

# Ionic Liquids in Carbohydrate Chemistry – Current Trends and Future Directions

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**Abstract:** Room Temperature Ionic Liquids (RTILs) have recently been introduced as new solvents in the chemical and biotechnological arenas. Carbohydrates are important natural products that play important biological and commercial roles as foods, drugs and chemical feedstocks. They have two properties that complicate their use a low solubility in most solvents and complex, highly chiral structures. We are currently witnessing a rapid increase in novel applications for newly discovered RTILs. This account reviews the application of RTILs in carbohydrate chemistry and biochemistry as a mono / biphasic solvent, a solvent / catalyst and a product retrieval media.

**Keywords:** Carbohydrates, room temperature ionic liquids, green chemistry, catalysis.

## INTRODUCTION

### Ionic Liquids

Ionic liquids (ILs) also referred to “neoteric solvents” and “designer solvents” were first introduced in chemical applications in the middle and late 1990’s. Over the past decade there has been an exponential increase in the number of publications describing the synthesis and application of ionic liquids (Fig. 1). ILs consist entirely of ions. Sodium chloride, common table salt is the prototypical IL. When heated beyond its melting point (810°C), sodium chloride becomes an IL consisting of Na<sup>+</sup> and Cl<sup>-</sup> ions with a net system charge of zero. Some salts that are liquid at room temperature are referred to as room temperature ionic liquids (RTILs). The increasing importance of RTILs is associated with their desirable properties. These properties include almost no vapor pressure, resulting in their low volatility, non-flammability, odorlessness, thermal stability and recyclability. Other important properties of RTILs including their density, viscosity, melting point, polarity, refractive index can be tuned by modifying the structures of their cation and anion components [1]. The cation (usually organic) (Fig. 2) and anion (usually inorganic) (Fig. 3) present in the ILs [2] are designed so that the resulting salts cannot pack compactly. As a result, ILs do not easily crystallize and remain liquid through a wide range of temperatures. ILs are not often involved in the processes of solvolysis and solvation, usually associated with aqueous and organic solvents. ILs can also be designed to solubilize either polar or non-polar molecules. Hence, ILs are attracting attention as potential replacements for the conventional volatile, environmentally harmful, conventional molecular solvents used in catalytic and organic reactions [3,4]. As salts, ILs conduct and, thus, are of increasing interest in electrochemical applications [5-7].

There are a number of desirable properties that make RTILs of particular interest and importance.

### *The Ability to Design Specific Physical and Chemical Properties*

Arguably the most useful property of RTILs is the ability to ‘design’ or ‘tune’ a set of specific desirable physical and chemical properties through the simple adjustment of the side chains of the cation (R groups in Fig. 2) and/or the appropriate selection of the anion (Fig. 3) [8]. The range of physical and chemical properties available with RTILs is considerably wider than those of commonly used organic solvents. Thus, an appropriate “Task Specific Ionic Liquid (TSIL)” can be designed with the precise physical and chemical properties desired by the end user.

### *Low or Near Zero Vapor Pressure*

RTILs are salts, and hence, have a very low or a nearly zero vapor pressure. Because of this property very little RTIL is lost into the environment through evaporation. Even when RTILs are used at elevated temperatures as solvents and /or catalysts little RTILs is lost.

### *Low Melting Point*

Most of the RTILs have a very low melting point, enabling them to be liquids at or below room temperature. This low melting point can be attributed to the asymmetrical nature of the ions making up these salts. This asymmetry prevents the compact packing of the ions. The RTIL, 1-ethyl, 3-methyl imidazolium benzoate for example has a melting point of -61°C [9].

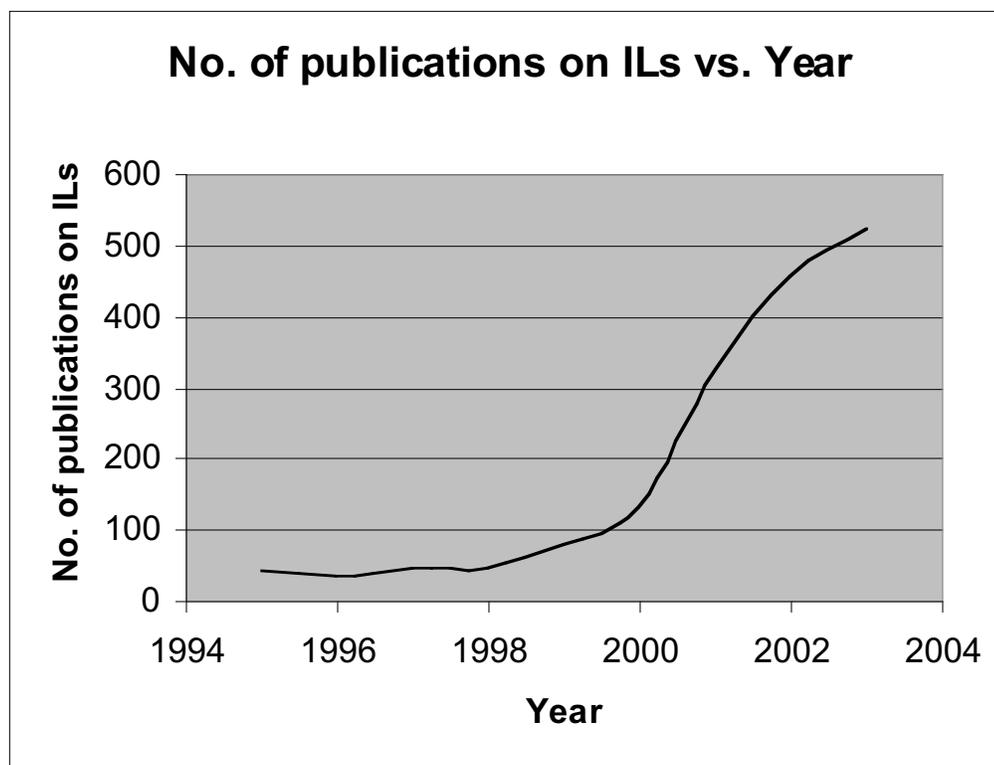
### *Water Miscibility*

Some RTILs are water miscible and some are not. This property can be switched ON and OFF according to the process requirements by modifying the cation structure of a RTIL or by changing its anion. The anion chosen plays a prominent role in RTIL water miscibility. [PF<sub>6</sub>]<sup>-</sup>, [(CF<sub>3</sub>SO<sub>2</sub>)<sub>2</sub>N]<sup>-</sup> for example are generally water immiscible anions, and [CH<sub>3</sub>COO]<sup>-</sup>, [CF<sub>3</sub>COO]<sup>-</sup>, [NO<sub>3</sub>]<sup>-</sup>, Br<sup>-</sup>, I<sup>-</sup>, and Cl<sup>-</sup> are generally water miscible anions.

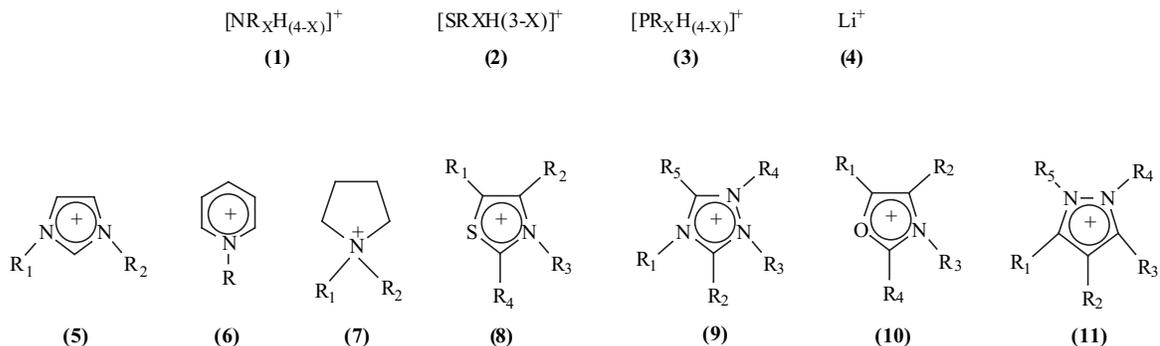
### *Recoverability and Reusability*

Since the miscibility property of RTILs differs significantly based on RTIL structure the products of many

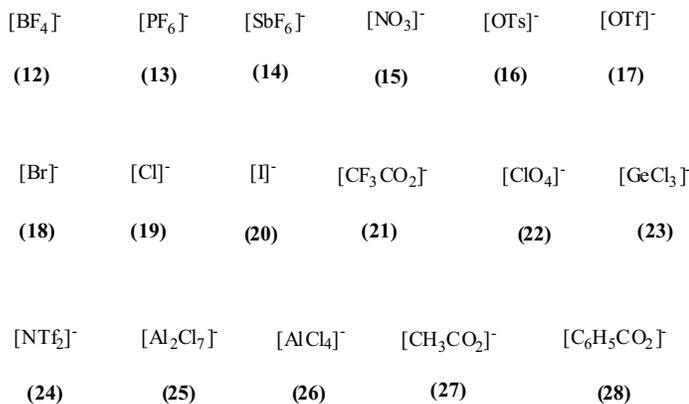
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**Fig. (1).** Increase in the number of publications relating to ILs.



**Fig. (2).** Examples of cations currently used in the preparation of RTILs. (1) ammonium, (2) sulfonium, (3) phosphonium, (4) lithium, (5) imidazolium, (6) pyridinium, (7) picolinium, pyrrolidinium, (8) thiazolium, (9) triazolium, (10) oxazolium (11) pyrazolium.



