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Reviews

Applications of Ionic Liquids in Carbohydrate Chemistry: A Window of Opportunities

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Ionic liquids (ILs) are composed only of ions. Of special interest to this review are those where at least one ion (the cation) is organic and whose melting points are below or not far above room temperature. ILs are designated as "green" solvents because they have extremely low vapor pressure, are noninflammable, and thermally and chemically stable. Therefore, many of them can be, in principle, recycled into the process indefinitely. The objective of the present review is to discuss different aspects of the use of ILs in carbohydrate chemistry, in particular, dissolution and functionalization of simple sugars, cyclodextrins, cellulose, starch, and chitin/chitosan. The molecular structure and synthesis of ILs most frequently employed in carbohydrate chemistry are discussed with an emphasis on imidazolium and pyridinium cations with different counterions. The physicochemical properties of ILs that are relevant to the dissolution and functionalization of carbohydrates, in particular their polarities and hydrogen-bonding abilities, are discussed. Dissolution of simple saccharides and biopolymers in ILs is presented with an emphasis on the mechanism of carbohydrate−IL interactions. Finally, the very interesting novel applications of the solutions obtained are addressed. These include, inter alia, spinning of the dissolved biopolymer into fibers, extrusion into slabs and rods, formation of matrixes for a myriad of substrates, including biomacromolecules, formation of nanocomposites, and functionalization to produce important derivatives. The use of ILs in many branches of science is expanding fast; it is hoped that this review will draw the attention of researchers to the "window of opportunities" that these green solvents open into carbohydrate chemistry.

1. Introduction

Ionic liquids are low-melting-point salts, thus forming liquids that consist only of cations and anions. The current convention is that a salt melting below the boiling point of water is known as an ionic liquid (IL) or by one of several synonyms, including ionic fluid, molten salt, fused salt, or neoteric solvent. With this proviso about the melting point of the IL, the use of the acronym RTIL, for room-temperature ionic liquid, becomes redundant. These electrolytes are liquids because their Gibbs free energies of solvation are negative. That is, the liquid state is thermodynamically favorable due to the large size and conformational flexibility of the ions, which leads to small lattice enthalpies and large entropy changes that favor the liquid state.[1] The first useful IL, ethylammonium nitrate, described by Walden, seems to have generated little interest; it was not until the 1980s that the physical and chemical properties of this salt were investigated. This was followed by the discovery that several tetraalkylammonium salts form air- and moisture-stable ILs of interesting properties; they were employed as solvents for spectroscopy, synthesis, and electrochemistry.[2]

Interest in developing and investigating the properties and applications of ILs in many fields of science and technology has been intensified as a result of the introduction of the principles of "green" chemistry. Briefly, this concept sets

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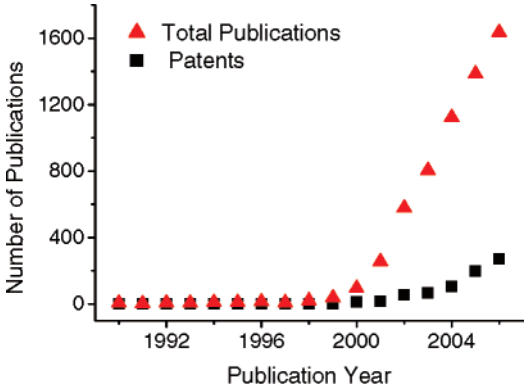


Figure 1. Evolution of the number of publications, including patents on ILs, in the period 1990−2006.

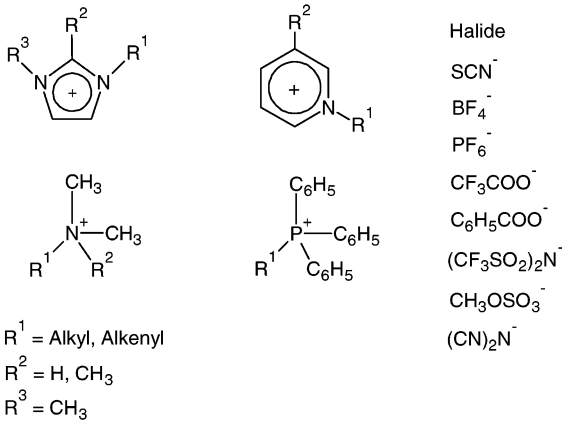


Figure 2. Structures of ILs most extensively employed.

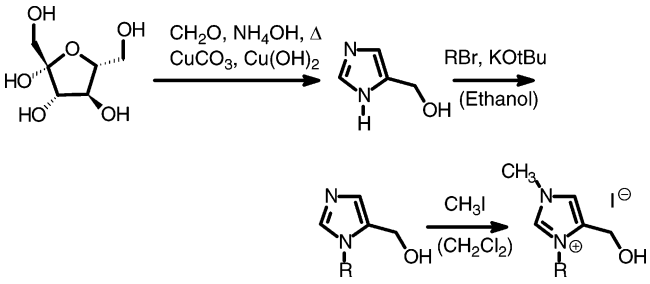
guidelines designed to secure sustainable development, while increasing process biocompatibility and economy. The emphasis is on an increase in and/or upgrading of: (i) process economy, by preventing waste generation (this represents a much superior approach to waste treatment); (ii) atom economy, by incorporating all reagents employed into the final product (this also contributes to reduction and/or elimination of waste); (iii) process safety, by using nontoxic, noninflammable solvents and reagents; (iv) process efficiency, by material recycling into the process, use of catalytic pathways, use of catalysts that can be regenerated and/or recycled, rational use of energy, and reduction of the number of intermediate steps; (v) environmental compatibility, by employing chemicals from renewable sources, and producing biodegradable end products.[3−5]

All of these principles call for a thorough understanding of the roles of all components of the chemical reaction/process including, naturally, the solvent or solvent mixture employed. The safety factor calls for a careful selection of the reaction medium; the use of aromatic and halogenated solvents has decreased noticeably in organic synthesis and industrial chemical processes. The introduction of the so-called "green" solvents, of which supercritical CO_2[6] and ILs[7−9] are promising examples, has increased our need to probe solute−solvent interactions at the molecular level; this understanding is one of the aims of this account.

There are several review articles on the synthesis, properties, and applications of ionic liquids,[2,7,10−14] including ILs in carbohydrate chemistry,[15] and a succinct evaluation of the potentials and drawbacks of the use of ILs in biopolymer-related industries.[16,17] To our knowledge, the use of ILs with either chitin/chitosan or starch has not been reviewed. This partial lack of information on the use of ILs in carbohydrate chemistry and the explosive growth in published research on ILs, as shown in Figure 1, justify updating and revisiting the subject. Equally important, we collect and discuss several pieces of information that are scattered in the literature but are of prime importance to the carbohydrate chemist, especially newcomers to the field. Examples are effects of impurities on the properties, hence performance of ILs; the heterogeneity of the structure of ILs on the nanoscale, and the relationship between the molecular structure of ILs and their physicochemical properties that are relevant to applications. Finally, we compare, where possible, the properties of ILs with those of other (classic) solvent systems employed in carbohydrate chemistry.

2. Synthesis and Properties of ILs

Figure 2 shows the structures of cations (mostly heterocyclic) and anions of ILs that are most extensively employed. Their synthesis involves one or two distinct steps: The first is an S_N (Mentschutkin) reaction between a tertiary halide, for example, 1-methylimidazole, and an alkyl halide or alkyl methanesulfonate (obtained by the reaction of alcohol and methanesulfonyl chloride) to yield ionic halides or methanesulfonates; these are termed "first generation" ILs. The second step (Finkelstein reaction) consists, in most cases, of metathesis (from the Greek words "meta" for change, and "tithemi" for place) of the halide or methanesulfonate counterion, leading to "second generation" ILs, containing bulkier anions, for example, BF_4^-, PF_6^-, $C_6H_5CO_2^-$, and $(F_3CSO_2)_2N^-$, having interesting properties such as lower melting points, different solubilities in classic organic solvents, viscocities, etc.[7−9,13,18,19] In some cases, the anion-exchange step can be avoided. Thus treatment of a 50% aqueous ethanolic solution of 1,3-dimethylimidazolium-2-carboxylate (synthesized by reacting 1-methylimidazole with dimethyl carbonate) with aqueous or alcoholic solutions of strong acids (HCl, HPF_6, H_2SO_4, and picric acid, respectively) leads to decarboxylation and production of $[C_1MeIm][X]$, where $X = Cl^-$, PF_6^-, HSO_4^-, and picrate, respectively.[20] An interesting example is a fructose-based IL, synthesized according to the following reaction scheme where R = 1-butyl. Metathesis was then



employed to introduce other anions, including Tos, AcO, TFA, $N(CN)_2$, and $N(TFMS)_2$, respectively. The products are liquids and are similar to their imidazole-based counterparts, for example, in physical properties (viscosities and miscibilities with water and classic organic solvents) and in performance (as solvents) in the Heck reaction between methyl acrylate and iodobenzene.[21] In addition to the above-shown anions, other "exotic" ones have been introduced, including saccharinate and acesulfamate; the corresponding ionic compounds (with [RMeIm], $R = C_4$ to C_9) are liquids at room temperature.[22]

Although the synthesis of ILs is generally not beset by any major problem, the cost can be high, and the synthesis is time-consuming. For example, metathesis with silver salts is expensive and leads to products that may be contaminated with colloidal silver.[23] The synthesis of $[C_4MeIm][Cl]$ takes as long

as 72 h; metathesis with a bulkier anion takes an additional 24−48 h, if purification prior to use is included.[24,25] The time required for synthesis can be reduced, for example, by the use of ultrasound or microwave irradiation.[26−30]

Due to their extremely low vapor pressure, vide infra, which renders their distillation unfeasible, the purification of ILs, for example, to measure their physicochemical properties is laborious and time-consuming. These difficulties may have led to some conflicting results, as illustrated by the following examples for "purified" ILs: mp of [C_2MeIm][BF_4], 5.8 °C,[31] 11 °C,[32] 12.0 to 12.5 °C,[33] 14.6 °C,[34] and 15 °C;[35] mp of [C_3MeIm]-[BF_4], −13.9 and −17 °C, respectively; mp of [C_4MeIm][BF_4], −81 and −71 °C, respectively;[2,9,36] viscosity of [C_2MeIm][BF_4], 37 and 66.5 mPa s, respectively;[2,36] viscosity of [C_8MeIm][PF_6], 691 and 866 mPa s.[2]

Depending on the method of synthesis, the impurities may include water, excess tertiary amine, excess alkyl halide, sulfate, or sulfonate, and, after metathesis, residual halide ion, RSO_3^-, or RSO_4^-. Water can be conveniently determined by Karl Fischer titration, cyclic voltametry,[37] or by near-IR (NIR) spectroscopy (overtone and combination transitions of the OH group at 1910 nm).[38] Residual 1-methylimidazole can be determined colorimetrically as a complex with $CuCl_2$[39] or by ^{1}H NMR spectroscopy; the latter method relies on integration of the ^{13}C satellites of (residual) 1-methylimidazole.[19] Simple ions, for example, Na^+, Br^-, or Cl^-, can be readily determined by the use of the appropriate ion-selective electrode,[40] ion chromatography,[41] or cyclic voltametry.[42,43] Methods of purification include extraction of the IL with a (cold) organic solvent, for example, acetone or ethyl acetate, extraction of the aqueous solution of the IL with an immiscible organic solvent, for example, CH_2Cl_2 or $CHCl_3$, or treatment of a solution of the IL in an organic solvent with activated charcoal, followed by flash column chromatography.[40,44−46]

Attention should be paid to the complete metathesis of the counterion; its presence in the IL can lead to one or more of the following problems:

•Conflicting physicochemical properties. In the presence of (residual) chloride ion, the viscosities of [RMeIm][BF_4] vary between 66.5 and 92.4 mPa s (R = C_2, molal [Cl^-] = 0.01, 1.8, respectively) and 154 and 201 mPa s (R = C_4, molal [Cl^-] = 0.01 and 0.5, respectively). The corresponding figures for [RMeIm][NO_3] vary between 67 and 222.7 mPa s (R = C_2, molal [NO_3^-] = 0.02 and 1.7, respectively) and 1238 and 8465 mPa s (R = C_4, molal [NO_3^-] = 0.01 and 2.2, respectively).[40]

•Dramatic decrease of the onset of thermal decomposition, occurring, at least, 100 °C below those of the same, halide-free samples.[47]

•Reduced solvation efficiency. The yield of glycosylation of cyclohexylmethanol in [C_6MeIm][N(TFMS)$_2$] is reduced from 90% to 6% in the presence of 5 mol % of (intentionally added impurity) [C_6MeIm][Cl]; the reaction ceased to occur when the impurity concentration was increased to 10 mol %![48]

Finally, water is another problematic impurity in ILs. The residual water contents (as determined by Karl Fischer titration) of a series of "dried" [C_4MeIm]-based ILs were found to be 2200, 1870, 4530, and 590 ppm for [Cl^-], [I^-], [BF_4^-], and [PF_6^-], respectively.[44] Note that the so-called hydrophobic ILs, for example, [C_8MeIm][BF_4], [C_8MeIm][PF_6] are, in fact, hygroscopic and absorb water at room temperature, for example, 1 wt % (0.16 mol fraction of water) over a 3 h period.[38,40]

The preceding discussion about impurities bears on the functionalization of carbohydrates in ILs. Increased IL viscosity hinders the swelling of biopolymers, hence their subsequent solubilization. Residual water in the IL leads to several undesired side reactions. At the outset, the presence of adventitious water renders the carbohydrate, for example, cellulose, insoluble! Whereas 3−10 wt % cellulose solutions in [C_4MeIm][Cl] can be easily prepared, the biopolymer is not soluble in the presence of 1% water.[49] Note that clear cellulose solutions are not necessarily molecularly dispersed; they may contain aggregates of still ordered cellulose molecules. Since water affects the aggregation state of dissolved cellulose, it also affects its reactivity.[50−53] Additionally, water consumes the functionalizing agent employed, for example, acyl chloride, acyl anhydride, or sulfonyl chloride. The acid liberated, especially HCl, decreases the DP of the original cellulose or that of the product or may decrease the DS of the latter due to acid-catalyzed ester hydrolysis. Some anions, in particular [PF_6^-] and [BF_4^-], hydrolyze (by residual water) at the relatively high temperatures employed for carbohydrate dissolution/functionalization (vide infra), liberating HF; this affects both DP and DS adversely. Hydrolysis of these anions at room temperature, for example, during extraction of the aqueous IL solution with an immiscible organic solvent has been referred to[54] and was detected by the solvatochromic polarity indicators RB and MePM, as shown in Figure 3.[55] In summary, the importance of the purity of ILs employed to carbohydrate dissolution/functionalization should not be underestimated.

