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RESEARCH LETTER

Novel biocompatible ionic liquids based on gluconate anion

Alexandra Costa, Andreia Forte, Karolina Zalewska, Gonçalo Tiago, Zeljko Petrovski and Luis C. Branco*

Departamento de Química, Faculdade de Ciências e Tecnologia, REQUIMTE, Universidade Nova de Lisboa, Caparica, Portugal

A sustainable organic synthetic methodology for the preparation of novel biocompatible ionic liquids (ILs) based on gluconate anion has been developed. Four functionalized methylimidazolium cations were efficiently combined with gluconic acid by acid-base neutralization reactions. All salts were obtained as RTILs in high yields (92–98%) and in high purity levels. Proton Nuclear Magnetic Resonance (^{1}H NMR) studies had proved the correct cation/anion proportion (1:1) and their chemical stability. These novel gluconate ILs can be applied for chemistry, material science, and medicine areas.

Keywords: gluconate; biocompatible; ionic liquids

1. Introduction

Ionic liquids (ILs) have emerged as a possible environmentally benign alternative to classic organic solvents, mainly due to their almost negligible vapor pressure, high thermal stability and ionic conductivity, large electrochemical window, insolubility in supercritical CO_2 (scCO_2), and dissolution of a large range of organic molecules and transition metal complexes (*1*). The physical and structural properties of the ILs are generally dependent on the combination of cation/anion structures. Applications of ILs (*2*) include their use as recyclable media for chemical processes, including bio- and chemical catalysis, CO_2 capture, biphasic extraction, gas chromatography, selective transport using supported liquid membranes, pervaporation, dissolution of cellulose, in fuel cells, and their potential use as a matrix for mass spectrometry or as solvent in nuclear electrical power plants, among others.

In the last decade, several synthetic ILs have been produced, characterized from the physical and chemical point of view and apply in several research areas (first generation) (*3, 4*).

Their extremely low volatility and high thermal and chemical stability as well as the possibility to incorporate desired functions or properties rendered the denomination of task-specific ILs (second generation) (*5, 6*).

Another recent class of ILs incorporating pharmaceutical drugs had been developed in order to open new platforms for pharmaceutical sciences (third generation) (*7, 8*).

Depending on the cation and anion combination it is possible to develop nontoxic and biodegradable ILs (*9*).

In this context, different examples of biocompatible organic cations or anions including amino acids, carbohydrates, and their derivatives have been used (*10*).

Our group has worked in all generations of ILs and the discovery of novel biocompatible cation/anion combinations for several applications (*11, 12*).

Gluconic acid and their derivatives are important for mammalian organisms as intermediates in the carbohydrate metabolism. Gluconate salts are natural substances readily nontoxic and biodegradable both in aerobic and in anaerobic conditions (*13*). They are listed as permitted food additives, which may be added to all food stuffs as long as no special regulations restrict their use (*14*).

In recent years, gluconic acid and its salts have been used in the formulation of food, pharmaceutical, and hygienic products (*15*).

The manufacturing of gluconic acid is based on a fermentation process (*16*). It is possible to produce gluconic acid from glucose through a dehydrogenation reaction catalyzed by glucose oxidase (*17*). Oxidation of the aldehyde group on the C-1 of D-glucose to a carboxyl group results in the production of glucono-d-lactone and hydrogen peroxide (*18*). Production of gluconic acid using the enzyme has the potential advantage that no product purification steps are required if the enzyme is immobilized (*19*). However, this approach is not yet common in the industry.

R = n-ethyl (-C₂H₅),[EMIM]; n-butyl (-C₄H₉),[BMIM];
ethylmethoxymethyl (C₂H₄OCH₃), [C₃OMIM];
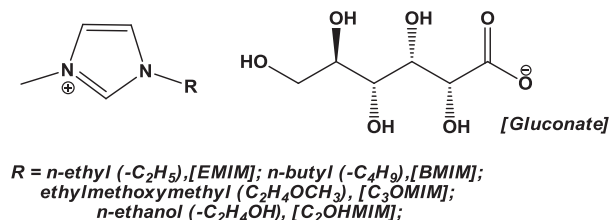n-ethanol (-C₂H₄OH), [C₂OHMIM];

Figure 1. Structure of novel gluconate ILs prepared.

