


 Cite this: *RSC Adv.*, 2020, 10, 14299

Synthesis of novel carbohydrate based pyridinium ionic liquids and cytotoxicity of ionic liquids for mammalian cells†

 Melanie Reiß,^a Andreas Brietzke,^b Thomas Eickner,^b Florian Stein,^a Alexander Villinger,^a Christian Vogel,^a Udo Kragl^a and Stefan Jopp^{a*}

The large pool of naturally occurring carbohydrates with their diversity in chirality and structure led to the idea of a systematic investigation of carbohydrate based ILs. To this end, we investigated the influence of different ether groups, mainly methyl or ethyl ether, on the secondary OH groups as well as different configurations on physical properties such as melting point, thermostability and especially the influence on cell toxicity. For this investigation we chose α - and β -methyl-, β -allyl- and β -phenyl D-glucopyranose as well as four 1-deoxy-pentoses. In order to be able to classify the results, more ionic liquids with different structural motives were examined for cytotoxicity. Here, we present data that confirm the biocompatibility of such ILs consisting of naturally occurring molecules or their derivatives. The synthesized carbohydrate based ILs were tested for their suitability as additives in coatings for medical applications such as drug-eluting balloons.

Received 12th February 2020

Accepted 18th March 2020

DOI: 10.1039/d0ra01370f

rsc.li/rsc-advances

Introduction

In recent years, ionic liquids have aroused the interest of scientists in the medical research field due to their wide variety of structures and potential applications.¹ Current areas of investigation include IL based drugs (Active Pharmaceutical Ingredients-Ionic Liquids)² as well as other applications of ILs in the pharmacological field such as drug delivery systems.^{1,3} In such systems, the IL serves as a solvent or solvent promoter for sparingly water-soluble drugs and can thus enhance pharmacokinetic and pharmacodynamic properties considerably.

Another interesting medical application are drug-eluting balloons, which are typically used in re-stenotic lesions.⁴ Previous works of our group have shown that the ionic liquid cetylpyridinium salicate [CetPyr][Sal] is a potential candidate for such an application.⁵ This IL however, while showing good properties in drug release and homogenous coating ability, is not suited for an actual application due to cytotoxicity.

Thus we decided to further look into ILs based on natural products like amino acids⁶ and carbohydrates⁷ Especially carbohydrate based ionic liquids have piqued our interest as

potential ILs with low cytotoxicity. While there have been a few previous studies on carbohydrate based ILs,⁷⁻¹⁰ most of them focused on the synthesis. Examples of previous ILs based on carbohydrates are shown in Fig. 1.

While the use of some of these carbohydrate based ILs as solvents or for asymmetric induction⁹ has been studied, a study for potential medical application has yet to be done.

Results and discussion

Synthesis

The first part of our strategy was the synthesis of four new ionic liquids derived from pentoses. We chose the peracetylated species of D-ribose **1a**, D-lyxose **2a**, D-xylose **3a** and L-arabinose **4a** as starting materials, which were prepared by procedures known from literature.¹¹ Fig. 2 shows the general synthetic pathway exemplary for D-ribose.

Starting from the peracetylated D-ribose **1a** we investigated a direct reduction of the anomeric center using TMSOTf and Et₃SiH.¹² While this strategy successfully led to the 1-deoxy-

^aInstitute of Chemistry, University of Rostock, Albert-Einstein-Straße 3a, 18059 Rostock, Germany. E-mail: stefan.jopp@uni-rostock.de

^bInstitute of Biomedical Engineering, University of Rostock, Friedrich-Barnewitz-Straße 4, 18119 Rostock, Germany

† Electronic supplementary information (ESI) available: Including experimental data for all products as well as ¹H, ¹³C and ¹⁹F NMR spectra for key intermediates and all final ionic products. CCDC 1914143 1916778 1916780. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra01370f

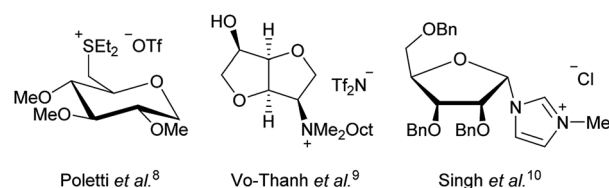


Fig. 1 Examples of carbohydrate based ILs from the literature.