**Fig. (3).** Examples of anions currently used in the preparation of RTILs. (12) tetrafluoroborate, (13) hexafluorophosphate, (14) hexafluoro antimonate, (15) nitrate, (16) tosylate, (17) triflate, (18) bromide, (19) chloride, (20) iodide, (21) trifluoroacetate (22) perchlorate (23) germanium chloride, (24) bis(trifluoromethylsulfonyl) imide, (25) aluminium chloride, (26) aluminium tetrachloride, (27) acetate, (28) benzoate

reactions can often be recovered from RTILs by means of extraction. Supercritical CO<sub>2</sub>, water or organic solvents can be used to recover products and enable the recycling of RTIL for subsequent reactions.

### **Large Liquidus Range and Thermal Stability**

RTILs have a very large liquidus range, and they are very stable with respect to elevated temperatures. For example, 1-ethyl, 3-methyl imidazolium bis(trifluoromethylsulfonyl) imide has a liquid range of 471 degrees, with a melting point -15°C and a decomposition temperature a 455°C [10]. This property makes RTILs useful for reactions that need to be maintained at either low-high or both low and high temperatures.

### **Other Useful Properties**

In addition to the properties listed, RTILs have high air and water stability, high ionic conductivity and a large electrochemical window.

### **Uses of ILs in Biotechnology**

The use of RTILs is promising in the area of biotechnology, particularly in chemistry involving biocatalytic processes. For example, in the reaction converting 1,3-dicyanobenzene to 3-cyanobenzamide and 3-cyanobenzoic acid catalyzed by whole cells of *Rhodococcus* R312, the biphasic 1-butyl, 3-methyl imidazolium hexafluorophosphate /water medium decreases the substrate and the product inhibition observed in water by acting as a reservoir for the substrate and product [11]. In another example, an isolated enzyme has been used to catalyze reactions in ionic liquid medium [12]. A variety of other examples highlighting the application of RTILs in biocatalytic processes are presented in recent reviews [13,14].

## **Carbohydrates**

Carbohydrates are organic compounds containing carbon, hydrogen and oxygen in a typical ratio 1:2:1. Carbohydrates are highly oxidized organic molecules containing a large number of hydroxyl groups. Because of these hydroxyl groups, carbohydrates can interact with the aqueous environment, by participating in hydrogen bonding. The simplest carbohydrates contain either an aldehyde moiety (an aldose) or a ketone moiety (a ketose). Carbohydrates can also contain amino, carboxyl phospho and sulfo groups imparting a net charge and further enhancing their hydrophilic nature.

### **Biological Significance**

A clear understanding of the fundamental roles of the carbohydrates in biology is the focus of the newly constituted field of glycobiology and requires indepth knowledge of the structure and properties of biologically significant carbohydrates. Carbohydrates were first viewed simply as the reservoirs for the storage of the excess cellular energy in various forms such as glycogen in animals. Specialized sugars, such as glucose in the blood, galactose and lactose in milk, sucrose in plant sap carry this stored energy within multicellular organisms. The second major role of carbohydrates is to maintain the structural integrity of most living organisms. Unbranched polysaccharides contain highly ordered secondary structures that are essential

structural components in plant (e.g., cellulose and pectins) and animal (e.g., glycosaminoglycan chains of proteoglycans molecules) tissues [15]. Cellulose has the unique distinction of being the most abundant polymer on the planet and also one of the most highly crystalline least soluble and hence most stable natural products. There is a clear need for new solvents that can dissolve such crystalline polysaccharides. A third and most recently discovered biological role for carbohydrates results from their preferential localization in the extracellular domain and their high level of chirality. These properties make carbohydrates ideal binding partners for proteins involved in intercellular communication. Glycosylation of carrier molecules, such as proteins and lipids, afford glycoproteins, proteoglycans and glycolipids that serve to display carbohydrates in their extracellular environment. These glycosylation modifications can result in very important biological activities. Erythropoietin (EPO), for example, is a glycoprotein that is a principal regulator of red blood cell formation. Glycosylation itself, rather than the specific type of glycosylation, can sometimes be sufficient for activity as in the case of EPO [16]. In contrast, in the heparan sulfate proteoglycan, a specific and unique sequence is required to maintain the fluidity of blood within the vascular lumen [17]. The large number of essential, but involuntary functions taking place in the body, which are regulated by carbohydrates, has given rise to the field of glycobiology, the study of biological activities mediated by carbohydrates [18,19]. Glycoproteins, proteoglycans and glycolipids are only soluble in a limited number of solvents. The metal salts of the sulfated sugars found in proteoglycans, for example, are insoluble in all of the organic solvents except water and formamide [20]. Even low molecular weight, neutral carbohydrates are soluble in a relatively small number of polar and hydrogen bonding solvents, such as, pyridine, dimethylsulfoxide, dimethylformamide and water. This property of carbohydrates prevents their use in various applications and complicates their structural determination, making it difficult to elucidate the structure-activity relationships (SAR) of carbohydrates. Thus, new solvents for these glycoconjugates are needed.

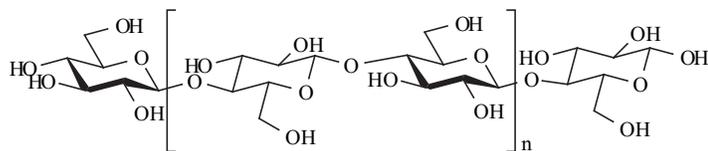
## **Carbohydrates and ILs**

RTILs are solvents capable of dissolving numerous polar and non-polar compounds, offering promise as solvents for the dissolution of carbohydrates. These solvents also offer a unique opportunity to study carbohydrate structure and properties using a variety of modern spectroscopic and analytical methods. Moreover RTILs are solvents in which carbohydrates can be chemically and enzymatically converted into useful new chemicals and materials with many potential applications including textiles, building materials and paper. Over the past few years, carbohydrate chemists have witnessed the use of RTILs in variety of important reactions. This report reviews the current applications and speculates on the potential applications of RTILs in the fields of glycochemistry, glycobiology and glycototechnology.

### **Treatment of Carbohydrates in RTILs**

#### **Solubility Studies**

Spear and coworkers [21] reported the solubility data of various mono and disaccharides such as xylose, fructose,

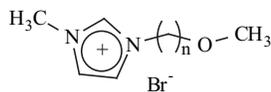


**Fig. (4).** A typical cellulose (**29**) polymer chain with  $n = 400 - 1000$ .

glucose and sucrose in an RTIL, 1-hexyl, 3-methyl imidazolium chloride. Their solubility ranged from 0.005 g/mL for sucrose to 0.062 g/mL for fructose. Difference in the carbohydrate solubility was attributed to differences in the carbohydrate molecular weight. Interestingly, the same sugars were insoluble in an RTIL having same imidazolium cation but different anion hexafluorophosphate. These data serve as examples of the tunable properties of RTILs. Spear and coworkers [22] have also reported the dissolution of the crystalline polysaccharide – cellulose (**29**) in ionic liquids (Fig. 4). They employed conventional heating, microwave radiation and sonication as tools in assisting its dissolution in various RTILs. A high level of cellulose solubility (25 wt %) was demonstrated in 1-butyl, 3-methyl imidazolium chloride by using microwave irradiation. Other ionic liquids gave 5 to 10% solutions of cellulose.

Dissolution of cellulose in RTILs can be attributed to their ability to break the extensive network of hydrogen bonds present in cellulose. The presence of high chloride concentration in the RTIL enhances its ability to disrupt hydrogen bonding. Furthermore, the longer the alkyl chains of the cation component of the IL, the lower its efficiency in cellulose dissolution. The presence of residual water in IL also reduces the solubility of cellulose, probably by forming competing hydrogen bonds to the cellulose microfibrils. This study clearly demonstrates RTILs as unique nonderivatizing solvents for crystalline polysaccharides such as cellulose.

Ether-based ionic liquids (**30**, **31**) (Fig. 5) also dissolve carbohydrates including,  $\beta$ -D-glucose,  $\alpha$ -cyclodextrin, amylose, agarose, and a glycoprotein, glucose oxidase [23]. Dissolution requires heating and the solubility varied from 10 mg/mL (agarose in RTIL,  $n = 1$ ) to 450 mg/mL ( $\beta$ -D-glucose in RTIL,  $n = 1$  or 2)



**Fig. (5).** Ether-based RTILs,  $n = 1$  (**30**), 2 (**31**).

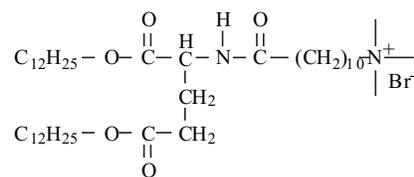
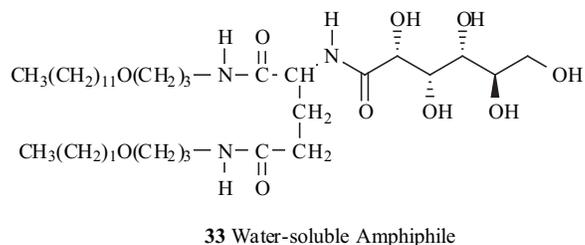
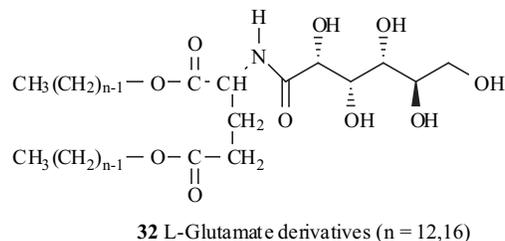
This study demonstrates a very high solubility of amylose, a coiled polysaccharide composed of  $\alpha$ -1,4-glucosyl units in these ionic liquids. It is important to note that amylose is only slightly soluble in water (< 0.5 mg/mL). The glycoprotein, glucose oxidase, is also soluble in these ionic liquids at a concentration of 1 mg/mL. Proteins (without glycosylation) including cytochrome c, myoglobin, hemoglobin and catalase, were insoluble. The reasons for these solubility differences appear to be due to the presence and extent of glycosylation (the more the glycosylation, the greater the solubility). The ability of ether-based RTILs (Fig. 5) to dissolve carbohydrates has resulted in these RTILs being called, “Sugar-philic” ionic

liquids [23]. In contrast to the report of Spear and coworkers [22], the presence of water had no significant effects on the dissolution of these saccharides in RTILs.