Estimation of the worldwide industrial production per year for all the derivatives of gluconate salts is around 100,000 tones.

The properties of sodium gluconate are attractive in particular for this high sequestering power. It is a good chelator at alkaline pH and, in general, better than ethylenediaminetetraacetic acid (EDTA), nitrilo-triacetic acid (NTA), and other commercial available chelators (20). Aqueous solutions of sodium gluconate are resistant to oxidation and reduction at high temperatures. Another relevant characteristic of sodium gluconate is related with this biodegradability and the possibility to use as efficient plasticizer and inhibiting bitterness in foodstuffs (21). It is well suited for removing calcareous deposits from metals and other surfaces, including milk or beer scale on galvanized iron or stainless steel. Its property of sequestering iron over a wide range of pH is exploited in the textile industry (22), where it prevents the deposition of iron and for desizing polyester and polyamide fabrics. It was also used in detergent industry, bottle and dish washing, cleaning of machinery, equipment and transport cages used in food processing, cleaning agent for ceramic surface, among others.

In pharmaceutical field, some gluconate salts showed relevant antiseptic properties as well as potential interest for drug formulation (23).

Herein, we described the sustainable synthesis of novel biocompatible ILs based on gluconate anion combined with different functionalized methylimidazolium cation as indicated in Figure 1.

2. Materials and methods

2.1. Materials and instruments

All commercial organic solvents were used as supplied from Sigma-Aldrich in analytical purity grade.

Gluconic acid and sodium gluconate (99%, Alfa Aesar), Amberlite IRA-400-OH anionic resin (Sigma-Aldrich), and chloride or bromide functionalized methylimidazolium salts in particular [EMIM][Br], [BMIM][Cl], [C₂OHMIM][Cl] and [C₃OMIM][Cl] (Solchemar, >98%) were used as supplied.
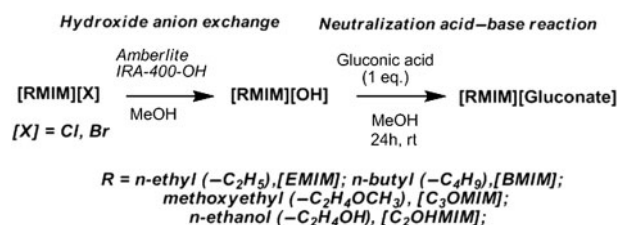
Hydrogen-1(1H) and Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Bruker AMX400 spectrometer. Chemical shifts are reported downfield in parts per million using MeOD or D₂O as deuterated solvents. Sodium gluconate was checked by NMR for comparison with gluconate ILs. The removal of the volatile solvent was performed with rotary evaporator equipment (Bruker) accomplished under high vacuum.

Differential scanning calorimeter (DSC) analysis was carried out by using a TA Instruments Q-series TM Q200 DSC with a refrigerated cooling system. The sample is continuously purged with 50 mL/min nitrogen gas, and 2–8 mg of salt was crimped into an aluminum standard sample pan with lid. The samples were submitted to an isothermal step (40°C, 10 minutes) and then heated to 250°C (10°C/min). The melting point and the decomposition temperatures were determined in the heating process. The decomposition temperature was determined using the inflection point of the endothermic behavior.

2.2. Synthesis of biocompatible ILs based on gluconate anion

The selected methylimidazolium organic cations in chloride or bromide form ([EMIM][Br]; [BMIM][Cl]; [C₂OHMIM][Cl]; [C₃OMIM][Cl]; 2.1 mmol) were dissolved in methanol and passed through an anion-exchange column Amberlite IRA-400-OH (5 eq., flux rate 0.133 mL/mL.min). Then, the prepared hydroxide cation solution was slowly added to gluconic acid (2 mmol) dissolved in methanol. The mixture was stirred at room temperature for 1–2 hours after complete dissolution. Finally, methanol was evaporated and then the desired pure products were dried in vacuum for 24 h. All the final products were obtained in high yield and purity levels as room temperature ILs (RTILs) (Scheme 1).