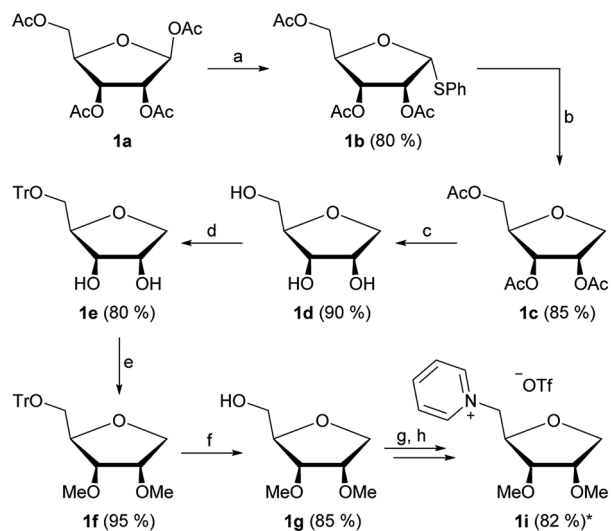


Fig. 2 Synthesis of 1-deoxy-ribose based ionic liquid **1i**; the same synthetic strategy was applied for lyxose (**2a–i**), xylose (**3a–i**) and arabinose (**4a–i**). (a) Thiophenol, $\text{BF}_3 \cdot \text{OEt}_2$, DCM, $0^\circ\text{C} \geq \text{r.t.}$, 2 h; (b) Bu_3SnH , AIBN, toluene, reflux, 2.5 h; (c) MeOH, Na, r.t., 4 h; (d) trityl chloride, NEt_3 , DMAP, DCM, r.t., overnight; (e) NaH, MeI, DMF, $0^\circ\text{C} \geq \text{r.t.}$, overnight; (f) AcOH (70%), 70°C , 45 min; (g) Tf_2O , pyridine, DCM, 0°C , 10 min; (h) pyridine, reaction at rotary evaporator, 700 mbar, 40°C ; *yield over two steps.

ribose derivative **1c** in a high yield of 92%, it could not be applied for the other three starting materials **2–4a**. The yields were low and the products impure. Thus we switched to a two-step strategy of first introducing a thiophenyl group at the anomeric center followed by reduction with tributyltin hydride (Fig. 2a and b). This strategy could be applied for all four products in yields from 50 to 85%.

The next four steps were the deprotection of the acetyl groups, 5-O-tritylation, introduction of the methyl ether groups on the secondary OH groups and lastly deprotection of the 5-O-trityl group, leading to the products **1–4g** (Fig. 2c–f). These steps were generally performed with high yields ranging from 80 to 95%.

Our strategy was finalized by converting the unprotected 5-OH group into a triflate, directly followed by the quaternization reaction with pyridine, yielding the products **1–4i** in overall high yields after an 8-step synthesis (Fig. 2g and h).

By using **1d** and **1e** as starting materials in a similar pathway as shown in Fig. 1 we were furthermore able to produce four additional 1-deoxy-ribose based ILs with varying groups in positions 2 and 3.

The isopropylidene protection of **1d** (Fig. 3a) allows the production of ionic liquid **1k**, which has free OH groups in the positions 2 and 3. Due to the instability of the isopropylidene group under acidic conditions, the synthesis of an isopropylidene protected 1-deoxy-ribose based IL was not possible at first. Said group was partly cleaved during the introduction of the 5-O-triflate group, thus a full cleavage of the isopropylidene group was performed after quaternization (Fig. 3b–d). We were however able to produce the isopropylidene protected 1-deoxy-ribose based IL **1x** by using mesylate instead of triflate (Fig. 4).