The solubility of two glycolipids (Fig. 6) in ether based RTILs (Fig. 5) has been reported [23]. Glycolipid **32** (Fig. 6) is insoluble in water even at low concentrations (1 mM). Glycolipid **33**, a water soluble amphiphile, with three amide bonds and flexible ether linkages, improves the stability and molecular orientation of bilayers. Glycolipids **32** and **33** dissolve in the ether-based ionic liquids on heating and these solutions are stable for up to three months. Cationic amphiphile **34**, related to these glycolipids but not containing glycan, was completely insoluble in ether-based RTILs. This observation demonstrates the favorable solvating interactions between carbohydrates and ether-based ionic liquids.

#### Gelation

Gelation was observed when the agarose solution in ether-based RTILs was cooled to room temperature. The resulting gel is called “Ionogel” [23]. Gelation also resulted



**Fig. (6).** Glycolipids (**32** and **33**) and the cationic amphiphile (**34**).

when glycolipid **33** was dissolved in both the ether-based RTILs at concentrations above 10 mM. Optical Microscopy suggested the formation of fibrous nanostructures. Other lipids examined in RTILs did not result in gel formation, suggesting the special importance of carbohydrates in gelation in RTILs.

### Ionic Liquid-Catalyzed Reactions of Carbohydrates

In addition to enhancing the dissolution of carbohydrates of difficult-to-dissolve complex structure, many RTILs can also act as catalysts. The nature of the cation and the anion tune the catalytic properties of RTIL as well as their water miscibility. Recently, a variety of carbohydrate-involved organic reactions have been reported, which use RTILs as catalyst or solvent/catalyst affording improved performance and easier product recovery.

#### Peracetylation of Simple and Protected Monosaccharides

Forsyth and coworkers [24] reported the rapid, clean and mild *O*-acetylation of carbohydrates in dicyanamide **35** based ILs (Fig. 7). The RTILs used in this study ([emIm] dicyanamide and [bmIm] dicyanamide) were both effective solvents and active base catalysts. Reactions resulted in very good yields, for example a 98% yield in 10 min at 50°C was reported for the peracetylation of  $\alpha$ -D-glucose. Similarly, methyl- $\beta$ -glucopyranoside was *O*-acetylated in 92% yield. An RTIL with the same cation [bmIm], but the bis(trifluoromethanesulfonyl)amide anion failed to afford products even after 24 h. This observation is consistent with the tunability of RTIL properties by adjusting the structures of anion and cation.

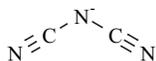


Fig. (7). Dicyanamide anion (**35**) (24).

Our laboratory reported [25] the peracetylation of simple sugars in the RTIL, [emIm][ba] (Fig. 8 - 36). The peracetylation of simple sugars such as  $\alpha$ -D-glucose,  $\beta$ -D-glucose,  $\alpha$ ,  $\beta$  mixture of D-mannose and  $\alpha$ ,  $\beta$  mixture of D-galactose was achieved in excellent yields, ranging from 71% for  $\alpha$ ,  $\beta$  mixture of D-galactose to a quantitative yield for  $\beta$ -D-glucose. The difference in product yields was attributed to the differences in sugar anomeric purity, leading to differences in the degree of crystallinity.

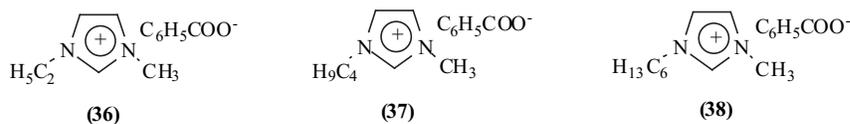


Fig. (8). (36) [emIm][ba], (37)[bmIm][ba] and (38)[hmIm][ba].

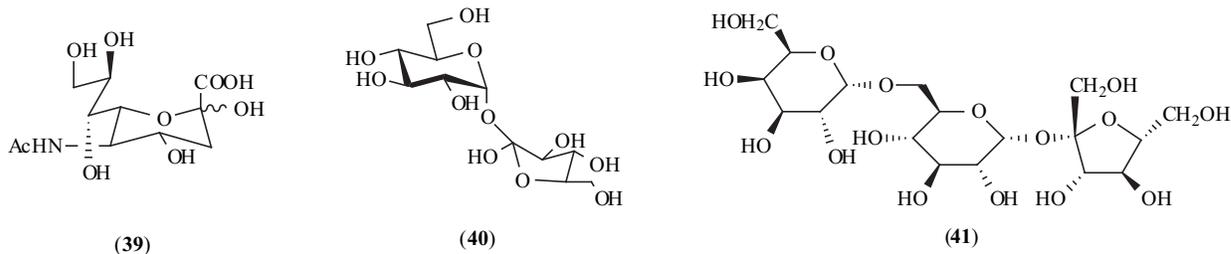


Fig. (9). (39) N-acetylneuraminic acid, (40) sucrose, (41) raffinose.

The ionic liquids [bmIm][ba] **37** and [hmIm][ba] **38** were also studied as a catalyst for the peracetylation of  $\beta$ -D-glucose and the results were compared with that of [emIm][ba]. Yields decreased (from 100% to 82% to 68%) and the reaction time increased (from 4h to 5h to 7h) with an increase (from ethyl to butyl to hexyl) in the RTIL cation alkyl chain length. These differences were attributed to an increase in IL viscosity with increased alkyl chain length, thereby decreasing the mobility of the reacting species.

#### Peracetylation of di- and tri-Saccharides

Forsyth and coworkers [24] also reported the *O*-acetylation of disaccharides including N-acetylneuraminic acid **39** (72% yield) and sucrose **40** (93% yield), and the trisaccharide, raffinose **41** (90% yield) in [emIm][dca] and [bmIm][dca] RTILs. Peracetylation (Fig. 9) resulted within 24 h at room temperature and the reaction time could be decreased with an increase in reaction temperature. This report also compared the results for the peracetylation of  $\alpha$ -D-glucose in RTILs with the same reaction in conventional organic solvents including acetone, acetonitrile, DMF in the presence of the added catalysts, pyridine, sodium acetate and triethylamine. Longer reaction times were required and lower yields were obtained in conventional solvents, further demonstrating the utility of dicyanamide-based RTILs.

#### Peracetylation of Sulfated Saccharides

Our laboratory has reported [25] the peracetylation of sulfated monosaccharides using benzoate-based ionic liquids. The sodium salts of sulfated sugars are insoluble in most of the organic solvents and are difficult to peracetylate [20]. Water and formamide are the only conventional solvents that dissolve these sugars. However, sulfated monosaccharides such as, phenyl-4-*O*-sulfo- $\beta$ -D-glucopyranoside and phenyl-6-*O*-sulfo- $\beta$ -D-glucopyranoside, were completely soluble in the [emIm][ba] RTIL, facilitating their peracetylation in excellent yields. This property of benzoate based RTILs to dissolve sulfated sugars makes these solvents potentially important tools for the chemical modifications of glycosaminoglycans.

#### Perbenzoylation of Simple Saccharides

Benzoate-based RTILs are also useful for the perbenzoylation of simple sugars such as  $\alpha$ -D-glucose,  $\beta$ -D-glucose and  $\alpha$ ,  $\beta$  mixture of D-mannose [25]. While, the

conventional, toxic and odoriferous benzoylation reagent, benzoyl chloride was found to give only the starting material after 24 h, benzoic anhydride afforded good product yields with anomeric stereoselectivity.

### Enzyme Catalysis of Sugars in ILs as Solvents

Some enzymes, such as hydrolases and oxidoreductases reportedly retain their activities when suspended in ILs [26]. Enzymes that work well in organic solvents are often capable of catalyzing reactions in ILs. RTILs containing  $\text{BF}_4^-$ ,  $\text{PF}_6^-$  and  $\text{NTf}_2^-$  anions are the most useful in enzymatic catalysis, while those having  $\text{Cl}^-$ ,  $\text{NO}_3^-$ ,  $\text{CF}_3\text{SO}_3^-$ ,  $\text{CF}_3\text{CO}_2^-$ ,  $\text{CH}_3\text{CO}_2^-$  anions are generally less suitable for use with enzymes [27]. The difference in the utility of these RTILs has been attributed to the difference in the hydrogen-bond ability of their anions. Lower hydrogen bonding by RTIL, affords improved enzyme-compatibility, possibly due to decreased interference with the internal hydrogen bonds in the enzyme catalyst. However, it is interesting to note that this hydrogen-bonding ability of RTIL anions favors the dissolution of carbohydrate polymers such as cellulose by RTILs. Thus, in enzyme catalyzed carbohydrate chemistry

the selection of a suitable IL is a trade-off between the substrate dissolution and the maintenance of enzymatic activity. Further, RTILs, which have polarities similar to that of the organic solvents, facilitating carbohydrate chemistry in solvents with polarity ranges that are unavailable in conventional aqueous solvents.