R = n-ethyl (−C₂H₅),[EMIM]; n-butyl (−C₄H₉),[BMIM];
methoxyethyl (−C₂H₄OCH₃), [C₃OMIM];
n-ethanol (−C₂H₄OH), [C₂OHMIM];

Scheme 1. Synthetic methodology for the preparation of novel ionic liquids based on gluconate anion.

1-ethyl-3-methylimidazolium gluconate, [EMIM][gluconate]: Yellow viscous liquid. Yield: 97% (0.59 g). ¹H NMR (400 MHz, MeOD): 1.48 (3H, t, *J* = 8 Hz), 3.26 (1H, m), 3.58 (1H, m), 3.75–3.68 (2H, m), 3.89 (3H, s), 3.97 (1H, m), 4.02 (1H, m), 4.23 (2H, *t*, *J* = 8 Hz), 7.59 (2H, *d*, *J* = 28Hz), 8.94 (1H, s)

¹³C NMR (100 MHz, MeOD): 136.91, 123.89, 122.27, 73.74, 72.36, 71.13, 70.87, 62.59, 45.03, 34.05, 14.60.

1-butyl-3-methylimidazolium gluconate, [BMIM][gluconate]: Pale yellow gel. Yield: 98% (0.65 g).
¹H NMR (400 MHz, MeOD): 1.01 (3H, t, J = 8 Hz), 1.41 (1H, m), 3.89 (2H, m), 3.33 (1H, m), 3.62 (1H, m), 3.83–3.71 (2H, m), 3.95 (3H, s), 4.04 (1H, m), 4.09 (1H, m), 4.24 (2H, t, J = 8 Hz), 7.59 (2H, d, J = 24 Hz), 8.96 (1H, s).
¹³C NMR (100 MHz, MeOD): 136.00, 123.30, 122.05, 73.70, 72.06, 71.02, 70.67, 62.19, 48.92, 35.51, 31.30, 18.60, 12.40.

1-ethanol-3-methylimidazolium gluconate, [C₂OHMIM] [gluconate]: Yellow viscous liquid. Yield: 93% (0.60 g).
¹H NMR (400 MHz, MeOD): 3.26 (1H, m), 3.57 (1H, m), 3.76–3.65 (2H, m), 3.83 (2H, t, J = 6 Hz), 3.89 (3H, s), 4.03 (1H, m), 4.26 (2H, t, J = 4 Hz), 7.52 (2H, d, J = 24 Hz), 8.92 (1H, s).
¹³C NMR (100 MHz, MeOD): 136.28, 123.31, 122.00, 73.97, 72.06, 71.73, 70.17, 62.09, 59.70, 45.94, 35.61.

1-ethylmethoxy-3-methylimidazolium Gluconate, [C₃OMIM][Gluconate]: Yellow gel. Yield: 92% (0.62 g).
¹H NMR (400 MHz, MeOD): 3.25 (1H, m), 3.55 (1H, m), 3.74–3.61 (2H + 1H, m), 3.87 (3H, s), 3.96 (1H, m), 4.02 (1H, m), 4.33 (2H, t, J =4 Hz), 7.50 (2H, d, J =20 Hz), 8.88 (1H, s).
¹³C NMR (100 MHz, MeOD): 138.01, 122.84, 121.90, 72.94, 72.46, 71.83, 71.07, 70.62, 62.59, 58.91, 47.08, 36.24.

Sodium Gluconate, [Na][Gluconate]: White powder.
¹H NMR (400 MHz, D2O): 3.58–3.54 (1H, m), 3.67 (1H, m), 3.71 (1H, m), 3.74 (1H, m), 3.94 (1H, m), 4.04 (1H, m).

3. Results and discussion

3.1. Synthesis of biocompatible ILs based on gluconate anion

In this work, a sustainable organic synthetic methodology was followed in order to obtain the desired ILs based on gluconate anion in high yields (92–98%) and purity levels (as indicated in Scheme 1).