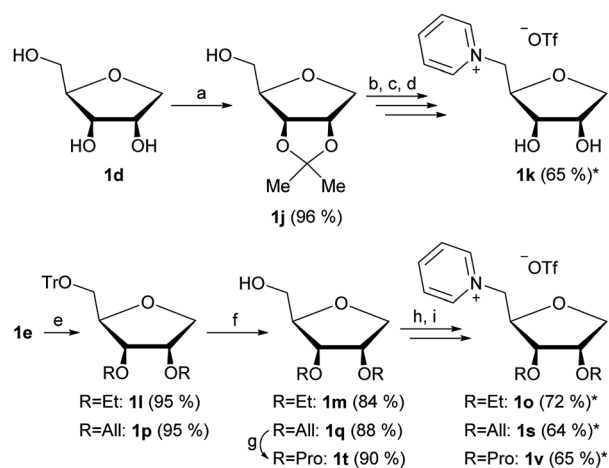


Fig. 3 Synthesis of alternative 1-deoxy-ribose ILs with varying 2- and 3-O-groups. (a) 2,2-Dimethoxy propane, camphorsulfonic acid, acetone, r.t., 1.5 h; (b) Tf_2O , pyridine, DCM, 0°C , 10 min; (c) pyridine, reaction at rotary evaporator, 700 mbar, 40°C ; (d) AcOH (70%), r.t., 20 min; (e) NaH, ethyl or allyl bromide, DMF, $0^\circ\text{C} \geq \text{r.t.}$, overnight; (f) AcOH (70%), 70°C , 45 min; (g) $\text{Pd}(\text{OH})_2$, MeOH, H_2 -atmosphere, r.t., 12 h; (h) Tf_2O , pyridine, DCM, 0°C , 10 min; (i) pyridine, reaction at rotary evaporator, 700 mbar, 40°C ; *yield over two steps.

By changing the reagent used for the introduction of the ether groups starting from **1e**, ethyl and allyl ethers **1l** and **1p** have also been synthesized successfully (Fig. 3e). By further reducing the allyl group to a propyl group and carrying on with the already established strategy of introduction of the triflate followed by quaternization with pyridine, products **1o**, **1s** and **1v** were achieved.

All nine new pyridine salts derived from pentoses are shown in Fig. 5. These ionic structures all classify as ionic liquids, as further shown under “Thermal analysis”.

Our second synthetic goal was to apply the established strategy for 1-deoxy-pentoses on different glucosides. Our starting materials were β -D-methyl, allyl and phenyl glucosides **5–7a** as well as α -D-methyl glucoside **8a**. Fig. 6 shows the general synthetic pathway exemplary for the β -D-methyl glucoside **5a**.

The 5-step reaction starts with the introduction of the 6-O-trityl group (Fig. 6a). This step was performed with yields from 66% when using the β -D-allyl glucoside up to 87% for the β -D-methyl glucoside. The follow-up reactions are, similar to the synthesis shown in Fig. 2, the introduction of the methyl ether groups and afterwards the 6-O-trityl deprotection. These two

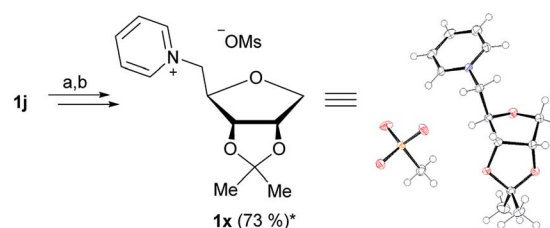


Fig. 4 Synthesis and ORTEP¹³ of **1x**. (a) Mesyl chloride, pyridine, r.t., 12 h; (b) pyridine, 125°C , 5 h; *yield over two steps.

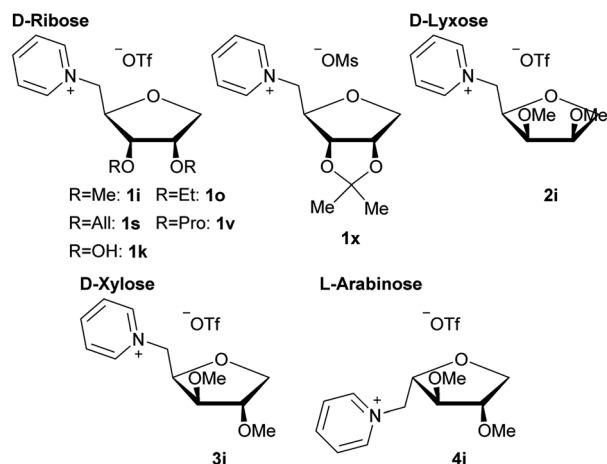


Fig. 5 Overview of 1-deoxy-pentose based ILs.