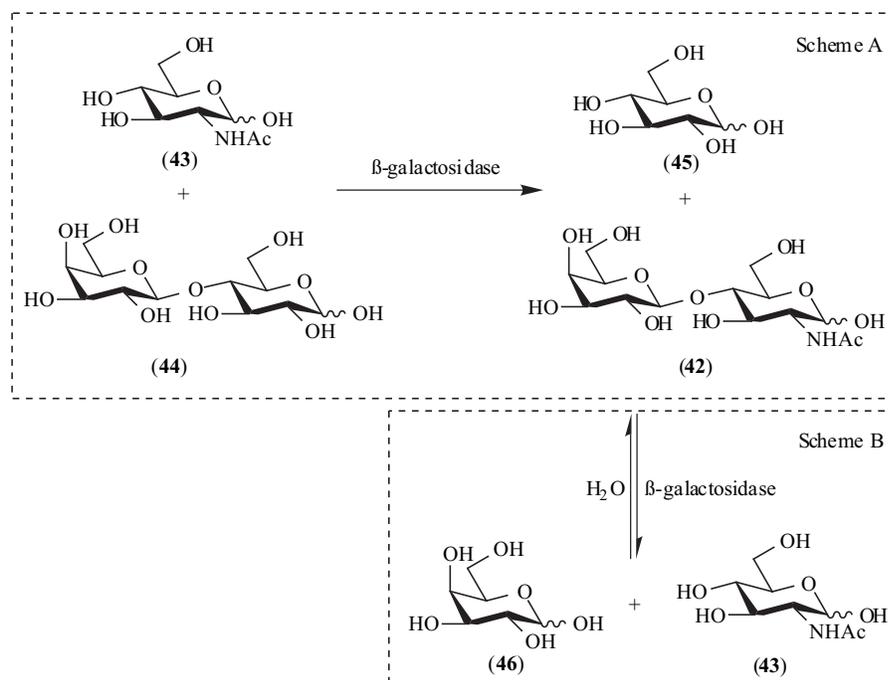
### Synthesis of N-Acetyl Lactosamine using $\beta$ -Galactosidase

Kaftzik and coworkers reported [28] an increase in both the product yield and the enzyme stability, when an optimal amount of IL was used in a transgalactosylation reaction. The enzyme activity ( $\beta$ -galactosidase) was first determined as a function of the amount of IL added and the percentage of the residual activity compared to enzyme activity in pure buffer solution was measured (Table 1). There was no clear correlation between the amount of RTIL and enzyme activity, which could be applied to all the ILs studied. Thus, the amount of the RTIL to be added in such mixed solvent systems, needs to be optimized individually for each ionic liquid.

N-acetyllactosamine **42** is formed by the  $\beta$ -galactosidase catalyzed transgalactosylation reaction of N-acetyl-

**Table 1. Enzyme Activity as a Function of the Amount of IL Present, Given as the % Residual Activity in Comparison to the Activity in Pure Buffer Solution [28]**

Ionic Liquid (% v/v)	$\beta$ -galactosidase		
	25	50	75
[MmIm][MeSO <sub>4</sub> ]	74	14	-
[BmIm][BF <sub>4</sub> ]	31	-	6
[EmIm][PhCO <sub>2</sub> ]	-	-	-
[BmIm][OctSO <sub>4</sub> ]	35	10	-



**Fig. (10).** Enzymatic synthesis of N-acetyllactosamine by  $\beta$ -galactosidase.

glucosamine **43** and lactose **44** when conducted in buffer solution (Scheme-A of Fig. 10). N-acetyllactosamine **42** also undergoes a secondary hydrolysis affording N-acetylgalactosamine **43** starting material and galactose **46** in buffer solutions, limiting the overall yield to 30% (Scheme-B of Fig. 10).

However, in the presence of the 25% (v/v) (optimized from Table 1) [MmIm][MeSO<sub>4</sub>] RTIL, the secondary hydrolysis of **42** is suppressed, improving the overall reaction yield to 58%. This represents an almost doubling in the yield of the desired product **42**, compared to that obtained from the reaction in conventional aqueous buffer. The suppression of secondary hydrolysis can be attributed to a reduction in water activity, caused by the addition of RTIL. The reaction velocity, was not improved by the presence of the ionic liquid. Interestingly, the enzyme was found to be more selective in the presence of the ionic liquid and the enzyme activity was maintained even after repeated by recycling suggesting an excellent enzymatic stability in aqueous solutions of RTIL.

#### Lipase Catalyzed Enantio- and Regioselective Acylation in Ionic Liquids

The enzymatic esterification of carbohydrates using lipases is often limited by the insolubility or very low solubility of carbohydrates in non-aqueous organic solvents. Dialkyl imidazolium based ionic liquids are useful solvents for the lipase catalyzed acylation reactions (Fig. 11) [29]. In this context, it is interesting to note that polar solvents,

showed it to dissolve ~100 times more of glucose than did THF or acetone. They observed the anomerization of product sugars at the elevated reaction temperature, and suggested that traces of acetic acid (a byproduct of this reaction) were responsible. Regioselective acylation of a disaccharide, maltose monohydrate in 50% yield, was also reported by this laboratory. The increase in the regioselectivity of the lipase catalyzed reaction was due to the increased solubility of the reactant in RTIL. Our laboratory [25] demonstrated the peracetylation of simple sugars in an RTIL in which the reactant was insoluble. These reactions proceeded to completion affording a quantitative yield of the peracetylated products. These high yields were accounted for by a biphasic reaction facilitated by RTIL. Differences between this study [25] and that of Park and coworkers [29] might reflect fundamental differences between chemically and enzymatically catalyzed reactions.

#### Oxidase - Peroxidase Catalyzed Sulfoxidation in ILs

Peroxidases are usually deactivated by their primary substrate, hydrogen peroxide (if present in excess). Hence, hydrogen peroxide is often introduced slowly to retain catalytic activity and reaction stereoselectivity. Okrasa and coworkers [30] developed an approach in which hydrogen peroxide was gradually generated *in situ* by the reaction between glucose and oxygen by glucose oxidase and used by peroxidase to oxidize sulfides **48** to chiral sulfoxides **49** (Fig. 12).

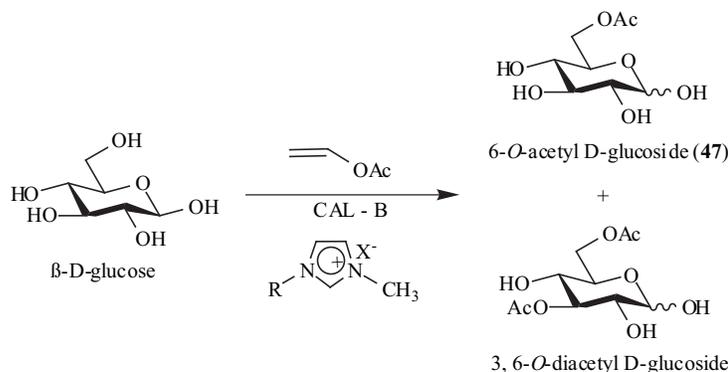


Fig. (11). Lipase-catalyzed acylation of  $\beta$ -D-glucose in dialkyl imidazolium ILs.

such as methanol and N-methylformamide, having polarities similar to these ionic liquids, usually inactivate lipases.

Using conventional organic solvents, it has been very difficult to synthesize 6-acyl glucose derivatives with good yields in lipase catalyzed reactions. This is the result of secondary acylation of the 6-acyl product to form 3, 6-diacyl derivatives. The low solubility of the glucose reactant in these conventional organic solvents has been viewed as the primary reason for this low selectivity and the consequent low yields. In contrast, RTILs give improved regioselectivity of 6-acyl glucose. Furthermore, higher yields are obtained, for example 6-O-acetyl glucopyranoside **47** could be prepared in 99% in seven different RTILs having the [BF<sub>4</sub>] anion.

The optimum RTIL was determined to be 1-methoxy ethyl, 3-methyl imidazolium BF<sub>4</sub>. Park and coworkers [29]

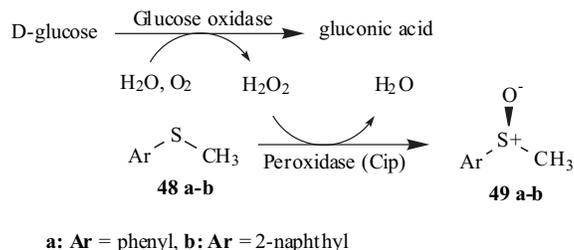


Fig. (12). Oxidase peroxidase catalyzed sulfoxidation.

