulose, and sugar-based biomass); (2) lignin (woody biomass); (3) fats and oils of animal sources (triglycerides); and (4) proteins.

Table 4. Sources of Biomass To Obtain Green Solvents

source of biomass	biopolymer	ref
corn, wheat, starch crops	starch	147
green plants, paper, switchgrass	cellulose	148, 149
sorghum, woody biomass	lignin	150
beet molasses, shrimp shells	chitin	151 152,
sugar cane, vegetable oils, seaweed, animal feedstocks	lipids, proteins	153 154 155,
wood residues	polyhydroxyalkanoates	156

There are several recent specialized reviews on the conversion of biomass to useful chemicals.[79b,144,145] The most difficult type of biomass to break down into chemically useful fragments is lignin due to its structure, a combination of aromatic polymers resulting from the oxidative combinatorial coupling of 4-hydroxyphenylpropanoids. Therefore, pyrolysis is one common way to process it.[146] In contrast, other types of biomass components, such as polysaccharides, triglycerides, and proteins, can be more easily degraded into their constituent building blocks of monosaccharides, fatty acids plus glycerol, and amino acids, respectively. Scheme 6 shows chemical structures of the most common products obtained from the above-mentioned types of biomass.

2.5.1. Carbohydrates: Starch and Sugar-Based Biomass. Probably the most popular biomass feedstock to produce solvents or specialty chemicals is carbohydrates.[157] Carbohydrates account for approximately 95% of the biomass produced annually. Carbohydrates exist primarily in the form of polysaccharides, including starch and cellulose. Traditionally, starch has been used as a basic organic raw material by chemical industries. Many bulk chemicals and polymers can be produced by chemical modification or fermentation of starch and its monosaccharide derivative D-glucose (Scheme 7).

Depolymerization of glycosidic bonds by catalytic hydrolysis can produce monosaccharides for subsequent conversions. Several intermediates and different reaction paths were identified for the acid-catalyzed conversion of fructose and glucose to 5-hydroxymethyl-2-furaldehyde (HMF) in different solvents. Acid-catalyzed hydration of HMF results in levulinic acid (LA) and formic acid, which can be converted to γ-valerolactone (GVL) in the presence of Shvo's catalyst (Scheme 7).[158,159] GVL is considered a sustainable liquid, since it is renewable and has

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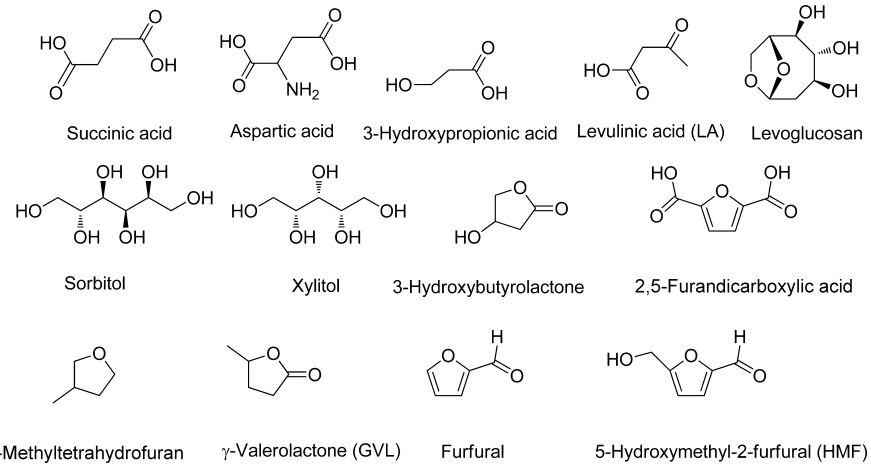
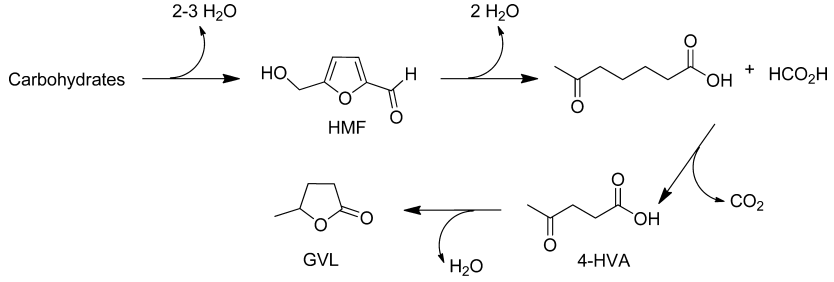
Scheme 6. Chemicals Obtained from Treatment of Biomass



Scheme 7. Pathway To Obtain γ-Valerolactone



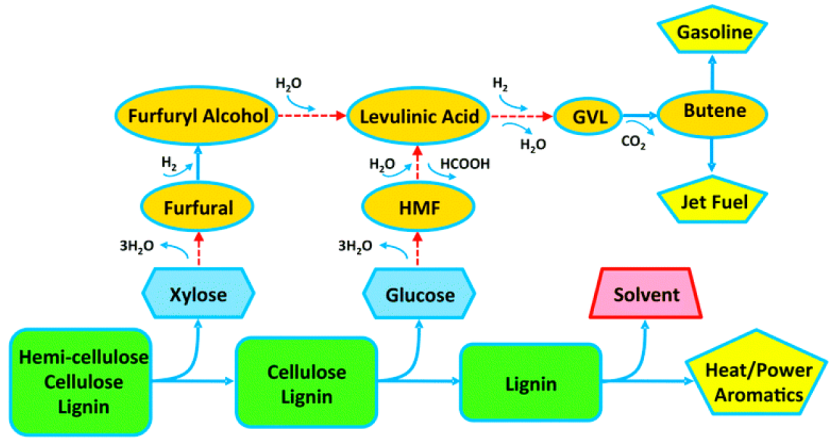


Figure 2. Conversion of lignocellulosic biomass to chemicals (ovals) after passage through the intermediate formation of xylose or glucose. Reproduced with permission from ref 172. Copyright 2012 Royal Society of Chemistry.

several very attractive properties.[160] GVL occurs naturally and has been used by the food industry. Its vapor pressure is low even at higher temperatures, it does not hydrolyze at neutral pH, and it does not form peroxides in the presence of air, making it a safe material for large-scale use. GVL can be also utilized for the production of energy.

A catalytic method[161] for conversion of carbohydrate biomass to GVL in acidic aqueous media has been developed. Water-soluble iridium complexes were observed to be extremely catalytically active for providing GVL in high yields with high turnover numbers. The homogeneous catalysts can also be recycled and reused by applying a simple phase-separation process.

D-Glucose is the most abundant monosaccharide in nature, and its oxidation can produce a variety of acids and keto acids. Oxidation of D-glucose to D-gluconic acid is the process most extensively studied.[162] The biodegradable D-gluconic acid is widely used in the pharmaceutical and food industry as a complexing or acidifying agent. The fermentation of glucose and fructose also gives precursors of green solvents. Lactic acid (2-hydroxypropionic acid) can be produced by chemical synthesis or by fermentation of different carbohydrates such as glucose (from starch), maltose (produced by specific enzymatic starch conversion), sucrose (from syrups, juices, and molasses), lactose (from whey), etc. Lactic acid is commercially produced today mainly through fermentation of glucose. One important solvent derived from lactic acid is ethyl lactate.[163] It is synthesized

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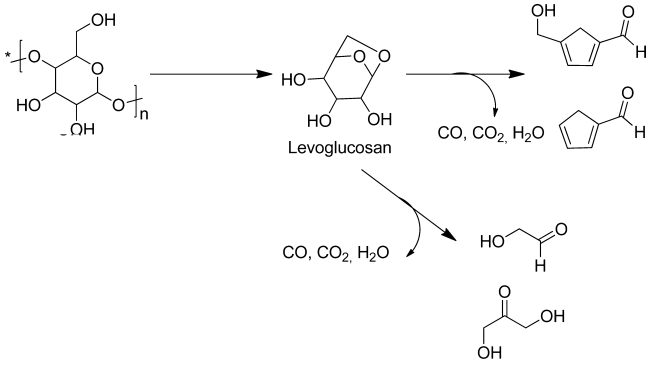
through the esterification reaction between ethanol and lactic acid, both reactants generated from biomass raw materials.[164] Its high boiling point, low vapor pressure, and low surface tension make ethyl lactate a substitute for acetone and xylene in several chemical processes. Ethanol and methanol, which are widely used solvents in organic chemistry, can also be obtained from polysaccharide biomass biorefining.[165]

2.5.2. Cellulosic, Lignocellulose, and Lignin Biomass-Derived Solvents. Cellulosic biomass comes from wood and herbaceous plants and major crop residues such as sugar cane bagasse, wheat straw, rice straw, and corn stover. Lignocellulosic materials are composed mainly of cellulose, hemicellulose, and lignin. Hemicellulose is an amorphous and heterogeneous group of branched polysaccharides (copolymers of any of the monomers glucose, galactose, mannose, xylose, arabinose, and glucuronic acid). Hemicellulose surrounds the cellulose fibers and is a linkage between cellulose and lignin (about 28%), a highly complex three-dimensional polymer of different phenyl-propane units bound together by ether and carbon−carbon bonds. Lignin is concentrated between the outer layers of the fibers, leading to structural rigidity and holding the fibers of polysaccharides together (about 27%). Most of the biomass on earth is in the form of lignocellulose that is an ideal source of raw sugars for industrial processes since it does not affect food supplies and price. Biopolymers such as cellulose, hemicellulose, and lignin may be converted to useful products (Figure 2), either by direct functionalization of the polymers or depolymerization to monomers (hydrolysis or pyrolysis),[166] and further treated to convert to useful chemicals[167] (Scheme 8).

Scheme 8. Obtaining Furfural, Levoglucosan, and HMF from Cellulose Treatment



The high crystallinity of cellulose, high reactivity of carbohydrates and lignin, insolubility of cellulose in conventional solvents, and heterogeneity in native lignocellulosic materials and in lignin itself sometimes make conversion of biomass to useful chemicals difficult. For instance, furfural is one of the most promising platform chemicals derived from lignocellulosic biomass.[168] Furfurals are important intermediates in the chemical industry. They are typically produced by homogeneous catalysis in aqueous solutions. However, heterogeneously catalyzed processes would be beneficial in view of the principles of green chemistry: the elimination of homogeneous mineral acids makes the reaction mixtures less corrosive, produces less waste, and facilitates easy separation and recovery of the catalyst.[169] Finding an active and stable water-tolerant solid acid catalyst still poses a challenge for the production of furfural and HMF. Furfural is produced in the dehydration of xylose, and HMF is formed from glucose and fructose in the presence of an acidic catalyst. Bases are not active in the dehydration reaction but do catalyze the isomerization of monosaccharides, which is favorable when glucose is used as a raw material. In addition to the desired dehydration of monosaccharides, many undesired side reactions take place, reducing the selectivity and deactivating the catalyst. In addition, the catalyst properties play an important role in selectivity. In this review, catalytic conversion approaches are summarized,[170] focusing on the heterogeneously catalyzed formation of furfural. The attractiveness of catalytic concepts is evaluated, with productivity, sustainability, and environmental footprint kept in mind.

MeTHF can be obtained from furfural and levulinic acid, and it is considered an alternative, environmentally benign solvent.[63] A new route to convert various biomass-derived oxygenates[171] (cellulose, starch, and sugars) into GVL without use of any external H_2 supply has been reported. LA can be selectively reduced to GVL instead of 1,4-pentanediol by tuning the base and ligand in Ru-based catalytic systems. More importantly, the hydrogenation process can be accomplished only in the presence of the formic acid produced from the original acidic dehydration step. The success of the new route not only improves the atom economy of the process but also avoids the energy-costly separation of LA from the mixture of LA and formic acid in aqueous solution.

Recently, Carrasquillo-Flores et al.[173] reported a mechanically driven acid-catalyzed depolymerization of solid biomass that overcomes the problems posed by the recalcitrance of lignocellulose. The solid-state reaction leads to water-soluble oligosaccharides, which display higher reactivity than cellulose and hemicellulose. These water-soluble oligosaccharides are useful feedstock for the high-yield production of HMF and furfural in biphasic reactors. Good results were obtained for beechwood and sugar cane bagasse.

A diverse range of highly attractive products[174] and building blocks could be derived from LA, which is accessible from wood-based feedstocks, and itaconic acid, which can be obtained from green biomass. Again, the cyclic ester GVL can also be obtained from lignocellulosic biomass.[172] Among the cyclic ethers, MeTHF is advocated as an alternative solvent in the pharmaceutical industry[63,65a] and is also considered a fuel component.[175] Hydrogenation routes have been proposed involving heterogeneous catalysts to produce GVL, 2-MeTHF, or 3-MeTHF. Organometallic catalysts based on iridium[161] and ruthenium phosphine[171] systems reportedly allow the conversion of succinic acid and LA into GVL. Direct transformation[176] of cellulose into HMF was carried out by use of a combination of metal chlorides in the IL [EMIM][Cl]. From high-throughput screening of various metal chlorides, a combination of $CrCl_2$ and $RuCl_3$was found to be the most effective catalyst. HMF was directly afforded from cellulose in nearly 60% yield. Gram scale-up synthesis of HMF was successfully performed from cellulose with $CrCl_2$ and $RuCl_3$. Furthermore, lignocellulosic raw material could be directly converted into HMF and furfural in reasonable yields under these conditions.

2,5-Dimethylfuran, also considered a green solvent, can be obtained from fructose,[177] from cellulosic biomass, or by isomerization of glucose.[178] Compared to ethanol, 2,5-dimethylfuran has higher energy density (by 40%) and higher boiling point (by 20 K) and is not soluble in water.

Fructose has also been used[179] as the starting material for preparation of a new class of ILs. These liquids exhibit tunable solvent properties similar to those of conventional imidazole-

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based ILs. The most abundant sugars in cellulose and hemicellulose represent the natural resources from which these ILs can be sustainably derived. These highly functionalized molecules need to be defunctionalized, by means of dehydroxylation, in order to be feedstocks for the chemical industry and yield suitable renewable chemicals.[180]

There are reports[181] of selected chemicals and fuels that can be produced from microbial fermentation of plant-derived cell-wall sugars and directed engineering for improvement of microbial biocatalysts. Lactic acid and ethanol production are highlighted, with a focus on metabolically engineered *E. coli*.

In the conversion of lignocellulosics to products, a combination of factors can result in highly heterogeneous depolymerization products, making their efficient separation difficult. ILs have been used to dissolve them, allowing homogeneous reaction conditions.

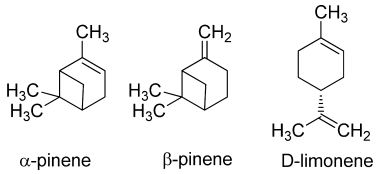
Functionalization,[151] characterization, and successful application of sulfonated hyperbranched poly(arylene oxindole)s for direct catalytic conversion of cellulose to LA has also been reported. The use of water-soluble hyperbranched polymers in combination with ultrafiltration is conceptually novel and opens new horizons in the aqueous-phase processing of cellulose substrates with various degrees of crystallinity. Compared to most conventional types of acid catalysts, these highly acidic polymers demonstrate superior catalytic performance in terms of both activity and selectivity. Additionally, this molecular approach can be successfully transferred to the acid-catalyzed degradation of other abundant biomass resources, including starch, inulin, and xylan.

The dehydration of D-fructose to 5-hydroxymethylfurfural[182] was studied under single-phase conditions in the low-boiling solvent 1,4-dioxane at moderate temperatures in the presence of the solid acid catalyst Amberlyst-15. The reaction was first examined and optimized under batch conditions, where levoglucosan (1,6-anhydro-β-D-glucopyranose),[149] the most abundant product of cellulose pyrolysis (60% of total), is deoxygenated within molten biomass to form products with higher energy content (pyrans and light oxygenates). The yield of these products can be increased by a factor of 6 under certain reaction conditions, for example, using long condensed-phase residence times encountered in powder pyrolysis. Finally, copyrolysis experiments with deuterated glucose reveal that hydrogen exchange is a critical component of levoglucosan deoxygenation.

2.5.3. Solvents Derived from Fats and Oils of Animal Sources (Triglycerides). Biodiesel is the main product of oils (rapeseed, soyabean, vegetable oil) and animal sources. Triglycerides are the main components of this type of biomass that undergoes tranesterification reactions with methanol to produce biodiesel (methyl esters of fatty acids) and glycerol. Glycerol, a byproduct of the biodiesel industry, has been recently proposed as a valuable green solvent.[183] It has a very high boiling point and negligible vapor pressure. It can dissolve many organic compounds and is miscible with water.

Terpenes are derivatives of isoprene that are ubiquitous in the plant world. A vast majority of them are essential oils, and they can also be a source of green solvents.[184] Those most commonly used as solvents are turpentine (a mixture of α- and β-pinene) and D-limonene (Scheme 9). They are both immiscible with water and they can easily substitute for methylene chloride or toluene.

Scheme 9. Green Solvents from Plant Essential Oils



2.6. Water

Water in principle could be considered as the ideal green solvent[185] because of its nontoxic nature, being naturally occurring, inexpensive, nonflammable, and having a high specific heat capacity where exothermic reactions can be more safely controlled. However, there are still some disadvantages to its use, such as energy-intensive distillation processes, sometimes difficult treatment of its waste, and difficulty of controlling heat and cool processes due to its high specific heat capacity. High-pressure water and scH_2O have found many applications in industry in extraction and separation processes. For example, the homogeneous catalysts (H_2SO_4 and NaOH) and heterogeneous catalysts (TiO_2 and ZrO_2) on glucose reactions were examined in hot compressed water (473 K)[186] by a batch-type reactor. From the homogeneous catalyst studies, the acid catalyst promoted dehydration, while isomerization of glucose to fructose was catalyzed by alkali. TiO_2 was found to act as an acid catalyst to promote formation of HMF. Zirconia (ZrO_2) was a base catalyst to promote the isomerization of glucose. Effects of the additives were also confirmed through fructose reactions.