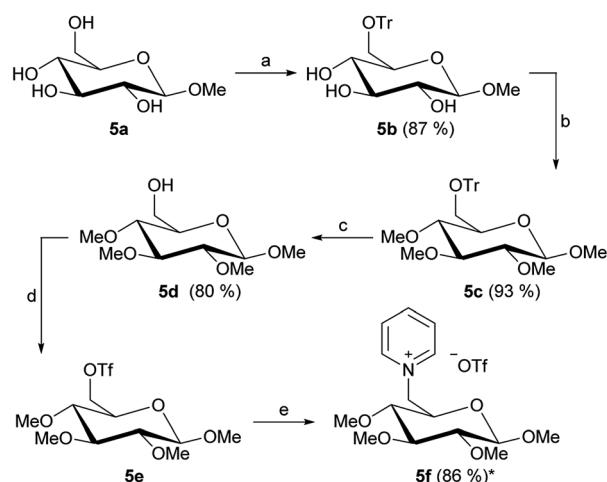
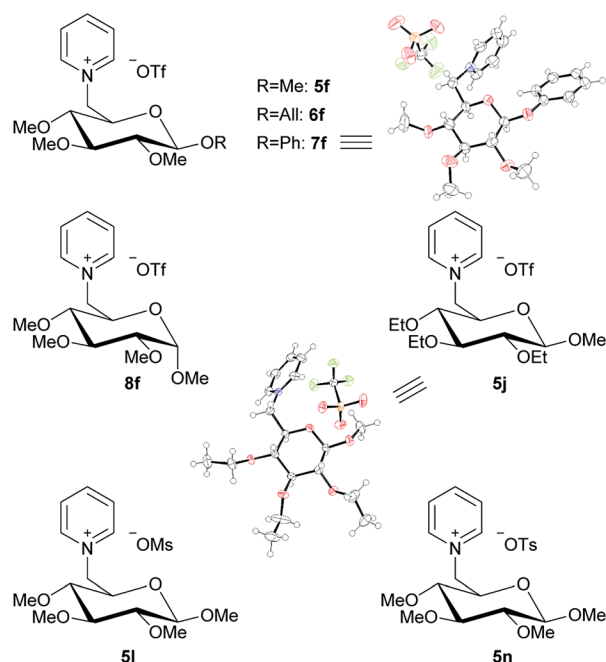


Fig. 6 Synthesis of ionic liquid **5f** from β -D-methyl glucoside **5a**; the same strategy was applied for β -allyl glucoside (**6a–f**), β -phenyl glucoside (**7a–f**) and α -methyl glucoside (**8a–f**). (a) Trityl chloride, NEt_3 , DMAP, DCM, r.t., overnight; (b) NaH, MeI, DMF, $0^\circ\text{C} \geq \text{r.t.}$, overnight; (c) AcOH (70%), 70°C , 45 min; (d) Tf_2O , pyridine, DCM, 0°C , 10 min; (e) pyridine, reaction at rotary evaporator, 700 mbar, 40°C ; *yield over two steps.

steps were generally performed in high yields up to 94% (Fig. 6b and c). The resulting free 6-OH group of the products **5–8d** was then converted into a triflate group followed by quaternization with pyridine, leading to the carbohydrate-based pyridinium triflate salts **5–8f** (Fig. 6d and e).

By following the same idea as applied before for the 1-deoxy-pentoses, the methyl ether groups were also changed to ethyl ether groups on the β -D-methyl glucoside structure. This leads to product **5j** (Fig. 7). Lastly, two further salts were derived from **5d** by changing the leaving group to mesylate or tosylate, leading to **5l** and **5n**, respectively (Fig. 7).

All seven new pyridine salts derived from glucosides are shown in Fig. 7. Most of these new products classify as ionic liquids, as further shown under “Thermal analysis”.

Fig. 7 Overview of glucoside-based pyridinium salts and ORTEPs¹³ of **7f** and **5j**.

Biocompatibility

For biocompatibility measurements, several commonly known ILs, whose cytotoxicity has already been thoroughly explored,¹⁴ have been studied in comparison to the new carbohydrate based ILs we synthesized. A few examples of these additionally tested ILs are shown in Fig. 8.

Cell viability assay revealed a strong impact on cell viability at 0.1 mol L^{-1} molar concentration for the predominant share of the evaluated ionic liquids (Fig. 9A–F). According to that only [AlaC₁][Lac], choline dihydrogenphosphate and sodium chloride, which was tested for comparison, exhibit no cytotoxic effects. Due to the natural occurrence of these substances in cells, this meets our expectations.