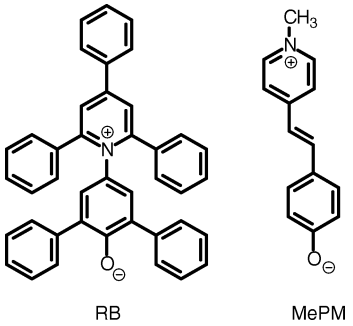


Figure 3. Solvatochromic polarity indicators.

3. Relevant Properties of ILs: "Green" Solvents

The following question now arises: What are the characteristics of ILs that make their use as solvents in carbohydrate chemistry both challenging and exciting? In answering this question we cite a number of advantages of ILs with reference, where possible, to classic solvent systems for carbohydrates, for example, LiCl/DMAc.

3.1. ILs: "Green" Solvents. In one sense, very low vapor pressure ILs constitute "liquid solids". It is important to note that the use of solid supports for chemical functionality is of enormous technological importance, for example, solid acid catalysts and scavenging reagents for solution-phase synthesis. Additionally, in many cases the key drivers for using solid reagents are their lack of vapor pressure or their phase heterogeneity, the latter facilitating product isolation. Still, solid reagents are fraught with drawbacks of their own, including heterogeneous kinetics and susceptibility to deactivation;[56] these drawbacks are not relevant to ILs. Very low vapor pressure is a very convenient feature because cellulose dissolution and activation are usually carried out at high temperatures, sometimes at the boiling point of the classic solvent, in particular DMAc.[57]

An early report that the 1:1 system [C_2MeIm][Cl]/$AlCl_3^-$ has no measurable vapor pressure has led to the belief that ILs, in general, possess no vapor pressure. However, the same system

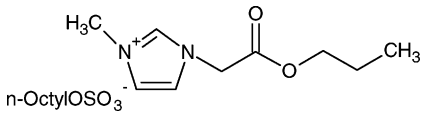


Figure 4. Typical molecular structure of a biodegradable ester group-carrying IL.

with an excess of $AlCl_3$ (>2:1) has a detectable vapor pressure of Al_2Cl_6 above 191 °C.[58] More recently, several imidazolium-based ILs have been slowly distilled under very low pressures. For example, $[C_6MeIm][N(TFMS)_2]$ distills at 155 ± 5 °C at ≤0.001 mbar, without degradation, probably by volatilization of the IL as intact ions, either alone or aggregated.[59] This conclusion has been corroborated by mass spectroscopy experiments, carried out under atmospheric pressure, via thermal desorption ionization (APTDI-MS) or chemical ionization (APCI-MS). Thus, APTDI-MS of $[C_2MeIm][BF_4]$ and $[C_1MeIm][CH_3SO_4]$ has indicated the presence, in the gas phase, of the corresponding imidazolium ions, and their aggregates;[60] the same conclusion was arrived at by examining six ILs, including $[C_4MeIm][X]$, X = methyl sulfonate and $N(TFMS)_2$, by APCI-MS. Therefore, when heated, imidazolium-ion-based ILs vaporize as discrete neutral clusters of the type $[RMeIm]_n[X]_n$.[61]

Heterocyclic-based ILs are not expected to be physiologically "inert", since many quaternary nitrogen compounds have antibacterial properties. Indeed, their cytotoxicities are comparable to those of many classic solvents, as shown by the following data for the human cell line HeLa (human cervical carcinoma epithelial cells): EC_{50} values after 24 h of incubation are 12.3, 13.9, and 0.6 mM for $[C_4MeIm][X]$, X = Cl^-, PF_6^-, and BF_4^-, respectively. The same figures for CH_2Cl_2, phenol, xylenes, and ethanol (after 3 h of incubation) are 71.4, 42.7, 52.4, and 1501.4 mM, respectively.[62] The relationship between the molecular structure of ILs and their toxicities toward two aquatic organisms, *Vibrio fischeri* and *Daphnia magna*, has been determined for ILs derived from Py, 3-MePy, 3,5-Me_2Py, MeIm, piperidine, 4-*N*,*N*-dimethylaminopyridine, trialkylamines, trialkylphosphines, and choline. The toxicity results showed the following trends: an increase as a function of increasing the chain length of the alkyl group; a slight increase with the number of nitrogen atoms in the cation; a decrease with ring methylation.[63] The toxicity toward *D. magna* and *Photobacterium phosphoreum* and biodegradability, "closed bottle" and "CO_2 headspace" tests of several ILs, have been determined. The compounds studied included [RMeIm][X] and [1-(alkyloxycarbonyl)methyl-3-methylimidazolium][X], R or RO = C_1-C_8; X = Br^-, BF_4^-, PF_6^-, $^-N(TFMS)_2$, $^-N(CN)_2$, *n*-$C_8H_{17}SO_4^-$; see Figure 4. The series [RMeIm][X] proved to be more toxic to both bacteria than classic organic solvents, namely, methanol, ethanol, 2-propanol, acetone, acetonitrile, chloroform, and dichloromethane, respectively. ILs carrying the ester side chain were found to be more biodegradable than those with alkyl groups; those with the *n*-octylsulfate anion were the most biodegradable within the same series.[64,65]

The relatively high toxicity of ILs (toward bacteria) and the poor biodegradability of (most extensively employed) 1,3-dialklyimidazolium-based ILs call for more studies on these two environmentally important aspects and careful attention to the disposal of ILs. The fact, however, is that the lack of volatility greatly reduces the chances of exposure, other than by direct physical contact, for example, through spills; this is a distinct advantage over classic, usually volatile, organic solvents.

3.2. ILs Are Noninflammable and Thermally Stable. In addition to being noninflammable, ILs are usually described as thermally stable. For example, $[C_2MeIm][N(TFMS)_2]$ has been claimed to be stable up to 455 °C.[44] More recent differential scanning calorimetry (DSC) results have shown, however, that the thermal stability threshold is much lower; e.g., $[C_2MeIm][X]$, where X = $N(TFMS)_2^-$, $N(MS)_2^-$, and Br^-, start their degradation at 307, 199, and 187 °C, respectively.[66] The relevant point, however, is that this stability threshold is well above the temperatures employed for dissolution and functionalization of carbohydrates: ≤150 °C.[67,68] However, the solubilization and functionalization of carbohydrates in classic solvent systems may be adversely affected by their relatively low thermal stability. For example, amber to brown solutions were obtained by heating cellulose under reflux in LiCl/DMAc; the color change was attributed to oxidative degradation of the polymer at temperatures as low as 90 °C. This is due to the formation of the *N*,*N*-dimethylketeniminium ion ($CH_2{=}C{=}N^+(Me)_2$), whose precursor is the enol tautomer of DMAc, $CH_2{=}C(OH)N(Me)_2$. This cation is an extremely reactive electrophile, capable of random chain cleavage, resulting in pronounced and rather fast changes in the M_r distribution of cellulose.[69]

3.3. ILs Are Reasonably Chemically Inert and Highly Polar. An important limitation to the use of the solvent system TBAF/DMSO for cellulose functionalization is that the electrolyte is very hygroscopic; its drying is time- and energy-consuming, because it cannot be dried by heating due to the Hofmann elimination reaction.[70−72] To our knowledge, there are no reports on a similar degradation of, for example, $[C_4MeIm][Cl]$, most certainly because the chloride ion, acting as a base, is not "naked" but is "solvated" via hydrogen-bonding to H2 and H4 of the imidazolium cation, as shown in Figure 5.[73]

However, the polarities of ILs, as measured by using solvatochromic probes, for example, RB of Figure 3, are relatively high, being situated between those of dipolar aprotic solvents and protic ones. Table 1 shows the solvent empirical polarities, $E_T(30)$ in kcal/mol, for some classes of ILs as well as those of organic solvents.[74] Note that polar solvents are associated with high $E_T(30)$ values.

Recently, the relative permittivities, ϵ_r, of a series of imidazolium-, pyridinium-, pyrrolidinium-, and alkylammonium-based ILs have been calculated from the frequency-dependent dielectric dispersion curves in the microwave regime, extrapolated to quasi-static conditions.[75] Interestingly, the values calculated for ϵ_r, 10−12, are lower than those of all classic solvents of Table 1, e.g., 24.55, 20.56, and 37.78 for ethanol, acetone, and DMAc, respectively.[76] That is, the high carbohydrate solubilizing power of ILs and their favorable effect on functionalization of the biopolymers dissolved (vide infra) is most probably connected with their polarities rather than their (relatively low) ϵ_r. As will be discussed below (eq 1), "polarity" is the sum of several solvent properties.

Table SI-1 of the Supporting Information (Table SI-1) shows some properties of individual ILs relevant to the dissolution and functionalization of carbohydrates. The properties listed, where available, include T_g, mp, decomposition temperature, viscosity, polarity, and the different solvatochromic parameters, vide infra, eq 1; all are considered as "must know" properties of ILs.[11]

3.4. Structure of ILs Is Deceptively Simple. At first glance, it would appear that ILs are assemblies of cations and anions. Consequently, their physicochemical properties and the relationship between their molecular structures and macroscopic properties could be rationalized by considering electrostatic interac-

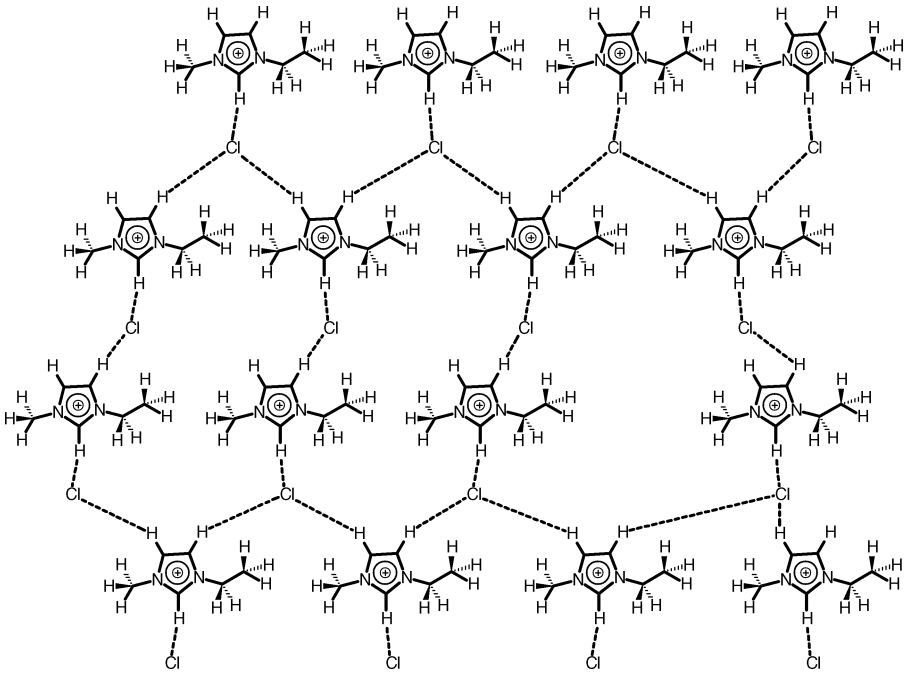


Figure 5. Schematic representation of hydrogen-bonding in a typical [RMeIm][Cl]. Adapted from ref 73. Copyright 2006 American Chemical Society.