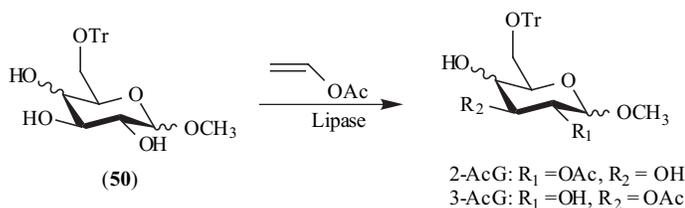
ILs afford increased solubility for both oxygen and organic substrates when compared to aqueous solutions offering advantages for peroxidase chemistry [31]. The hydrophobic RTIL, 1-butyl, 3-methyl imidazolium hexafluorophosphate, which is immiscible with water and ether, but readily miscible with ethyl acetate and

dichloromethane was used in these studies. The efficiency of an enzymatic reaction in non aqueous media, such as ILs often depends on the water activity of the media [32,33]. The percentage of water in RTIL was optimized for the conversion of glucose to gluconic acid. At 10% v/v water in RTIL, a yield of 66% was obtained. Hydrogen peroxide release increased when the reaction temperature was elevated from rt to 40°C, but the yield was reduced to 46%, suggesting that excess of hydrogen peroxide inhibited peroxidase.

#### Enzymatic Selective Acylation of Glycosides in Ionic Liquids

Monoprotected glycosides, such as  $\alpha$ - and  $\beta$ -methyl-6-*O*-trityl glucoside and galactoside **50**, have been selectively acylated through enzymatic catalysis (Fig. 13) using *Candida rugosa* lipase in RTILs [34]. The results were compared with those obtained in the conventional organic solvents, THF and chloroform.

These lipase catalyzed reactions took place more rapidly in ([bmIm][PF<sub>6</sub>] and [moemIm][PF<sub>6</sub>]) ILs, giving higher yields than those obtained in organic solvents. Another important observation was that the reactions of  $\alpha$ -glycosides proceeded rapidly (3-11 h) and gave excellent regioselectivity (>98:1 = 2-*O*Ac: 3-*O*Ac), in contrast to the  $\beta$ -glycosides



**Fig. (13).** Lipase - catalyzed acylation of glycosides.

(50-120 h and 90:10 to 95:5). This regioselectivity shows the merits of using RTILs compared with conventional organic solvents. ILs can also be recycled and reused in the subsequent reactions resulting in excellent yields (~92%). The enhanced reactivity in RTIL has been attributed to an increased solubility of the substrates in these more polar RTIL solvents, consistent with the suggestions made by Park and coworkers [29].

#### Inactivation and Unfolding of Cellulase from *Trichoderma Reesei*

Turner and coworkers [35] reported the RTIL induced unfolding and inactivation of cellulase from *Trichoderma reesei*. This work was a follow-up on their previous studies [22] that demonstrated the dissolution of unmodified cellulose in [bmIm][Cl] with the aid of microwave heating. The activity of the enzyme cellulase in various solvents, has been reported as a function of concentration [35]. Cellulose azure was used as a substrate to measure enzyme activity. The solvents studied included ionic liquids, [bmIm][Cl] and [bmIm][BF<sub>4</sub>], and 5% lithium chloride - 95% dimethylacetamide, a common solvent for cellulose. The results of these studies showed that the concentration of ionic liquid was inversely proportional to the cellulase activity. Even very small amounts (22 mM) of [bmIm][Cl] reduced enzyme activity. The concentration of Cl<sup>-</sup> ion also

reduced enzyme activity, as confirmed using NaCl solution. This is a predictable result, as the Cl<sup>-</sup> concentration in this RTIL is equivalent to a concentrated brine solution. This observation is consistent with the earlier report [27].

Protein renaturation of cellulase was attempted in both [bmIm][Cl] and NaCl solutions. Cellulase refolding is inversely proportional to [bmIm][Cl] concentration. In contrast, refolding in NaCl solution results step-wise changes in the conformation. The refolded enzyme, however lacks activity. The enzyme activity apparently is influenced by both unfavorable RTIL anion - enzyme interactions and the immediate environment of the enzyme.

In general, ILs with hydrogen bond donating and/or hydrogen bond accepting ability similar to a protic organic solvent as well as hydrophobic RTILs, capable of isolating the enzyme into aqueous microdomains, give the most favorable immediate environment to the enzyme for optimal enzyme stability [35].

#### *ILs as Reaction Medium/Solvent for Reactions of Carbohydrates*

RTIL solvents are widely used in cases in which the product yield must be improved to a level greater than accessible in "non-green" conventional organic solvents.

#### Glycosylation in ILs

Using 2,3,4,6-tetra-*O*-benzoyl- $\alpha$ -D-mannopyranosyl trichloroacetamidate (**51** in Fig. 14) as a glycosyl donor in [bmIm][PF<sub>6</sub>] with trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalyst, an array of *O*-glycosylated products (**52** (93% yield), **53** (68%), **54** (70%), **55** (77%) and **56** (53%)) have been prepared [36]. The glycosyl acceptors were allyl and benzyl alcohols, methyl 6-hydroxyhexanoate, methyl 2, 3-*O*-isopropylidene- $\beta$ -D-ribofuranoside (**57**), and glucofuranose derivative (**58**).

Glycosylations carried out with 2,3,4,5-tetra-*O*-acetyl- $\alpha$ , $\beta$ -D-glucopyranosyl trichloroacetamidate as glycosyl donor (**59** in Fig. 15) and allyl alcohol, benzyl alcohol, methyl 6-hydroxyhexanoate and **57** as acceptors afforded the products **60**, **61**, **62**, **63**, **64** and **65** (Fig. 15). The reaction of **59** with allyl and benzyl alcohols proceeded smoothly yielding products. However, column chromatography was used to purify the crude products gave two fractions. The less polar fraction contained peracetylated  $\alpha$ , $\beta$ -glycosides, **60** and **62**, while the more polar (slow moving) fraction comprised of a mixture of  $\alpha$ - and  $\beta$ -products (**61** and **63**) that were deacetylated at the 2- position, as confirmed by H<sup>1</sup> NMR.

Glycosylation carried out using 2,3,4,6-tetra-*O*-acetyl- $\alpha$ , $\beta$ -D-galactopyranosyl trichloroacetamidate (**66** in Fig. 16)

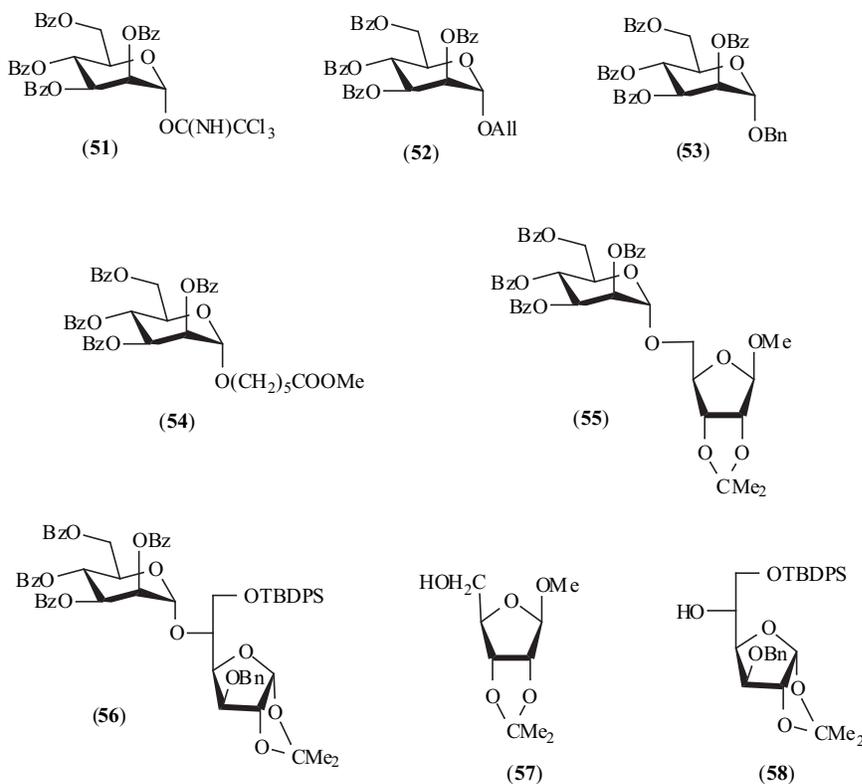
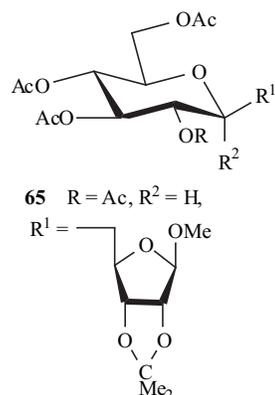


Fig. (14). Glycosylation in RTILs (Compounds 51 – 58).