2.7. Solvent-Free Conditions: Microwave, Pressure, Ultrasound, and Mechanochemistry

Polysaccharides, which contain abundant hydroxyl groups, are polar molecules particularly suitable for microwave (MW) applications. MW-assisted transformations reported in the literature typically include either reactions involving hydroxyl groups for the production of novel entities or dehydration reactions leading to the formation of furfural and related platform molecules. Ultrasound radiation[187] has also been used to increase the dissolution rate of glucose in ILs and to promote enzyme activity in the synthesis of glucose esters. Ultrasound has been reported as well to be helpful for dissolution of cellulose.[188]

3. GREEN SOLVENTS IN CARBOHYDRATE SYNTHESIS

3.1. Carbohydrates in Chemicals

Current carbohydrate syntheses under green conditions reported in literature include no-solvent conditions, where one of the reagents can dissolve the other substrates in a nonsolvent system, which is considered greener than classical reactions performed in organic solvents,[189] or in the absence of liquid medium by use of mechanochemical methods,[190] or microwave-assisted reactions.[187a,191] The use of green solvents and cosolvents as reaction media for carbohydrate synthesis and modification (chemical or enzymatic) can involve ILs[7b,192] or BDS.[193] In this section we summarize the use of green solvents in chemical or enzymatic synthesis and modifications of carbohydrates for chemical applications.

3.1.1. Chemical Synthesis. When carbohydrate chemical synthesis and modification requires specific solvents for the desired reaction, DES and particularly ILs are mainly used.[88,102,194] Current carbohydrate chemical modifications applied in the chemical industry and described in the literature have shown three major areas of use: (1) polysaccharide-based

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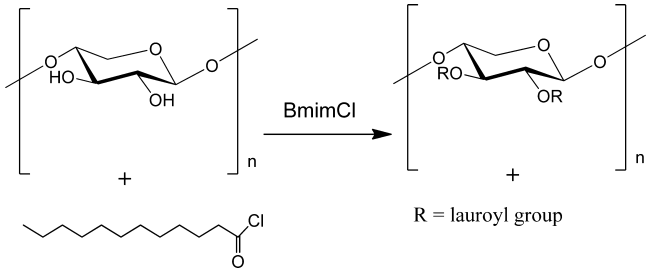
materials as substrates, (2) acetylation/deacetylation of saccharides for building block purposes, and (3) IL-catalyzed reactions of carbohydrates.

3.1.1.1. Polysaccharide-Based Materials as Substrates. Cellulose is often used as a raw material for chemical modification. A simple, green transformation of cellulose to afford carboxylate-functionalized cellulose was described by Zhang et al.[195] In their work, they performed a solvent-free and room-temperature reaction between cellulose from wood and succinic anhydride using mechanochemistry. This modified cellulose was used for removal of Pb^{2+} from aqueous solution, with adsorption capacity of 422 mg/g, which is higher than for unmodified cellulose.

Cellulose acetate is a nontoxic, inexpensive, and biodegradable cellulose-derived material.[196] This modified polymer has been used in the preparation of biodegradable thin-film polymer electrolytes, which are often applied to electrochemical devices and mainly lithium polymer cells under environmentally friendly conditions. In this chemical synthesis, cellulose acetate was dissolved in a mixture with DES (prepared from choline chloride) and lithium bis(trifluoromethanesulfonyl)imide.[136,140] Cellulose polyelectrolytes have also been synthesized from cellulose in the presence of acrylamide, NaOH, and urea in aqueous solution, resulting in polyelectrolytes functionalized with two different groups: acylamino and carboxyl groups.[197]

ILs are recognized for their ability to dissolve cellulose and hemicellulose;[198] among these, butylmethylimmidazolium chloride, [BMIM][Cl], has been featured as a solvent for wool, cellulose, hemicellulose, and chitin.[198e,199] Due to its properties, this compound has been employed for the development of new carbohydrate materials. In 2009, cellulose from sugar cane was succinylated in the presence of [BMIM][Cl] and succinic anhydride, although the greenness of the process was affected by the use of 4-dimethylaminopyridine as a catalyst.[196] In 2012, preparation of lauroylated hemicelluloses in the presence of [BMIM][Cl] was reported by Wang et al.,[199c] and they developed a chemical modification of hemicellulose isolated from poplar tree, which possesses 32% hemicellulose polysaccharide. A 3.3% solution of hemicellulose in [BMIM][Cl] was prepared at 90 °C and then lauroyl chloride was added. The esterification reaction mixture was incubated up to 90 min and then cooled and precipitated with ethanol (Scheme 10).

Scheme 10. Esterification with Lauroyl Groups of Hemicellulose in [BMIN][Cl][199c]



Recently cellulose−chitosan composites have been synthesized in [BMIM][Cl] for the removal of microcystin, a deadly toxin released by cyanobacteria in drinking water.[200] [BMIM][Cl] was employed to dissolve the carbohydrate raw material (1%) under argon atmosphere at 100−110 °C, and then new portions of polysaccharide were added until 10% cellulose and 4% chitosan concentrations were reached. Several solutions with different concentrations were cast on glass slides and stored at room temperature until a gel was formed. In their work, the authors removed and recycled [BMIM][Cl] from the composite films, recovering up to 88% of this solvent. The absorbent properties of the resultant materials were also tested and showed 4-fold better absorption of microcystin than the best absorbent previously reported.

Chitosan is a polymer with a wide variety of applications in material science.[199b,201] Several procedures for the production of chitosan-based materials have been developed in the presence of ILs as solvents: some recent examples include homogeneous acetylation of chitosan in 1-allyl-3-methylimidozolium chloride [AMIM][Cl] and acetyl chloride,[202] preparation of chitosan fibers in a glycine chloride spinning solution,[203] and synthesis of alkylated chitosan derivatives in the presence of [BMIM][OH] with the aim to developed new compounds with antibacterial activities.[203] The alkaline [BMIM][OH] was reported as solvent for the synthesis process,[204] and then several alkyl halides were used as substrates for the alkylation of chitosan. According to their results, the authors reported three compounds with excellent antibacterial activities against *Pseudomonas aeruginosa*.

ILs have been used as solvents for dehydration of carbohydrates to obtain 2-furaldehydes[205] and 5-hydroxymethylfurfural.[202,206] Meanwhile, these solvents have been considered as reaction media for glycosylation of trichloroacetimides of different glycopyranoses with excellent yields. Generally, the use of ILs was considered green due to the possibility to recycle the solvent.[207] In addition, the combined application of ILs and MW radiation has been used for cellulose/calcium silicate nanocomposites.[208]

Dehydration of lignocellulosic pentoses to furfural was also reported in the green solvent cyclopentyl methyl ether by Campos Molina et al.[209] These authors employed xylose and *Cynara cardunculus* (cardoon) as carbohydrate source and cyclopentyl methyl ether as cosolvent for the reaction medium (70% cyclopentyl methyl ether and 30% H_2O), and they found an important increase in furfural yields related to NaCl concentration in the reaction medium. Finally, the transformation of pentoses into furfural was close to 100% under specific reaction conditions: 1% H_2SO_4, 4% biomass, 40% NaCl, and 30 min of reaction at 443 K.

3.1.1.2. Acetylation and Deacetylation of Saccharides. Acetylated sugars are important building blocks for the synthesis of complex oligosaccharides and glycoconjugates, and per-*O*-acetylation is a useful organic reaction to protect hydroxyl groups in carbohydrate chemistry.[210] Traditionally per-O-acetylation of sugars has been carried out with acetic anhydride and pyridine. In recent decades, some Lewis acids have been used for this purpose as inorganic alternatives. Recently, γ-Al_2O_3 nanoparticles functionalized with sulfonic acid in the presence of a stoichiometric quantity of acetic anhydride catalyzed a solvent-free condition of per-*O*-acetylation of several carbohydrates.[210b,211]

Alkyl glycosides have been prepared with moderate to good yields (19%−70%) from peracetylated pyranoses (glucose and galactose) and long-chain fatty alcohols under solvent-free conditions by using zeolite as catalyst for the first time. In that work, different types of β-zeolites were tested and the best results were obtained with Fe^{3+}−β-zeolite. Although there is no clear explanation about the role of zeolite in the catalyst, the authors considered the main features of zeolite, such as greater acid strength and larger pore openings and channel intersections, as

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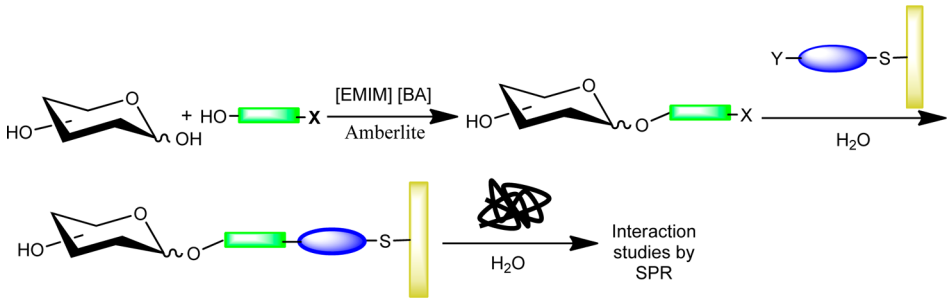

Figure 3. Green glycosylation approach using IL to prepare alkyl glycosides for studying carbohydrate−protein interactions by surface plasmon resonance.

the most probable effects of this compound related to this catalytic process.[211]

3.1.1.3. IL-Catalyzed Reactions of Carbohydrates. In addition to enhancing the dissolution of carbohydrates, many ILs can also act as catalysts. The nature of the cation and anion tune the catalytic properties of IL as well as its water miscibility. Recently, a variety of carbohydrate-involved organic reactions have been reported that use ILs as catalyst or solvent/catalyst, affording improved performance and easier product recovery.

Forsyth et al.[212] reported a rapid, clean, and mild *O*-acetylation of carbohydrates in dicyanamide (DCA)-based ILs. The ILs used in that study ([EMIM][DCA] and [BMIM][DCA]) were both effective solvents and active base catalysts, and reactions proceeded successfully in very good yields. For example, the peracetylation of α-D-glucose was reported in 98% yield at 50 °C for 10 min. Similarly, methyl β-glucopyranoside was *O*-acetylated in 92% yield while another IL, with the same cation BMIM but the bis(trifluoromethanesulfonyl)amide anion, failed to afford products even after 24 h. This observation is consistent with the tunability of IL properties by adjusting the structures of anion and cation.

Murugesan et al.[213] reported the peracetylation of simple sugars in the IL 1-ethyl-3-methylimidazolium benzoate, [EMIM][BA]. Peracetylation of simple sugars such as α-D-glucose, β-D-glucose, α/β mixture of D-mannose, and α/β mixture of D-galactose was achieved in excellent yields, ranging from 71% for α/β mixture of D-galactose to quantitative yield for β-D-glucose. The variations in product yields were attributed to the variations in sugar anomeric conformations, leading to nonconstant degree of crystallinity.

The ILs 1-methyl-3-methylimidazolium benzoate, [BMIM]-[BA], and 1-hexyl-3-methylimidazoliumbenzoate, [HMIM]-[BA], were also studied as catalysts for the peracetylation of β-D-glucose, and the results were compared with those for [BMIM][BA]. Decrease of the yields (from 100% to 82% to 68%) was associated with increasing reaction time (from 4 to 5 to 7 h) and increasing IL cation alkyl chain length (from ethyl to butyl to hexyl). These differences were attributed to an increase in IL viscosity with increased alkyl chain length, thereby decreasing the mobility of the reacting species.

Forsyth et al.[212] also reported the *O*-acetylation of disaccharides, including *N*-acetylneuraminic acid (72% yield) and sucrose (93% yield), and the trisaccharide raffinose (90% yield) in [EMIM][DCA] and [BMIM][DCA] ILs. Peracetylation was completed within 24 h at room temperature, and the reaction time could be decreased with an increase in reaction temperature. This report also compared the results for peracetylation of α-D-glucose in ILs with the same reaction in conventional organic solvents including acetone, acetonitrile, and *N*,*N*-dimethylformamide (DMF) in the presence of added catalysts, pyridine, sodium acetate, and triethylamine. Longer reaction times were required and lower yields were obtained in conventional solvents, further demonstrating the utility of DCA-based ILs.

Murugesan et al.[213] have reported the peracetylation of sulfated monosaccharides using benzoate-based ILs. The sodium salts of sulfated sugars are insoluble in most organic solvents and are difficult to peracetylate. Water and formamide are the only conventional solvents that dissolve these sugars. However, sulfated monosaccharides such as phenyl 4-*O*-sulfo-β-D-glucopyranoside and phenyl 6-*O*-sulfo-β-D-glucopyranoside were completely soluble in [EMIM][BA], facilitating their peracetylation in excellent yields. This property of benzoate-based ILs to dissolve sulfated sugars makes these solvents potentially important tools for the chemical modification of glycosaminoglycans. Benzoate-based ILs are also useful for the perbenzoylation of simple sugars such as α-D-glucose, β-D-glucose, and α/β mixture of D-mannose.[213] While the conventional, toxic and odoriferous benzoylation reagent benzoyl chloride was found to give only the starting material after 24 h, benzoic anhydride afforded good product yields with anomeric stereoselectivity.

Glycosylation reactions in the synthesis of complex carbohydrates are known as the major challenge areas in carbohydrate chemistry. There are multiple factors that need to be considered when the synthesis of glycosides is carried out, including presence and choice of a leaving group at the anomeric position of the donor, manipulation of protecting groups in both donor and acceptor, architecture of donor and acceptor, solvent system, and choice of promoter.[214] Glycosylation with unprotected and unactivated donors is often preferred, as it can reduce the number of steps, enhance reactivity, allow different stereochemistry, and increase prospects for further process modifications.[215] The chemical synthesis of unprotected carbohydrates possesses a number of challenges, particularly due to their poor solubility in most conventional solvents. It is important to investigate new solvent systems that dissolve carbohydrates and support glycosylation reactions of unprotected sugars. Park et al.[216] reported the synthesis of benzyl glycosides and disaccharides of glucose, mannose, and *N*-acetyllactosamine in the IL [EMIM][BA] with Amberlite IR-120(H^+) as promoter. The benzyl glycosides were synthesized from unactivated donors in good yield in a single synthetic step. Glycosylation of partially protected monosaccharide acceptors gave the expected disaccharides with α-stereoselectivity and without protection or covalent activation of the glycosyl donor.

Muñoz et al.[69f] describe a similar approach for the direct functionalization of monosaccharides such as glucose and *N*-

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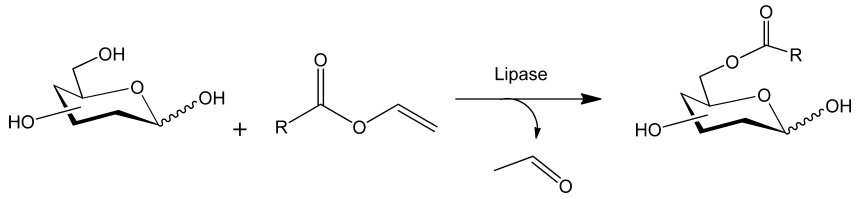
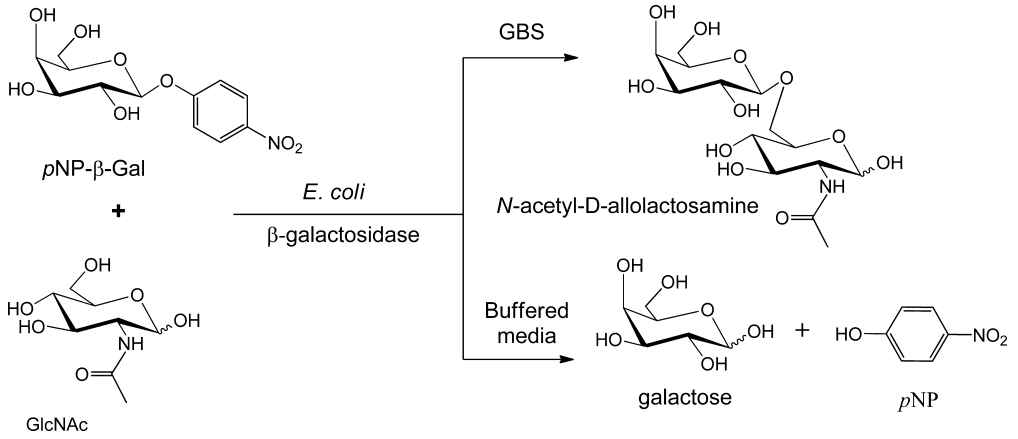
Scheme 11. Lipase-Catalyzed Acylation of Saccharides



Scheme 12. Glycerol-Based Solvent Effects in Enzymatic Activity of *β*-Galactosidase from *E. coli*



acetylgalactosamine and disaccharides such as lactose with different linker chains. Despite the modest yields obtained, the decrease in the number of steps made it a green alternative to traditional carbohydrate chemistry. Amino-functionalized *N*-acetylgalactosamine was directly synthesized in the presence of [EMIM][BA] and further immobilized on an alkanethiol-coated surface. The interaction of immobilized *N*-acetylgalactosamine derivative with a carbohydrate binding protein was studied, and kinetic parameters of the procedure were determined (Figure 3).