Table 1. Polarities of Different Chemical Classes of Ionic and Molecular Liquids[a]

chemical class of ionic liquids	range of $E_T(30)$ (kcal/mol)	$E_T(30)$ of molecular liquid with corresponding polarity (kcal/mol)
primary and secondary alkylammonium salts; $RN^+H_3X^-$ and $R_2N^+H_2X^-$	57−66	water, 63; F_3CCH_2OH, 60
tertiary alkylammonium salts; $R_3N^+HX^-$	57	ethylene glycol, 56; formamide, 56
quaternary alkylammonium salts; $R_4N^+X^-$	43−51	2-butanol, 47; acetonitrile, 46
quaternary alkylphosphonium salts; $R_4P^+X^-$	42−45	acetone, 42; DMAc, 43
RMeImX	48−55	ethanol, 52; $CH_3CONH(CH_3)$, 52
RPyX and 1,4-R_2PyX	51−53	ethanol, 52; $CH_3CONH(CH_3)$, 52

[a] Reprinted with permission from ref 74. Copyright 2005 The Royal Society of Chemistry.

tions. Available evidence has indicated that this (molten-salt-based) simplified picture is not adequate to explain several experimental results, including the dependence on IL concentration of ^{1}H NMR chemical shifts, conductivities, and enthalpies of dilution in acetonitrile and chloroform,[77] self-diffusion coefficients of neutral and charged electroactive probes in dry and wet ILs,[78] and the dependence on the length of R (from C_1 to C_8) of conductivity, self-diffusion coefficient, viscosity, and spatial distribution of the coherent anti-Stokes Raman scattering.[79,80] The relationship between the viscosity of the IL and the length of R is instructive; the former property increases as a function of increasing the latter. This is surprising because as the length of R increases one expects a decrease in the overall contribution of electrostatic interactions and hydrogen-bonding, coupled with an increase in the (weaker) dispersive, or London interactions; i.e., the viscosity is expected to decrease; this is not the case. Additionally, X-ray diffraction studies have indicated that solid ILs consist of extended networks of ions, connected together by hydrogen bonds;[77,81] such networks appear to persist in the liquid phase and in solutions of ILs in (classic) solvents.[82] All of these results and molecular dynamics simulations of the structures of several ILs[83−86] support the following picture: The main difference between ILs and simple molten salts is the molecular asymmetry built into (at least one of) the ions, usually the cation. Whereas the polar domain has the structure of a tridimensional network of ionic channels, the nonpolar one is arranged as a dispersed microphase for short R and as a continuous one for longer chains, $>C_6$; the 1-butyl group appears to mark the onset of transition from one type of structure to the other. When R is short, the equilibrium distance between the cations is determined by headgroup Coulombic interactions. These have less influence when R becomes long, and the structure of the IL is noticeably affected by dispersion interactions between the tails. Therefore, ILs and possibly their solutions in some classic solvents should be considered as heterogeneous on the nanoscale, akin to normal and inverse micellar aggregates in solution.

4. Applications of ILs in Carbohydrate Chemistry: A Window of Opportunities

The preceding discussion shows that ILs constitute a particularly useful class of solvents for a variety of applications; these will be shown by examining the use of ILs in: Dissolution of carbohydrates and their recovery from solutions; incorporation into nanocomposites; transformation into important derivatives, in particular esters and ethers. All of these applications are summarized in Table SI-2 of the Supporting Information.

4.1. IL-Assisted Solubilization of Carbohydrates. There is considerable current interest in the utilization of carbohydrates as readily available, relatively inexpensive, and renewable feed stocks, for example, for sugar-based surfactants,[87] and the fatty esters of sugars.[88] The derivatization of native carbohydrates is still a challenging task, because of their low solubilities in almost any solvent but water; see Table 2. The organic solvents listed in the latter include Py, which is expected to dissolve carbo-

Table 2. Solubility of Several Carbohydrates in Organic Solvents

carbohydrate	solvent	concentration (wt %)	*T* (°C)	reference
glucose	2-methyl-2-propanol	0.03	25	89
sucrose	acetone	0.007	30	90
	2-methyl-2-propanol,	0.05	60	91
	pyridine	6.45	26	92
galactose	pyridine	5.45	26	92
lactose	pyridine	2.18	26	92
mannose	pyridine	0.47	26	92

Table 3. Solubility of Different Carbohydrates in Ionic Liquids

carbohydrate	solvent	solubility (g/L)	*T* (°C)	reference
glucose	$[C_1OCH_2MeIm][N(TFMS)_2]$	0.5	25	89
	$[C_1OCH_2MeIm][BF_4]$	4.4	25	89
	$[C_1OC_2H_4MeIm][BF_4]$	5	55	96
	$[C_1OCH_2MeIm][N(CN)_2]$	66	25	89
	$[C_1OC_2H_4MeIm][N(CN)_2]$	91	25	89
	$[C_2OC_2H_4MeIm][N(CN)_2]$	70	25	89
	$[C_4MeIm][N(CN)_2]$	145	25	89
	$[C_4MeIm][Cl]$	50	70	97
fructose	$[C_4MeIm][Cl]$	50	70	97
	$[C_4MeIm][Cl]$	560	110	98
	$[C_4Me_2Im][Cl]$	400	120	98
sucrose	$[C_1OC_2H_4MeIm][TFMS]$	2.1	25	89
	$[C_1OCH_2MeIm][N(CN)_2]$	249/352	25/60	89
	$[C_1OC_2H_4MeIm][N(CN)_2]$	220	25	89
	$[C_2OC_2H_4MeIm][N(CN)_2]$	50/240	25/60	89
	$[C_4MeIm][N(CN)_2]$	195/282	25/60	89
	$[C_4MeIm][Cl]$	50	70	97
	$[C_4MeIm][Cl]$	180	110	98
	$[C_4Me_2Im][Cl]$	140	120	98
lactose	$[C_4MeIm][N(CN)_2]$	51/225	25/75	89
α-CD	$[C_1OCH_2MeIm][Br]$	350	*a*	99
β-CD	$[C_4MeIm][N(CN)_2]$	450	75	89
	water	18.5	25	100
agarose	$[C_1OCH_2MeIm][Br]$	20	*a*	99
amylose	$[C_4MeIm][N(CN)_2]$	4	25	89
	$[C_1OCH_2MeIm][Br]$	30	*a*	99
	water	<0.5	25	89
amylopectin	$[C_4MeIm][Cl]$	50	70	97

[a] Not listed.

hydrates because of hydrogen bonding between the saccharide OH groups and the lone electron pair of the heteroatom; this is not the case.

Few classic solvents, for example, DMF and DMSO, dissolve saccharides. These, however, have some undesirable characteristics; e.g., they can deactivate the enzyme employed in enzyme-mediated esterifications[93] and are not compatible with many intended applications of the derivatized carbohydrate, especially in consumer products.

The first report on the dissolution of cellulose in an IL, molten *N*-ethylpyridinium chloride in the presence of nitrogen-containing bases, dates back to 1934;[94] this report was treated as a novelty of little practical importance, because of the high mp of the salt, 118−120 °C. Later, it has been shown that the mp can be lowered to 77 °C by mixing the IL with 50% DMF or DMSO; the mixtures thus obtained dissolve cellulose.[95] The introduction of the principles of green chemistry and the recognition of the potential of ILs as solvents has revived interest in their use. A comparison of the results listed in Tables 2 and 3 clearly shows the power of ILs, relative to classic solvents, in dissolving low- and a few high-M_r carbohydrates.

A similar compilation for other high-M_r carbohydrates, for example, cellulose and chitosan, will not be attempted. The reason is that the dissolution of these biopolymers is dependent on their DP, Ic, and the conditions of preparation, including the method and time of heating. Additionally, carrying out derivatization at the solubility limits of biopolymers in ILs is usually not carried out. The reason is that the solutions obtained are either extremely viscous (paste formation was also reported); this renders subsequent functionalization difficult, at best.

A few examples, however, suffice to demonstrate the power of ILs in dissolving biopolymers. A mixture of $[C_4MeIm][Cl]$/DMSO, 84:16 wt %, dissolves pine, eucalyptus, and oak wood shavings after heating at 100 °C for several hours. In all cases, the swelling of wood particles was observed immediately after they came into contact with the IL-based solvent. After filtration of the insoluble solids, cellulose samples were readily constituted (as flocs) from the resulting clear, amber-colored solution by rapid mixing with solvents that dissolve lignin, for example, dichloromethane or acetonitrile.[101] Thus treatment of wood by ILs constitutes a single-phase "organosolv" delignification process. The last conclusion is corroborated by the high solubilization of lignin, 9.7 wt % at 110 °C, in ILs, e.g., $[C_4MeIm][Cl]$.[98]

At 25 °C, the breakage length and elongation at breakage (measures of strength) of paper (90 g/m^2) decreased after impregnation by the following ILs: $[RMeIm][BF_4]$, R = C_8, C_{10}; $[ROCH_2MeIm][BF_4]$, R = C_4, C_5, C_6, C_7, C_8, respectively; $[ROCH_2MeIm][N(TFMS)_2]$, R = C_4, C_5, C_6, C_7, C_8, C_9, respectively. This decrease in paper strength was attributed to the weakening of hydrogen bonding between the biopolymer chains as a result of the corresponding (competitive) interaction with the ILs.[102] The rates of cellulase-catalyzed hydrolysis of microcrystalline cellulose, dissolved in $[C_4MeIm][Cl]$, were between 52 and 55 times faster than that of the untreated sample.[103] All of these results show that cellulose interacts appreciably with ILs, even at room temperature.

Conventional heating of cellulose (DP ≈ 1000) produced clear solutions containing 3 wt % (70 °C) or 10 wt % (100 °C) in $[C_4MeIm][Cl]$ or 5 wt % (100 °C) in $[C_6MeIm][Cl]$. A 5 wt % solution of the same cellulose in $[C_4MeIm][Cl]$ was obtained by sonication at 80 °C; microwave heating produces a 25 wt % viscous paste.[49] Note that ILs are heated with exceptional efficiency by microwaves,[104] so care must be taken to avoid excessive localized heating that can induce chain degradation of the biopolymer during its dissolution. Indeed, recent results have indicated not only decomposition but also incomplete dissolution when microcrystalline or filter-paper celluloses were heated by microwave irradiation in $[C_4$-2,3-$Me_2Im][Cl]$ (20 min; 100−120 °C; 300 W power).[98]

The data listed in Table 4 were obtained after cellulose dissolution for 12 h at 10 °C higher than the mp of the IL.[105,106]

The efficiency of $[C_4MeIm][Cl]$ as a solvent is demonstrated by the fact that it dissolves bacterial cellulose, DP = 6493. As seen under the microscope, swelling of a single cellulose fiber appeared after 5 min of contact with the solvent; complete dissolution was observed after 20 min at 80 °C.[68]

As a solvent for cellulose, the IL [AllylMeIm][Cl] has generated interest because its mp (17 °C) is much lower than that of the saturated alkyl group counterpart, namely, $[C_3MeIm]$-[Cl], 60 °C. Solutions of 2.9−5 wt % cellulose in [AllylMeIm]-[Cl] can be obtained after 15 min of heating without prior activation of the biopolymer.[67] Note that this solvent is not "new", as claimed.[107,108] Real-time observation of the dissolution of cellulose fibers (DP = 650) in [AllylMeIm][Cl] was carried out at 80 °C by using polarized light microscopy. Solution viscosity depended on the concentration of the dissolved cellulose, being 110 and 1480 mPa s, at 80 °C, for 4 and 8 wt

Table 4. Dissolution of Different Celluloses in ILs

	weight; DP[a]				
cellulose; DP	[C_2MeIm][Cl]	[C_4MeIm][Cl]	[C_4-2,3-Me_2Im][Cl]	[C_4MePy][Cl]	BDTACl
microcrystalline; 286	12%; 329	18%; 307	9%; 342	39%; 172	5%; 327
spruce sulfite pulp; 593	6%; 580	13%; 544	6%; 622	37%; 412	2%; 527
cotton linters; 1198	4%; 1181	10%; 812	4%; 1102	12%; 368	1%; 966

[a] Weight percent of cellulose dissolved; DP after regeneration of the biopolymer.

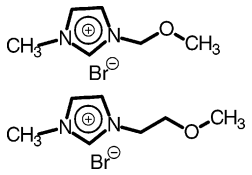


Figure 6. Structures of some ILs with an ether linkage in the side chain.