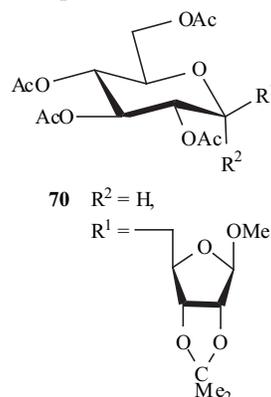
- 59a: R = Ac, R<sup>1</sup> = H, R<sup>2</sup> = OC(NH)CCl<sub>3</sub>  
 β: R = Ac, R<sup>1</sup> = OC(NH)CCl<sub>3</sub>, R<sup>2</sup> = H  
 60a: R = Ac, R<sup>1</sup> = OAlI, R<sup>2</sup> = H  
 β: R = Ac, R<sup>1</sup> = H, R<sup>2</sup> = OAlI  
 61a: R = H, R<sup>1</sup> = OAlI, R<sup>2</sup> = H  
 β: R = H, R<sup>1</sup> = H, R<sup>2</sup> = OAlI  
 62a: R = Ac, R<sup>1</sup> = H, R<sup>2</sup> = OBn  
 β: R = Ac, R<sup>1</sup> = OBn, R<sup>2</sup> = H  
 63a: R = H, R<sup>1</sup> = H, R<sup>2</sup> = OBn  
 β: R = H, R<sup>1</sup> = OBn, R<sup>2</sup> = H  
 64a: R = Ac, R<sup>1</sup> = H, R<sup>2</sup> = O(CH<sub>2</sub>)<sub>5</sub>CO<sub>2</sub>Me  
 β: R = Ac, R<sup>1</sup> = O(CH<sub>2</sub>)<sub>5</sub>CO<sub>2</sub>Me, R<sup>2</sup> = H

Fig. (15). Glycosylation in RTILs (Compounds 59 – 65).

donor and the same set of acceptors afforded both  $\alpha$ - and  $\beta$ -anomers with no deacetylated products. In both the reactions involving **57** (with **59** and **66**), only  $\beta$ -anomer was formed with a yield of 49% and 52%, respectively. Once the product was extracted from the ionic liquids, the ionic liquid was recovered by washing with toluene, and water and then by dissolution in acetone followed by the filtration through a pad of Celite. After the evaporation of all the volatile compounds, the remaining ionic liquid was dried at 70°C under reduced pressure.

The recovery of RTIL after acylation is not always so easy [25]. Adding water at reaction completion can rupture the ionic liquid, precipitating the benzoic acid from the benzoate ionic liquids along with the insoluble peracetylated sugars; hence column chromatography was an inevitable downstream step, required for product purification. Optimal

recovery of RTIL requires the careful selection of a suitable task specific - anion.



- 66a: R<sup>1</sup> = H, R<sup>2</sup> = OC(NH)CCl<sub>3</sub>  
 β: R<sup>1</sup> = OC(NH)CCl<sub>3</sub>, R<sup>2</sup> = H  
 67B: R<sup>1</sup> = OAlI, R<sup>2</sup> = H  
 a: R<sup>1</sup> = H, R<sup>2</sup> = OAlI  
 68B: R<sup>1</sup> = OBn, R<sup>2</sup> = H  
 a: R<sup>1</sup> = H, R<sup>2</sup> = OBn  
 69B: R<sup>1</sup> = O(CH<sub>2</sub>)<sub>5</sub>CO<sub>2</sub>Me, R<sup>2</sup> = H  
 a: R<sup>1</sup> = H, R<sup>2</sup> = O(CH<sub>2</sub>)<sub>5</sub>CO<sub>2</sub>Me

Fig. (16). Glycosylation in IL (Compounds 66 – 69).

In another study, trichloroacetamidate donors were used in glycosylation reactions in [bmIm][PF<sub>6</sub>] and [emIm][OTf] with alcohols (Fig. 17) and with other monosaccharide derivatives (Fig. 18) [37].

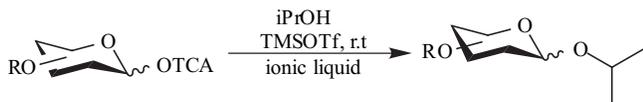


Fig. (17). Synthesis of isopropyl glycosides in ionic liquids.

In the reaction of isopropanol, with donor **73** (Fig. 18), the stereochemistry of the product was strongly solvent and catalyst dependent. When [bmIm][PF<sub>6</sub>] was used,  $\alpha$ -anomer was favored ( $\alpha$ : $\beta$  = 76:24), in contrast when [emIm][OTf] was used  $\beta$ -anomer was favored ( $\alpha$ : $\beta$  = 20:80). Donors **74** and **76**, lacking a participating group at C-2, favored the  $\beta$ -anomer ( $\alpha$ : $\beta$  = 37:63) and  $\alpha$ : $\beta$  = 16:84, respectively, when [emIm][OTf] was used as solvent, leading to the implication that RTIL might assist the reaction mechanism.

The recycling of RTIL from the reaction medium and subsequent re-use afforded similar yields. Recovered RTIL was also found to retain the acidic promoter so that there was no need to add it again. The formation of glycosidic linkage has also been tested in these RTILs. Donors **72** and **76** were used with acceptors **77**, **78**, **79** and **80** (Fig. 19) to afford disaccharides with yields ranging from 54% to 98%.

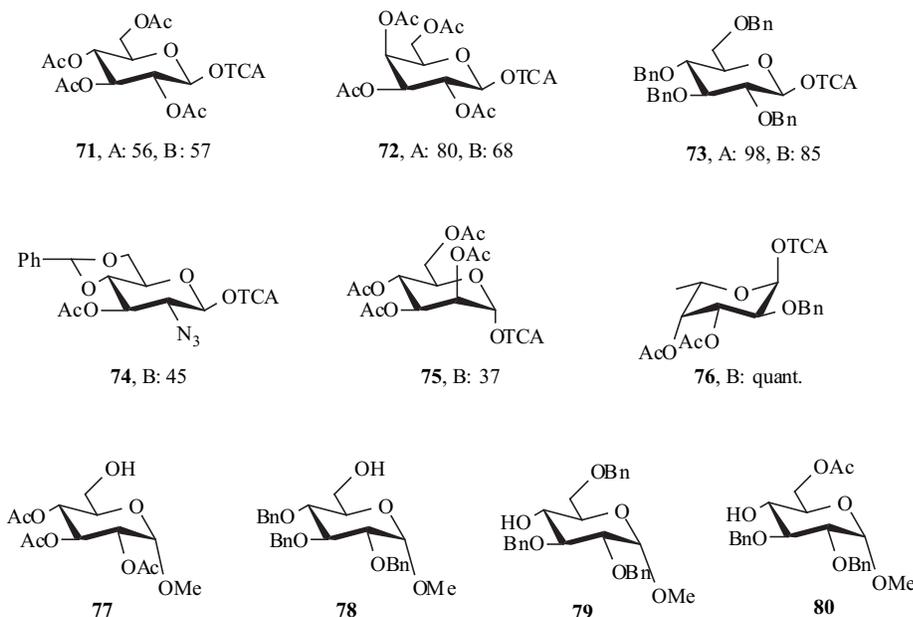


Fig. (18). Various glycosyl donors (**71** – **76**) in glycosylation reaction and their yield when reacted with isopropanol, and the acceptors (**77** – **80**) used for the disaccharide synthesis (A = [bmIm][PF<sub>6</sub>] and B = [emIm][OTf]).

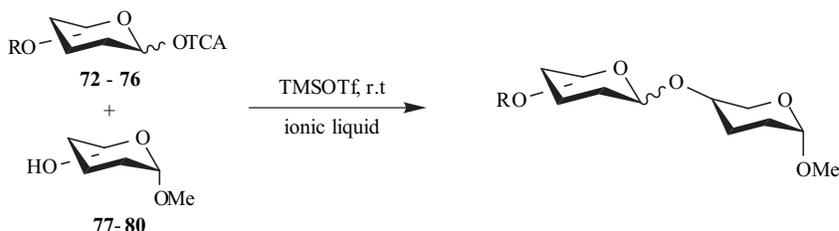


Fig. (19). Disaccharide synthesis in ionic liquids.

The notable observation was that better product yields resulted with less reactive acetylated acceptors than with more reactive benzylated acceptors. Trichloroacetamidate derivatives were very effective donors for the glycosylation reactions of both alcohols and monosaccharides in RTILs.

### Synthesis of 2, 3 Unsaturated Glycopyranosides

Yadav and coworkers [38] relied on a novel and recyclable catalytic medium, dysprosium triflate immobilized in ILs, for the very efficient synthesis of *O*-glycopyranosides from tri-*O*-acetyl derivatives of D-glucal and alcohols, phenols and hydroxyl  $\alpha$ -amino acids.

First, the reaction of 3,4,6-tri-*O*-acetyl-D-glucal **81** with a group of alkyl alcohols using 5 mol% Dy(OTf) in [bmIm][PF<sub>6</sub>] afforded the corresponding 2, 3-unsaturated glycosides **82** (Fig. 20). The reactions took place at high yields (86% to 95%) affording the  $\alpha$ -anomer as the major product. Similarly, **81** was glycosylated with phenols in the presence of Dy(OTf)<sub>3</sub> in the same ionic liquid to afford the corresponding aryl 2,3-unsaturated glycosides in very good yields (85% to 95%) with an exclusive  $\alpha$ -selectivity. The promising results with the alkyl and the aryl acceptors led to the applications of N-Boc protected threonine and serine as acceptors for glycosylation (Fig. 21) with **81**, affording the corresponding *O*-glycopyranosides **83**.

The nature of the anion of the ionic liquid is believed to strongly influence the catalytic activity of dysprosium

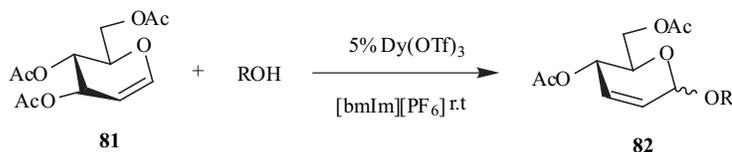


Fig. (20). Glycosylation of D-glucals using alkyl and aryl alcohols.

