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Separable fluorous ionic liquids for the dissolution and saccharification of cellulose†

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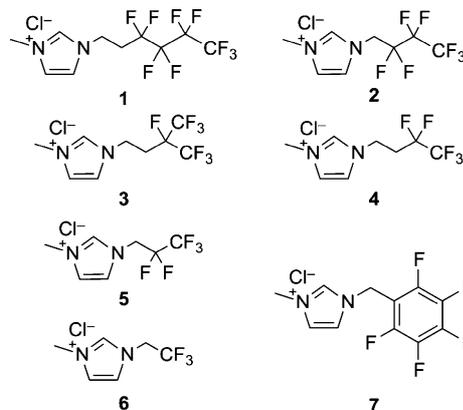
Ionic liquids are an attractive class of solvents for biomass conversion processes. The same properties that make them advantageous—high polarity, water solubility and negligible vapor pressure—hinder their recovery from carbohydrates. We report on the synthesis of seven fluorous imidazolium chloride ionic liquids and on their ability to dissolve cellulose. One of these ionic liquids, 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride, dissolves cellulose. We found this fluorous ionic liquid to be suitable for use in cellulose hydrolysis reactions, and we achieved its recovery from glucose.

Introduction

The implementation of a viable fuel and energy alternative to sources such as coal, natural gas and petroleum is rapidly becoming critical for a sustainable future. Lignocellulosic biomass, both abundant and renewable, is one such alternative resource. Its primary component, cellulose, can be hydrolyzed to glucose, then transformed into the platform chemical 5-(hydroxymethyl)furfural (HMF)¹ or used as a feedstock for the growth of engineered microbes. Unfortunately, the polymeric, crystalline nature of cellulose makes it highly recalcitrant to dissolution, and few organic solvents accomplish this feat.² The desire to utilize environmentally benign solvents for cellulose dissolution aggravates the problem further.

Ionic liquids are an attractive class of solvents as they are polar, water-soluble molten salts with negligible vapor pressure.³ Importantly, ionic liquids can accomplish cellulose dissolution. The crystallinity of cellulose results from a complex network of intrastrand and interstrand hydrogen bonds.² To dissolve cellulose, a solvent must compete for

these intermolecular hydrogen bonds. Ionic liquids accomplish dissolution because their charged species disrupt the hydrogen bonding network by forming electron donor–electron acceptor complexes with the hydroxyl groups.^{3c,4} This results in separation of the polymer chains, allowing dissolution. Dialkylimidazolium chlorides, in particular, demonstrate the capacity to dissolve high concentrations of cellulose,⁵ and have been used in cellulose conversion processes.⁶ For example, we accessed HMF in one step from lignocellulosic biomass using a chromium catalyst in 1-ethyl-3-methylimidazolium chloride ([EMIM]Cl)^{6c} and fermentable sugars from lignocellulosic biomass by hydrolysis in an [EMIM]Cl/HCl/H₂O system.^{6c} Schüth and co-workers utilized solid acid catalysts in 1-butyl-3-methylimidazolium chloride ([BMIM]Cl) for the depolymerization of cellulose to cello-oligomers.^{6b} Amarasekara and Owerh accomplished cellulose hydrolysis to glucose and other reducing sugars in the Brønsted acidic ionic liquids 1-(1-propylsulfonic)-3-methylimidazolium chloride and 1-(1-butylsulfonic)-3-methylimidazolium chloride.^{6d} We realized that the physical properties that make ionic liquids ideal as a reaction medium for these biomass conversion processes hinder their separation and recovery from the desired carbohydrate products. Yet, as ionic liquids are more expensive than traditional organic solvents, it is imperative that they be recovered if they are to serve as reaction media in economical processes.



Fluorous tags are being increasingly employed to facilitate the separation of products and catalysts in organic synthesis.⁷ They have a high affinity for fluorous phases, which are distinct from

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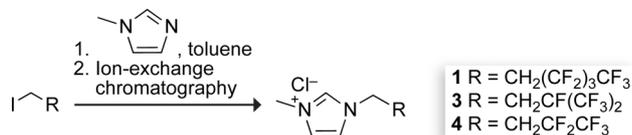
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polar/non-polar and hydrophilic/hydrophobic phases.^{7c} Heavy fluorous tags containing >60% fluorine enable the extraction of a tagged compound.^{7e} Light fluorous tags (typically C₃F₇ to C₁₀F₂₁) are suited for solid-phase extraction with a C₈F₁₇-bonded phase (as in fluorosilica gel) or isolation by fluorosilica HPLC.^{7e} We envisioned that these same separation strategies could be used with fluorosilica ionic liquids.