% cellulose, respectively. More concentrated solutions (10 wt %) show strong light anisotropy, probably due to the formation of a lyotropic liquid-crystalline phase.[109] A structurally related solvent, [Allyl-2,3-Me_2Im][Br] also dissolves cellulose, 12, 4, and 4 wt %, for microcrystalline cellulose, spruce sulfite pulp, and cotton linters, respectively.[106]

The IL series [RMeIm][FmO] and [REtIm][FmO], where R = Et, 1-propyl, and allyl, respectively, are interesting because of their low viscosities and the high basicity of the counterion. Thus, the viscosities are 66, 67, and 2090 mPa s for [AllylMeIm][FmO], [AllylEtIm][FmO], and [AllylMeIm][Cl], respectively. The very low viscosities of the formates were attributed to the small size and flat shape of the anion. Additionally, the anion basicity, as measured by the solvatochromic parameter β, vide infra, eq 1, is stronger than that of the chloride ion, $\beta = 0.99$ and 0.83, respectively. These characteristics should make this series of ILs suitable to dissolve biomacromolecules, where low viscosity and high basicity are important. A 10 wt % solution of a microcrystalline cellulose, DP ca. 250, in [AllylMeIm][FmO] was obtained by heating at 60 °C versus 100 °C for the corresponding [AllylMeIm][Cl]. At 85 °C, the solubility of the same cellulose in the former IL reached 22 wt %. Amylose (DP ca. 1000), dextrin (DP ca. 70), inulin (DP ca. 35), pectin (DP ca. 1500), and xylan (DP ca. 3000) also dissolve in [AllylMeIm][FmO]. The solubilities of amylose, dextrin, and inulin increased noticeably as a function of increasing temperature between 20 and 100 °C. This was attributed to hydrogen bonding of the anion with the hydroxyl groups of the biomacromolecule. The much smaller temperature effect on the solubilities of pectine and xylan agree with this explanation, because of the relatively low density of OH groups of these compounds.[110]

At 25 °C, β-cyclodextrin (β-CD) has comparable solubilities in water and in [C_4MeIm][BF_4], 1.85 and 1.88 wt %, respectively.[111] Structurally complex carbohydrates, for example, glycosaminoglycans, including heparin ($M_r = 12\,500$), heparin sulfate ($M_r = 14\,800$), chondroitin-6-sulfate, and hyaluronic acid ($M_r = 10^6$) dissolve in several ILs (in the range of 0.1 to 1 wt %), including [C_4MeIm][BF_4], [C_2MeIm][BzO], and [C_4MeIm][BzO], respectively.[112] As shown in Table 3, ILs that carry the ether linkage in one of the side chains attached (Figure 6) are efficient in dissolving carbohydrates, for example, glucose, α-CD, amylose, and agarose. Gelation (formation of a physical gel) was observed when a solution of the latter was cooled to room temperature.[99]

Konjac glucomannan is a polysaccharide, consisting of glucose and mannose in the ratio of ca. 1:1.6. A sample of this carbohydrate ($M_r = 77\,503$) is only slightly soluble in 2-methyl-2-propanol (0.12 wt %) but is more soluble in ILs, 2.66, 3.36, 1.91, and 1.62 wt % for [C_2MeIm][BF_4], [C_4MeIm][BF_4], [C_8MeIm][BF_4], and [C_4MeIm][PF_6], respectively.[113] Chitin and chitosan (partially N-deacetylated chitin) dissolve in [C_4MeIm][X] (X = Cl^- and BF_4^-).[114,115] Viscous solutions of chitin (10 wt %, clear) or chitosan (degree of N-deacetylation, 88%, $M_r = 3 \times 10^5$ to 4×10^6; 10 wt %, semiclear) can be obtained by dissolving the biopolymer at 110 °C. Results of X-ray diffraction have shown that the former solution is completely disordered, whereas some order is still present in the solutions of chitosan.[115] The swelling of chitosan hydrogel films by mixtures of water plus [C_2MeIm][X] (X = SCN^- and TFA^-), [C_3MeIm][I], [C_4MeIm][X] (X = Cl^-, BF_4^-), and [C_6MeIm][Cl] has been studied. Dried chitosan hydrogel films were prepared by dissolving chitosan (degree of N-deacetylation, 76 wt %, $M_r = 2 \times 10^5$) in dilute acetic acid, followed by casting, washing of the films, and drying. These films were brought into contact with water−IL binary mixtures, and the water retention was measured at different water contents. The results show a clear dependence on the counterion; swelling by [C_4MeIm][BF_4] is more efficient than that by contact with pure water.[116]

Starch and zein protein are soluble in [C_4MeIm][Cl] and [C_4MeIm][$N(CN)_2$]. After heating at 80 °C, extremely viscous solutions were obtained, containing up to 15 wt % dissolved material.[117] The effects of heating in water or in [C_4MeIm][Cl] on the morphology, amylopectin M_r, and thermal properties of corn, rice, wheat, and potato starches were recently studied. Dispersions of all starches in water or the IL (15 min at 80 °C) are opaque or translucent. Heating the dispersions of all starches for 1 h at 100 °C produced translucent (water) or clear products (IL). Dissolution in hot ILs resulted in a decrease of the M_r of all starches, ranging from 59.4% (rice) to 38.6% (potato), with concomitant formation of several degradation products, detected by size exclusion chromatography (SEC). Thus [C_4MeIm][Cl] may have limited applications as a solvent for starch. The onset and peak temperatures and the enthalpy change of native starches and those dispersed in water or IL were determined by DSC. Except for potato starch in the IL, dispersion in either solvent has transformed the remaining starches into gelatinized form.[118]

A series of results can be employed to rationalize the mechanisms of IL-induced solubilization of carbohydrates. Near-IR spectroscopy has been employed to determine the binding constants between phenol and α-, β-, and γ-CD in [C_4MeIm][Cl]. The phenol−CD binding constants were much lower in the IL than its counterparts in aqueous solution (phenol/CD/water), because the cation of the IL forms inclusion complexes with the cyclodextrin, thereby preventing phenol from being included into the cavity of the oligosaccharide.[119,120] A combination of techniques has been employed to probe the solubilization of β-CD in [C_4MeIm][BF_4]. The results indicated that β-CD enhances the solubility of the IL in water, because of its mutual interaction with both solvents. The dependence of solution conductivity of the (partially soluble) IL in water on β-CD indicated the formation of 1:1 CD−IL complex. A fine crystalline powder is formed when β-CD is mixed with IL;

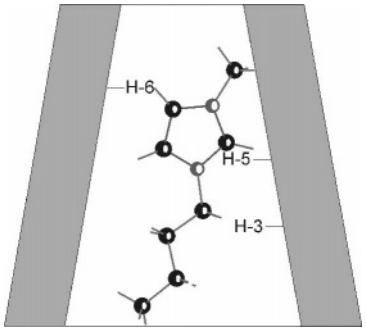


Figure 7. Structure suggested for the penetration of the cation of IL into the cavity of β-CD. Adapted with permission from ref 111. Copyright 2005 Wiley-VCH.

X-ray diffraction of this powder showed a pattern typical of a cage structure. Finally, both solid-state ^{13}C NMR of these crystals, and liquid-state ^{1}H NMR of the CD−IL mixture indicated the formation of hydrogen bonds between the cation of the IL and C3-OH, C5-OH and C6-OH groups of the glucose units of β-CD. On the basis of these data, Figure 7 was suggested for the penetration of the IL into the cavity of the CD.[111] The dependence of chitosan hydrogel swelling by aqueous ILs on the molecular structure of the IL has also been explained on the basis of the penetration of the latter into the hydrogel network.[116]

Insight into the mechanism of dissolution of carbohydrates in ILs was achieved by applying NMR spectroscopy. ^{13}C NMR signals of cellulose dissolved in [C_4MeIm][Cl] were recorded at 80 °C, and the spectrum obtained was compared with that of the same cellulose in a typical nonderivatizing solvent system, DMSO/TBAF. The similarity of the chemical shifts of the anhydroglucose unit (AGU) carbon atoms indicated that the IL is a nonderivatizing solvent for cellulose.[105] The same technique was applied to solutions of celluloses (DP = 400−1000), and the oligomers cellobiose, cellotriose, and cellohexaose in D_2O (where the carbohydrate is soluble) and in [C_4MeIm][Cl] containing 15 wt % DMSO-d_6; the latter was added to reduce solution viscosity. The spectra obtained indicated that cellulose oligomers are disordered in the IL/DMSO solution. This result is similar to that observed for aqueous solutions, despite the considerable differences of the two media.[121] To further probe carbohydrate−IL interactions, the same authors determined the NMR longitudinal (T_1) and transverse (T_2) relaxation times of [C_4MeIm][Cl], both for the cation (^{13}C), and the anion ($^{35/37}Cl$), respectively. These relaxation times were determined as a function of the concentrations of cellobiose (model for cellulose), glucose, and glucose pentaacetate; the latter lacks hydrogen-bond donors. Variations in relaxation times usually yield information about molecular dynamics of the compound investigated.[122] These variations are particularly pronounced for the chloride ion, as both ^{35}Cl and ^{37}Cl have a spin number of $^{3}/_{2}$.[123] The effects of increasing temperature (from 40 to 90 °C) on T_1 and T_2 of both nuclei (^{13}C and $^{35/37}Cl$) of the pure IL indicated the expected weakening of ion-pair interactions. Investigation of the relaxation times as a function of increasing cellobiose concentration has indicated that the interactions between the IL cation and sugar are negligible. However, those with the anion were found to be very strong. That these interactions are due to hydrogen bonding of Cl^- to the OH groups of the sugar was confirmed by studying the dependence of relaxation times on glucose and glucose pentaacetate concentrations. Whereas the former interacted strongly with the anion, the latter shows almost no effect on the relaxation rate of ^{35}Cl. The stoichiometry of the interaction was calculated to be 7.8 and 4.9 for cellobiose and glucose, respectively, corresponding to 1 IL molecule/sugar OH group.[124]

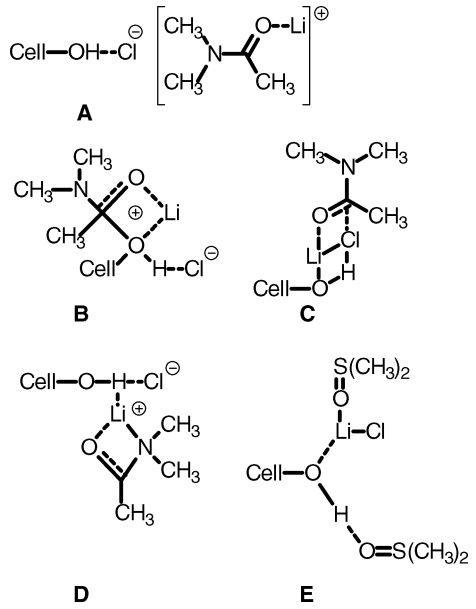


Figure 8. Structures suggested for explaining the interactions of cellulose with LiCl/aprotic solvent systems. For simplicity, partial charges are not shown. Adapted with permission from ref 53. Copyright 2005 Springer Verlag.

The above-discussed dissolution mechanism probably applies to other carbohydrates. Formally, it is similar to the mechanism of cellulose dissolution in LiCl/dipolar aprotic solvent, where possibilities for the biopolymer/solvent system interactions are depicted in Figure 8.

The relative importance of the halide ion−HO−Cel interactions can be inferred from application of the Taft−Kamlet−Abboud equation to the UV−vis absorbance data of solvatochromic probes, Figure 3, dissolved in cellulose solutions in different solvent systems, including LiCl/DMAc.[125] In this treatment, the microscopic polarity measured by the indicator; E_T(indicator) is correlated with the properties of the solvents, as shown in eq 1

$$E_T(\text{indicator}) = \text{constant} + s(\pi^*) + a\alpha + b\beta \qquad (1)$$

That is, the polarity is modeled as a linear combination of a dipolarity/polarizability term [$s(\pi^*)$], two hydrogen-bonding terms, in which the solvent is the hydrogen-bond donor ($a\alpha$) or the hydrogen-bond acceptor ($b\beta$). The parameters π^*, α, and β are known as solvatochromic parameters, because they are determined by the use of solvatochromic indicators.[76,126] The results obtained have revealed that the most important solvatochromic parameters are α_{Cel} (the hydrogen-bond donation ability of cellulose) and $\beta_{LiCl/DMAc}$ (the basicity of the solvent system). Therefore, the most dominant interaction is Cl^-−HO−Cel. In other words, carbohydrate dissolution in LiCl/DMAc or in ILs can be pictured as a chloride-ion-driven exchange of cellulose for DMAc in the coordination sphere of the lithium ion[127] or for the organic cation in case of ILs. Note that the cations and most anions of ILs (that are employed to dissolve carbohydrates) are large and asymmetric, leading to loosely packed ionic network.[128] Consequently, the ions of ILs are expected to be freer to interact with the OH groups of the carbohydrate than, e.g., the ions of LiCl in DMAc. This leads to higher solubilities in ILs than in classic solvent systems.

4.2. Applications of Carbohydrate Solutions in ILs. We start by showing applications where the biopolymer is not

chemically modified (i.e., is not functionalized). Regeneration of the biopolymer dissolved is the first application that comes to mind. Indeed, cellulose can be precipitated from its solutions in ILs as monoliths, fibers, and films by the addition of water, alcohol or acetone.[16,129] In addition to the biopolymer, the solution in IL may contain other additives, e.g., dyes and metal complexing agents. The additive-containing cellulose matrix, obtained by extrusion, can then be employed, e.g., for remediation in aqueous media.[130]

Cellulose solution in [C_4MeIm][Cl] was extruded into thin fibers by contact with water. SEC analysis has shown that the dissolving pulp was regenerated without significant change in its DP, or polydispersity. Examination by scanning electron microscopy (SEM) revealed that the morphology of the fibers obtained has changed significantly, displaying a rough, but conglomerate texture in which the fibers are fused into a relatively homogeneous macro-structure.[49] As shown in Table 4, the same trend, little effect of solubilization on DP of the bioploymer, has also been reported for other celluloses in several ILs.[105] Note that the negligible effect of solubilization on DP has been demonstrated for cellulose solutions in LiCl/DMAc.[131] It appears, however, that dissolution of some carbohydrates in ILs may result in degradation. As shown in Table 4, dissolution of cellulose in [C_4MePy][Cl] has decreased the DP of the biopolymers to 44.4, 71.0, and 30.7% of their starting values, for microcrystalline cellulose, spruce sulfite pulp, and cotton linters, respectively. Also, dissolution of cellulose from sugarcane bagasse in a mixture of [C_4MeIm][Cl] and DMSO (4:1) and in pure [AllylMeIm][Cl] (100 °C, 12 h) has resulted in DP decrease of 42.7 and 28.7%, respectively.[132] Stirring native barley starch in [C_4MeIm][Cl], at 100 °C gave depolymerized amylose products, but amylopectin remained intact.[133]

Electrospinning is a widely used technique to obtain micron- to nanometer-sized fibers of various polymers.[134] In this method, the polymer solution is held by its surface tension at the tip of a capillary. Application of high voltage (10−20 kV) causes the solution at the tip to elongate, until a fine jet is ejected from the apex of the cone. Cellulose solution, 10 wt %, in [C_2MeIm]-[Cl] and cellulose-heparin solution (10 and 7 wt %, respectively) in [C_2MeIm][BzO] were subjected to electrospinning; the fibers and composite fibers formed were washed with ethanol and dried. SEM characterization showed the formation of highly branched, nanometer-to-micron-sized fibers. It is noteworthy that the heparin present in the composite fiber maintained its bioactivity (as anti-clotting agent) even after exposure to the high voltage required for electrospinnig.[135]

A very important application is to use the carbohydrate−IL composite as a matrix for a myriad of substrates, including biopolymers. The general approaches that are employed to attach substrates to supports, e.g., matrices in forms of films or beads, are shown in Figure 9 and are discussed blow:

(i) The first approach is by inclusion into the matrix during preparation of the latter, Figure 9A. In encapsulation of biopolymers, this strategy may result in loss of bioactivity by several mechanisms: heat-induced denaturing during drying of the composite; IL-induced denaturing, as shown for cellulase in the presence of [C_4MeIm][Cl] and [C_4MeIm][BF_4]; constrained local environment, imposed by the support matrix and/or decreased diffusion of the substrate into the composite film.[136]

(ii) Simple physical adsorption onto the film surface is shown in Figure 9B; this process is reversible and is associated with substrate leaching.