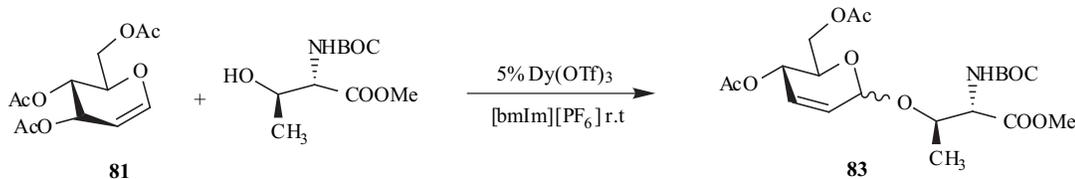


Fig. (21). Glycosylation of D-glucals using N-Boc protected amino acids.

triflate. This catalyst is only slightly soluble in hydrophobic RTILs leading to a suspension. However, in hydrophilic RTILs, this catalyst is completely soluble. The recovery of RTILs was achieved by a simple extraction of products using ether. Recovered catalyst suspended or immobilized in RTIL still had catalytic activity resulting in high yields in subsequent reactions. The [bmim][BF<sub>4</sub>] RTIL was tested alone in the absence of Dy(OTf)<sub>3</sub>, for catalytic activity in the glycosylation reactions at 80°C for 5-8 h. The yields obtained ranged from 60-75%. The catalytic activity is attributed to the mild Lewis acidity of RTIL. The presence of water in trace amounts in ionic liquids did not significantly affect glycosylation. Other lanthanide triflates such as scandium and ytterbium triflates were also found to be equally effective as catalysts in these glycosylation reactions. These studies [38] add the advantage of the simple recovery of the catalyst/ionic liquid system and reuse, to this excellent method of RTIL based glycosylation reactions.

β-anomeric product **85**. Reactions studied using this system containing varying concentrations of protic acid, showed an optimum concentration of 1 mol% in ionic liquid. The same reaction was also performed in organic solvents for comparison.

RTIL [hmIm][NTF<sub>2</sub>] performed better than ether and toluene, and comparable to acetonitrile and methylene chloride on the basis of stereoselectivity, and better than all organic solvents on the basis of chemical yield. The purity of the ionic liquid was next examined. Halides are the most common impurity in RTILs as they are often carried through the synthesis of RTIL. Varying amounts of chloride was added to examine its effect on the product yield. It was found that the presence of even 5 mol% [hmIm][Cl] significantly decreased product yield, resulting from the basicity of the chloride ion [40]. The recovery and reuse of the acid-RTIL proved its efficiency for five sequential reactions after the recovery of the product.

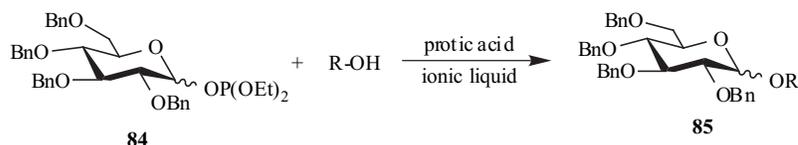


Fig. (22). Glycosidation of glycosyl phosphite in an acid- IL system.

#### Glycosidation of Glucopyranosyl Diether Phosphate and Alcohols

Sussaki and coworkers [39] recently reported the glycosidation of various alcohols, including cyclohexanol, *n*-octanol, phenol and isopropanol, in an acid-RTIL system. Glycosyl phosphite was selected as the glycosyl donor because of its capability of being activated by both weak Lewis acids and protic acids. A higher alkyl chain length in IL cation was preferred because decreased hygroscopicity and reduced water miscibility. The 1-*n*-hexyl substituted imidazolium-based RTILs were examined in conjunction with three different anions BF<sub>4</sub>, trifluoromethanesulfonate and trifluoromethanesulfonimide. HBF<sub>4</sub>, HOTf or HNTf<sub>2</sub> were used in RTILs as protic acids. Reaction between glucopyranosyl diethyl phosphate **84** and cyclohexylmethanol was carried out in these acidic solvent systems (Fig. 22). The most efficient system was found to be [hmIm][NTf<sub>2</sub>] and HNTf<sub>2</sub>, giving 91% yield of primarily the

#### Dehydration of Fructose into 5-Hydroxymethylfurfural

5-Hydroxymethylfurfural (HMF) **86** is an important starting material for the preparation of non-petroleum-derived polymers. Fructose **87** is one of the most widely used starting materials for the preparation of HMF. Lansalot-Matras and coworkers [41] reported the dehydration of fructose into HMF in the presence of RTILs (Fig. 23).

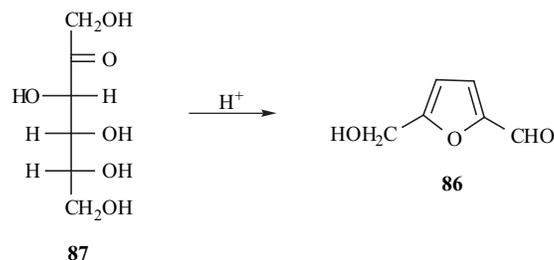


Fig. (23). Dehydration of fructose into HMF.

The RTILs studied included the hydrophobic [bmIm][PF<sub>6</sub>] and the hydrophilic [bmIm][BF<sub>4</sub>]. DMSO was also used as a co-solvent to enhance the solubility of reactants in these RTILs. In pure DMSO, *i.e.* in the absence of both ionic liquid and protonic catalyst (Amberlyst-15), **86** was observed only in trace amounts after 44 h. With the addition of RTIL, the yield increased to 27% after 15 h and 36% after 32 h. The presence of Amberlyst-15 further increased the yield to 75% in 32 h at 80°C. By doubling the amount of catalyst, the yield was further elevated to 87% in 32 h. Both hydrophobic and hydrophilic RTILs gave similar results and the yield reduced in the absence of co-solvent.

### RTILs made of Carbohydrates

#### Solvents from Biorenewable Sources

Most currently known RTILs are made from synthetic organic substrates. An important advance in green chemistry would result from making even RTILs from a biorenewable source. Handy and coworkers [42] reported the synthesis of RTILs from **87**, a simple monosaccharide, using a method developed by Trotter and coworkers [43] but requiring some downstream modifications (Fig. 24).

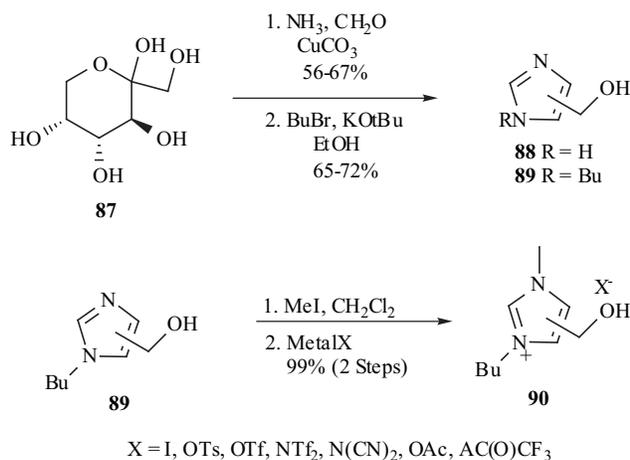


Fig. (24). Synthesis of ionic liquids from Fructose.

The use of the conventional solution phase alkylations in ethanol with potassium tert-butoxide as the base afforded **89** in 65-72% yield. This reaction resulted in an inseparable 9:1 mixture of regioisomers of **88** and **89**. Nuclear Overhauser effect (NOE) spectroscopy demonstrated that the major isomer was the one alkylated at the nitrogen away from the hydroxymethylene group. The second alkylation with methyl iodide in methylene chloride afforded the iodide salt **90** in nearly quantitative yield. A standard anion metathesis reaction was used to prepare a variety of new RTILs including the low viscosity BF<sub>4</sub>, triflimide and dicyanamide ions. The triflimide salt was completely immiscible in water, and miscible with acetonitrile, acetone, methylene chloride, ethyl acetate and ether. The dicyanamide salt was immiscible with ether, toluene and hexane, and miscible with water, methanol, acetonitrile, acetone and methylene chloride.

These fructose-derived ionic liquids were tested for their efficiency as a protic solvent, in the Heck reaction (Fig. 25). These reactions afforded product yields of >95% in 1 h at 100°C. The solvent and the catalyst gave similar yields even after being reused 8 times after recycling.

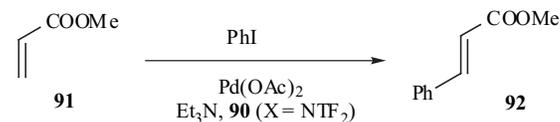


Fig. (25). Heck reaction in fructose-derived ionic liquid.

#### Fructose-Derived ILs as Recyclable Homogenous Supports

Fructose-derived ionic liquids were also investigated as homogenous supports for solution phase reactions [44]. The advantages of these ionic liquids as supports are that their molecular weight is very low, increasing the possible effective loading to > 2 mmol/g compared to effective loading of < 1 mmol/g for conventional homogenous supports such as PEG. Moreover, the solvent properties of these RTILs can be tuned by choosing a proper anion and the alkyl chain lengths of the cation. The triflimide-based fructose-derived RTIL **93** (**90** in Fig. 24 with X = Ntf<sub>2</sub>) was selected for this purpose in an acrylate-derived Diels-Alder reaction. The required acrylate **94** was synthesized (Fig. 26) by acylation at low temperature in the presence of triethylamine.