Fluorous ionic liquids are not available from commercial vendors. A variety, however, have been synthesized, not only to avail potential fluorine-fluorine interactions, but also to modulate the physical properties of the ionic liquids.⁸ Modification of the fluorine-containing portion of the cation can have a substantial impact on melting point, viscosity, density, conductivity, solubility and thermostability.^{8d} Additionally, the identity of the anion can be modified to alter the properties of an ionic liquid. The versatility is great, and a number of imidazolium fluorosilica ionic liquids, in particular, have been synthesized and tested as surfactants in gas separations and in metal-ion extraction.^{8a-c,e-g,9} Nonetheless, fluorosilica ionic liquids have not been employed in biomass- or bioproduct-conversion processes, and no fluorosilica ionic liquids have been synthesized with the chloride counterion necessary for cellulose dissolution. Herein, we report on the synthesis of seven fluorosilica imidazolium chloride ionic liquids (1–7) and on their capabilities as biomass solvents. To our knowledge, ionic liquid 3 is novel. The other six fluorosilica imidazolium groups have been described previously (though not as chloride salts)^{8e,9,10} but have not been used in a bioprocessing application.

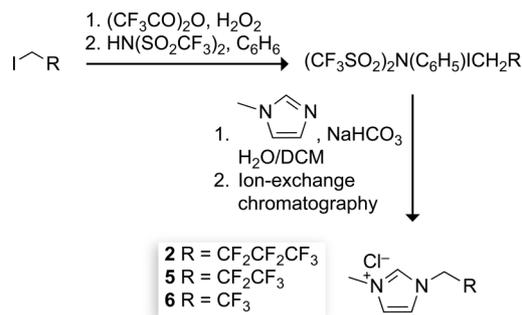
Results and discussion

As its separation from non-fluorous molecules would be enhanced by a high fluorine-content,^{7f} we initially targeted an ionic liquid with nine fluoro groups, 3-methyl-1-(3',3',4',4',5',5',6',6',6'-nonafluorohexyl)-imidazolium chloride (1). Following the procedure of Noble and co-workers (Scheme 1),^{8e} ionic liquid 1 was synthesized by the reaction of a fluoroalkyl iodide precursor with 1-methylimidazole. Ion-exchange chromatography yielded ionic liquid 1 as a highly viscous oil. This ionic liquid was soluble in polar solvents such as water, methanol and acetonitrile, but demonstrated limited solubility in toluene. We found cellulose to be insoluble in ionic liquid 1, even with heating.



Scheme 1

Next, we synthesized 1-(2',2',3',3',4',4',4'-heptafluorobutyl)-3-methylimidazolium chloride (2), a fluorosilica ionic liquid containing a smaller fluorosilica tag. The steric bulk of the proximal fluoroalkyl group made the 1-position of heptafluorobutyl iodide especially resistant to nucleophilic attack. Hence, a hypervalent iodonium alkylating agent invented by DesMarteau and co-workers was employed as an intermediate (Scheme 2).^{9,10b}



Scheme 2

We again found the ionic liquid to be soluble in polar solvents but unable to dissolve cellulose.

Then, we sought to consolidate the fluoro groups so as to minimize alteration to the dialkylimidazolium core structure. Hence, we synthesized 3-methyl-1-(3',4',4',4'-tetrafluoro-3'-trifluoromethyl-butyl)-imidazolium chloride (3) as a viscous oil by following the procedure of Noble and co-workers.^{8e} Once again, while the ionic liquid was soluble in polar solvents, it was unable to dissolve cellulose.

The behavior of ionic liquids 1–3 was unexpected, as ionic liquids containing a chloride anion are typically able to dissolve at least low concentrations of cellulose. We reasoned that the size of the perfluorinated alkyl side chain on ionic liquids 1–3 could be hindering cellulose dissolution. A steric effect had been observed previously, as imidazolium ionic liquids with *N*-alkyl groups containing >8 carbons demonstrate a marked decrease in cellulose solubility.^{5a,5b} Perfluorinated alkyl groups are significantly more bulky than the corresponding alkyl groups, which would explain why our fluorosilica ionic liquids were unable to dissolve cellulose, unlike their corresponding alkyl ionic liquids. For example, *A*-values indicate that a trifluoromethyl group is at least as large as an isopropyl group; Taft-type steric parameters indicate it to be as large as an isobutyl group.¹¹ Therefore, we sought to synthesize fluorosilica ionic liquids with smaller fluorosilica side chains (Table 1).