(iii) Chemical attachment of the substrate to the film surface via a covalent bond, is depicted in Figure 9C.

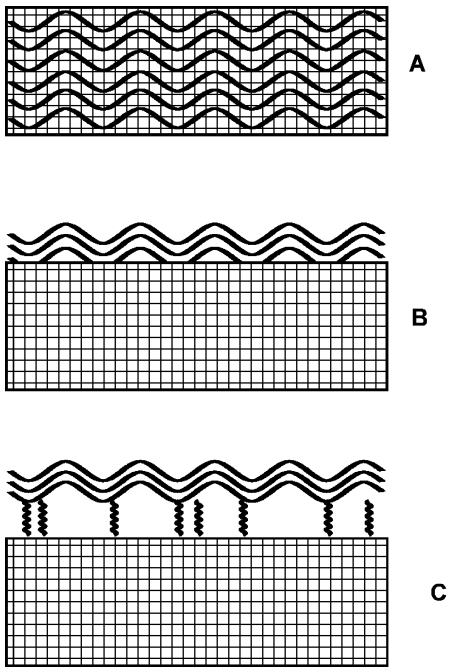


Figure 9. Schematic representation of methods employed to attach substrates to carbohydrate matrices. Parts A, B, and C correspond to inclusion into the carbohydrate matrix, physical adsorption, and covalent attachment, respectively.

In any of these approaches, carbohydrate−IL composite substitutes for the simple carbohydrate matrix; this entrapment of the highly polar IL solves the problem of poor conductivity of the carbohydrate film, an important requirement for application in biosensors.

Several examples of approach i will be listed; first we consider encapsulation of simple substrates, then that of biomacromolecules. Complexing agents for metal ions were prepared as follows: Solutions of microcrystalline cellulose or filter-paper celluloses were dissolved in [C_4MeIm][Cl] or [C_4-Me_2Im][Cl] ILs. Metal-complexing agents, e.g., PAN, were then added, the composite was casted into film, and the latter was washed with water and dried. The resulting films removed metal ions, e.g., Mn^{2+}, Ni^{2+}, and Zn^{2+} from aqueous solutions. They were also employed for the quantitative determination of these ions, with detection limits of 1.6, 1.6, and 2.2×10^{-6} mol/L, respectively.[98] "Magnetic" cellulose was obtained as follows: A 5 wt % solution of microcrystalline cellulose was prepared in [C_4MeIm][Cl] by conventional (110 °C) or microwave heating (3−5 s pulses at 700 W). The solution was cooled to 70 °C, and magnetite, 0.5 to 2.5 wt %, was added, under vigorous stirring. X-ray diffraction of the gray or black flocs or beads of magnetic cellulose showed the presence of crystalline and amorphous cellulose and magnetite. The negligible shifting of the magnetite X-ray peaks as a function of its concentration in the composite indicated little interaction with cellulose and that it is incorporated without undergoing chemical change during the formation of the composite. All samples examined exhibited ferromagnetism.[137] TiO_2 nanostructures of controlled properties are important because of their potential applications in photocatalysis, dye-sensitized solar cells, etc.[138,139] Mesoporous TiO_2 films have been obtained by the following procedure: Cellulose was first dissolved in [AllylMeIm][Cl] to give 1, 5, and 10 wt % solutions. Titanium tetrabutyloxide was then added, followed by calcinations of the resulting solutions. The samples produced showed similar X-ray diffraction patterns. The following results were observed as a function of increasing the cellulose content

of the solution: an increase in the specific surface area (from 30 to 44 m^2/g); an increase in the pore volume (from 0.10 to 0.13 cm^3/g); a decrease in the average pore size (from 16.0 to 5.5 nm). That is, the composition of the original Cel/IL solution can be employed to control the properties of mesoporous TiO_2 nanofilms.[140]

The encapsulation of biomacromolecules into solid support materials has been studied extensively as a simple mean of protein stabilization, as well as catalyst separation and recovery from reaction systems. Cellulose- and chitin-supported enzyme membranes are attractive because the matrices are hydrophilic, inert under physiological conditions and biocompatible. Imidazolium salt of heparin was dissolved in [C_2MeIm][BzO]; the resulting solution added to another of cellulose in [C_4MeIm][Cl]. After homogenization, the resulting heparin/Cel/IL was fabricated into biomaterials of different shapes, including membranes (by casting), micro- or nanospheres (by atomization), or micro- or nanofibers (electrospinning). Once solidified, the resulting bio-composites were washed with ethanol and dried. SEM micrographs of cellulose and heparin−Cel films showed material with smooth surfaces and uniformly distributed nanopores (20−40 nm); heparin is strongly attached to the Cel matrix. Activated partial thromboplastin time and thromboelastography demonstrate that the heparin−Cel composite is superior to other existing heparinized biomaterials in preventing clot formation in human blood plasma and whole blood. Membranes made of these bio-composites allow the passage of urea, while retaining albumin, representing a promising blood-compatible biomaterial for hemodialysis.[141] Another example is the encapsulation into cellulose-IL composite of the enzyme laccase from *Rhus vernifecera* (a redox enzyme, responsible for the degradation of phenolic compounds, e.g., lignin).[142] Microcrystalline cellulose was dissolved in [C_4MeIm][Cl] to give a 4.75 wt % solution. This was cooled to room temperature to form a supercooled solution (the mp of the IL is 66 °C). Aqueous laccase solution was then added, the solution homogenized, casted as a film, washed with water to dissolve the IL, and air-dried (enzyme activity was lost on drying the film at 100 °C). Alternatively, the enzyme was precoated with another IL, e.g., [C_4MeIm][N(TFMS)$_2$] before being added to the supercooled solution of cellulose in the IL. Native laccase retained 18% of its original activity (syringaldazine oxidation in bulk water) when encapsulated in the cellulose matrix, compared with 29% when precoated with a "protective film" of IL, before being added to the Cel/IL solution. There was no observable leaching of the enzyme from its cellulose matrix.[143]

The above-mentioned loss of enzyme activity, relative to that of laccase in bulk water, can be traced to either loss of conformational flexibility or decreased diffusion of the substrate, as a result of encapsulation in the cellulosic matrix. Consequently, surface immobilization of the protein alleviates this problem, either by physical adsorption (approach ii) or covalent attachment to the surface (approach iii). This latter was used by the same research group to attach laccase to a cellulose matrix. First, films and beads of surface-functionalized cellulose were prepared by adding polyamine polymers, e.g., branched or linear poly(ethyleneimine) to a supercooled Cel solution in [C_4MeIm][Cl]. The solution was casted into films or dispersed into beads; the products were washed with water. The Cel composite materials were "activated" by glutaraldehyde, the resultant imine bonds were reduced, and the enzyme was attached. Depending on the polyamine employed, the specific activities of the Cel-composite films ranged from 15% to 63% of that of the enzyme in bulk water. The same technique was employed to attach lipase to Cel beads. The activity of the surface-immobilized enzyme as a catalyst for transesterification of ethyl butyrate with 1-butanol compared favorably, 87% conversion, to that of a commercial lipase sample.[144]

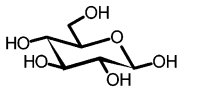
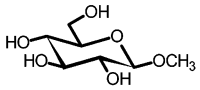
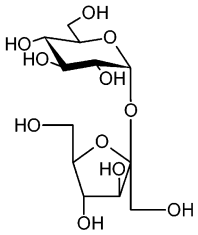
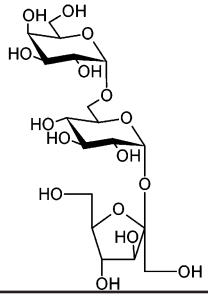
In principle, similar immobilization schemes for biomacromolecules can be employed for composites of chitin and/or chitosan with ILs. Thus an aqueous solution of hemoglobin was dissolved into a solution of chitosan in [C_4MeIm][BF_4]; the resulting solution was casted as a thin film on the surface of a glassy carbon electrode. The position and intensity of the Soret absorption band of heme (Fe) indicated no denaturing as a result of its entrapment in the chitosan−IL composite and negligible heme diffusion through the film. A pair of well-defined, quasi-reversible redox peaks of hemoglobin was observed, indicating efficient electron transfer between the protein and the electrode. The composite film electrode is stable and has dramatically enhanced the biocatalytic activity of heme in reduction of oxygen and trichloroacetic acid.[145] A horseradish peroxidase biosensor was constructed by entrapping the enzyme into chitosan/[C_4MeIm][BF_4] composite film, followed by deposition of the latter on the surface of a glassy electrode. A pair of stable, well defined, quasi-reversible redox peaks of the enzyme was observed. The biosensor exhibited good sensitivity, reproducibility, and linear response to H_2O_2 concentration, from 0.75 to 135 μM, and was found to be free from interference by organic solutes, ethanol, glucose, sucrose, uric acid, or ascorbic acid, respectively.[114]

Heck olefination reaction has been carried out in the presence of Pd/chitosan/IL nanocomposites. The ILs employed were TBABr, tetrabutylphosphonium bromide, [C_4MeIm][BF_4], [C_4MeIm][Br], or [C_4Py][BF_4]; all reactions were carried out in the presence of TBAA as a base. The metallic catalyst, Pd(0) and Pd(II) was generated by chemical or electrochemical reduction of Pd(AcO)$_2$ in the presence of chitosan/IL. Examination of the catalyst by TEM showed that it is of the cortex type, Pd(0) being surrounded by a shell of chitosan. Bromobenzene and butyl acrylate react rapidly (15 min) at 130 °C in the presence of the above-mentioned catalyst; a high yield (99%) of *trans*-butyl cinnamate was obtained. The reaction products were extracted with cyclohexane, and the catalyst/IL was recycled. Due to the high reaction temperature, however, the catalytic efficiency decreased after each cycle, due to Hofmann decomposition of TBABr, which destabilizes the nanocomposite (Pd/chitosan). The more reactive iodobenzene reacts with *n*-butyl acrylate at a lower temperature, 105 °C, and the catalyst was recycled 11 times, with an overall conversion of 94%.[146]

4.3. Synthesis of Functionalized Carbohydrates in ILs. A clear understanding of the roles of carbohydrates in biology is the focus of the newly constituted field of glycobiology, the study of biological activities mediated by carbohydrates. Thus carbohydrates play an important role in biology, e.g., as reservoirs for the storage of excess cellular energy and for maintaining the structural integrity of most living organisms.[144−149] Additionally, carbohydrates are ideal binding partners for proteins involved in intracellular communication. Glycosylation of carrier molecules, such as proteins and lipids, afford glycoproteins, proteoglycans and glycolipids that serve to display carbohydrate in their extracellular environment. These glycosylation modifications can result in very important biological activities.[150,151]

Investigation of the above-mentioned activities is often dependent upon the synthesis of complex carbohydrates, and these synthons frequently rely on selective functionalization of one or more of the hydroxyl groups present.[152] On the basis of

Table 5. Acetylation of Carbohydrates with Acetic Anhydride in Ionic Liquids

carbohydrate	solvent	time (h)	*T* (°C)	yield (%)	ratio of α/β-anomers
	$[C_4MeIm][N(CN)_2]$	0.2	room temperature	89	1.17/1
	$[C_4MeIm][N(CN)_2]$	24	50	98	1/1.10
	$[C_4MeIm][N(TFMS)_2]$	24	room temperature	0	
	$[C_4MeIm][N(CN)_2]$	0.2	room temperature	92	
	$[C_4MeIm][N(CN)_2]$	24	room temperature	93	
	$[C_4MeIm][N(CN)_2]$	24	room temperature	90	

the unique properties of ILs, it is only natural that their use as solvents for functionalization of low- and high-M_r carbohydrates has been recognized and exploited, as shown below.