Besides that, further discriminations between the ionic liquids presented herein can be made. Comparison between the different glucose derivatives (Fig. 9A) shows almost no viability for any substance at $c = 0.1 \text{ mol L}^{-1}$, whereas major differences

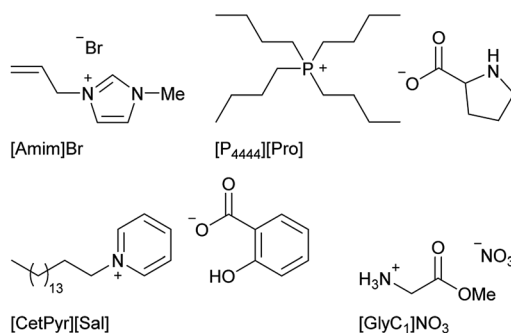


Fig. 8 Examples of additional ILs used in cell viability assay.

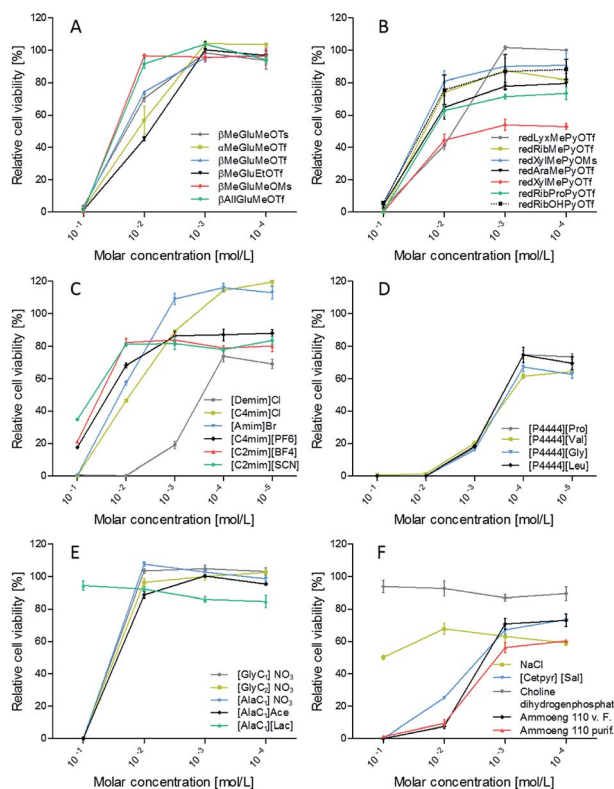


Fig. 9 Relative cell viability of L929 mouse fibroblasts after 48 h cultivation in a dilution series of the ionic liquids compared to the pure cell culture medium control ($n = 4$, mean \pm SEM). (A) Glucoside based ILs; (B) 1-deoxy-pentose based ILs; (C) imidazolium based ILs; (D) ILs based on tetrabutylphosphonium cation and amino acids as anion; (E) ILs based on amino acids as cation; (F) further natural salts and ILs.

can be found at a concentration of 10^{-2} mol L $^{-1}$. A change of the anomeric form from β -glucose to α -glucose results in a decreased viability.

Moreover, results indicate a major impact of the sort of anion on biocompatibility. For β MeGluMePyr $^{+}$ viability rises for following anions in the order: $^{-}OTs < ^{-}OTf < ^{-}OMs$. This effect is supported by redXylMePyr $^{+}$ with the counterions $^{-}OTf < ^{-}OMs$ (Fig. 9B). Surprisingly, the substitution of the methyl group by an allylic group at the anomeric center diminishes the cytotoxicity of the triflate anion.

For 1-deoxy-pentoses different viabilities could be observed in the following order: lyxose \leq xylose $<$ arabinose $<$ ribose. Ribose derivatives are naturally found in all nucleotides (DNA, RNA) and hence in all cells, while lyxose can be found in the cell walls of few bacteria and xylose and arabinose in the polysaccharides of plants. Hence, ribose derivatives should be tolerated better by cells with mammalian origin.

Thus, the use of substances with biological origin such as carbohydrates and amino acids is a promising approach for improving the biocompatibility of ionic liquids. To test this, a common tetrabutylphosphonium cation [P $_{4444}$] was counteracted with four different anions derived from proteinogenic hydrophobic amino acids: proline, valine, glycine and leucine (Fig. 9D). The resulting ionic liquids exhibit cytotoxic effects

over the whole concentration range. There are no significant differences between the different anions.