3.1.2. Enzymatic Synthesis. For the enzymatic synthesis of carbohydrates, the main types of green solvents are ILs,[4,7b,193,217] biosolvents,[7b,62,193] or the absence of solvent. ILs are used, in part, due to their polarity and their multiplicity of possibilities (of cations and anions) for the design of optimal reaction medium, allowing the preparation of enzyme stabilizing solutions and solubilizing sugar mixtures.[218] Mainly two classes of biocatalysts are used for the enzymatic synthesis of glycosides with these solvents: lipases and glycosidases. Lipase generally catalyzed acylation of sugars by using vinyl esters, which promotes the irreversible reaction toward the acylation of the saccharide (Scheme 11).[219] As products of the enzymatic reaction, sugar fatty esters are obtained, and these are nonionic surfactants with potential application in several industrial fields.[220]

The main drawback for synthesis of sugar fatty esters is the low solubility of carbohydrates in organic solvents used to avoid the production of homogeneous medium for biocatalysis reactions. In 2005, Ganske and Bornscheuer[219b,c] synthesized a glucose fatty ester by using immobilized lipase B from *Candida antarctica* (CAL-B) in the presence of pure 1-butyl-3-methylimidazolium tetrafluoroborate [BMIM][BF_4] and in pure 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM][PF_6]. Subsequently in 2008, Lee et al.[219d] investigated the acylation of glucose with commercial Novozym 435 lipase and IL mixtures, achieving the synthesis of 6-*O*-lauroyl-D-glucose. In the same year, a strategic alternative to improve yields in enzymatic acylation of glucose was inspired out of this new approach. The first step is to dissolve the sugar in an aqueous solution and then transfer it into an IL. The water was removed from the mixture and a supersaturated glucose solution in ILs was prepared. This solution was used for the enzymatic acylation, achieving better yields from the lipase-catalyzed reaction.[219e] More recently, the use of lipase-catalyzed reaction in ILs was extended to enzymatic acylation of saccharides with nonactivated fatty acids.[221]

ILs have been employed as cosolvents for several enzymatic modifications of carbohydrates, including recent advances in the synthesis of arylalkyl *β*-D-glucopyranosides catalyzed by *Prunus domestica* (prune) seed meal,[222] esterification of 6- and 6′-hydroxyl groups of maltose with linoleic acid by *Pseudomonas cepacia* and *Candida antarctica* lipases,[223] and synthesis of starch palmitate catalyzed by *Candida rugosa* lipase.[224]

An important lipase employed for the preparation of sugar fatty esters is Novozym 435, which is an immobilized form, in acrylic resin, of CAL-B. There have been several recent publications about catalyzed reactions using this commercial enzyme, including synthesis of mannosyl myristate by transesterification from vinyl myristate in 1-butyl-1-methylpyrrolidinium trifluoromethanesulfonate, [Bmpyrr][TFO];[225] synthesis of myristoyl maltose ester from maltose and myristic acid in the presence of *tert*-butanol[226] and also in ionic liquids;[225] synthesis of sialic acid derivatives from nonanoic anhydride and sialic acid in the presence of acetonitrile;[227] and synthesis of starch ester from vernonia oil methyl ester (an epoxy ester) and cassava starch in a mixture of 1-butyl-3-methylimidazolium hexafluorophosphate, [BMIM][PF_6], and dimethyl sulfoxide, DMSO.[228]

Based on the capability of ILs to dissolve cellulose,[194b,229] several strategies to alter some structural characteristics of this polymer and facilitate the enzymatic treatment of cellulosic materials have been carried out; for example, pretreatment of cellulose with IL for further enzymatic hydrolysis[230] and MW-assisted pretreatment of cellulose in IL that showed an important enhancement of enzymatic hydrolysis of substrate.[230a] A series of useful enzymes for hydrolysis of cellulose related to IL

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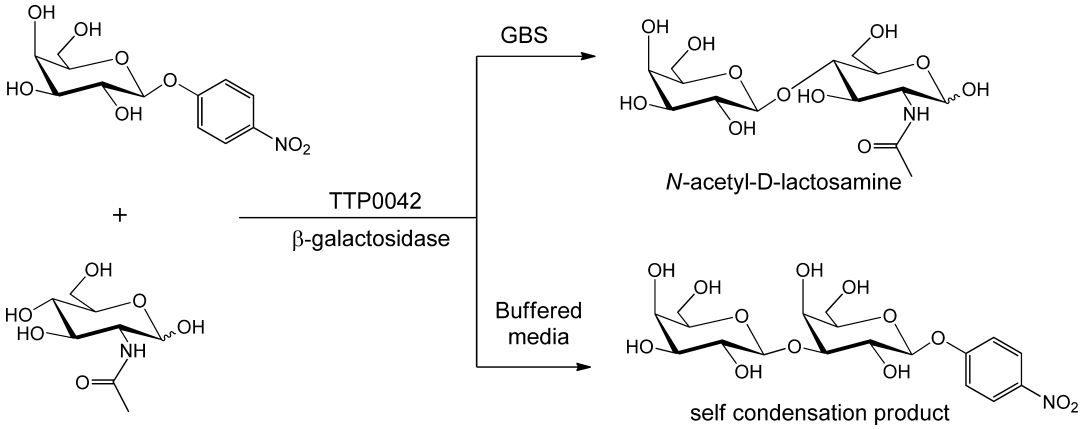
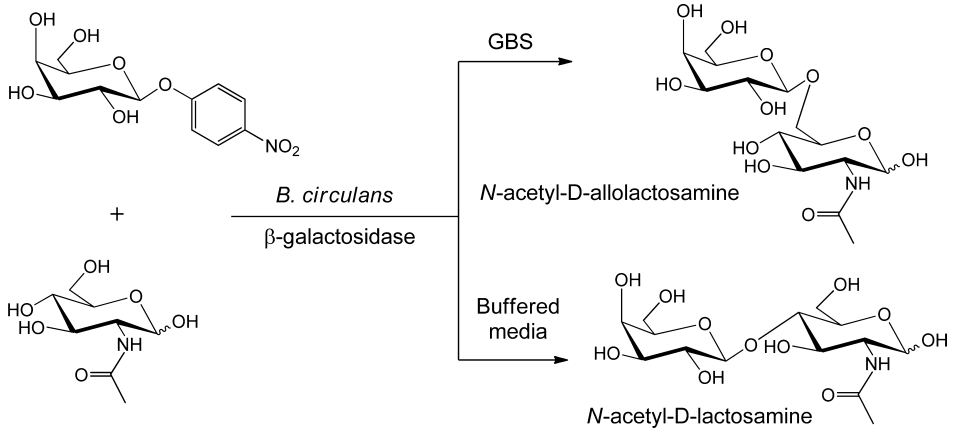
Scheme 13. Glycerol-Based Solvent Effects in Transglycosylation Reaction Catalyzed by *T. thermophilus* β-Galactosidase TTP0042



Scheme 14. Glycerol-Based Solvent Effects in Transglycosylation Reaction Catalyzed by *B. circulans* β-Galactosidase



treatments are cellulase from *Trichoderma reesei*[230a,231] and endo-1,4-β-D-glucanase from *Aspergillus niger*,[231c,232] as well as their immobilized commercial forms, Spezyme CP (*T. reesei*) and Novozyme 188 (*A. niger*).[230b]

Nowadays, research on biosolvents and their applications for the enzymatic synthesis of carbohydrates by use of glycosidases is ongoing. Some of these biosolvents, such as glycerol and MeTHF, are available from commercial sources, although their use in biocatalysis is only beginning.

Glycerol is considered a green solvent due to its ready availability from renewable sources, low toxicity, and biodegradability.[61a−c] Increased production of glycerol has resulted in a dropping price and the need to exploit it in new applications.[233] Thus, the use of glycerol and glycerol-based solvents (GBSs) has become a greener alternative, reducing the use of classical organic chemistry solvents (from petroleum) and developing new chemical syntheses in these green solvents.

Glycerol-based solvents have been used as cosolvents for the transglycosylation of *p*-nitrophenyl β-D-galactopyranoside (*p*NP-β-Gal, donor) in the synthesis of several disaccharides with *N*-acetyl-D-glucosamine (GlcNAc) as acceptor. In all cases studied, the presence of a cosolvent shifted the classical regioselectivity (in buffered medium) toward better synthetic results.[193] In that sense, β-galactosidase from *E. coli* reduced the hydrolytic activity of the enzyme and increased the amount of products from synthesis (transglycosylation), as shown in Scheme 12.[234] This result was explained by molecular dynamic studies comparing pure water and water−GBS systems. According to these simulations, the authors found more flexibility in some parts of the protein in a water system, while in the system containing the solvent G9 they found a shorter distance between C-1 of the donor, docked to the glutamic catalytic residue (as galactose) in the enzyme, and O-6 from the acceptor (GlcNAc).

Similar results have been observed with *Thermus thermophilus* β-galactosidase, which is a thermophilic biocatalyst that promotes the synthesis of *N*-acetyl-D-lactosamine [Gal-β(1→4)-GlcNAc] in buffered medium. However, these aqueous conditions lead to high amounts of self-condensation product derived from the donor [Gal-β(1→3)-Gal-β-*p*NP].[235] The presence of cosolvents affected the reaction by improving the regioselectivity of the enzyme, reducing self-condensation reactions, and increasing the synthesis of disaccharide (see Scheme 13). GBSs have an effect in the synthesis of disaccharides, as the solvent appears to modify the tertiary and secondary structures of the enzyme.[235b]

Glycerol-based solvents also affect the enzymatic activity of β-galactosidase from *Bacillus circulans*, which has been studied by several groups. The conventional synthesis affords *N*-acetyl-D-lactosamine as major product and *N*-acetyl-D-allolactosamine [Gal-β(1→6)-GlcNAc] as minor product when the reaction is performed in buffered medium.[236] The addition of GBS (at 2 M) to the reaction medium altered the product ratio, affording *N*-acetyl-D-allolactosamine as the main product (up to 100%) and reducing the yield of *N*-acetyl-D-lactosamine (see Scheme 14).[237,238] Apparently, the presence of GBS impacted the disposition of the substrate in the active site of the enzyme, and

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this effect promotes nucleophilic attack of the acceptor toward the O-6 position of the docked donor in the active site.

Analogous results have been found with *B. circulans* ATCC 31382 β-galactosidase. This enzyme recognizes GlcNAc and GalNAc as acceptors and is used to synthesize Gal-β-(1→3)-GalNAc and Gal-β-(1→3)-GlcNAc with high regioselectivity but low yield.[239] The use of GBS allows good catalytic activity in the synthesis of these disaccharides, with yields of 99% for Gal-β-(1→3)-GlcNAc and 95% for Gal-β-(1→3)-GalNAc, respectively. This process prevents hydrolysis with full regioselectivity. Furthermore, reaction scale-up and biosolvent recycling are feasible without loss of catalytic activity.[240]

Biomass-derived solvents offer excellent properties to be used in the enzymatic synthesis of carbohydrates with glycosidases. ILs, as a large category of green solvents, have been involved in the application of glycosidases as well. ILs have been used as water cosolvents for glycosidase-catalyzed reactions. Kaftzik et al.[241] have described the use of [MMIM][$MeSO_4$] as solvent for the enzymatic synthesis of *N*-acetyllactosamine. An efficient transglycosylation reaction with lactose and *N*-acetyl-D-glucosamine as substrates, catalyzed by β-galactosidase from *B. circulans*, was observed in good yield (60%).

Similar results have been reported with *T. thermophilus* β-galactosidase and with *B. circulans* ATCC 31382 β-galactosidase. In both cases, β-galactosidase exhibited the best result in a fluorinated IL: [BMIM][PF_6] for the enzyme from *T. thermophilus*[70] and [OMIM][PF_6] for the one from *B. circulans* ATCC 31382[242] containing 30% (v/v) buffer. β-Galactosidase from *T. thermophilus* improved the synthesis of *N*-acetyl-D-lactosamine when ILs were used, instead of the traditional self-condensed products obtained in buffer. Sandoval et al.[70] performed a molecular interaction study by surface plasmon resonance, fluorescence, and molecular modeling studies to understand the possible effect of these solvents on the synthetic behavior of the enzyme. They concluded that the enzyme becomes more flexible in an IL−water mixture and that it allows stabilization of the GlcNAc molecule in the active center of the enzyme, affording a new product based on the original regioselectivity of the reaction. β-Galactosidase from *B. circulans* ATCC 31382, was also used in the synthesis of Gal-β-(1→3)-GalNAc and Gal-β-(1→3)-GlcNAc in different ILs as cosolvent. These reactions took place in IL−buffer mixtures with excellent yields (up to 97%), without obvious hydrolytic activity and with excellent regioselectivity, representing a considerable improvement over the use of aqueous medium. Furthermore, reaction scale-up and IL recovery and recycling are feasible without loss of catalytic action.[242]

In a recent work, lipase from *Pseudomonas stutzeri* catalyzed regioselective deacylation of peracetylated β-pyranosides.[243] In that study the enzyme was used for deacylation of per-O-acetylated sugars in aqueous buffered medium (hydrolysis reaction) in the presence of green solvents from several sources: GBS, BDS (biosolvents), and fluorous solvents. Then some alcohols were tested for the same deacetylation (alcoholysis reaction); in both cases, the enzyme performed a regioselective deacetylation of substrates at the β-anomeric position, while α-anomers were not recognized by the enzyme. This result was explained due to specific interactions between substrate and the active site of the enzyme. Some alcohols with bulky residues (i.e., *t*-butyl, *i*-propyl) were not able to perform the reaction, and this effect was explained due to the size and shape of the active site of the enzyme.

3.2. Carbohydrates in Food and Nutraceuticals

Many carbohydrates are present in food and beverages as main natural constituents or as additives that provide desired properties to the final food products.[244] Therefore, they are of great importance in the food industry,[245] and new enzymatic methods[246,247] and their use in synthesis are valuable for the development of green processes. Enzymatic methods are also useful for analysis of the carbohydrate content of many foodstuffs. These methods are rapid, highly specific, and sensitive to low concentrations and are therefore ideal for determination of carbohydrates in foods.[248,249] The two methods most commonly used to determine carbohydrate concentration include allowing the reaction to go to completion and measuring the concentration of the product, which is proportional to the concentration of the initial substrate, and measuring the initial rate of the enzyme-catalyzed reaction because the rate is proportional to substrate concentration.[250] Labeling of the carbohydrate content of food is required by legislation to ensure that costumers are receiving accurate information on the chemical composition of a given food product.

Food carbohydrates can be classified according to structure or digestibility. Chemically, they are classified as mono-, di-, oligo-, and polysaccharides. By convention, IUPAC (International Union of Pure and Applied Chemistry) defines polysaccharides as molecules containing 10 or more monomeric residues. Low-molecular weight carbohydrates often consist of mono-, di-, and oligosaccharides, the latter having 3−9 monomeric residues. Glucose and fructose are the main dietary monosaccharides found in fruits, berries, and drinks, whereas free galactose is found in fermented milk products. Sucrose and lactose are the main disaccharides, with maltose occurring mainly in glucose syrups. The main forms of oligosaccharides are the raffinose[251] series of galactosides, fructo-oligosaccharides[252] from vegetables, and malto-oligosaccharides,[252] especially from starch hydrolysis. Polysaccharides can be divided into starches and non-starch polysaccharides (NSPs). NSPs consist of cellulose, which is a linear β-glucan, and a range of heteropolysaccharides without α-glucosidic linkages. Plant cell walls are the main source of dietary NSP. Noncellulosic NSP can be classified according to many different criteria, for example, neutral (containing mainly neutral sugar residues), acidic (containing mainly uronic acid residues, also referred to as pectic substances), and hemicelluloses A, B, and C, depending on solubility at various pH. Gums and mucilages, naturally occurring in some plant foods and used as polysaccharide food additives, contribute to the dietary intake of NSP. The relative proportions of main monomeric residues—rhamnose, xylose, arabinose, galactose, glucose, mannose, and uronic acids—is another common way to characterize and name food polysaccharides, for example, arabinoxylans, galactans, galactomannans, and rhamnogalacturonans.

In general, food-grade oligosaccharides are not pure products but mixtures containing oligosaccharides of different degrees of polymerization, the parent poly- or disaccharide, and monosaccharides. Most manufacturers produce several classes of products: higher grades contain pure oligosaccharide mixtures with lower levels of mono- and disaccharides or polysaccharides. A number of more recently introduced carbohydrate food ingredients include maltose and dextrins from glucose syrups, inulin, polydextrose, various oligosaccharides, polyols, and starches that are chemically modified.

A major source of glucose and fructose since the mid-1900s has been starch, which is produced by most green plants on the earth as an energy store.[253] Besides starch, sugars, pentosans,

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fibers, proteins, amino acids, and lipids are also present as crucial parts of the plant. In the beginning, starch was hydrolyzed into glucose syrups by acid treatment as discovered by Kirchhoff. In 1921, Newkirk described a commercial process for the production of glucose from starch; that procedure includes the granulating release of amylopectin and amylose from starch followed by treatment with enzymes. Nowadays, almost all production of glucose is obtained by enzymatic treatments, and generally four significant enzymes are involved (Figure 4).[10a]

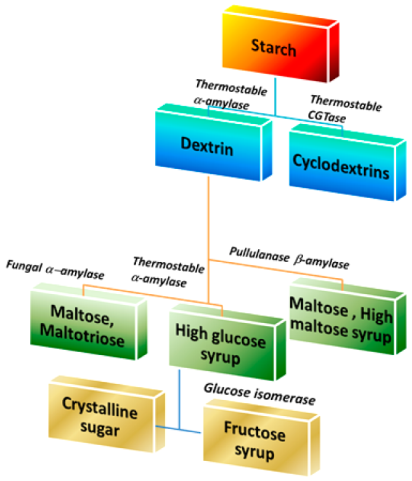

Figure 4. Enzymatic production of glucose, maltose, and fructose from starch.

The first step is liquefaction into soluble and short-chain dextrins. A dry solid (30−35%) starch slurry of pH 6 is mixed with α-amylase and passed through a jet cooler, after which the temperature is maintained at 95−105 °C for 90 min. Temperatures above 100 °C are preferred to ensure the removal of lipid−starch complexes. Initially α-amylase from *Bacillus amyloliquefaciens*[254] was used, but this has been replaced by α-amylase from *Bacillus stearothermophilus*[255] or *Bacillus licheniformis*.[256] The drawback of the α-amylases used currently is that they are not active at pH below 5.9 at the high temperatures used. Therefore, the pH has to be adjusted from the natural pH 4.5 of the starch slurry to pH 6 by adding NaOH.[257] Ca^{2+} is also required, because of the Ca^{2+} dependency of these enzymes. *Pyrococcus furiosus*[258] has an extracellular α-amylase enzyme that shows promising characteristics for applications in the starch industry. The enzyme is highly thermostable in the absence of metal ions, remains active even at a temperature of 130 °C, and shows a unique product pattern and substrate specificity.

The second step is saccharification of the starch−hydrolysate syrup to highly concentrated glucose syrup, with more than 95% glucose. This is completed by use of an exo-acting glucoamylase, which hydrolyzes 1,4-α-glycosidic bonds from the nonreducing end of the chain. Most commonly used are glucoamylases of *Aspergillus niger* or a closely related species. These enzymes have a pH optimum of 4.2 and are stable at 60 °C. The pH of the starch−hydrolysate syrup is adjusted to 4.5 with hydrochloric acid to run an efficient saccharification process. Depending on the specifications of the final product, this step is performed for 12−96 h at 60−62 °C. A practical problem in this process is that the glucoamylase is specialized in cleaving α-1,4-glycosidic bonds and slowly hydrolyzes, α-1,6-glycosidic bonds present in maltodextrins. This will result in accumulation of isomaltose. A solution to this problem is to use a pullulanase that efficiently hydrolyzes α-1,6-glycosidic bonds. A prerequisite is that the pullulanase has the same pH and temperature optimum as the glucoamylase.