The finding that ILs with the $^-N(CN)_2$ counterion appear to be unique, thus far, among families of ILs in their efficiency as solvents for mono-, di- and polysaccharides[89] has led to work on the use of these ILs for O-acylation of alcohols and carbohydrates. This reaction is widely employed not only for the protection of the hydroxyl groups but also for the purification and structural elucidation of natural products. Per-O-acetylation is most frequently achieved by use of acetic anhydride along with, inter alia, a tertiary base, e.g., pyridine,[153] or a Lewis acid, e.g., $ZnCl_2$.[154] Alternatively, this reaction can be carried out in an IL with or without a base catalyst. As shown in Table 5, several saccharides were successfully O-acetylated by reaction of acetic anhydride with the sugar in $[C_4MeIm][N(CN)_2]$.[155]

Although the preceding reactions were carried out in the presence of an IL/saccharide molar ratio between 2 and 6, acetylation of α-D-glucose has been successfully carried out with a IL/saccharide ratio of only 0.5. The presence of a base catalyst, sodium acetate or pyridine, has no effect on the yield of penta-*O*-acetyl-D-glucopyranose, indicating that the solvent anion is acting as a base catalyst.[155] A reaction of similar importance is O-acylation of sulfated sugars because the products have proven useful in the synthesis of glycosaminoglycans.[23]

Ultrasound-mediated acetylation of primary and secondary alcohols and peracetylation of α-D-glucose and D-mannitol were successfully carried out in $[C_4BuIm][X]$, where $X^- = Br^-$, Cl^-, ClO_4^-, BF_4^-, and PF_6^-, respectively. Except for 1-hexanol and 1-octanol, all acteylations preceded at room temperature in short times, 5−30 min, to give excellent yields, 80−95%. The role of ultrasound in promoting O-acetylation is evident from the fact that lower yields, 50−91%, were obtained when the reaction was carried out under nonsonicated (silent) conditions.[28] O-Peracetylation of various saccharides, glucose, mannose, galactose, and phenyl 4-*O*-sulfo-β-D-glucopyranoside was achieved by using Ac_2O in [RMeIm][BzO], R = ethyl, 1-butyl, and 1-hexyl, respectively as solvents. The yields obtained were high but decreased as a function of increasing the length of R, being 100% and 68% for β-D-glucose in $[C_1MeIm][BzO]$ and $[C_6MeIm]$-[BzO], respectively. An indication that the benzoate counterion plays a catalytic role is the fact that no product was obtained for the O-peracetylation of β-D-glucose in $[C_4MeIm][BF_4]$ and $[C_4MeIm][PF_6]$, respectively. O-Perbenzoylation of glucose and mannose was also carried out in $[C_2MeIm][BzO]$; the yields were 53 to 55%, respectively.[23]

Cyclic 1,2-orthoesters of carbohydrates are important synthons that are employed, e.g., as protecting groups for C1-OH and C2-OH groups, as glycosyl donors, and in oligosaccharide synthesis. When treated with a Lewis acid, the *n*-pentenyl orthoesters are converted into highly stabilized ambident dioxolenium ions. Depending on the hardness of the nucleophile that reacts with these intermediates, the product may be a (kinetically controlled) glycoside or a (thermodynamically controlled) orthoester; the latter is used in the glycosidation reaction. The classical methods of preparing 1,2-orthoesters are by reacting peracteylated or perbenzoylated glycosyl bromides with quaternary ammonium salts or silver triflate. Under these conditions, the reactions are slow, requiring reflux in CH_2Cl_2 for one or more days. Alternatively, perbenzoylated glucopyranosyl bromide was reacted with alcohols and 2,6-lutidine in $[C_4MeIm][PF_6]$ for 8 h, Figure 10. The yield of the 1,2-orthoesters obtained varies from 52% (2-propanol) to 80% (4-penten-1-ol). Satisfactory yields were obtained for the reactions of galactose and mannose, 68−82% and 59−70%, respectively.[156]

Although strategies for the synthesis of oligosaccharides are well established, many are laborious and require purification of the reaction product after each step.[157,158] Recent advances include solid-phase synthesis,[159] the use of polymer-supported synthesis (polyethylene glycol, fluorinated supports),[160,161] and IL-supported synthesis. In the last technique, the substrate is

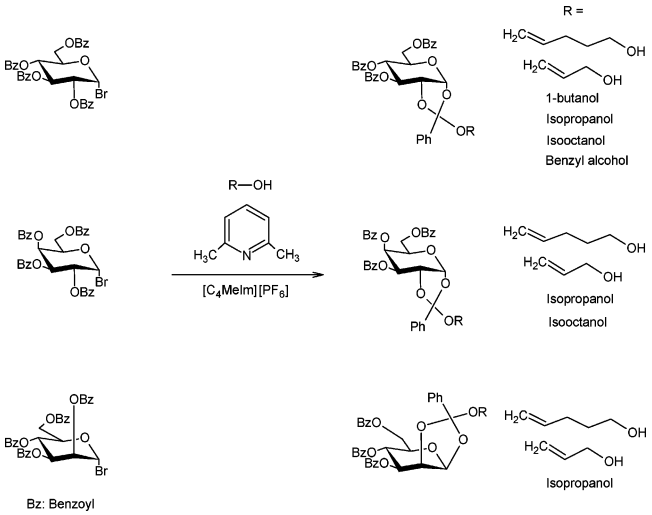


Figure 10. Scheme for the synthesis of cyclic 1,2-orthoesters. Adapted with permission from ref 157. Copyright 2005 Georg Thieme Verlag KG.

covalently attached to the IL; the resultant product undergoes the reaction desired; the product is detached from the IL and separated, as shown in the following reaction scheme in which phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-β-D-glucopyranoside is converted into the trimer phenyl-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside; Figure 11.[162]

Alkyl glycosides are important intermediates and products in the synthesis of biologically active natural compounds and surfactants.[163−165] A variety of reagents have been employed in the formation of the glycoside bond, including glycosyl halides, thioglycosides, and pentenyl glycosides. In a recent study, methyl 2,3,4,6-tetra-*O*-acetyl-α-D-thiomannopyranoside and methyl 2,3,4,6-tetra-*O*-acetyl-β-D-thiogalactopyranoside were employed as glycosyl donors to a series of acceptors, including 2-propanol, cyclohexanol, benzyl alcohol, and perbenzoylated methylglucopyranoses. The reaction was carried out in $[C_4MeIm][X]$, $X = BF_4^-$, PF_6^-, and $CH_3SO_4^-$, plus methyl trifluoromethane sulfonate as the donor activator, Figure 12. Only the first IL gave satisfactory results, with yields from 55% to 81% for alcohols and 39% to 76% for the disaccharides. In addition to its role as a solvent, the IL also acted as a drying agent, or "molecular sieve". Thus the yield was not affected by the presence of intentionally added water until the water/trifluoromethane sulfonate molar ratio exceeded 1:1. That the IL inhibits the hydrolysis of the activator has been demonstrated by comparing the reaction in the IL with that in $CDCl_3$ and DMSO. After 2 h of stirring at room temperature, in the presence of equivalent concentrations of water and catalyst, the extent of hydrolysis of the latter was found to be 55%, 9.9%, and 1.2%, for DMSO, $CDCl_3$, and $[C_4MeIm][BF_4]$, respectively.[166]

The glycosylation of several alcohols including cyclohexanol, cyclohexylmethanol, 2-propanol, and 1-octanol by perbenzylated glycosyl phosphite was investigated in classic organic solvents and in ILs containing Brønsted acids, Figure 13. Each IL, $[C_6MeIm][X]$, $X = BF_4^-$, $N(TFMS)_2^-$, and $TFMS^-$, respectively, and the corresponding protic acid catalyst employed had a common anion, e.g., $[C_6MeIm][BF_4]/(HBF_4)$, etc. The dependence of the yield of glycosylation of cyclohexylmethanol on the catalyst concentration was investigated; 1 mol % catalyst to IL gave the best result. Other alcohols gave similar good yields, ranging from 63% to 99%. Under comparable experimental conditions, glycosylation of cyclohexylmethanol gave a better yield in $[C_6MeIm][TFMS]$, 91%, than in organic solvents, diethyl ether, toluene, acetonitrile, or dichloromethane, 84%, 84%, 85%, and 89%, respectively. The reason for using an IL with a long-chain alkyl group (C_6) is to decrease its water miscibility, hence making product separation and IL recovery easier. The products were extracted with hexane/ethyl acetate, and the IL was recycled five times without loss of yield.[48]

Other compounds, e.g., O-perbenzylated glycosyl fluorides were also investigated as glycosyl donors. The ILs employed were $[C_6MeIm][X]$, $X = BF_4^-$, $N(TFMS)_2^-$, $TFMS^-$, and ClO_4^-, respectively, associated with Brønsted acid catalyst with the same anion (as the IL). The reaction was found to be stereoselective; its outcome depended on the IL/protic acid employed. For example, at 25 °C, the yields of glycosylation of cycohexylmethanol with glucopyranosyl fluoride (α/β = 1/20) were found to be 86% and 89%, with the α/β anomer ratios of 2.13/1 and 1/3.17 for the reactions carried out in $[C_6MeIm][N(TFMS)_2]/(CF_3SO_2)_2NH$ and $[C_6MeIm][TFMS]/(CF_3SO_3H)$, respectively. The corresponding figures for the reaction of the above-mentioned glycosyl donor with methyl 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranoside (in a mixture of two ILs, 0 °C, 24 h) and methyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside ($[C_6MeIm][TFMS]/(CF_3SO_3H)$, 25 °C, 1 h) were 99% and 54% and 13/87 and 42/58, respectively.

Subsequent studies on the glycosylation of the same alcohol in the presence of IL/protic acid with different anions, e.g., $[C_6MeIm][TFMS]/(CF_3SO_2)_2NH$ indicated that the IL not the Brønsted acid is responsible for the predominance of the β-anomer in the product. Effects of other experimental variables on the stereoselectivity of glycosylation of cyclohexylmethanol were investigated, namely, reaction temperature and the structure of the alkyl group of the IL. Because $[C_6MeIm][TFMS]$ is solid at 0 °C, its mixtures with $[C_6MeIm][N(TFMS)_2]$ were employed. At this temperature, the product α/β anomer ratio were 1.08/1, 1/2.33, and 1/3 for pure $[C_6MeIm][N(TFMS)_2]$ and for $[C_6MeIm][N(TFMS)_2]/[C_6MeIm][TFMS]$ ratios of 5/5 and 2/8, respectively. With regard to the molecular structure of the alkyl group, use of $[C_2OC_2H_4MeIm][TFMS]$ offered no stereoselectivity (α/β = 1.08/1), whereas $[CNC_3H_6MeIm][TFMS]$ gave 1/3.35. Thus the stereochemical outcome of carbohydrate functionalization reactions can be controlled by a judicious choice of the molecular structure of the IL.[167]

O-Perbenzoylated mannopyranosyl trichloroacetimidate, O-peracetylated glucopyranosyl trichloroacetimidate, and O-peracetylated galactopyranoside trichloroacetimidate in $[C_4MeIm][PF_6]$/trimethylsilyl trifluoromethane sulfonate catalyst were also employed as glycosyl donors to allyl alcohol, benzyl alcohol, and methyl-6-hydroxyhexanoate (Table 6).[169]

Under the same experimental conditions, a disaccharide was obtained by the reaction of O-peracetylated glucopyranosyl trichloroacetimidate with methyl ribofuranoside. Recovery of the IL included extraction of the products, washing the IL with water and toluene, filtration in Celite, and drying under reduced pressure. The IL recovered was used once in the preparation of allyl mannoside, with some loss of yield, from 93% to 82%, respectively.[168] Similar results were obtained for the reaction of 2-propanol with O-peracetylated and O-perbenzylated trichloroacetimidates in $[C_4MeIm][PF_6]$ or $[C_2MeIm][TFMS]$, by using trimethylsilyl trifluoromethane sulfonate as a promoter. Interestingly, the ILs were recycled by extracting the product with toluene or chloroform; a new reaction was carried out in the recycled IL, up to four times, without the addition of fresh acidic