In contrast amino acid derivatives from alanine and glycine as cations exhibit no cytotoxic effects at a concentration of 10^{-2} mol L $^{-1}$ (Fig. 9E). There is also no difference between methoxy- or ethoxy esters in the glycine derivatives. According to the counter ion no significant differences between nitrate and acetate can be found.

Hence, using naturally occurring substances and their derivatives to generate the cation opens up new fields of application, such as biomedical applications. It is worth noting that the IL [AlaC $_1$][Lac] shows good viability already at concentrations of 0.1 mol L $^{-1}$, but compared to the other [AlaC $_1$] derivatives a slightly worse impact on the biocompatibility at lower concentrations. Further studies have to be performed to shed light on this phenomenon (Tables 1 and 2).

Thermal analysis

The analysis of the melting points of our 16 new carbohydrate based pyridinium salts allows the categorization into the class of ionic liquids, which are per definition salts with a melting point under 100 $^{\circ}$ C.

As such, only β PhGluMePyrOTf **7f**, β MeGluEtPyrOTf **5j** and β MeGluMePyrOTs **5n** do not qualify as ionic liquids, while all other glucoside- and 1-deoxy-pentose products exhibit melting points under 100 $^{\circ}$ C, with many of them even being room temperature ionic liquids (Tables 3 and 4).

While most of the 1-deoxy-pentose based ILs are liquid at room temperature (Table 4) and such don't allow a direct comparison of the impact of configuration and varying groups on the melting point, such comparisons can be made for the glucoside based products (Table 3).

The type and configuration of the group at the anomeric center has a high influence on the melting point. A trend of β OME $<$ β OAl \leq β OPh was found for the glucosides **5-7f**. The double bonds of allyl and phenyl groups allow more interactions between the cations than the methyl group, leading to this trend. Furthermore, β MeGluMePyrOTf **5f** is liquid at room

Table 1 Relative cell viability of L929 mouse fibroblasts with carbohydrate based ILs

No.	Cation	Anion	EC $_{50}$ [mmol L $^{-1}$]
1i	redRibMePyr	OTf	46.40
2i	redLyxMePyr	OTf	25.19
3i	redXylMePyr	OTf	38.65
4i	redAraMePyr	OTf	40.37
1k	redRibOHPrPyr	OTf	54.80
1v	redRibPrPyr	OTf	136.62
5f	β MeGluMePyr	OTf	41.73
6f	β AllGluMePyr	OTf	36.40
7f	β PhGluMePyr	OTf	n.m. ^a
8f	α MeGluMePyr	OTf	49.88
5l	β MeGluMePyr	OMs	57.60
5n	β MeGluMePyr	OTs	51.49

^a **7f** was not measured due to its very poor solubility in water.

Table 2 Relative cell viability of L929 mouse fibroblasts with several ILs^{15–18}

Cation	Anion	EC ₅₀ [mmol L ⁻¹]
P ₄₄₄₄	Pro	0.575
P ₄₄₄₄	Val	0.775
P ₄₄₄₄	Gly	0.875
P ₄₄₄₄	Leu	0.725
GlyC ₁	NO ₃	35
GlyC ₂	NO ₃	20
AlaC ₁	NO ₃	20
AlaC ₁	Lac	25
Choline	H ₂ PO ₄	30
Amim	Br	15
C ₂ mim	BF ₄	4
C ₂ mim	SCN	8
C ₄ mim	Cl	10
C ₄ mim	PF ₆	7
C ₁₀ mim (demim)	Cl	0.035
Ammoeng 110®	—	1.07
Ammoeng 110® purif.	—	3.08
Cetpyr	Sal	0.038
Na	Cl	51.85

Table 3 Melting points and decomposition points of glucoside based products

No.	Cation	Anion	mp [°C]	dp [°C]
5f	βMeGluMePyr	OTf	Liquid at r.t.	225
6f	βAllGluMePyr	OTf	66–70	205
7f	βPhGluMePyr	OTf	164–168	225
8f	αMeGluMePyr	OTf	95–100	242
5j	βMeGluEtPyr	OTf	118–120	215
5l	βMeGluMePyr	OMs	60–63	250
5n	βMeGluMePyr	OTs	135–138	242

Table 4 Melting points, decomposition points and glass transition temperature of 1-deoxy-pentose based products