A final step in industrial starch processing is the conversion of high-glucose syrup into high-fructose syrup. Fructose is an isomer of glucose and is almost twice as sweet as glucose. This conversion is done by use of the enzyme D-xylose−ketol isomerase (EC 5.3.1.5), better known as glucose isomerase.[259] The high-glucose syrup is first refined, carbon-filtered, concentrated to over 40% dry solids, and adjusted to pH 7−8. In a continuous process, this adjusted high-glucose syrup is passed over an immobilized column containing glucose isomerase on a solid support. Maximum levels of fructose are about 55%. Starch,[260] although considered fully digestible, has been challenged, and starch is found to be partly indigestible in the gastrointestinal tract of humans. This fraction of starch, resisting digestion in vivo, is known as resistant starch. Due to its excellent fermentative capacity in the gut, especially yielding butyric acid, resistant starch is considered a new tool for the creation of fiber-rich foods, which are of nutraceutical importance. By careful control of processing conditions, the content of resistant starch, a man-made fiber, can be increased to as high as 30%.

Arabinoxylans are the major endospermic cell wall polysaccharides of cereals. In wheat they are found complexed with ferulic acid esters, which after oxidative coupling in vivo, mediated by H_2O_2 and peroxidases or even by photochemical means, give cross-linked diferuloyl derivatives. The latter confer strength and extensibility to the cell wall and offer resistance to digestibility by ruminants. They also help block the ingress of pathogens. The ester-bound ferulic acid, after oxidation in vivo, generates reactive oxygen species that contribute to fragmentation of non-starch polysaccharides (hemicelluloses) and thereby reduce product viscosity, a property seen during long-term storage of rice. In plant tissues, arabinogalactans are implicated in such diverse functions as cell−cell adhesion, nutrition of growing pollen tubes, and response to microbial infections and also as markers of identity expressed in the terminal sequences of saccharide chains.

3.2.1. Enzymatic Synthesis of Food Oligosaccharides. Oligosaccharides have increased their presence in the food industry due to their prebiotic properties.[261] Prebiotics are nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of bacteria in the colon. The ingredients are carbohydrates, in general the more nondigestible oligosaccharides. A combination of probiotic (bacteria that grow in the intestinal tract)[262] and prebiotic food ingredients are the so-called symbiotic ingredients. They are produced in bulk via enzymatic procedures. The two types of enzymes used are glycosyltransferases and glycosidases. More recently, the glycosynthases,[263] engineered mutant glycosidases[264] built by mutation of the catalytic nucleophile of a retaining glycosidase of a small nonnucleophilic residue, have been reported. Their advantage is that they cannot hydrolyze glycosidic bonds and are capable of synthesizing oligosaccharides. Table 5 shows enzymes involved in industrial production of oligosaccharides.

Lactulose[265] is one of the structural isomers of lactose that has many applications in both pharmaceutical and food industries. Lactulose increases the prevalence of *Bifidobacterium* in feces of breast-fed infants in comparison to bottle-fed ones and also does not cause tooth decay, and it can be used as an antidecaying and noncaloric sweetener due to its exclusive digestion by anaerobic *Bifidobacterium* in the large intestine. In addition, lactulose is now

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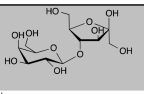
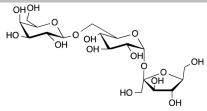
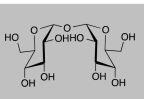
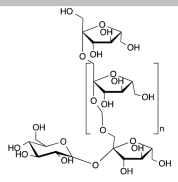
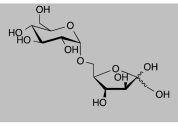
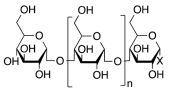
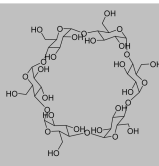
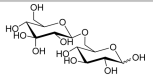
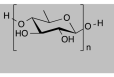
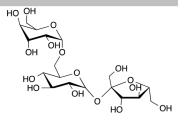
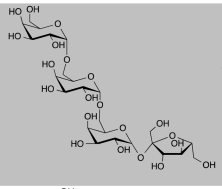
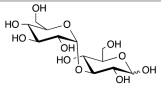
Table 5. Food-Grade Oligosaccharides and Enzymes Involved in Their Synthesis

Oligosaccharides	Structure	Enzymes	References
Lactulose		β-galactosidase	257,259,260
Lactosucrose		β-Galactosidase	262,263
Tetrahalose		Tetrahalose synthase	264,265
Inulin		β- Fructosyltransferase	272,273
Palatinose		Sucrose isomerase tranglucosidase	273, 274
Malto-oligosaccharide and isomaltose oligosaccharides			275, 276
Cyclodextrins		Cyclodextrin glucosyl transferases	277,278
Gentiooligosaccharides		β-Glucosidases	281
Xylooligosccharides		β-Xylosidase	282
Raffinose		α–Galactosidases	284,285
Stachyose		α-Galactosidases	284,285
Nigerooligosaccharides		α-Glucosidase	287

commonly used as a pharmaceutical drug for prevention and treatment of portal systemic encephalopathy and chronic constipation. The preparation of lactulose was first described by Montgomery and Hudson[266] in 1930, making use of the aldose to ketose rearrangement. Enzymatic synthesis[267] with clean production has been reported, where glycosidases were used to produce lactulose by a new enzymatic method. A continuous enzymatic process for production of the prebiotic disaccharide lactulose through transgalactosylation was developed that uses free and immobilized β-glycosidase from *Pyroccocus furiosus*.[268] The hyperthermostable β-glycosidase (CelB) was immobilized onto an anion-exchange resin (Amberlite IRA-93) or onto Eupergit C with immobilization yields of 72% and 83%, respectively. The immobilized biocatalysts demonstrated specific activities of 920 and 1500 nkat·(g of dry carrier)$^{-1}$ at 75 °C with *p*-nitrophenyl β-D-galactopyranoside as substrate. Maximum lactulose yields of 43% related to the initial lactose concentration were reached with the carrier-bound CelB preparations. The corresponding productivities were 52 g of lactulose·L^{-1}·h^{-1} (Amberlite IRA-93) and 15 g of lactulose·L^{-1}·h^{-1} (Eupergit C). The free enzyme tested in an enzyme membrane reactor showed a product yield of 41% and a productivity of 12 g of lactulose·L^{-1}·h^{-1} in the first day. While both carrier-bound CelB preparations were 100% stable for at least 14 days, the half-life of the free CelB in the enzyme membrane reactor was only about 1.5 days. Recently a novel pilot plant[269] scale process was reported where lactulose was synthesized enzymatically, operating at a maximum batch volume of 170 L.

Lactosucrose is a trisaccharide that is more soluble in water than lactose and has a high moisture-retaining capacity, making it useful in the food industry. It is enzymatically produced from lactose by transglycosylation. β-D-Galactosidase from *B. circulans* was a suitable biocatalyst for the production of lactosucrose [β-D-Gal*p*-(1→4)-α-D-Glc*p*-(1→2)-β-D-Fru*f*] and its analogues from lactose and sucrose.[270] Tetrahalose[271,272] is synthesized by use of tetrahalose synthase,[272] maltooligosyltrehalose synthase, and trehalose-6-phosphate synthetase.[272,273]

The biofunctional applications of fructooligosaccharides are many, due to the following three properties that make them important food ingredients: (1) they encourage the growth of the bifidobacteria; (2) they suppress the growth of harmful bacteria in the gut, possibly due to the formation of lactic, acetic, and other short-chain organic acids that may be antagonistic to the potentially pathogenic intestinal competitors; and (3) they reduce levels of serum cholesterol, phospholipids, and triglycerides. Fructooligosaccharides derived from inulin[274] are referred to as inulooligosaccharides. Inulin is the storage carbohydrate in the roots and tubers of plants such as Jerusalem artichoke, chicory, and dahlias. Inulin is a linear compound consisting of β-(2,1)-linked D-fructofuranose units and one terminal α-(1,2)-linked-D-glucopyranose unit. It is resistant to hydrolysis by pancreatic amylase and saccharidases (sucrase, maltase, isomaltase, or lactase) in the upper gastrointestinal tract, and it reaches the large intestine unabsorbed and is utilized as a carbohydrate substrate for the growth of indigenous *Bifidobacterium*. In a broader context, fructans are carbohydrate polymers in which fructosyl−fructose linkages constitute the majority of linkages. Fructans includes small oligomers, polymers with more than 10 000 residues, and dimeric inulobiose. There are several types of fructans depending on their chemical structure and the organisms producing them. Fructans are categorized as follows: inulin, levan, phlein, graminan, kestoses, and kesto-*n*-oses. Levan is primarily found as a microbial exopolysaccharide and is a fructose biopolymer mainly linked by β-(2,6)-glycosidic bonds, with β-(2,1)-linked side chains Levan is also a fructan of higher plants that has mostly (2,6)-fructosyl−fructose linkages and high degree of polymerization (DP > 100) polymers such as those found in bacterial systems. Phleins are plant-derived compounds, which contain mostly the (2,6)-fructosyl−fructose linkage and

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are of lower molecular weight (DP < 100). Inulin-type fructans are either extracted from plants (chicory, dahlias, and artichokes)[275−277] in the form of inulin[278] or synthesized from sucrose through the combined action of microbial enzymes,[279] sucrose−sucrose 1-fructosyltransferase (EC.2.4.1.99), and fructan−fructan 1-fructosyltransferase (EC 2.4.1.100).[280]

Isomaltulose (trade name Palatinose) is a disaccharide made of glucose and fructose (6-*O*-α-D-glucopyranosyl-D-fructose) that is a natural constituent of honey and sugar cane and has a very sweet natural taste. It has been used as a sugar substitute in Japan since 1985. Industrial bioconversion of sucrose to isomaltulose is possible via the enzymatic activity of sucrose isomerases (SIases, EC 5.4.99.11) from various microbial sources.[281] A recent report[282] shows the efficient enzymatic synthesis of a homologous series of isomaltulose-derived oligosaccharides with DP = 3−9 through transglycosylation by use of a dextransucrase from *Leuconostoc mesenteroides* B-512F.

Isomaltooligosaccharides are known as prebiotic, branched oligosaccharides that are obtained from starch. Branched oligosaccharides are one of the major prebiotic carbohydrates, including isomaltose, panose, isopanose, branched maltotetraose, and branched isomaltopentaose. Branched oligosaccharides are produced via a two-stage reactor system having two different enzymes. Isomaltooligosaccharides are composed of glucose monomers linked by α-1,6 (and rarely α-1,4) glucosidic linkages and are produced from starch by the action of three separate enzymes.

Starch is hydrolyzed to maltooligosaccharides by α-amylase (EC 3.2.1.1) and pullulanase (EC 3.2.1.41), and α-glucosidase (EC 3.2.1.20) is added to catalyze a transfer reaction that converts the α-1,4-linked maltooligosaccharide into α-1,6-linked isomaltooligosaccharides. Isomaltooligosaccharides are prepared on an industrial scale by three different approaches: (1) using glucoamylase to catalyze high concentration glucose to form maltose and isomaltose; (2) using transglycosylation to synthesize isomaltose and panose from maltose; and (3) using α-amylase to hydrolyze starch to produce a mixture of maltose, panose, and isomaltooligosaccharides.[283]

Co-immobilization of dextransucrase[284] and dextranase into calcium alginate includes the coentrapment of soluble dextransucrase and adsorbed dextranase. Dextransucrase converts sucrose into dextran, which is the substrate for dextranase, so that isomaltooligosaccharides are followup products of dextran hydrolysis. The boundary conditions for successful preparation were investigated with respect to choice of dextranase adsorbate, surface modifications with blotting agents, and optimal enzyme activity ratios. Product formation at various cosubstrate/substrate concentrations and at different dextranase/dextransucrase ratios was discussed. Moreover, the complexity of the bienzymatic system can be reduced by consideration of the molar ratios of cosubstrate/substrate (glucose/sucrose). Based on these factors, a mechanistic kinetic model is developed, which distinguishes the corresponding contributions of the two enzymes upon overall product formation. In general, at low glucose/sucrose ratios, isomaltose synthesis is featured primarily by dextranase action. Yet with increasing amounts of glucose, both the quantity and quality of dextranase substrate changes, so that its contribution to product formation decreases in an exponential manner; still the overall product yield continuously increases due to enhanced dextransucrase contribution.

Cyclodextrins[285,286] are cyclic oligomers used in the food industry to provide encapsulation of lipophilic food ingredients, which improves the stability of flavors, vitamins, colorants, and unsaturated fats in both a physical and a chemical sense, leading to extended product shelf life. Accelerated and long-term storage stability test results showed that the stability of cyclodextrin-entrapped food ingredients surpassed that of traditionally formulated ones. The use of cyclodextrins in foods and food processing technologies are also manifested in improved sensory, nutritional and performance properties. Cyclodextrin glycosyltransferase[287] (CGTase; EC 2.4.1.19) is an enzyme that converts starch into cyclodextrins, which are closed-ring structures having six or more glucose units joined by means of α-1,4 glucosidic bonds. CGTase is classified in the α-amylase family and is known to catalyze four different transferase reactions: cyclization, coupling, disproportionation, and hydrolysis. Three major types of cyclodextrins are produced by CGTase depending on the number of glucose units: α-, β-, and γ-cyclodextrins.

Gentiobiose is well-known as a sugar having a bitter taste. This bitterness makes gentiobiose useful as a taste improver for certain beverages. Gentiooligosaccharide is a new functional oligosaccharide that consists of more than two D-glucoses linked with β-1,6-glycosidic bonds. The main components of gentiooligosaccharide are gentiobiose and small amount of trisaccharide and tetrasaccharide. Gentiooligosaccharide is low in calories and has low risk of causing dental caries. Moreover, gentiooligosaccharide promotes the proliferation of probiotics such as *Bifidobacterium* and *Lactobacillus*, whose functions involve vitamin syntheses, promoting immune response, inhibiting the growth of harmful bacteria, and inhibiting tumors as well as promoting nutrient uptake and metabolism.[288] There are only limited reports on the industrial-scale production of gentiooligosaccharides with starch as the feedstock. In Japan, some β-glucosidases (EC 3.2.1.21) that have transglycosylation activities have been used to synthesize gentiooligosaccharides. With high concentrations of glucose as the substrate, β-glucosidase transfers free glucose to other sugar substrates through β-1,6-glycosidic bonds and synthesizes gentiooligosaccharides.[289] This process is mild, safe, low cost, and causes only low levels of pollution. In addition, the end product is easy to isolate from the reaction mixture. Also, these enzymes are tolerant to a wide range of pH and the reaction conditions are mild.

Xylooligosaccharides are sugar oligomers made up of xylose units, which are found in bamboo shoots, fruits, vegetables, milk, and honey. These emerging prebiotic sugars can be prepared either from enzymatic degradation of xylan[290] or through treatment of wheat bran insoluble dietary fiber with the commercial xylanase Sunzyme.[291]

Two oligosaccharides of nutritional importance are raffinose and stachyose,[292] which are found in beans and other legumes. They are nondigestible since they are degraded only by α-galactosidases,[293] which are not present in the human intestinal tract; therefore they are responsible for flatulence. They are now used in the food industry as prebiotics.[294]

Nigerooligosaccharides are oligosaccharides derived from glucose with a high number of α-(1→6)-O-glycosidic bonds including the isomaltooligosaccharide group. They are synthesized from maltose[295] by transglucosidation reactions catalyzed by α-glucosidase enzymes from different microorganisms. Recently, sucralose (Splenda) has been introduced as a supersweetener. It was discovered in 1976 by scientists at Tate and Lyle; chemically speaking, it is a partially chlorinated sucrose (Scheme 15). It is 600-fold sweeter than sucrose and 3.3-fold sweeter than aspartame (Equal).

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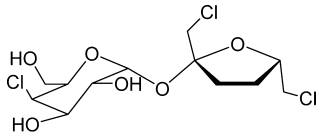
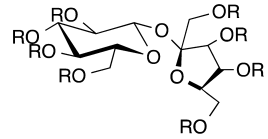
Scheme 15. Chemical Structure of Sucralose



Chemical synthesis of sucralose from sucrose involves the selective protection of hydroxyl groups (acetylation), followed by chlorination and deprotection. Many efforts have been made to improve production of the acetylated intermediate sucrose-6-acetate[296] to replace the traditional multistep chemical route for sucralose biosynthesis, which uses cross-linked enzyme aggregates of Lipozyme TL 100 L. Chaubey et al.[297] have reported the bioconversion of sucrose-6-acetate by use of microbial immobilized whole cells of *Arthrobacter* sp. and *Bacillus subtilis* (RRL-1789) in a bioreactor. The biotransformation was performed in water and the final sucraolose product was directly concentrated under vacuum as a crystalline powder. Other enzymatic procedures have been used to obtain sucralose from starting materials other than sucrose. Bennett et al.[298] started with chemical chlorination of raffinose to form a novel tetrachlororaffinose intermediate (6,4′,1″,6″-tetrachloro-6,4′,1″,6″-tetradeoxygalactoraffinose), followed by enzymatic hydrolysis of the α-1,6-glycosidic bond to give sucralose and 6-chlorogalactose.

The food industry has increasingly introduced the use of fat substitutes in foods as reduced- or zero-calorie ingredients. Many are based on starches, gums, and emulsifiers that thicken with water to give a feeling of thickness in the mouth, and some are based on proteins broken into micrometer-size particles on the tongue to feel like fat. Those fat replacers are limited by heat stability, texture, taste, and marketing. One of the first molecules widely used in the food industry is Olestra (Procter and Gamble), which is prepared through esterification of sucrose molecules with fatty acids from edible oil (Scheme 16).

Scheme 16. Olestra and Its Chemical Structure



R= Fatty acid CH_3-$(CH_2)_n$COOH

Olestra exhibits functional and physical properties that resemble conventional triglycerides but contributes no calories to the diet. Other methyl glucoside polyesters[299] (Scheme 17) also have potential fat-substitute properties. They consist of a methyl glucoside molecule with four fatty acids attached to the hydroxyl groups.