First, four functionalized methylimidazolium cations previously prepared in the chloride or bromide form ([EMIM][Br]; [BMIM][Cl]; [C₂OHMIM][Cl]; [C₃OMIM][Cl]) were efficiently converted into hydroxide using Amberlite IRA-400-OH anionic resin. This step was optimized through the use of

Table 1. Characterization of gluconate salts including prepared ILs.

Salts	Yield (%)	Physical state	Mp (Td) °C
[H][Gluconate]	n.d.	White solid	131 (200)
[Na][Gluconate]	n.d.	White powder	200 (200)
[EMIM] [Gluconate]	97	Yellow viscous liquid	RTIL (>250)
[BMIM] [Gluconate]	98	Pale yellow gel	RTIL (>250)
[C₂OHMIM] [Gluconate]	93	Yellow gel	RTIL (>230)
[C₃OMIM] [Gluconate]	92	Yellow viscous liquid	RTIL (>230)

appropriate quantity of resin and adequate pH control in order to convert completely the initial bromide or chloride salts. Then, hydroxide organic cations were slowly added to gluconic acid in methanol solution. The final gluconate salts were obtained as room temperature ILs (viscous liquids or gels) in high purity after complete drying in vacuum. This sustainable synthetic strategy avoids the use of metal salts for anion-exchange methods which in general involve several steps of purification and lower reaction yields.

The possibility to apply with success a neutralization acid–base reaction requires the chemical stability of hydroxide organic cations as well as the use of strong or mild organic or inorganic acids. In this case, methylimidazolium cations are stable in different chemical conditions such as in acidic, basic, oxidative, and reduction media, while gluconic acid is enough strong for effective neutralization reaction.

Table 1 summarizes all the prepared gluconate ILs comparing with initial gluconic acid and its sodium salt.

3.2. Characterization of novel gluconate-based ILs

All novel biocompatible ILs based on gluconate anion were obtained as viscous liquids or gels comparing with initial solids of gluconic acid (131°C) or its sodium salt (205°C). The exchange of initial inorganic cation to organic bulky cation based on methylimidazolium units allowed a significant reduction of their melting point. Additionally, a thermal stability improvement was achieved in the case of gluconate ILs (higher than 230°C) comparing with initial gluconate salts (lower than 200°C).

A detailed ¹H NMR study was performed in order to check the chemical stability of cation and anion and their correct proportion (1:1 cation/anion) as well as the final purity of the salts (indicative purity level

according to the presence of protons in NMR spectra). For ^{1}H-NMR spectra of different ILs based on gluconate was selected methanol as deuterated solvent allowing a simplest NMR profile (OH groups from gluconate do not appear in the spectra).

A chemical shift to the left was observed for protons in pendant substituent group of cations and protons close to carboxylate group from gluconate anion in which it is more pronounced in the case of hydrophilic organic cations in particular [C$_2$OHMIM] and [C$_3$OMIM] examples.

Also, acidic proton (H-2) from the imidazolium ring should interact with gluconate anion by hydrogen bonding. All characteristic carbons from different ILs based on gluconate anions can be identified by analysis of ^{13}C NMR spectra.

Depending on the selected organic cation combined with the gluconate anion, it is possible to tune different chemical, physical, and thermal properties. Viscosity, density, water and organic solvent solubilities, polarity, and thermal behavior can be modulated through the appropriate selection of functionalized methylimidazolium cation.

4. Conclusion

Novel biocompatible chiral ILs based on the efficient combination of functionalized methylimidazolium cation and gluconate anion have been developed.

All high pure gluconate salts have been obtained as RTILs by sustainable organic synthetic methodology based on anionic resin process followed by an acid–base neutralization reaction.

According to the adequate cation/anion combination, it should be possible to tune physical–chemical properties of final gluconate salts. In this context, these novel biocompatible gluconate RTILs can be applied for asymmetric catalysis or chiral recognition processes, taking advantage of gluconate chirality as well as food or pharmaceutical formulations.

A detailed study of physical, chemical, thermal, and biological properties is required in order to elucidate the potential interest of these novel biocompatible RTILs.

Taking advantage of the peculiar properties of ILs and gluconate salts separately, the combination of these ionic forms can open novel perspectives for future applications in chemistry, medicine, material science, and similar research areas.

Acknowledgments

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