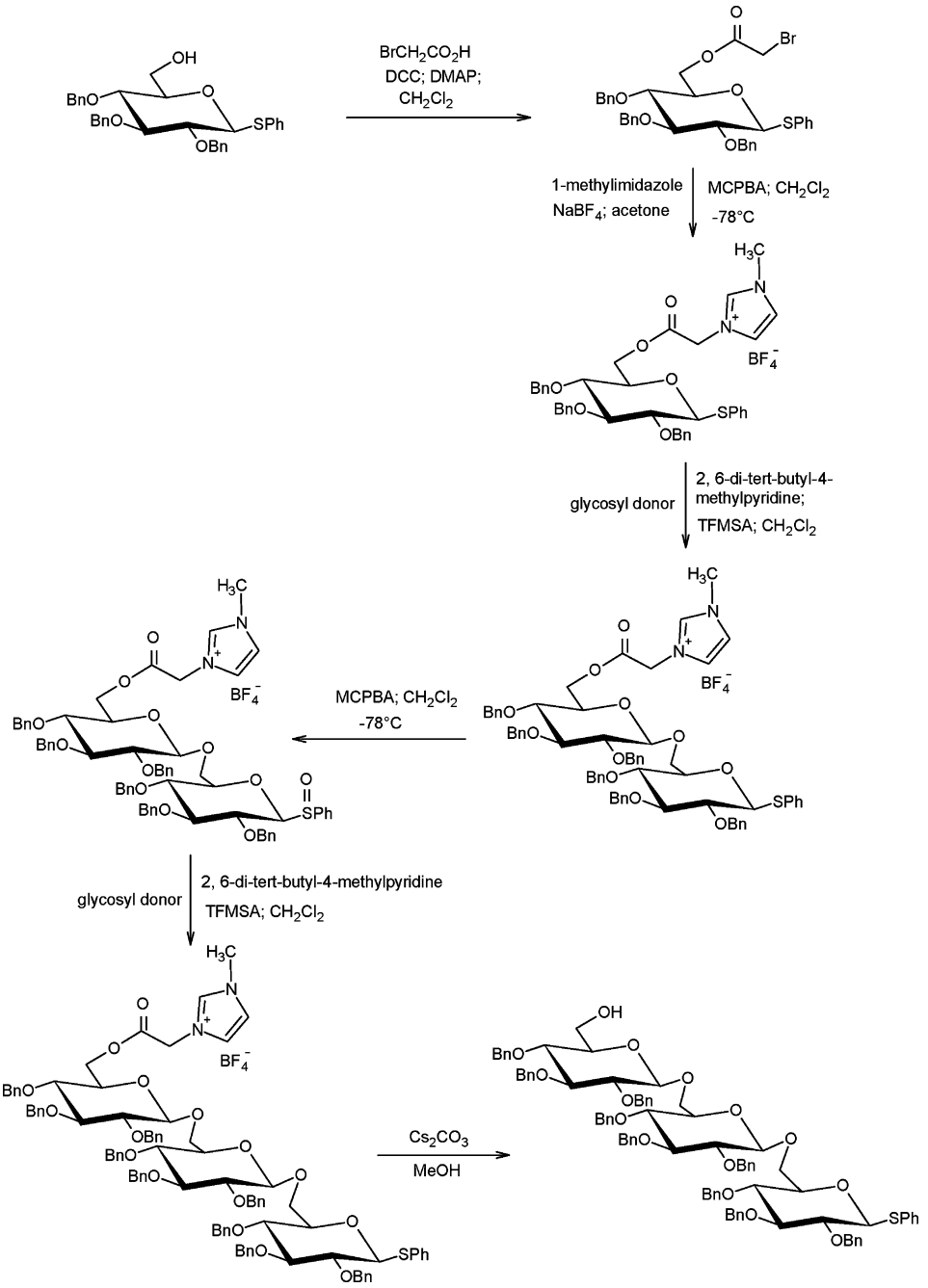


Figure 11. Representative IL-supported synthesis of oligosaccharides. Adapted with permission from ref 162. Copyright 2006 Georg Thieme Verlag KG.

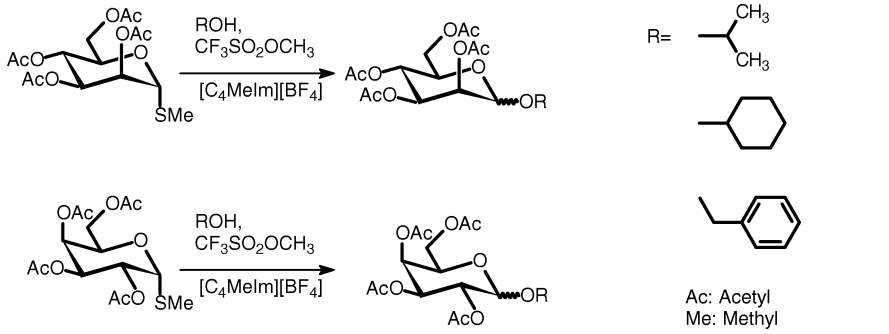


Figure 12. Glycosylation of mono-saccharide derivatives in ILs. Adapted with permission from ref 167. Copyright 2006 BioMed Central.

promoter or loss of yield. This result shows the capability of the IL to retain the catalytic properties of Lewis acids.[169]

Glycosides may be also obtained by enzyme-catalyzed transglycosylation, involving the formation of a covalent glycosyl−enzyme intermediate; this reacts with water (hydrolysis) or another nucleophile (Nu) to yield a glycosidic product. As expected, the ratio of transglycosylation/hydrolysis depended on rate constants, and concentrations of the receptors, (k_{Nu}/k_{water})

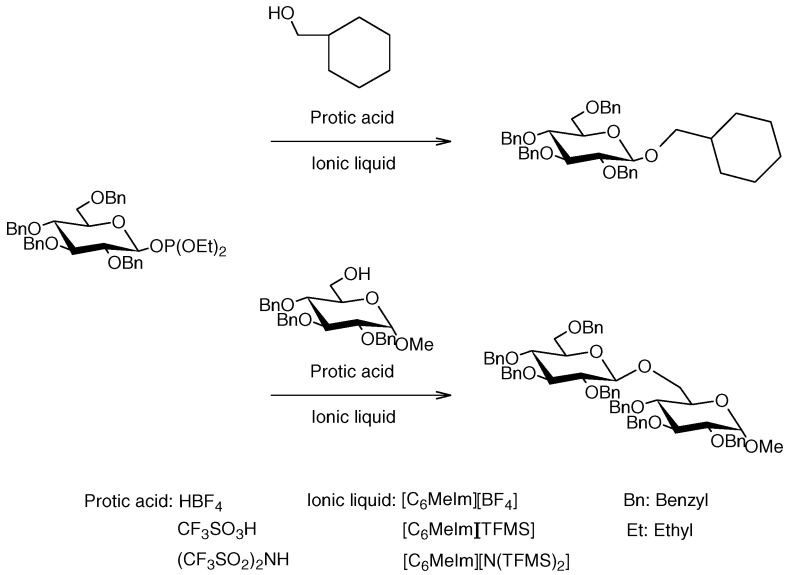


Figure 13. Brønsted acid-catalyzed glycosylation of cyclohexylmethanol by perbenzylated glycosyl phosphate in ILs. Adapted with permission from ref 48. Copyright 2003 Elsevier.

Table 6. Yields of Glycosides, Obtained by the Reaction in $[C_4MeIm][PF_6]$, in the Presence of Trimethylsilyl Trifluoromethane Sulfonate Catalyst[a]

	glycosyl acceptor[b] (trichloroacetimidate of)		
glycosyl donor	allylalcohol	benzylalcohol	methyl-6-hydroxy hexanoate
mannopyranose	93%	70%	77%
glucopyranose	62%; 1/6	50%; 1/8	52%; 1/3.2
galactopyranose	67%; 1/7.6	60%; 1/6.4	66%; 1/10.6

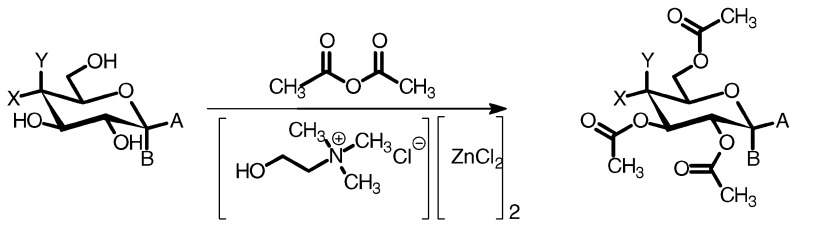
[a]Reprinted from with permission from ref 169. Copyright 2003 Georg Thieme Verlag KG. [b] In each column, the first and second figure refer to product yield (%) and product α/β anomer ratio, respectively.

and ([Nu]/[water]), respectively. Aqueous ILs can be used as a media for this reaction because they reduced the activity of water, provided that they do not deactivate the enzyme. The almost 2-fold increase in the yield of *N*-acetyllactosamine, induced by β-glycosidases from *E. coli* and *Bacillus cirulans*, in 25% $[C_1MeIm][MeSO_4]$ in water was attributed to the efficient suppression of the hydrolysis side reaction.[170] A similar reaction (synthesis of β-D-galactosides), catalyzed by the hyperthermostable enzyme β-glycosidase from the archaeon *Pyrococcus furiosus*, was studied at 80 °C in the absence and presence of ILs. Because the activity of the enzyme was much more inhibited by $[C_4MeIm][BF_4]$ than by $[C_1MeIm][MeSO_4]$, the latter IL was employed, along with lactose as the galactosyl donor and lactose, D-xylose, glycerol, 1,2-ethanediol, 1-propanol, 1-phenylethanol, benzyl alcohol, and 2-propyl-β-D-thio-galactopyranoside as acceptors. Except for one compound, benzyl alcohol, the transgalactosyl efficiency increased in the presence of 45% or 50% (by volume) of the IL. The effect of the IL was found to be strongly dependent on the molecular structure of the acceptor, suggesting that interactions of the latter with the solvent molecules, water, or IL, make a major contribution to the observed transgalactosylation efficiency of the enzyme.[171]

Some ILs have polynuclear anions that are particularly air- and moisture-sensitive, e.g., $Al_2Cl_7^-$ and $Al_3Cl_{10}^-$; other complex anions are water-insensitive, e.g., $ZnCl_3^-$ and $Zn_2Cl_5^-$, but are Lewis acids of sufficient strength to catalyze the Fisher indole synthesis and cationic polymerizations.[172] They are expected to be sufficiently acidic to catalyze the esterification of carbohydrates. Several methyl glucopyranosides were found to be soluble (at 90 °C) in the IL $[HOCH_2CH_2N(Me)_3][Zn_2Cl_5]$, prepared from a 1:2 molar ratio mixture of choline chloride and $ZnCl_2$. Interestingly, the sugars were O-acetylated by acetic anhydrides in high yields, 78−81%, although, in principle, acetylation of choline (present in ca. 20:1 molar excess with respect to the substrate) is a potential side reaction; see Figure 14. The yield was not appreciably decreased, 66%, when the reaction was carried out in the acetylcholine analogue of the above-mentioned IL, i.e., $[MeCO_2CH_2CH_2N(Me)_3][Zn_2Cl_5]$. Similar high yields, 88% and 68%, were also observed for acylation by propionic and 2-methylpropionic anhydrides, respectively. Other interesting results include: specific acteylation of the sugar at the C4-OH group, 96%, when the acetic anhydride/sugar molar ratio was reduced from 5:1 to 1:1; very small yields, 5%, when a structurally similar IL, albeit with no Lewis acidity, $[HOCH_2CH_2N(Me)_3][urea]_2$, was employed. IL recovery was possible by extraction of reaction products by ethyl acetate, followed by removal of volatiles under reduced pressure. The IL recovered was employed four times in the acetylation of methyl α-D-glucopyranoside without loss in product yield.

Acetylation of microcrystalline cellulose (DP ca. 200) in the same IL has also been studied, with an emphasis on obtaining products of low DS. Dissolution of the biopolymer (to obtain 3 wt %) has been achieved either by microwave heating or by heating for 3 h at 90 °C. A SEM micrograph of the cellulose regenerated (by precipitation in water) showed noticeable loss of structure, an important polymer morphology modification required for its efficient functionalization. The product DS (after removal of some triacetate) was between 0.42 and 1 for 1:1 and 20:1 Ac_2O/AGU molar ratios, respectively.[173]

One commonly employed strategy for the synthesis of saccharides specifically functionalized at positions 2 and 3 of the hexapyranose ring is their transformation into the corresponding 4,6-O-bezylidenated derivative. Glucose, several methyl glycosides, and maltose were reacted with benzaldehyde dimetyl acetal, in the presence of toluene sulfonic acid catalyst in ILs, namely, $[C_2MeIm][BF_4]$, $[C_4MeIm][X]$, $X = BF_4^-$, $MeSO_4^-$, and phosphate, respectively. The yields were highest (61% to 99%) for $[C_4MeIm][BF_4]$ and lowest (<5%) for $[C_4MeIm][MeSO_4]$, showing the important effect of the anion of IL. Recycling of the IL was examined; the products were



1: X= OH, Y=H, A= H, B=OMe
2: X=H, Y=OH, A=H, B=OMe
3: X=H, Y=OH, A=OMe, B=H
4: X=OH, Y=H, A=H, B=OH

1a: X= OAc, Y=H, A= H, B=OMe
2a: X=H, Y=OAc, A=H, B=OMe
3a: X=H, Y=OAc, A=OMe, B=H
4a: X=OAc, Y=H, A, B=H, OAc

Ac: Acetyl
Me: Methyl

Figure 14. Per-O-acetylation of sugars in acidic IL. Adapted with permission from ref 174. Copyright 2005 The Royal Society of Chemistry.

extracted with toluene, the IL was washed with water and passed through a pad of Celite, and the volatiles removed under reduced pressure. The benzylidenation reaction was repeated five times without loss in efficiency.[174]

Using acid catalysis, ion-exchange resin, or 4-toluene sulfonic acid, it was possible to obtain 5-hydroxyfurfural and 2,5-disusbtituted furanic derivatives by dehydration of fructose. This reaction was studied in DMSO, ILs [C_4MeIm][BF_4], [C_4MeIm]-[PF_6], and [C_4MeIm][BF_4] plus DMSO (to increase solubility of fructose in the IL), respectively. In the absence of catalyst, only traces of 5-hydroxyfurfural were obtaind in DMSO, whereas 36% was obtained in a mixture of [C_4MeIm][BF_4] plus DMSO after 32 h, demonstrating the catalytic effect of the IL. This yield increased to 52% and 75% in the presence of acid catalyst in pure [C_4MeIm][BF_4], and in its mixture with DMSO, respectively. Higher yield, 80%, was obtained for the reaction in more hydrophobic IL [C_4MeIm][PF_6].[175]

The fact that ILs solubilize high-M_r carbohydrates to produce clear solutions, akin to those in obtained in LiCl/DMAc and TBAF/DMSO, has led to intensive research on biopolymer functionalization, in particular, acylation in these media. As discussed above, hydrogen bonding between the anion of the IL and the OH groups of the AGU is crucial to solubilization, this being the reason that most ILs employed have a chloride counterion. Thus 2.9 and 4 wt % solutions of cellulose (DP = 650) were acetylated by acetic anhydride in [AllylMeIm][Cl], at 80 °C and a 5:1 Ac_2O/AGU molar ratio. The DS of the product increased as a function of increasing reaction time 0.94, 2.49, and 2.74 for 0.25, 8, and 23 h, respectively. For 2.9 wt % cellulose solution in the same solvent, the DS increased from 1.99 to 2.30 for Ac_2O/AGU ratios of 3:1 to 5:1, respectively. With regard to the properties of the products, the following was reported: All samples (DS 0.94 to 2.74) were soluble in DMSO; samples with DS > 1.86 were soluble in acetone, those with DS ≥ 2.30 were soluble in chloroform; the order of reactivity is C6-OH > C3-OH > C2-OH, similar to that observed in acteylation in LiCl/DMAc.[131] The reaction in recycled IL (obtained by removal of volatiles under reduced pressure) gave products of similar DS.[67]

The reaction of Cel from sugarcane bagasse with succinic anhydride in a mixture of [C_4MeIm][Cl] and DMSO (4:1) was studied at different temperatures, 85−100 °C, reaction times, 5−120 min, and [succinic anhydride]/AGU of 1:1 to 12: 1, respectively; the DS obtained were from 0.037 to 0.53.[132] The reason for this inefficient esterification (DS = 0.26), even under favorable reaction conditions, [succinic anhydride]/AGU = 4:1, reaction temperature = 100 °C, reaction time = 2 h is, however, unclear.