3.3. Carbohydrates in Pharmaceuticals

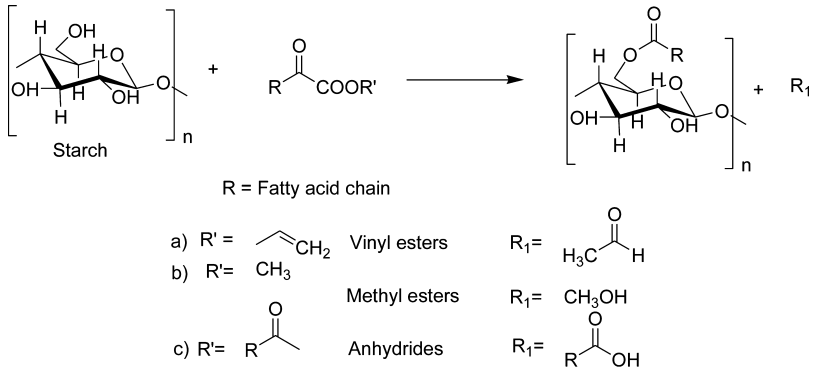
Carbohydrates are the most abundant natural products. Besides their role in metabolism and as structural building blocks, they are fundamental components of every cell surface, where they are involved in vital cellular recognition pathways. Carbohydrates are relatively unexploited sources of new drugs, so that there are many new research opportunities in the field of therapeutic glycans. Advances in the functional understanding of carbohydrate−protein interactions have enabled the development of a new class of small-molecule drugs known as glycomimetics.[300−302] These compounds mimic the bioactive function of carbohydrates and address the drawbacks of many carbohydrate leads, namely, their low activity and/or insufficient druglike properties.[301,302]

The development of efficient and general synthetic routes for carbohydrates remains a major challenge because of the complexity of their structures.[301,302] Because of the polyhydroxyl nature of carbohydrates, a major challenge in carbohydrate synthesis is to modify specific hydroxyl groups in the presence of others. Nevertheless, a number of powerful methods including metal-catalyzed synthesis, one-pot glycosylation, and automated solid-phase synthesis have been developed to address the challenges of synthetic carbohydrate chemistry. Conventional nonenzymatic methods have been widely employed, but the exploitation of enzymatic or chemoenzymatic approaches represent an attractive and valuable strategy for synthesizing carbohydrates and glycomimetics. Chemoenzymatic methods combine the flexibility of chemical synthesis with the efficiency and selectivity of biocatalyzed transformation to obtain diverse complex carbohydrate families. The enzymes more commonly used are glycosidases, aldolases, oxidoreductases, lipases, and their mutants with or without sugar nucleotide biosynthetic enzymes.[303]

3.4. Carbohydrates as Materials

Polysaccharides are fundamental structural components for most organisms, providing for their structural integrity. This is especially true for terrestrial plants, where cellulose and lignin are their major structural constituents. Cellulose is the most abundant biopolymer on the earth, existing in wood, cotton, hemp, and other plant-based materials and serving as the

Scheme 17. Methyl Glucoside Polyester



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dominant reinforcing phase in plant structures. Cellulose is also synthesized by algae, tunicates, and some bacteria. Cellulose, a β-(1→4)glucan, has been used to produce paper for centuries. Nowadays, the application of cellulose has expanded to the field of modification of synthetic polymers. The production of nanoscale cellulose fibers[304] and their application in composite materials has gained increasing attention due to their high strength and stiffness combined with low weight, biodegradability, and renewability. Two main types of cellulose nanofibers can be produced: cellulose nanowhiskers[305] and microfibrillated cellulose.[306] These natural fillers are distinguished by their size, crystallinity, and aspect ratios.

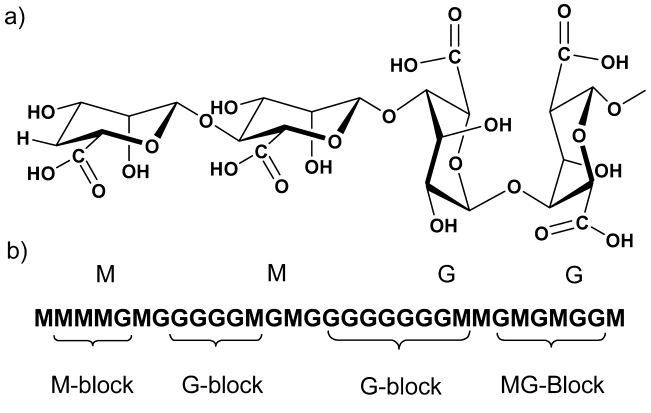
Chitin[307] is the world's second most important natural polymer. The main sources of chitin are two marine crustaceans, shrimp and crabs. Its morphology in the native solid state, methods of identification and characterization, and chemical modification, as well as the difficulties in utilizing and processing it for selected applications, make it difficult to use as biomaterial. Chitosan, partially de-N-acetylated chitin, is the most important chitin derivative. Chitosan, a cationic polysaccharide, is easier to process since it is soluble in acidic aqueous media. Chitin[308] and its derivatives show various functional properties that make them useful in many fields including food,[309] cosmetics,[310] biomedicine,[311] agriculture, environmental protection,[312] and wastewater management.[313] Furthermore, the biodegradable, nontoxic, and nonallergenic nature of chitosan has encouraged its potential use as a bioactive material. Even though chitosan is known to have important functional activities, its poor water solubility at neutral pH values makes it difficult to use in food and biomedicinal applications. In contrast, chitosan oligosaccharides are readily soluble in water due to their shorter chain lengths and unsubstituted amino groups. The reduced viscosity and excellent solubility of chitosan oligosaccharides at neutral pH have attracted the interest of many researchers.

Chitosan can be further functionalized through its amino groups, resulting in products with improved properties. Genipin has been used as a cross-linker to functionalize chitosan to prepare matrices for use in supporting cell growth.[314] Additional chitosan cross-linkers including glutaraldehyde,[315] hexamethylene-1,6-diaminocarboxysulfonate,[316] and epichlorohydrin[317] have been reported.

Alginate[318] is a biomaterial (Scheme 18) that is often applied for use in a variety of biomedical and engineering applications because of its favorable properties, including biocompatibility and ease of gelation. Alginates are unbranched polysaccharides consisting of (1→4)-linked β-D-mannuronic acid (M-block) and its C-5 epimer α-L-guluronic acid (G-block). The natural copolymer is an important component of algae, such as kelp, and is also an exopolysaccharide of bacteria including *P. aeruginosa*. Alginate hydrogels[319] have been particularly attractive in wound healing, drug delivery, and tissue engineering applications to date, as these gels retain structural similarity to the extracellular matrices in tissues and can be manipulated to play several critical roles.

Scaffolds derived from naturally occurring polysaccharides have attracted significant interest in bone tissue engineering due to their excellent biocompatibility and hydrophilic nature favorable for cell attachment. Composite scaffolds of cationic chitosan complexed with an anionic polysaccharide, such as alginate[318] or chondroitin 4-sulfate,[320] that include a biomimetic apatite surface layer have been used to deliver progenitor cells (i.e., bone marrow stromal cells) and model proteins.

Scheme 18. (a) Monomers of Alginate. (b) Structure of Alginate



4. GREEN SOLVENTS IN CARBOHYDRATE EXTRACTION, SEPARATION, PURIFICATION, AND ANALYSIS

Green solvents, as previously discussed, have been widely applied to various steps of carbohydrate processing. Water is the principal solvent used in processing sugars, polysaccharides, and glycoconjugates, as it is readily able to dissolve most carbohydrates. However, aqueous solvents have several disadvantages, including high energy requirements for drying; codissolution of salts, peptides, and other substances; and difficulties associated with extraction, purification, and analysis in aqueous solvents. This section examines the use of green solvents in extraction, separation, purification, and analysis of carbohydrates.

4.1. Carbohydrate Dissolution and Extraction

4.1.1. Ionic Liquid Applications. ILs have been widely used for the dissolution and extraction of carbohydrates. ILs have also been applied as solvents for biorefining carbohydrates[321] (Table 6). The solubility of biomass-derived compounds in ILs is an important parameter for design of future processes incorporating ILs as solvents for biorefining. Sugar alcohols such as sorbitol and xylitol, reduced carbohydrates important in the food industry, have been identified as building blocks (renewable feedstocks for use in green solvents) for biorefining. The solubility of these sugar alcohols was experimentally measured and modeled, in the temperature range 288−433 K, in three ILs: [EMIM][$EtSO_4$], *N*-methyl-*N*,*N*-dioctyloctan-1-ammonium chloride or [Aliquat 336][Cl], and [Aliquat 336][NO_3]. A thermodynamic study on phase diagrams of D-sorbitol and xylitol with dicyanamide-based ILs relied on both experimental and theoretical studies of thermodynamic properties of three ILs based on dicyanamide anion (Figure 5).[322] The dicyanamide-based ILs used in this study included 1-butyl-3-methylimidazolium dicyanamide, [BMIM][DCA]; 1-butyl-1-methylpyrrolidinium dicyanamide, [BMPyr][DCA]; and 1-butyl-1-methylpiperidinium dicyanamide, [BMPip][DCA]. Experiments on these ILs and their binary mixtures were conducted to assess their applicability for dissolution of these sugar alcohols.

The IL solubility of monosaccharides obtained from biomass processing has also been experimentally studied and modeled.[321] ILs have demonstrated a capability to act as selective solvents and catalysts for biomass processing. The solubilities of monosaccharides such as D-glucose, D-fructose, D-xylose, and D-galactose in two ILs were measured in a temperature range from

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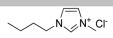
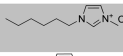
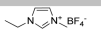
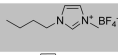
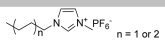
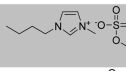
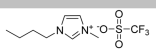
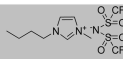
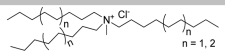
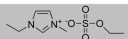
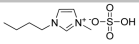
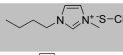
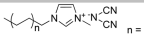
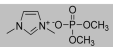
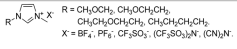
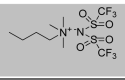
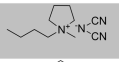
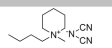
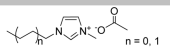
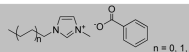
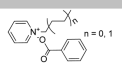
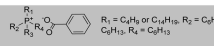
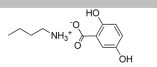
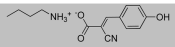
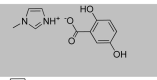
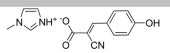
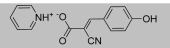
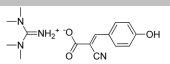
Table 6. Structures of Room-Temperature Ionic Liquids Used for Carbohydrate Extraction, Purification, Separation, and Analysis

RTIL	Structure	References
1-Ethyl-3-methylimidazolium Chloride [EMIM]Cl		323, 364
1-Butyl-3-methylimidazolium Chloride [BMIM]Cl		82, 90, 110, 231, 322, 335, 343, 357, 364, 365
1-Hexyl-3-methylimidazolium Chloride [HMIM]Cl		82, 90
1-Ethyl-3-methylimidazolium Tetrafluoroborate [EMIM]BF_4		117, 355
1-Butyl-3-methylimidazolium Tetrafluoroborate [BMIM]BF_4		90, 355
1-Butyl/Hexyl-3-methylimidazolium Hexafluorophosphate [B/HMIM]PF_6	 n = 1 or 2	90, 329, 355
1-Butyl-3-methylimidazolium Methyl sulfate [BMIM][$MeSO_4$]		342, 343
1-butyl-3-methylimidazolium Trifluoromethanesulfonate [BMIM][TfO]		355
1-Butyl-3-methylimidazolium Trifluoromethylsulfonyl imide [BMIM][NTf_2]		117, 355
N-Methyl-N, N-dioctyloctan-1-ammonium Chloride [Aliquat 336]	 n = 1, 2	321
1-Ethyl-3-methylimidazolium Ethyl sulfate [EMIM][$EtSO_4$]		321
1-Butyl-3-methylimidazolium Hydrogensulfate [BMIM][HSO_4]		349
1-Butyl-3-methylimidazolium Thiocyanate [BMIM][SCN]		90, 349
1-Butyl-3-methylimidazolium Dicyanamide [BMIM][$N(CN)_2$]	 n = 0 or 1	322, 334, 349
1-Methyl-3-methylimidazolium Dimethyl phosphate [DMIM][DMP]		323, 333, 348
[RMIM][X]	 R = CH_3OCH_2, $CH_3OCH_2CH_2$, $CH_3CH_2OCH_2CH_2$, $CH_3CH_2CH_2CH_2$ X = BF_4^-, PF_6^-, $CF_3SO_3^-$, $(CF_3SO_2)_2N^-$, $(CN)_2N^-$	107
Butyltrimethylammonium Bis(trifluoromethylsulfonyl) imide [N114][N		352

RTIL	Structure	References
1-Butyl-1-methylpyrrolidinium chloride [BMPyr]Cl		323
1-Butyl-1-methylpyrrolidinium Dicyanamide [BMPyr][DCA]		322
1-Butyl-1-methylpiperidinium Dicyanamide [BMPip] [DCA]		322
1-Allyl-3-methylimidazolium Chloride [AMIM]Cl		110
1-Ethyl/Butyl-3-methylimidazolium Acetate [E/BMIM][OAc]	 n = 0, 1	106, 110, 333, 342, 346, 347, 366
1-Methyl/Ethyl/Butyl-3-methylimidazolium Benzoate [M/E/BMIM][Ba]	 n = 0, 1, 2	324, 357, 364, 365
N-methyl/ethylpyridinium Benzoate [M/EP][Ba]	 n = 0, 1	324
Trihexyltetradecylphosphonium Benzoate [THTDPH][Ba]	 R_1 = C_6H_{13} or $C_{14}H_{29}$, R_2 = C_6H_{13}, R_3 = C_6H_{13}, R_4 = C_6H_{13}	324
Butylammonium 2,5-Dihydroxybenzoates [DHBB]		336
Butylammonium α-Cyano-4-hydroxycinnamates [CHCAB]		336
1-Methylimidazolium 2,5-Dihydroxybenzoates [IMDHB]		336
1-Methylimidazolium α-Cyano-4-hydroxycinnamates [ImCHCA]		336
Pyridinium α-Cyano-4-hydroxycinnamates [PyCHCA]		336
1,1,3,3-Tetramethylguanidinium α-Cyano-4-hydroxycinnamates [G2CHCA]		337

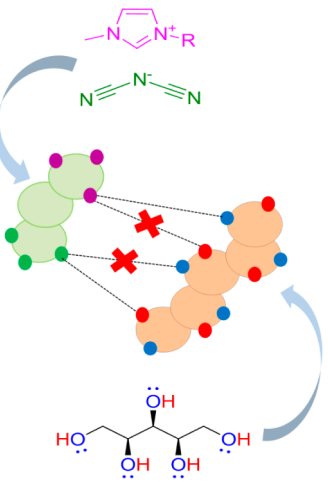


Figure 5. PC-SAFT (perturbed-chain statistical associating fluid theory) molecular and association schemes adopted for the investigated compounds. Dashed lines correspond to allowed intermolecular interactions via cross-association. Interactions designated by red crosses are not permitted.

288 to 328 K to address the absence of experimental data on phase equilibria of biomass-derived carbohydrates in ILs. The two ILs examined showed a solubility ranking of D-fructose > D-xylose > D-glucose > D-galactose. Dissolution of glucose in ILs and its extraction by use of an antisolvent (an IL-miscible solvent in which the solute, glucose, is insoluble) has been also evaluated.[323] The solubility of D-glucose in four ILs was measured in the temperature range from 283 to 373 K, again to overcome the lack of experimental data on phase equilibria of biomass-derived carbohydrates in ILs.

Some ILs can dissolve carbohydrates at high concentrations.[107] ILs based on the DCA anion are highly effective, nonprotic solvents that dissolve carbohydrates from glucose to starch and even cellulose in large amounts. Enzymatic acylation with a fatty acid can also take place in such a medium. ILs can even dissolve highly charged anionic polysaccharides, such as glycosaminoglycans, if they are prepared in the appropriate salt forms prior to their dissolution.[324]

The recovery of carbohydrates, such as cellulose and hemicellulose, from biomass is also possible by use of ILs. Aqueous biphasic systems composed of a water-stable IL ([BMIM][CF_3SO_3])[117] have been shown to undergo phase separation. Phase diagrams, tie lines, and tie-line lengths at 298 K were determined, and the densities and viscosities of the coexisting phases were determined to evaluate the adequacy of such systems for liquid−liquid extractions and their suitability in scale-up processes. ILs are important nonderivatizing solvents for cellulose.[90] ILs incorporating anions, which are strong hydrogen-bond acceptors, were most effective in dissolving cellulose, especially when these were combined with microwave heating. In

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contrast, ILs containing "noncoordinating" anions, such as $[BF_4]^-$ and $[PF_6]^-$, do not dissolve cellulose. Chloride containing ILs appears to be the most effective solvents, presumably by solubilizing cellulose through hydrogen bonding of hydroxyl functions to anions of the solvent (Table 7).

Table 7. Solubility of Dissolving Cellulose in Ionic Liquids

IL	method	solubility (%)
$[C_4MIM]Cl$	heat (100 °C)	10
$[C_4MIM]Cl$	heat (70 °C)	3
$[C_4MIM]Cl$	heat (80 °C) + sonication	5
$[C_4MIM]Cl$	microwave, 3−5 s pulses	25[a]
$[C_4MIM]Br$	microwave	5−7
$[C_4MIM]SCN$	microwave	5−7
$[C_4MIM][BF_4]$	microwave	insoluble
$[C_4MIM][PF_6]$	microwave	insoluble
$[C_6MIM]Cl$	heat (100 °C)	5
$[C_8MIM]Cl$	heat (100 °C)	slightly soluble

[a]Clear viscous solution.

4.1.2. Applications of Supercritical Fluids and Deep Eutectic Solvents. Supercritical fluids have also been applied to dissolution of carbohydrates. Carbohydrates have been referred to as CO_2-philes because of their ability to be dissolved in CO_2.[325] In particular, peracetylated sugar derivatives show high solubility in supercritical liquids such as $scCO_2$.[123] Peracetylated sorbitol and β-D-galactose are soluble under mild conditions in $scCO_2$, while high pressures are required to dissolve peracetylated β-cyclodextrin, and peracetoxyalkyl chains impart CO_2 solubility to amides.

Developing new green solvents is one of the key subjects in green chemistry. Natural deep eutectic solvents have been used to dissolve glycans.[135] Many abundant plant primary metabolites change their state of matter from solid to liquid when they are mixed in proper ratios. Natural deep eutectic solvents may play a role as alternative media to water in living organisms, and a wide range of natural products have been tested, resulting in the discovery of over 100 deep eutectic solvents from nature. Interactions between molecules were investigated by NMR spectroscopy to establish their deep eutectic nature. Novel natural deep eutectic solvents discovered in that study were applied to the solubilization of a wide range of biomolecules such as non-water-soluble bioactive natural products, the protein gluten, the carbohydrate starch, and DNA. In most cases the solubilities of the biomolecules evaluated in that study were much higher than their values in water.