No.	Cation	Anion	mp [°C]	dp [°C]	T _g [°C]
1i	redRibMePyr	OTf	48–51	345	–18
2i	redLyxMePyr	OTf	Liquid at r.t.	325	–41
3i	redXylMePyr	OTf	32–36	345	–28
4i	redAraMePyr	OTf	Liquid at r.t.	340	–38
1o	redRibEtPyr	OTf	Liquid at r.t.	316	–26
1s	redRibAllPyr	OTf	Liquid at r.t.	301	n.m.
1v	redRibPrPyr	OTf	Liquid at r.t.	235	–27
1k	redRibOHPyr	OTf	Liquid at r.t.	297	–30
1x	redRibIsoPyr	OMs	92–94	296	n.m.

temperature, while αMeGluMePyrOTf **8f** has a melting point close to 100 °C, showing that the configuration of the anomeric center alone has a high impact on the melting point. The change of methyl ether groups in **5f** to ethyl ether groups in **5j** also heightens the melting point significantly. Lastly the corresponding anion also has a high influence, showing a clear trend of OTf < OMs ≤ OTs.

The decomposition points of the glucoside products vary from 205 to 250 °C, while the 1-deoxy-pentose products have higher values with 297 to 345 °C. In general, these new products have a good thermal stability.

Glass transition temperatures we measured for the 1-deoxy-pentose based IL's to acquire further information of the influences of configuration and varying groups on physical properties. Here we see a trend of lyxose **2i** < arabinose **4i** < xylose **3i** < ribose **1i**. The impact of the varying groups in positions 2 and 3 on the glass transition temperature is small, with the methyl ether product **1i** having the highest and the free OH group product **1k** the lowest T_g in direct comparison.

Methods

Cell viability assay

In order to evaluate the biocompatibility of the carbohydrate-based ILs cytotoxicity was tested with Cell Viability Assay Kit (BioAssay systems, Hayward, CA, USA).

L929 mouse fibroblasts (CCL-1, ATCC) were cultured in DMEM (PAN BIOTECH, Aidenbach, Germany) with 4.5 mg glucose and 10% fetal calf serum (FCS), 1% Penicillin/Streptomycin and 3.7 g L⁻¹ NaHCO₃.

For screening tests 2 × 10⁴ L929 mouse fibroblasts were seeded in a 96-well microtiter plate with 200 μL culture medium per well and incubated under cell culture conditions (37 °C, 5% CO₂) for 24 hours.

To proof cell viability CellQuanti-Blue Cell Viability Assay Kit (BioAssay systems, Hayward, CA, USA) was implemented. 10% CellQuanti-Blue supplement was added to the wells followed by an incubation of another 2 hours under same conditions. The reductive activity of the cells conducts the metabolic turnover from resazurin to the fluorescent resorufin (absorption 544 nm, emission 590 nm) which was detected with the Fluostar optima (BMG LABTECH, Ortenberg, Germany).

Thermal analysis

Melting points were determined with a micro heating stage (Mikroheiztisch BOETIUS, Dresden, Germany).

Decomposition points have been measured *via* thermogravimetric analysis using a Labsys 1600 TGA-DSC (SETARAM Instrumentation, Caluire, France).

The differential scanning calorimetry using a Pyris 1 DSC (PerkinElmer, Waltham, USA) allowed the analysis of glass transition temperatures.

Conclusion

In this work we presented a reproducible strategy to synthesize new carbohydrate based pyridinium salts. Said synthetic pathway was successfully applied on 4 different 1-deoxy-pentoses as well as 4 different glucosides, leading to overall 16 new products with varying configurations and groups.

Thermal analysis shows that 13 of these new carbohydrate based pyridinium salts qualify as ionic liquids per definition, with most of them even being room temperature ionic liquids.

Further biocompatibility tests have proven that these ionic liquids are suitable for biomedical applications, as they exhibit a much higher viability than common imidazolium or phosphonium based ILs, which have been tested in comparison. A potential application currently under testing is the usage of these new carbohydrate based ionic liquids as additives in coatings for drug-eluting balloons.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Prof. H. Ohno for providing us the four tetrabutylphosphonium ILs paired with amino acid anions, which we used in the biocompatibility tests. We also thank Prof. Schick of the University of Rostock for conducting DSC with our samples. This work was supported by the European Union (ESF/14-BM-A55-0048/16) as well as by the Federal Ministry of Education and Research (BMBF) project REMEDIS (FKZ:03IS2081).

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