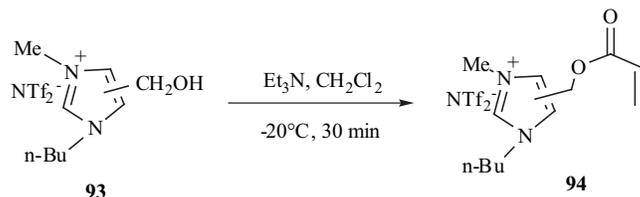


Fig. (26). Synthesis of ionic support by acylation.

Diels-Alder reaction was then investigated (Fig. 27) using the acrylate support with various dienes containing varied alkyl substituents. In all cases, the **95** was readily formed in yields ranging from 29% (for the diene with R<sub>1</sub> = CH<sub>3</sub>, and R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> = H) to 91% (for the diene with R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> = H, R<sub>5</sub>, R<sub>6</sub> = CH<sub>2</sub>). The conditions used for this conversion were toluene, reflux, 4 h or hydroquinone, 120°C, 12 h. The product was cleaved from the ionic support using catalytic KCN in methanol, forming **96** in good yield (Fig. 27). Recycling of these recovered ionic supports in subsequent reactions also resulted in good yields.

### Potential Applications of ILs

The utility of RTILs can also be extended to applications that facilitate the structural study and purification of complex carbohydrates.

#### Light Scattering of ILs

Light scattering experiments are useful in studying the extent of solvent-solute interactions in a solution. Further, a measurement of the solute dimensions can also be done by using light scattering experiments. RTILs have the property of dissolving many polar solutes such as carbohydrate polymers. In this regard, polysaccharides with negligible solubility in conventional organic solvents might be studied by using RTILs.

#### Crystallization

There are a very few x-ray crystal structures of carbohydrates as these polar molecules are quite difficult to

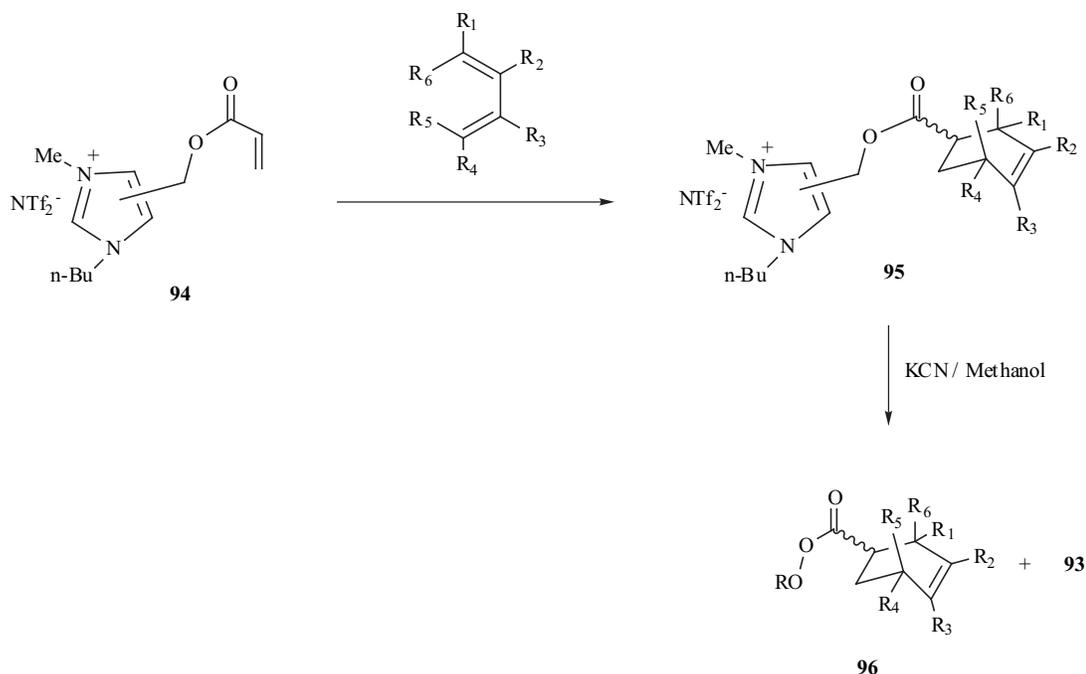


Fig. (27). Diels-Alder reaction followed by the cleavage of the ionic support.

crystallize. One of the problems associated with carbohydrate crystallization is due to the limited choice of the solvents that can dissolve carbohydrates. Carbohydrates, such as glycosaminoglycans, are soluble only in water, formamide, DMF and DMSO. This limited choice of solvents decreases the chance of successfully crystallizing these carbohydrates. The imidazolium salt of the heparin glycosaminoglycan is freely soluble in 1-ethyl, 3-methyl imidazolium benzoate [45]. Further, due to the asymmetrical nature of this and other RTILs solvent ordering is required and solvent crystallization can be prevented. RTILs also have a very good liquidus range allowing temperature to be used in optimizing conditions for carbohydrate solute crystallizations. The high viscosity RTILs also offer a positive property for crystallization. In a highly viscous solvent, solute seed crystals will be more buoyant and their settling rate will be greatly reduced, simulating microgravity conditions that favor the formation of defect-free crystals. Another limitation to carbohydrate crystallization is the high degree of flexibility. RTILs might limit this mobility reducing conformational disorder and favoring crystal formation. These desired solvent properties suggest RTILs have a good potential as solvent for carbohydrate crystallization. Further, the results of light scattering experiments of carbohydrate polymers in RTILs should be useful in selecting optimum conditions for crystallization. The second osmotic virial coefficient  $B_{22}$  provides important information on solute-solvent interactions that can be used to intelligently design the crystallization studies.

#### MALDI-MS

Properties such as high solubilizing capability, vacuum stability, good UV absorbance and broad liquidus range are advantageous for using a solvent in Matrix assisted laser desorption ionization – mass spectrometry (MALDI-MS). This suggests that RTILs might be the ideal choices as MALDI matrices. Armstrong and coworkers [46] have

reported the use of ionic liquids as matrices in MALDI-MS with peptides, proteins and polyethyleneglycol. The application of RTILs might in the future be extended to study the carbohydrates by MALDI-MS.

#### Downstream Processing

RTILs as reaction solvents offer easier product work-up in the downstream processing. Recovery of carbohydrates from chemical and enzymatic reactions is sometimes a difficult process and that can adversely affect isolated reaction yield. The solvent properties of RTILs can be tuned by simply adjusting the anion and the alkyl substituents of the cation moiety, thus facilitating liquid-liquid extraction processes. By varying anions and cations it is possible to design  $\sim 10^{18}$  ILs [47]. Out of this large collection of solvents, it is likely that many will fit a specific task. Unfortunately, significant time and effort is required to design, prepare and screen so-called “Task Specific Ionic Liquids”. Furthermore, new developments are to improve recovery processes involving RTILs. For example, Krockel and coworkers [48] have recently developed a filtration process based on nanotechnology to recover the non-volatile compounds, including carbohydrates, from ionic liquids.

#### Challenges

Even though the number of applications of ILs is increasing exponentially, there are still a number of important issues about ILs that still need to be addressed. These issues may restrict the use of ILs for various applications.

#### Toxicity

Toxicity data on most ILs are not available, making the scientific community suspicious that ILs are actual “green” solvents. This lack of information prevents the widespread

application of RTILs in applications involving living systems. Recently, RTILs have been designed from nontoxic GRAS components such as saccharin and acesulfame [49]. Moreover, recent studies suggest that RTILs are generally orders of magnitude less toxic than conventional organic solvents [50]. Once the toxicity issue is better addressed, the application of ILs in the medical research will be inevitable.

### Biodegradability

The biodegradability of RTILs is another concern. The RTILs that are currently in use, such as [bmIm][BF<sub>4</sub>] and [bmIm][PF<sub>6</sub>] showed no biodegradation [51]. Low biodegradability may increase RTIL toxicity. However, the RTILs with ester groups incorporated in one of their side chains show increased biodegradation [51]. This has been attributed, in part, to an enzymatic hydrolysis leading to a pathway resulting in further breakdown products.

### Viscosity and other Limiting Properties

With the exception dicyanamide and tetrafluoroborate, most ILs are very viscous. This viscosity results in the mechanical loss of ILs in handling, reducing their recovery and recycle in downstream processing. High viscose ILs also results in a decrease in the mobility of the components in reactions limiting the application of RTILs as solvents. While high IL viscosity does have some benefits, such as utility in coating [52], high viscosity is generally viewed as a limiting property of these solvents.

RTILs often contain UV active chromophores limiting the use of these solvents in applications where UV transparency is required. Finally, current RTILs have a small polarity range further limiting their applications. Each of these limitations offer challenges in designing ILs with optimal characteristics.

### Costs

When considering the ILs as alternatives for the conventional organic solvents, the higher cost of preparing the solvents must be taken into account. The preparation of ILs is labor intensive when compared to the preparation of conventional organic solvents. This adds to the expense of using ILs restricting their applications to small scale processes and limiting their commercial applications to more heavily rely on the recyclable and reusable properties of RTILs to limit the amount and cost of RTIL solvents.

## CONCLUSIONS

The application of ionic liquids in the carbohydrate chemistry is increasing exponentially. Ionic liquids have applications as solvents, catalysts, catalyst/solvents in chemical reactions and as solvents for enzymatic reactions. In addition, RTILs are considered environmentally benign. ILs also show an enhanced performance when compared to the conventional organic solvents in a number of processes involving carbohydrates. With an increasing focus on the glycomics, this new class of RTIL solvents offers promising solutions in carbohydrate chemistry.

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