4.2. Carbohydrate Separation

The application of green solvents in separation processes involving carbohydrates has also been well-studied. Supercritical fluid extraction of glycans such as grape glycosides has been described.[326] Supercritical fluid extraction with methanol-modified CO_2 was used to extract glycosides from grapes. An optimization design involving 12 extraction variables was applied to achieve quantitative recoveries. The most important factor was the amount of organic modifier, a consequence of the high degree of glycoside polarity. The application of supercritical fluid extraction to fractionate complex carbohydrate mixtures has been evaluated.[327] Appropriate selection of the cosolvent employed, together with the most suitable extraction conditions (including temperature, pressure, and cosolvent flow rate), allows selective extraction of a prebiotic ketose with high selectivity and recovery. Scale-up and economic feasibility studies have also been performed on the isolation of prebiotic carbohydrates by supercritical fluid extraction.[328] Several processes have been studied that involve the use of supercritical fluid technology to fractionate and purify carbohydrate solid mixtures. The process optimized at laboratory scale to fractionate carbohydrate mixtures produced by enzymatic transglycosylation has been scaled up to an industrial level, and its economic feasibility has been simulated by employing AspenONE V7.3 software to obtain consistent data supporting the interest of a potential investment for prebiotics production at large scale by use of SCFs.

IL-based, surfactant-improved, dispersive liquid−liquid microextraction and derivatization have also been reported on aminoglycosides in milk samples.[329] Supercritical fluid chromatography can also be used in glycan purification.[330] Two new oligosaccharides isolated from the urine of a patient with GM gangliosidosis were purified by capillary supercritical fluid chromatography using a Brownlee syringe pump equipped with a 60-nL Valco injection valve.

Solid-phase carbohydrates have been applied in separations that use supercritical fluid chromatography. Chiral separation of three neonicotinoid insecticides by three polysaccharide-type stationary phases was achieved via high-performance liquid chromatography and supercritical fluid chromatography.[331] Enantioselectivity of polysaccharide-based chiral stationary phases in supercritical fluid chromatography has also used methanol-containing carbon dioxide mobile phases.[332] The enantioselectivity of 12 polysaccharide-based chiral stationary phases and four methanol-containing CO_2 mobile phases was investigated in supercritical fluid chromatography of a test set of 59 drug compounds.

4.3. Carbohydrate Analysis

Glycan analysis has also been accomplished with green solvents. ILs have been used for the analysis of biomass-derived glycans.[333] Analysis of mono- and oligosaccharides has been carried out in the IL-containing matrices [DMIM][DMP] and [EMIM][OAc]. This group studied how these two imidazolium-based, hydrophilic, cellulose dissolving ionic liquids impact standard analytical methods employed for mono- and oligosaccharides, typically produced through the hydrolysis of biomass. ILs have also been examined as solvents for the silylation of carbohydrates prior to their analyses by gas chromatography[334] (Figure 6).

ILs and SCFs have been used as NMR solvents for analysis of carbohydrates. ILs have been applied to study fruit ripening by high-resolution ^{13}C NMR spectroscopy, in a study referred to as "green solvents meet green bananas".[335] Banana pulps at any ripening stage are rich in polysaccharides and could be completely dissolved in [BMIM][Cl]. Variations in the

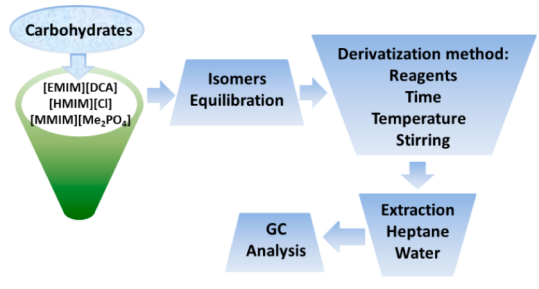

Figure 6. Carbohydrate silylation process in ionic liquids and gas chromatographic analysis.

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carbohydrate composition of the fruit were then directly analyzed in the resulting solutions by high-resolution ^{13}C NMR spectroscopy. A multinuclear NMR spectroscopic study has been performed on carbohydrates in *N*,*N*′-dialkylimidazolium ILs.[110] The results presented in that paper provide valuable new information regarding the solvation of carbohydrates by imidazolium ILs. Analysis of $^{35/37}Cl$ and ^{13}C relaxation data for sugar solutions in both imidazolium chlorides and [EMIM][OAc] clearly show that the anions in these ILs are involved in specific interactions with the solutes and, thus, govern the solvation process. High-pressure NMR characterization of triacetyl-β-cyclodextrin in supercritical carbon dioxide was performed to obtain information on the molecular structure and dynamics.[336] Triacetyl-β-cyclodextrin in $scCO_2$ at 313.15 K and 20 MPa formed inclusion complexes. The influence of $scCO_2$ on a number of NMR spectral parameters, such as chemical shifts, spin−spin coupling constants, nuclear Overhauser effect, and spin−lattice relaxation ($T1$), were also examined.

ILs have been applied as matrix-assisted laser desorption/ionization mass spectrometry (MALDI MS) matrices for the analysis of carbohydrates. While standard ILs could be used for analysis of highly sulfated oligosaccharides,[337] IL matrices specially designed for direct ultraviolet MALDI time-of-flight MS analysis of the sulfated oligosaccharides work even better.[338] A novel IL matrix, 1,1,3,3-tetramethylguanidinium salt of 2,4,6-trihydroxyacetophenone, was developed for MALDI MS analysis of glycopeptides and glycans out of total tryptic digests.[339] This matrix turned out to be particularly well-suited for the analysis of glycopeptides and glycans and overcame the well-known ionization suppression of carbohydrate structures in the presence of peptides. IL matrices can even be used for MALDI time-of-flight MS analysis of intact glycoproteins.[340] This study demonstrated that the chemical composition of an IL matrix very strongly influences the analysis of intact glycoproteins by MALDI time-of-flight MS. Ionization efficiencies and spot homogeneity were better when IL matrices with higher amounts of organic salt were used.

5. GREEN SOLVENTS IN PROCESSING OF CARBOHYDRATE POLYMERS INTO HIGH-VALUE FEEDSTOCKS AND MATERIALS

5.1. Value Products Derived from Biomass

Pretreatment of biomass is a critical step for its effective utilization as a feedstock for the production of biofuels, specialty chemicals, and materials. Biomass typically consists of highly crystalline cellulose, hemicelluose, and xylan and lignin components. A major objective in biomass pretreatment is the separation of biomass into its individual components, their recovery, and the reduction of cellulose crystallinity. RTILs have been proposed as green solvents for biomass treatment as they are designer solvents, nonvolatile, and should be completely recoverable and recyclable.[341]

The separation of biomass into its individual components relies on use of ILs designed to selectively dissolve the components of a particular type of biomass.[342] The dissolution of biomass with ILs as green solvents can provide lignocellulosic materials with appropriate mechanical and physical properties for the preparation of composite films.[343] In that study, two imidazole-based ILs, [BMIM][Cl] and 1,3-dimethylimidazolium dimethyl sulfate ([DMIM][$MeSO_4$]), were used to dissolve ball-milled poplar wood, chemimechanical pulp, and cotton linter to afford cellulose, hemicellulose, and lignin (Figure 7).

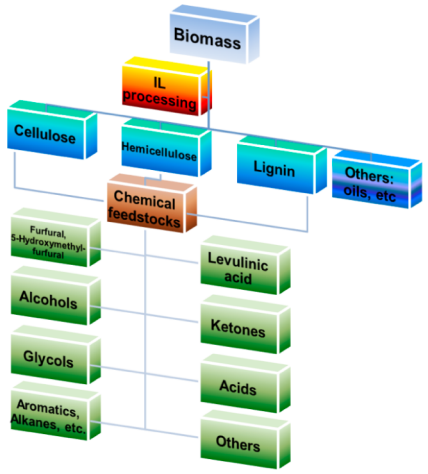

Figure 7. Applications of three major components from lignocellulosic biomass.

Algal biomass can be used to prepare lipids for food and fuel as well as fermentable sugars.[344] An IL-based chemical hydrolysis strategy was developed to obtain high-yielding soluble sugars from the biomass of the alga *Chlorella*.[345] Initial IL dissolution and subsequent HCl-catalyzed hydrolysis dissolved 75% of *Chlorella* biomass and released 88% of total sugars from *Chlorella* biomass (Figure 8).

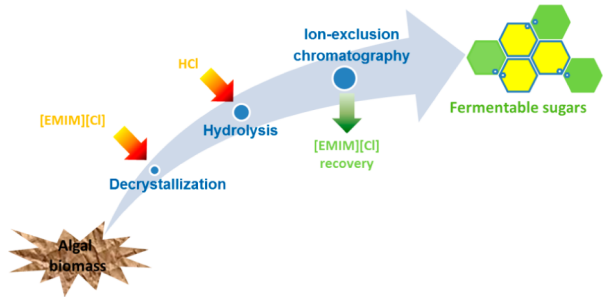

Figure 8. IL-based hydrolysis of *Chlorella* biomass for fermentable sugars.

The selective extraction of lignin from wood by use of ILs can lead to enhanced enzymatic cellulose hydrolysis by removing lignin inhibition of cellulases and reducing the crystallinity of cellulose substrate.[346] The facile pretreatment of lignocellulosic biomass at high loadings in ILs might offer a green and cost-effective approach for the utilization of otherwise intractable biomass.[347] Pretreatment of cellulose with ILs can improve the efficiency of hydrolysis by increasing the surface area of the substrates accessible to solvents and cellulases. However, the IL methods face challenges to separate the hydrolyzed sugar products as well as the renewable ILs from the complex hydrolysis mixtures. Alumina column chromatography was developed for the separation of hydrophilic IL *N*-methyl-*N*-methylimidazolium dimethyl phosphate ([MMIM][DMP]) and glucose, which was the main ingredient of the monosaccharide hydrolysate.[348] In an examination of wheat straw pretreatment with ILs, namely, [BMIM][HSO_4], [BMIM][SCN], and [BMIM][DCA], only [BMIM][HSO_4] was found to achieve

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macroscopic complete dissolution of wheat straw during pretreatment.[349]

A new generation of choline-derived ILs can dissolve and decrystallize microcrystalline cellulose within only a few minutes.[350] Within 5−10 min at 110 °C, these [CH][OAc]-based systems can dissolve approximately 2−6 wt % of microcrystalline cellulose. As compared with imidazodium-based ILs commonly used for decrystallization of microcrystalline cellulose, these new solvents have notable advantages: (1) a higher dissolution rate of microcrystalline cellulose, (2) a lower economical and ecological footprint, (3) availability in very large scale, and (4) good recyclability, thus offering great potential for large-scale applications (Figure 9).

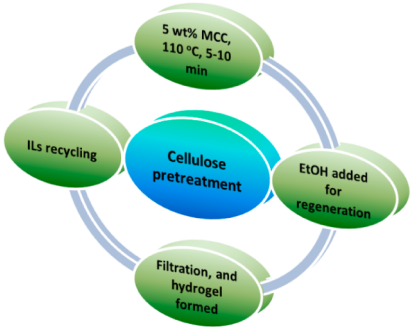

Figure 9. Graphical representation of the decrystallization process of cellulose in choline-derived ILs.

IL pretreatment and saccharification can be combined into a single-unit or one-pot process by use of a thermostable IL-tolerant enzyme cocktail.[351] The results of that study provide the foundation for developing an economically viable IL-based pretreatment technology for biofuels/chemical production based on one-pot pretreatment and saccharification (Figure 10).

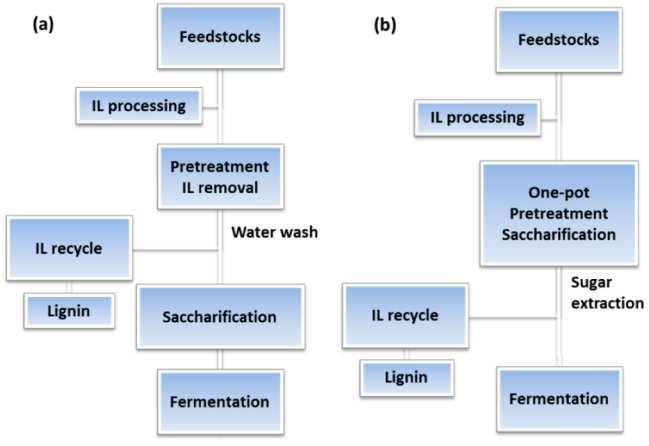

Figure 10. (a) Conventional and (b) one-pot pretreatment and saccharification process using ILs.

A sustainable cyclic process for enzymatic saccharification of IL-pretreated cellulose, in which the IL is recovered and recycled, has been developed.[231c] Homogeneous cellulose solutions in [BMIM][Cl] were used to prepare amorphous cellulose by antisolvent precipitation with water, ethanol, or equimolar water−ethanol mixtures as green molecular solvents. Furthermore, the cellulose regenerated in each cycle was an excellent substrate for enzymatic hydrolysis, permitting full hydrolysis (i.e., up to 98% hydrolysis after 4 h at 50 °C) by the combined action of both cellulase and cellobiase enzymes, providing a clear glucose solution. A novel stabilized cellulose derivative, obtained by coating immobilized enzyme particles with IL, was prepared and successfully used for saccharification of dissolved cellulose in [BMIM][Cl] (i.e., up to 50% hydrolysis in 24 h) at 50 °C and 1.5 (w/v) water content.[352]

Biomass pretreatment has also been accomplished by use of supercritical fluids. The green solvent $scCO_2$ was suitable as a mobile lignocellulosic biomass processor and was used to pretreat corn stover and switchgrass at various temperatures and pressures.[353] Pretreatment of corn stover with sc-CO_2 enhanced the glucose yield considerably. High-pressure vapor−liquid and vapor−liquid−liquid equilibria for binary and ternary systems containing supercritical carbon dioxide, water, and furfural.[354] From these data, operating conditions for the recovery of CO_2 and concentrations of furfural in the separator were obtained. Such data are useful for the production of chemical intermediates from biomass by use of SCF.

Subcritical water is widely accepted as an environmentally benign solvent, for extraction but also as a catalytic medium it therefore has the potential to support processing of multiple components found in biomass.[355] Modeling of continuous-flow subcritical water hydrolysis of biomass-derived components including lipids and carbohydrates successfully demonstrated the application of subcritical water-mediated hydrolysis of rice bran, a lignocellulosic biomass, within a continual flow process configuration for the first time.

ILs have also been applied to food processing applications.[356] Amylases are important in the processing of starch. The impact of two water-miscible ILs on the activity, stability, and structure of two related α-amylases from *Bacillus amyloliquefaciens* and *Bacillus lichiniformis* were studied.[82] This study demonstrated that both the activity and the stability of these α-amylases in aqueous buffer are affected by addition of ILs. Although the imidazolium-based ILs [BMIM][Cl] and [HMIM][Cl] have previously been shown to dissolve carbohydrates, they result in the loss of activity and stability of both α-amylases.

5.2. Materials Derived from Carbohydrates

Green solvents can be used to process carbohydrate polymers into fibers, films, particles and foams for a variety of commercial applications. Woven cellulose fibers coming from cotton have been important commercially for centuries, but recently attention has turned to nonwoven cellulose fibers coming from other forms of biomass. Electrospinning relies on the solubilization of a polymer in a conductive solvent that is ejected in a stream from a spinneret toward a target across a high-voltage gap, during which the solvent evaporates and a nanoscale fiber is formed and collected[357] (Figure 11).

While cellulose had been previously electrospun from volatile but generally toxic solvents, it was only recently that cellulose and other biopolymers were first electrospun from a nonvolatile, nontoxic IL and collected in a coagulation bath containing a second IL-miscible solvent (antisolvent),[358] such as water, allowing the collection of nanoscale fibers[357] (Figure 12A). In addition to being able to electrospin pure cellulose fibers of diameters from 100 nm to 1 μm, electrospining from RTILs into a coagulation bath can afford fiber nanomaterial composites with some very interesting properties with uses ranging from filtration[359] to electrical devices[360] to biology and medicine.[361] Fibers consisting of an internal conductive cable of multiwalled nanotubes with an external insulating surface of cellulose have

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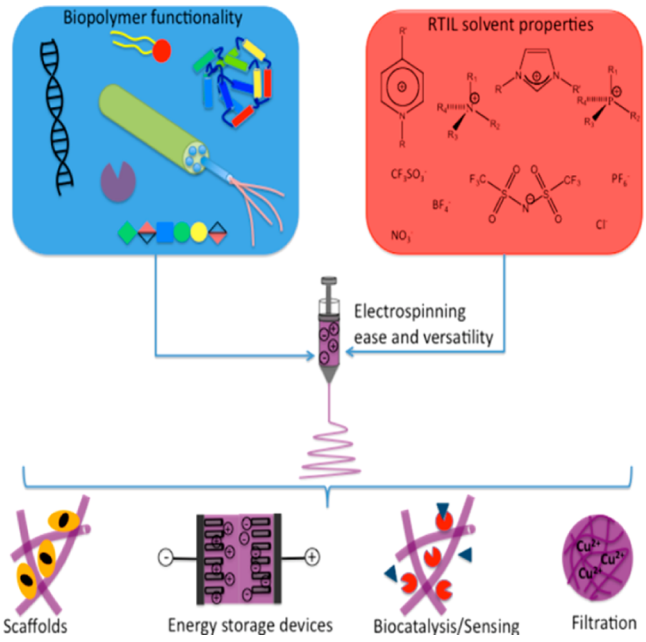

Figure 11. Schematic diagram of potential functional, biopolymer-based fibrous materials and composites fabricated by electrospinning from ILs for advanced applications. Reproduced with permission from ref 357. Copyright 2010 Royal Society of Chemistry.

been prepared by coaxial electrospinning (see Figure 12).[360] The resulting nanowires might one day be used in building nanoscale machines and devices. Electrospun cellulose nanofibers can be surface-modified and used as substrates for immobilization of other biomolecules. For example, lysostaphin-functionalized cellulose fibers display antistaphylococcal activity and might one day have wound-healing applications in bandages or be used to prepare antimicrobial fabrics such as hospital gowns.[362] Flexible electrospun cellulose fibers can be used as affinity packing materials in filtration and chromatography.[359] By coating electrospun chitosan cationic polysaccharide fibers with an anionic hyaluronan polysaccharide, novel matrices can be prepared for cell culturing or slow release applications.[363] Finally, inclusion of nanoparticles, either within electrospun cellulose fibers or on the exterior surface of fibers, can result in nanocomposites with important properties, such as flame-retardant nanocelluloses.[364]

Films and membranes of carbohydrate polymers, prepared from ILs by casting or coating, also offer new materials with appropriate properties for important applications. Cellulosic membranes are widely used in kidney dialyzers, but the formation of blood clots on these membranes remains a problem. Composite membranes of IL-cast cellulose and heparin, a polysaccharide anticoagulant, afford a novel blood-compatible membrane for kidney dialysis.[365] Charcoal beads are widely used in filters for drug detoxification but suffer from low biocompatibility. Heparin−cellulose films, coated on the surface of these beads, afford charcoal composites with improved properties for drug detoxification.[366] In nonmedical applications, synthetic wood composites have been prepared by use of ILs.[367] Regenerated cellulose short fibers/cellulose green composite films have been prepared by first dissolving cellulose in a green solvent of aqueous 7 wt % NaOH/12 wt % urea precooled to −12 °C, reinforcing them with different amounts (1−5%) of short regenerated cellulose fibers, and subsequently regenerating the spread films in an aqueous 5 wt % H_2SO_4 bath.[368] The effect of fiber loading on the optical, tensile, cell viability, and thermal stability properties was studied.