To access an ionic liquid with a smaller fluorosilica tag, we synthesized 3-methyl-1-(3',3',4',4'-pentafluorobutyl)-imidazolium chloride (4) as a viscous oil by following the procedure of Noble and co-workers.^{8e} This ionic liquid was unable to dissolve cellulose, despite its solubility in polar solvents. Seeking to truncate further the side chain of the cation, we synthesized 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (5) by following the procedure of DesMarteau and

Table 1 Imidazolium volumes of fluorosilica ionic liquids 1–7

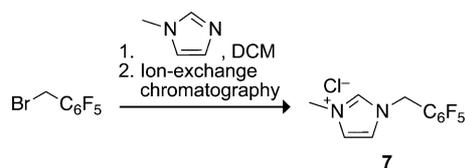
Fluorous ionic liquid	Number of fluoro groups	Imidazolium volume ^a (Bohr ³ mol ⁻¹)
1	9	1835
2	7	1669
3	7	1352
4	5	1303
5	5	1213
6	3	1089
7	5	1652

^a Calculated using Gaussian '03, see the ESI.†

co-workers.^{9,10b} This ionic liquid was obtained as a crystalline solid at room temperature but melts at moderate temperatures and is a viscous liquid at 100 °C. Importantly, upon heating to 140 °C, ionic liquid **5** demonstrated the dissolution of cellulose to ≥ 2 wt%, forming a viscous solution similar to that observed with typical dialkylimidazolium ionic liquids. Remarkably, this difference in cellulose solubility was accomplished upon deletion of a single methylene unit. This result demonstrates the profound influence of imidazolium size on solubilizing cellulose. Furthermore, as dialkylimidazolium acetates are also known to dissolve cellulose,^{5b,5c} we transformed **5** into its acetate counterpart. Again, a viscous solution formed upon heating and cellulose dissolution was observed to ≥ 2 wt%.

Encouraged by this success, we sought to decrease further the size of the fluoroalkyl side chain. Hence, we again followed the procedure of DesMarteau and co-workers^{9,10b} to synthesize 3-methyl-1-(2',2',2'-trifluoroethyl)-imidazolium chloride (**6**) as a viscous oil. Cellulose was soluble in this ionic liquid but somewhat less than in 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (**5**). Apparently, the imidazolium structure has subtle and (currently) inexplicable influences on interactions with cellulose.

As a final possibility, we were interested in testing a perfluorinated aryl-alkyl imidazolium ionic liquid as a solvent for cellulose. Aryl-alkyl ionic liquids allow for the potential to modulate the physicochemical properties of an ionic liquid *via* σ - and π -based electronic effects.¹² To this end, we synthesized 3-methyl-1-pentafluorophenylmethylimidazolium chloride (**7**) as a white solid by following the procedure of McGrandle and Saunders (Scheme 3).^{10a} Ionic liquid **7** demonstrated solubility in polar solvents but was insoluble in toluene and had a melting point of 150 °C. Due to its high melting point, we attempted cellulose dissolution utilizing varying concentrations of the ionic liquid in *N,N*-dimethylacetamide–LiCl.^{6c} Yet, even when heated to 140 °C, no cellulose dissolution was observed in these solutions.



Scheme 3

Given the demonstrated ability of ionic liquid **5** to dissolve cellulose, we next sought a method for its extraction. Ionic liquid **5** is highly soluble in water, and we did not recover an appreciable quantity in an organic phase (*e.g.*, ethyl acetate). Nonetheless, we investigated whether a fluorinated solvent (*e.g.*, perfluorinated hexane) could extract ionic liquid **5**. As typical fluorinated tags used in this way contain >20 fluoro groups, we did not expect our ionic liquids to separate into the fluorinated phase. Indeed, when tested for separation in water and perfluorinated hexane, no ionic liquid **5** was detected in the fluorinated solvent. Next, we turned to fluorinated solid-phase extraction (SPE) to remove our lightly fluorinated ionic liquid from water. Following a procedure from Fluorous Technologies (Pittsburgh, PA),¹³ we used water as our fluorophobic phase and methanol as our

fluorophilic phase on a FluoroFlash[®] SPE cartridge. Although the majority of ionic liquid **5** was retained on the cartridge after water elution, we could detect the ionic liquid in the water eluent. A methanol elution recovered the remaining ionic liquid. These results suggested that the fluorinated ionic liquid with only five fluoro groups is too polar and insufficiently fluorinated for standard fluorinated separation techniques. Fluorous SPE typically requires molecules to contain at least seven fluoro groups,^{7e} whereas our ionic liquid contained only five.