Because the temperatures required to dissolve and functionalize cellulose are relatively high, vide supra, ionic compounds whose mp's are higher than room temperature can also be employed, e.g., [C_4MeIm][Cl], [C_4MePy][Cl] and the surfactant BDTACl, mp's 73, 95, and 52 °C, respectively. The celluloses employed were microcrystalline cellulose, spruce sulfite pulp, and cotton linters, DPs, 307, 544, and 814, respectively. Cellulose dissolution was carried out at 10 °C above the mp of the IL. The derivatization reactions included acetylation by acetyl chloride or Ac_2O/pyridine at 80 °C for 2 h and carboxymethylation by NaOH powder/$ClCH_2CO_2Na$; the latter reaction was carried out in a 1:1.1 mixture (by weight) of IL and DMSO. In [C_4MeIm][Cl], depending on the molar ratio Ac_2O/AGU/pyridine, 3/1/0 to 10/1/2.5, cellulose acetates with DS ranging from 2.56 to 3.0 were obtained. Biopolymer reaction with acetyl chloride gave products with DS of ca. 3, for an acetylating agent/AGU ratio of 3 to 10/1. All products were soluble in DMSO; the ones with DS ≥ 2.85 were soluble in chloroform. Acetylation in the other two ILs was unsuccessful. Carboxymethyl cellulose (CMC) with DS = 0.49 was obtained by using a chloroacetate/AGU molar ratio of 1:1; the DS was not altered when the latter ratio was increased to 3:1.[105] The preparation of several cellulose ethers in ILs was claimed; only one example, CMC, was given.[176]

The success in dissolving bacterial cellulose of very high DP (6493) in [C_4MeIm][Cl] prompted work on its acetylation by Ac_2O and carbanilation by phenyl isocyanate; both reactions were carried out for 2 h (after cellulose dissolution) at 80 °C. The acetates were found to be soluble in DMSO; the order of reactivity of the AGU OH groups is C6-OH > C3-OH > C2-OH. All carbanilates, except that with DS = 0.29, were found to be soluble in DMSO; some were soluble in DMF and THF. The effect of the molecular structure of IL on acylation and carbanilation of cellulose was studied. The ILs employed included [C_2MeIm][Cl], [C_4MeIm][Cl], [C_4-2,3-Me_2Im][Cl], and [Allyl-2,3-Me_2Im][Br]. Acetylation gave products whose DS depended on the molar ratio of acetylating agent/AGU. For example, acetylation with Ac_2O in [C_4MeIm][Cl] gave DS of 1.87−3.0 for 3:1 to 10:1 ratios, respectively. Under comparable experimental conditions, the following dependence of DS, hence reactivity, on the IL was observed: [C_4MeIm][Cl] > [Allyl-2,3-Me_2Im][Br] > [C_4-2,3-Me_2Im][Cl] > [C_2MeIm][Cl].[68]

The reaction with lauroyl chloride in [C_4MeIm][Cl] gave DS of 0.34, 1.54, and 1.44 for acyl chloride/AGU molar ratios of 1:1, 3:1, and 5:1, respectively. Fully functionalized samples, DS = 3, were unattainable, probably because the system turns heterogeneous. The effect of the structure of the IL on this reaction, at an acyl chloride/AGU ratio of 3:1, showed the

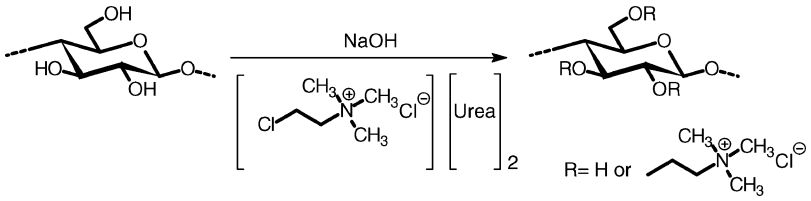


Figure 15. Cationic derivatization of cellulose in choline−urea eutectic mixture. Adapted with permission from ref 177. Copyright 2006 The Royal Society of Chemistry.

following order: [C_4MeIm][Cl] > [C_2MeIm][Cl] >[C_4-2,3-Me_2Im][Cl] > [Allyl-2,3-dimethylIm][Br].

The carbanilation reaction occurred smoothly in [C_4MeIm][Cl], without base catalyst (e.g., pyridine); the product DS ranged from 0.6 to 3.0, for phenyl isocyanate/AGU of 1:1 to 10:1, respectively; most samples were soluble in DMSO, DMF, and THF. The presence of adventitious water in the carbanilation reaction mixture led to the formation of aniline (detected by ^{13}C NMR); the latter may be removed from the product by washing, and the IL can be recovered.[106]

Cationic functionalization of cellulose, Figure 15, is important because the products can be employed, e.g., as filters for the removal of anionic dyes present in textile industry effluents. The IL employed to dissolve cellulose was a eutectic mixture of choline chloride and urea, molar ratio of 1:2, respectively. The reaction was carried out by treating cellulose with NaOH in this medium; the latter is acting as both a solvent and a reactant. The best conditions involved the reaction of the biopolymer for 15 h at 90 °C. One-half of the nitrogen present in the product is chemically bound as a quaternary ammonium group. The product formed was found to be efficient in removing a typical water-soluble dye, orange II.[177]

Successful acylation (by Ac_2O and propionic anhydride) of starch and benzoylation (by benzoyl chloride) of zein protein were carried out in [C_4MeIm][Cl]. In the former reaction, 10 wt % starch in the IL was obtained by heating for 40 min at 95 °C. Treatment of the solution resulted with different Ac_2O/pyridine molar ratios gave products whose DS ranged from 0.38 to 2.66. Zein solution in the same solvent reacted with benzoyl chloride to give the benzoylated product. Other ILs were also investigated as low-cost alternative solvents for starch. These included the acidic IL [MeIm][BF_4], eutectic mixtures of urea with $CaCl_2$ and with choline chloride, and choline chloride with citric acid, with $ZnCl_2$, or with oxalic acid, respectively. Starch gelation was observed for the first solvent system, viscous solutions were obtained for the next three solvent systems, and a dark solution was obtained for the oxalic acid system, indicating biopolymer degradation. Zein was not soluble in any of these solvents.[117]

5. Conclusions

The favorable characteristics of ILs make them a promising substitutes for classic solvents for carrying out reactions, according the principles of green chemistry, in several fields, including carbohydrate chemistry. From the application point of view, the extremely low vapor pressure, high polarity, and high chemical and thermal stabilities of ILs are very important properties because the reactions can be safely carried out at high temperatures. Additionally, all volatile substances present (water, residual reagents, and, where applicable, products) can be removed by extraction with an appropriate solvent or distillation under reduced pressure; this renders recovery and recycling of the IL feasible. The most important single factor is, perhaps, molecular structure versatility. The molecular structures, hence properties of ILs, can be "tailored" according to need by a judicious choice of the cation (e.g., aliphatic or heterocyclic), the length and nature of the alkyl chains attached (saturated or unsaturated), and the anion (simple or complex). Their power to dissolve large concentrations of saccharides and carbohydrate biopolymers has resulted in an explosive growth in research where they are employed as solvents, sometimes with a catalytic effect. Examples of these studies include the synthesis of functionalized mono- and disaccharides and of esters, carbanilates, and ethers of celIulose and starch. Our hope is that this account serves as a "road map" for further research in the field of applications of ILs in carbohydrates and biopolymers in general.

Abbreviations and Acronyms

The many structural possibilities for ILs may cause some difficulties to the carbohydrate chemist and to readers in general who are not familiar with the subject. Therefore, we have opted for employing longer, but self-explaining acronyms. We use C_1, C_2, C_3, C_4, etc. to refer to the number of carbon atoms of a saturated alkyl group attached to the heterocyclic ring. Thus C_1OCH_2-, C_2OCH_2-, $C_1OC_2H_4$-, and $C_2OC_2H_4$- refer to the methoxymethyl, ethoxymethyl, methoxyethyl, and ethoxyethyl group, respectively. Unless specified otherwise, the alkyl groups are *n*-alkyl. For clarity, the cation and anion are placed inside brackets, even when the latter is a simple ion, e.g., Cl^-. Therefore, [C_1MeIm][Cl], [C_4MeIm][BF_4], [C_1OCH_2MeIm]-[$N(CN)_2$], [C_4-2,3-Me_2Im][Cl], and [C_4Py][PF_6] refer to 1,3-dimethylimidazolium chloride, 1-(1-butyl)-3-methylimidazolium tetrafluoroborate, 1-methoxymethyl-3-methylimidazolium dicyanamide, 1-(1-butyl)-2,3-dimethylimidazolium chloride, and *N*-(1-butyl)pyridinium hexaflourophosphate, respectively.

AcO, acetate
Ac_2O, acetic anhydride
AGU, anhydroglucose unit
BDTACl, benzyldimethyltetradecylammonium chloride
BuIm, *n*-butylimidazolium
bp, boiling point
Bn, benzyl
Bz, benzoyl
BzO, benzoate
CD, cyclodextrin
Cel, cellulose
CMC, carboxymethyl cellulose
DCC, dicylohexylcarbodiimide
DMAc, *N*,*N*-dimethylacetamide
DMAP, 4-(*N*,*N*-dimethylamino)pyridine
DMF, *N*,*N*-dimethylformamide
DMSO, dimethylsulfoxide
DP, degree of polymerization of the native biopolymer
DS, degree of substitution of the fuctionalized biopolymer
DSC, differential scanning calorimetry.
EtIm, ethylimidazolium
E_T(30), empirical solvent polarity parameter; corresponds to the transition energy of the charge-transfer within the probe, in kcal/mol
FmO, formate

$HN(TFMS)_2$, bis(trifluoromethanesulfonyl)imide $(F_3CSO_2)_2NH$

HTFMS, trifluoromethane sulfonic acid; F_3CSO_3H

Ic, index of crystallinity of the biopolymer

IL, ionic liquid; In this review, IL refers to ionic compounds that are liquid at room temperature (referred to, sometimes, as RTILs) and those that melt below 100 °C.

MCPBA, 3-chloroperbenzoic acid

Me, methyl.

MeIm, 1-methylimidazolium.

MePM, (4-[2-(1-methylpyridinium-4-yl)ethenyl] phenolate

M_r, relative molecular mass of a simple compound or average molecular mass for a biopolymer

mp, melting point

$N(CN)_2$, dicyanamide anion

NIR, near-infrared spectroscopy

$N(MS)_2$, bis(methanesulfonyl)imide anion, $(H_3CSO_2)_2N^-$

$N(TFMS)_2$, bis(trifluoromethanesulfonyl)imide anion, $(F_3CSO_2)_2N^-$

Nu, nucleophile, other than water, e.g., alcohol and sugar

PAN, 1-(2-pyridylazo)-2-naphthol

Py, pyridinium.

SEC, size exclusion chromatography

SEM, scanning electron microscopy

RB, (2,6 dichloro-4-(2,4,6-triphenylpyridinium-1-yl)phemolate

RTIL, room-temperature ionic liquids

TBAA, tetra-*n*-butylammonium acetate

TBABr, tetra-*n*-butylammonium bromide

TBAF, tetra-*n*-butylammonium fluoride, xH_2O, $x \geq 3$

TEM, transmission electron microscopy

TFA, trifluoroacetate.

TFMS, trifluoromethane sulfonate; $F_3CSO_3^-$

TFMSA, trifluoromethylsulfonic acid anhydride

THF, tetrahydrofuran.

Tos, tosylate.

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Supporting Information Available. Properties and applications of ILs. This material is available free of charge via the Internet at http://pubs.acs.org.

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