As we have mentioned before, deep eutectic solvents have also been used to prepare cellulosic films. A series of polymer electrolytes composed of corn starch, lithium bis-(trifluoromethanesulfonyl)imide, and DES were fabricated by solution-casting technique.[140] The highest ionic conductivity was obtained for sample containing 80 wt % DES with a calculated ionic conductivity value of 1.04×10^{-3} S·cm^{-1} at room temperature. Biodegradable thin-film polymer electrolytes were developed by plasticizing the cellulose acetate/lithium bis-(trifluoromethanesulfonyl)imide/DES matrix with up to 60 wt % DES.[136] The highest plasticized sample cellulose acetate exhibits the highest ionic conducting and has the greatest ability to retain the property even after 30 days of storage, with a value of 5.89×10^{-5} S·cm^{-1}.

SCFs are useful in preparing particles and foams from carbohydrate polymers. Factors influencing the crystallization of α-lactose monohydrate from aqueous solution were studied by SCF solution-enhanced dispersion technique.[369] The SCF enhanced dispersion process is an efficient method for forming micrometer-sized particles of water-soluble compounds with controlled physicochemical properties. New natural chitosan polymer-based aerogels, cross-linked aerogels, were prepared by the sol−gel route with glutaradehyde, glyoxal, and formaldehyde as cross-linkers[370] and dried by $scCO_2$ fluid extraction. The sol−gel and subsequent $scCO_2$ drying process generate aerogels with high surface areas and mesopores, so that mesoporous chitosan-based aerogels were synthesized for the first time..

Green processing of carbohydrate polymers has combined ILs and SCFs. Porous chitin-based materials were developed by combining the processing of chitin, with ILs as a green solvent, with the use of supercritical fluid technology as clean technology.[105]

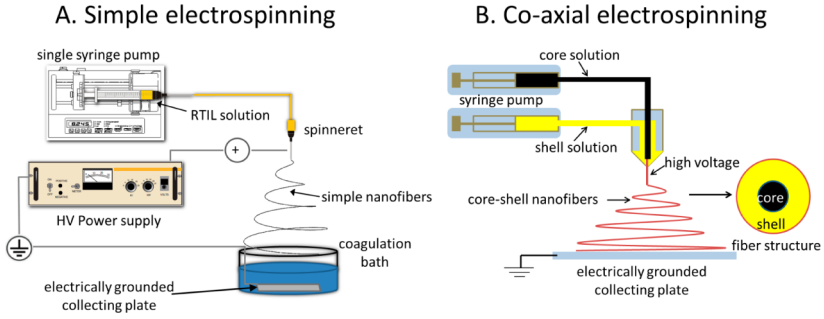

Figure 12. Schematic representation of (A) simple[357] and (B) coaxial[358] electrospinning from IL solutions.

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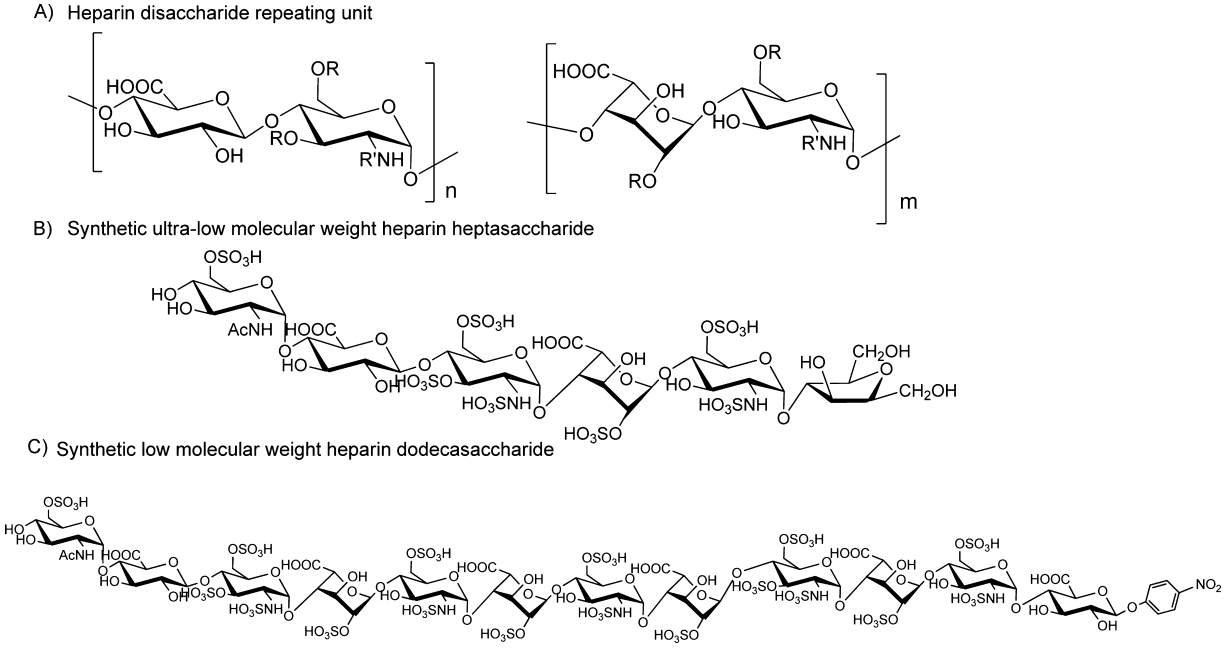
Table 8. Supercritical Fluid Drying of Carbohydrates: Selection of Suitable Excipients and Process Conditions

sample	cross-linker	mass ratio of chitosan to water	volume ratio of cross-linker to water	surface area (m^2/g)	pore diameter (nm)	pore volume (cm^3/g)	bulk density (g/cm^3)
1	glutaraldehyde	0.014	1:70	504	5.40	0.90	0.57
2	glutaraldehyde	0.014	1:35	392	3.62	0.40	0.78
3	glutaraldehyde	0.014	1:14	66	3.29	0.06	0.92
4	glutaraldehyde	0.018	1:70	569	4.59	0.78	0.51
5	glutaraldehyde	0.021	1:70	566	4.37	0.74	0.49
6	glyoxal	0.014	1:35	612	6.40	0.99	0.53
7	glyoxal	0.014	1:14	574	4.20	0.64	0.62
8	glyoxal	0.014	1:7	420	3.89	0.48	0.78
9	glyoxal	0.018	1:35	707	5.38	1.11	0.47
10	glyoxal	0.021	1:35	686	4.37	0.85	0.49
11	formaldehyde	0.014	1:35	747	8.50, 11.13	2.89	0.48
12	formaldehyde	0.014	1:14	716	6.87	1.48	0.52
13	formaldehyde	0.014	1:7	525	8.50	1.24	0.59
14	formaldehyde	0.018	1:35	821	10.16	3.46	0.38
15	formaldehyde	0.021	1:35	845	9.28	2.65	0.43

Scheme 19. (A) Chemical Structure of Heparin Disaccharide Repeating Unit, Where R is Sulfo or Hydrogen and R′ is Sulfo, Acetyl or Hydrogen. (B) Structure of Synthetic Ultra-Low-Molecular-Weight Heparin Heptasaccharide. (C) Structure of Synthesis Low-Molecular-Weight Heparin Dodecasaccharide



The processability of 15 commonly used carbohydrates, as excipients in supercritical fluid drying, was investigated (Table 8).[371] A wide metastable zone, solubility of 10−50% (w/w) in water at the process temperature, low viscosity of both the aqueous solution being sprayed and the saturated solution, and high T_g is a combination that is expected to lead to the production of amorphous powder. A number of analytical techniques were used to characterize the powder and to determine the stability of the amorphous product. Stable, sugar-based protein formulations could also be obtained by supercritical fluid drying.[372] In contrast to previous reports, supercritical fluid drying of aqueous solutions without the addition of ethanol proved to be feasible. Residual ethanol acts as a plasticizer in supercritical fluid dried powders, leading to decreased T_g values and increased tendency of amorphous sugar matrices to crystallize.

6. EXAMPLES OF INTEGRATED PROCESSES INVOLVING CARBOHYDRATES

6.1. Enzymatic Synthesis of Low-Molecular-Weight Heparins in Water and Chemoenzymatic Synthesis of Bioengineered Heparin

Heparin is a highly sulfated polysaccharide that consists of a disaccharide repeating unit of glucuronic (or iduronic) acid linked to a glucosamine. Both the iduronic acid and glucosamine residues are capable of carrying sulfo groups, and occasionally glucuronic acid residue can be sulfated (Scheme 19). Heparin is an anticoagulant drug widely used to treat thrombotic disorders or in many surgical procedures to prevent blood from clotting.[373] Heparin is a natural product that is isolated from pig intestine through a long and poorly regulated supply chain.[374] Several batches of contaminated heparin entered the U.S. market in 2007, leading to the deaths of more than 80 patients. This tragic

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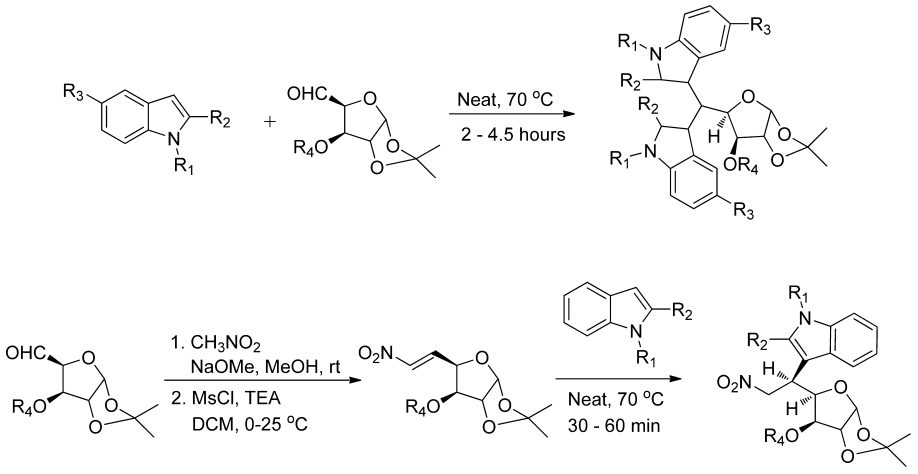
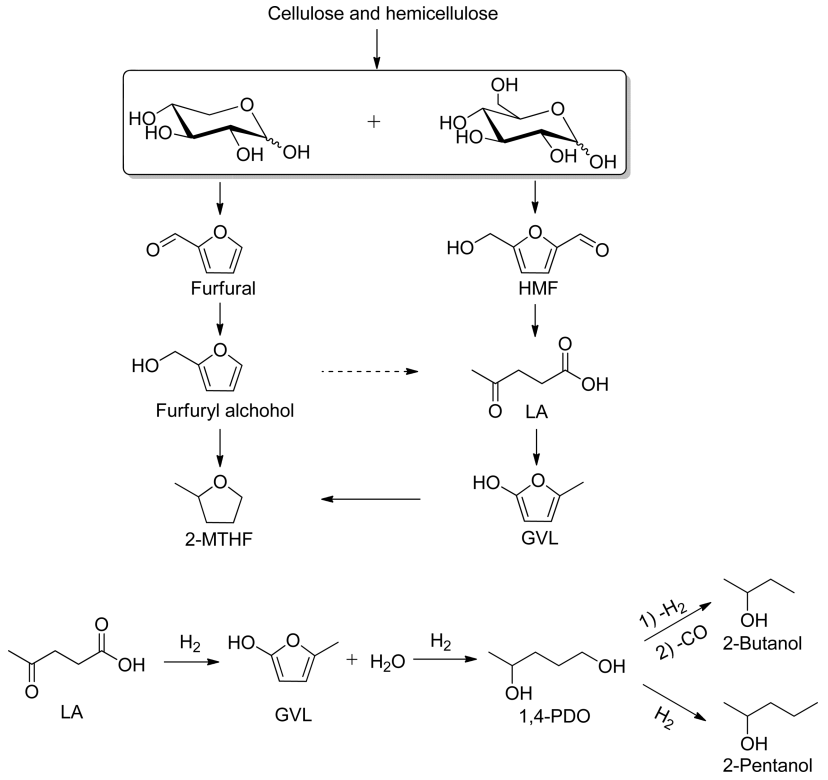
Scheme 20. Synthesis of Bis(indolyl)methanes and Glycosyl Nitroalkanes



Scheme 21. Preparation of 2-Methyltetrahydrofuran from Lignocellulosic Biomass and Catalytic Hydrogenation of Levulinic Acid in a One-Pot Reaction



event underscores an urgent need for a method to prepare synthetic heparin under a highly regulated process. Although chemical synthesis of short heparin fragments is possible, the efficiency is very low due to the involvement of a long synthetic route. A chemoenzymatic method has recently emerged as a promising alternative to prepare different sizes of heparin fragments with high efficiency.[375] The method uses heparan sulfate biosynthetic enzymes, including epimerase and several sulfotransferases, to prepare bioengineered heparin polysaccharides.[376]

In the case of bioengineered heparin, the goal is to prepare a generic version of the animal tissue-derived product. This bioengineered heparin would have identical structural microheterogeneity, molecular weight properties, polydispersity, and bioactivity as the natural product.[375] A bioengineered heparin relies on fermentation of *E. coli* K5 to obtain the backbone, heparosan, which is then chemically de-N-acetylated and N-sulfonated and enzymatically C-5 epimerized (converting D-glucuronic acid to L-iduronic acid) and O-sulfonated.[377] These enzymatic steps rely on *E. coli*-expressed recombinant animal enzymes (i.e., C5-epimerase, O-sulfotransferases) and the cofactor 3′-phosphoadenosine-5′-phosphosulfate (PAPS). These enzymes need to be immobilized[378] and a cofactor regeneration system[379] needs to be put in place in order to make the process scalable and commercially viable on the kilogram to ton production scale.

In addition, the method described is utilized to prepare structurally homogeneous ultra-low-molecular-weight heparin

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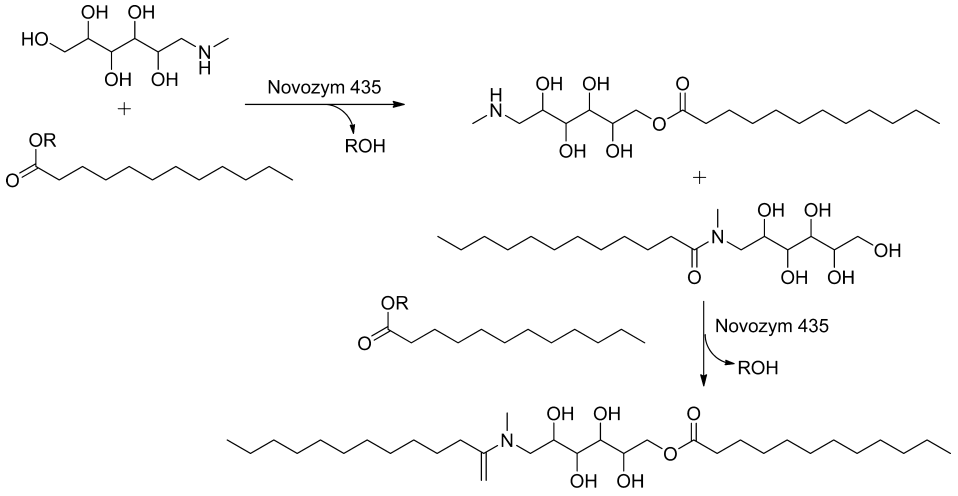
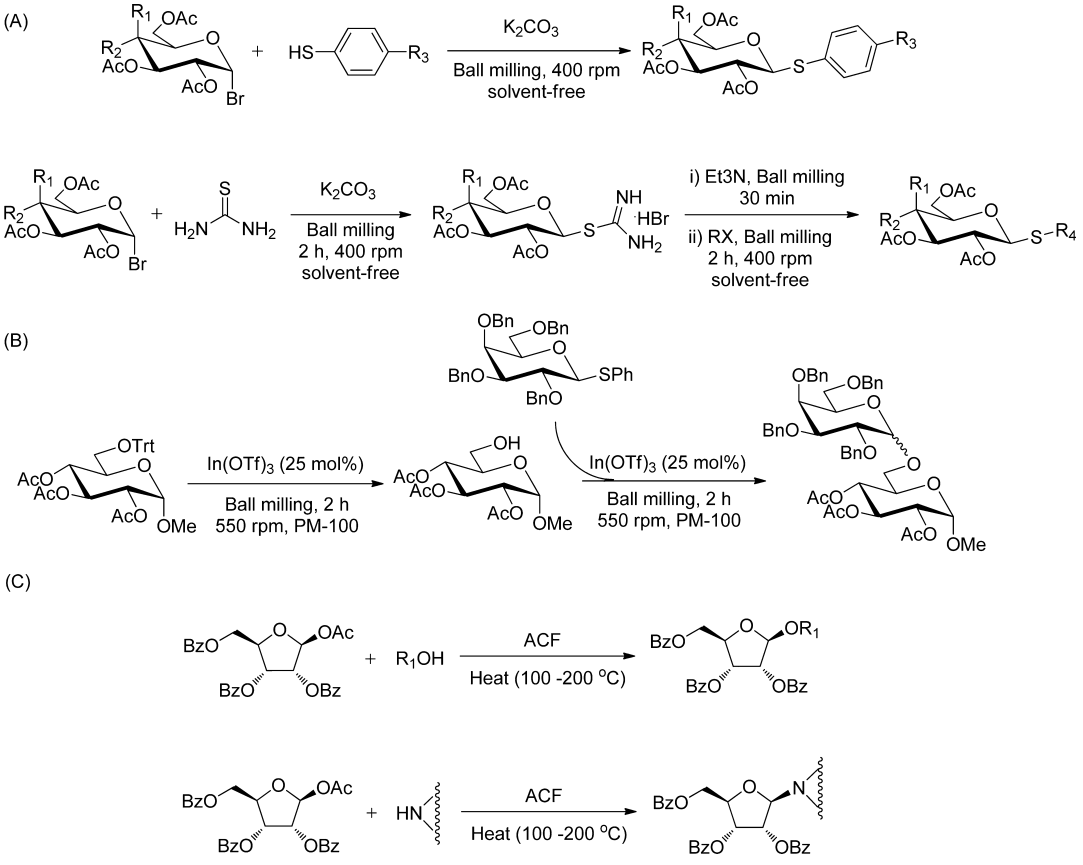
Scheme 22. Transformation Reaction Catalyzed by Lipase (Novozym 435)



Scheme 23. Examples of Synthesis of Carbohydrate Derivatives under Solvent-Free Conditions



heptasaccharide and low-molecular-weight heparin dodecasaccharide (Scheme 19B,C).[375] This synthesis also offers the opportunity to improve pharmacological effects of heparin. For example, the anticoagulant synthetic low-molecular-weight heparin dodecasaccharide can be reversed by protamine, a polypeptide drug approved by the U.S. Food and Drug Administration (FDA) to neutralize heparin. The anticoagulant activity of the currently marketed low-molecular-weight heparin drug cannot be completely reversed by protamine. Reversible low-molecular-weight heparin will undoubtedly reduce the bleeding side effects.