The moderate retention of the fluorinated ionic liquid on the fluorinated SPE cartridge led us to hypothesize that a chromatographic separation might be possible. To this end, we prepared a column using FluoroFlash[®] silica gel, as in the SPE cartridge. Using this column, we were able to separate ionic liquid **5** from glucose using water as the eluent (Fig. 1). To conclude that the fluorinated tag was responsible for the separation of the ionic liquid from the sugar, we performed a similar experiment using pentafluorobutyl ionic liquid **4** and its non-fluorinated counterpart 1-butyl-3-methylimidazolium chloride. The fluorinated ionic liquid again demonstrated a clean separation from glucose, while the non-fluorinated ionic liquid was not cleanly separated from the glucose. This result is consistent with the fluorinated tag enabling the separation of the ionic liquid from glucose.

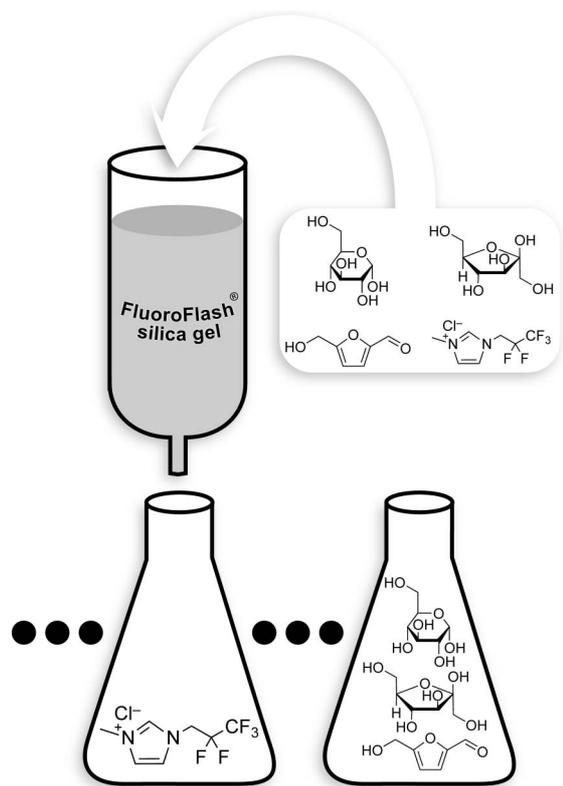


Fig. 1 Schematic of the isolation of ionic liquid **5** from sugars and furanics by chromatography using FluoroFlash[®] silica gel. The eluent is water.

With the successful separation of the fluorinated ionic liquids from glucose, we sought to determine if ionic liquid **5** could be used in a cellulose hydrolysis reaction. By following a modified procedure that we have employed previously,^{6c} we dissolved cellulose at 2 wt% in ionic liquid **5** and assessed the reaction

mixture at known time points. After 2 h, we detected the presence of both fructose and glucose in the reaction mixture at 27 and 11 mol%, respectively. After 4 h, we detected traces of HMF. Finally, we achieved separation of ionic liquid **5** from the reaction products by chromatography using FluoroFlash® silica gel (Fig. 1), recovering >95% of **5**. This result suggests that 3-methyl-1-(2',2',3',3',3'-pentafluoropropyl)-imidazolium chloride (**5**) can indeed be used in cellulose conversion.

Conclusions

We have synthesized seven fluorinated imidazolium chloride ionic liquids and assessed their ability to dissolve cellulose. We discovered that the ability of a fluorinated ionic liquid to dissolve cellulose is highly sensitive to the structure of the imidazolium cation, as only by decreasing the fluorinated tag to a pentafluoropropyl group was cellulose dissolution possible. An even smaller tag, trifluoroethyl, also allowed some cellulose dissolution to occur. Although the content of fluorine in these fluorinated tags is too small to allow for typical fluorinated SPE methods, we accomplished the separation of cellulose hydrolysis products from our optimal fluorinated ionic liquid by utilizing chromatography with FluoroFlash® silica gel. Finally, we tested the pentafluoropropyl ionic liquid in a cellulose hydrolysis reaction and discovered its support of monomeric sugar production. These results encourage the further development of fluorinated imidazolium chloride ionic liquids for biomass conversion processes.

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