6.2. Solvent-Free Processes

Development of novel solvents corresponding to the "green" principle has been a widely explored theme for the production of high-value materials and chemicals. In the case of nonconventional and greener conditions, solvent-free synthesis supplies higher atom-economic and more environmentally benign processes with less waste and fewer health hazards and is commonly considered as the most "green" of processes. The applications of solvent-free systems also eliminate potential issues that existed in aqueous or organic solvents such as low

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yields due to the insolubility and difficult handling under neat atmosphere.

A solvent- and catalyst-free strategy was developed for the construction of sugar-tethered bis(indolyl)methanes.[380] Michael addition was accomplished with high stereoselectivity by employing chiral Michael acceptors derived from carbohydrates and various indoles as donor. Michael adducts were successfully obtained under neat conditions in the absence of catalysts, either Lewis or Brønsted acid. Sugar-tethered isoxazoles and isoxazolines were synthesized as well from stereoselective carbohydrate substrates and the corresponding primary nitroalkanes (Scheme 20).

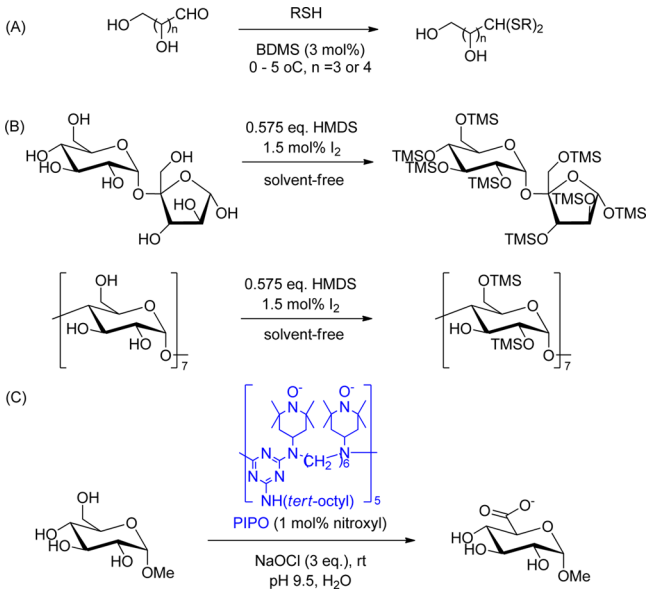
Hydrogenation catalyzed by Ru/C was applied in the conversion of 2-methyltetrahydrofuran (2-MeTHF) under solvent-free conditions (Scheme 21).[381] LA and GVL derived from biomass were transformed into 2-MeTHF at 190 °C (100 bar, 24 h) over Ru/C in a batch reactor, and further hydrogenation would induce the decomposition of 2-MeTHF into 2-pentanol. In a particular protocol, a one-pot synthesis was employed in two steps for the direct hydrogenation of levulinic acid, with removal of generated water being critical for full conversion to 2-MeTHF in yields up to 61%.

N-Alkanoyl-*N*-methylglucamide surfactant was prepared through enzymatic reaction in a solvent-free system.[382] In that study, Novozym 435 (N435) was utilized to catalyze the production of polyester, with comparable viscosity, at 80 °C (Scheme 22). Environmental assessment of *N*-alkanoyl-*N*-methylglucamide was performed by use of the freeware package Environmental Assessment Tool for Organic Synthesis and EcoScale to monitor energy usage and process variables, such as heating, stirring, and vacuum. The synthesis of triglycerides was accomplished in a solvent-free system, leading to high molar fraction and selectivity values.[383] Temperature has a marked effect on the reaction, and the best results were achieved at 60, 70, 80, and 90 °C for the syntheses of tricaprylin, tricaprin, trilaurin, and trimyristin, respectively.

Thioglycosides are highly valuable glycosyl donors in carbohydrate chemistry, and they are generally obtained with a phase-transfer catalyst and organic solvents. A planetary ball mill with solvent-free conditions[384] was used for the high-yield synthesis of aryl thioglycosides from the corresponding glycosyl halides through their thiuronium salt (Scheme 23A), which eliminates the consumption of hazardous organic solvents. Glycosylation and detritylation reactions were accomplished as well via ball milling under solvent-free conditions. $In(OTf)_3$-mediated[385] detritylation of carbohydrates was obtained for 3.5 h at 550 rpm with 25 mol % catalyst (Scheme 23B), which subsequently induced glycosylation in the same pot upon the addition of carbohydrate acceptor. Activated carbon fiber[386] was employed to display a novel system for O- and N-glycosylation under solvent-free conditions. Sterol and triterpene O-glycosides (saponin analogues), as well as nucleoside mimics, are efficiently synthesized at given times (0.5−24 h) and different temperatures (100−210 °C) (Scheme 23C). Analogously, sulfuric acid immobilized on silica gel (H_2SO_4−SiO_2)[387] is another efficient promoter, which has been explored for per-O-acetylation of carbohydrates with acetic anhydride under solvent-free conditions. The acetylation reaction was established under optimal conditions: 5 mg of catalyst B (0.8% mol) for 1 mmol of glucose, and the catalyst was completely recycled without any significant loss in reactivity.

Bromodimethylsulfonium bromide (BDMS)[388] has been explored for the preparation of diethyl and dipropyl dithioacetal derivatives of carbohydrates under solvent-free conditions, and optimized yields were obtained with 3 mol % BDMS at 0−5 °C (Scheme 24A). Bis(trimethylsilyl)amine,[190b] with the additional

Scheme 24. Preparation of Carbohydrate Derivatives with Catalyst under Solvent-Free Environments

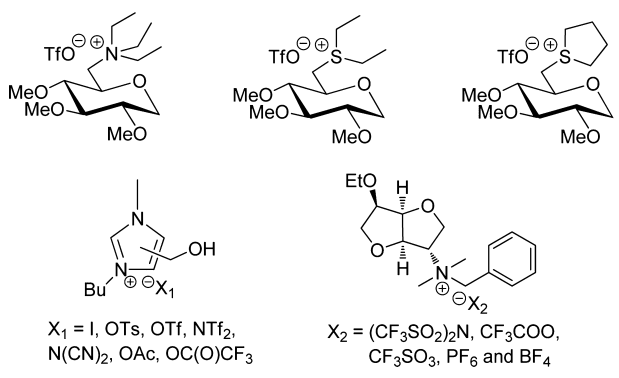


requirement of a catalytic amount (up to 2 mol %) of iodine under a solvent-free process (Scheme 24B), was also successfully investigated to protect carbohydrates with silyl groups. In addition, free radical (2,2,6,6-tetramethylpiperidin-1-yl)oxyl immobilized on polymer[389] was prepared and applied in the oxidation of methyl α-D-glucopyranoside, affording methyl α-D-glucopyranosiduronate in 70% yield (Scheme 24C), and this catalyst was subsequently identified to be truly heterogeneous after filtration experiments. Solvent-free system was explored for probing the structures of carbohydrate−peptide complexes,[390] which is another interesting area for carbohydrate research in the absence of solvent.

7. EMERGING APPLICATIONS

Novel ILs and DES green solvents based on renewable carbohydrates (Scheme 25) have been prepared. Glucose-based ILs have been synthesized starting from commercially available methyl-D-glucopyranoside, and they were fully characterized in their physicochemical properties.[114] They

Scheme 25. Carbohydrate-Derived Ionic Liquids



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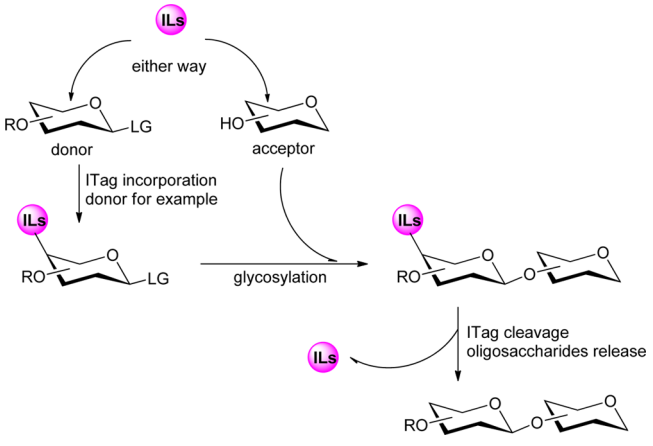
represent the first terms of a new class of chiral solvents from low-cost natural sources. Fructose has been used as the starting material for preparation of a new class of ILs.[179] These liquids exhibit tunable solvent properties much like conventional imidazole-based ILs. They have been applied as recyclable solvents for the Heck reaction of aryl iodides. Carbohydrate-based novel bis(ammonium) chiral ILs have been synthesized by following a straightforward protocol using the substrate isomannide, 1,4:3,6-dianhydromannitol, a derivative of mannose.[391] Their applications in chiral discrimination and optical resolution of racemates have been established in that paper. Deep eutectic solvents are considered nowadays as green IL analogues. A glucose-based DES of choline chloride [2-(hydroxyethyl)-trimethylammonium chloride] with the monosaccharide sugar D-glucose (anhydrous) was synthesized at different molar ratios.[138] Analysis of these physical properties revealed that these novel DES have the potential to be utilized for several possible industrial applications involving processing and separation of food constituents, pharmaceutical applications, and media for chemical reactions.

IL-based catch-and-release MS tags have been applied for carbohydrate analysis. A novel, inexpensive, and versatile IL-based catch-and-release MS tag (I-Tag) that facilitates substrate purification, fast, robust, and sensitive enzymatic reaction monitoring, and quantitative kinetic analysis has been developed.[392] The applicability of the system has been demonstrated in an enzymatic assay with β-1,4-galactosyltransferase. A new *N*-benzenesulfonyl-based IL mass spectroscopic label (I-Tag2) for covalent attachment to substrates has been prepared. I-Tag2 was used to monitor oligosaccharide elongation and serve as a purification handle.[393] Starting from chemically synthesized I-Tag2-labeled *N*-acetylglucosamine (GlcNAc), I-Tag2-LacNAc [Gal-β-(1→4)GlcNAc] and I-Tag2-LewisX [Gal-β-(1→4)[Fucα(1→3)]GlcNAc], which are oligosaccharides of biological relevance, were enzymatically prepared. The apparent kinetic parameters for enzyme-catalyzed transformations with β-(1→4)-galactosyltransferase [β-(1→4)-GalT] and fucosyltransferase VI (FucT VI) were measured by liquid chromatography–MS, demonstrating the applicability and versatility of the new I-Tags in enzymatic transformations with glycosyltransferases.

Glycosylation can also be accomplished with the support of an IL tag (Scheme 26). A new strategy to synthesize a trisaccharide by using IL as a soluble functional support has been demonstrated.[394] This approach appears to provide a way to construct oligosaccharides with greatly simplified purification, requiring no chromatography during the synthesis or at the end of cleavage of the tag. It offers the advantages of solution-phase synthesis, for example, homogeneous mass transportation and no temperature restriction, and may be suitable for large-scale synthesis. A strategy for the synthesis of an activated oligomannan that employs IL-support glycosylation methodology has been described that relies on an IL-tagged mannosyl fluoride donor.[395] This method is capable of rapidly producing linear α(1→6) oligomannan thioglycosides in a convenient and cost-effective manner without the need for column purification after each glycosylation step. An improved method for the synthesis of large and complex oligosaccharides on an IL support has been described. A strategy to attach the acceptor on the IL via a more stable ether linker was used to prevent undesirable decomposition and side products.[396] A dissolution–evaporation–precipitation procedure was also developed by combining the advantages of precipitation and solid–liquid extraction to reduce mechanical loss and purification time. This approach was successfully used for the rapid assembly of IL-supported homolinear α(1→2)-linked nonamannoside in 25% overall yield within 29 h. A general and efficient chromatography-free IL-supported catch-and-release strategy for oligosaccharide synthesis has been reported.[397] The methodology is compatible with current glycosylation strategies and amenable to protecting-group manipulations. A series of β-(1→6)- and β-(1→2)-linked glycan structures have been prepared to showcase the versatility of the strategy.

Scheme 26. General Strategy for Synthesis of Oligosaccharides Supported by Ionic Liquids (ITag)



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The authors declare no competing financial interest.

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Manuel Sandoval was born in Heredia, Costa Rica, in 1980. He received a B.Sc. in science education in 2005 (with honors) and a B.Sc. in industrial chemistry in 2007, both from the Universidad Nacional of Costa Rica. He moved to the Biotransformations Group at Universidad Complutense de Madrid in Spain in 2009 and received his Ph.D. in sustainable chemistry with honors in 2012 under the direction of Professor María José Hernáiz. In the same year he was hired as an associate professor at Universidad Nacional in Costa Rica. Since 2012 he has worked for the Biochemistry Research Laboratory and the Chemistry Education Program at this university. His research goals are to search for new hydrolases from microorganisms from the Costa Rican forests for industrial purposes and to improve the quality of high school chemical education in Costa Rica.

Yongmei Xu received her Ph.D. from Wuhan University in China. She is currently a research assistant professor in the Eshelman School of Pharmacy, University of North Carolina at Chapel Hill. Her research focuses on enzymatic synthesis of heparin and heparan sulfate and study of their biological function. She has published over 40 peer-reviewed publications.

Jian Liu received his Ph.D. from the University of Iowa under the guidance of Professor Robert Linhardt. He is currently the John A. and Deborah S. McNeil Jr. distinguished professor at the Eshelman School of Pharmacy, University of North Carolina at Chapel Hill. His research interest is in the investigation of biosynthetic mechanisms of heparin and heparan sulfate. He has published over 100 peer-reviewed publications.

Professor María J. Hernáiz received her B.C. (1992) and Ph.D. in pharmacy from the University Complutense of Madrid. After two postdoctoral stays in the Chemistry Department of Warwick University (U.K.) and in the Department of Medicinal and Natural Products Chemistry of the University of Iowa, working in the fields of carbohydrate chemistry and green chemistry, she returned to the

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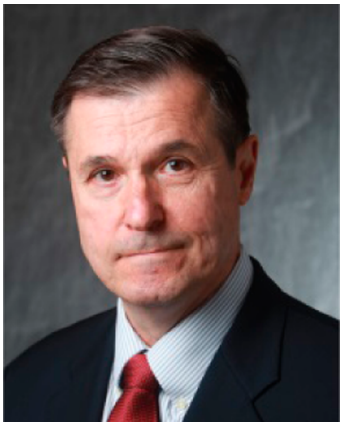
Spanish Research Council (CSIC, Spain) in the Bio-Organic Department, after which she became an assistant professor (permanent position, 2002) at the Faculty of Pharmacy, Complutense University of Madrid (Spain). In addition, she is the director of the Biotransformation Group, qualified as a research quality group in Spain. Her major research lines are the chemoenzymatic synthesis of carbohydrates and glycoconjugates, working mainly in sustainable conditions. She has published more than 100 scientific papers, reviews, and books in these fields. After being a member of Spanish Society of Biotechnology (SEBiot) in 2010, she was appointed its General Secretary.



Professor Robert J. Linhardt received his Ph.D. in chemistry from Johns Hopkins University in 1979 and did his postdoctoral studies at Massachusetts Institute of Technology. He is currently the Anne and John Broadbent, Jr. '59 Senior Constellation Chair in Biocatalysis and Metabolic Engineering at Rensselaer Polytechnic Institute. His research focuses on glycoscience, and he is an expert on glycosaminoglycans and their synthesis, biology, and analysis. He has received multiple honors, including the American Chemical Society Horace S. Isbell, Claude S. Hudson, and Melville L. Wolfrom Awards, the AACP Volwiler Research Achievement Award, and the Scientific American 10. He has authored over 680 research articles and holds over 50 patents.

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ABBREVIATIONS

CAL-B	*Candida antarctica* lipase
CGTase	glycosyltransferase
BDS	biomass-derived solvents
DES	deep eutectic solvents
G	α-C-glucuronic acid
GBS	glycerol-based solvents
GLV	γ-valerolactone
HMF	5-hydroxymethyl-2-furaldehyde
ILs	ionic liquids
LA	levulinic acid
M	β-D-mannuronic acid
MeTHF	2-methyltetrahydrofuran
NMR	nuclear magnetic resonance
MS	mass spectroscopy
MW	microwave
NSP	non-starch polysaccharides
PLA	poly(L-lactic acid)
$scCO_2$	supercritical carbon dioxide
scH_2O	supercritical water
SCFs	supercritical fluids

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