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Alternative Methods for Preparation of Gluconate Salts Using Heterogeneous Non-Metal Catalysts

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Abstract: Gluconate salts can be prepared using alternative non-metal catalysts based on methylene blue dye salt derivatives. Novel Methylene blue (MB) salts based on trifluoromethanesulfonate (TfO) and docusate (AOT) anions have been prepared and characterized by spectroscopic techniques, nuclear magnetic resonance (NMR), Fourier transform infrared spectroscopy (FTIR) and UV-Visible spectra) in order to proof their chemical structure stability as well as final purity. [MB][TfO] showed a similar behavior of commercial available [MB]Cl as homogenous catalyst for preparation of sodium gluconate. Contrarily, [MB][AOT] as non-toxic, lower melting point and water-immiscible dye salt has been used as efficient and recycled heterogeneous catalyst for preparation of sodium gluconate in shorter reaction time, higher yields and purity grade. This alternative method can be extended to other relevant gluconate salts such as calcium, barium, magnesium, potassium, lithium and several transition metals.

Key words: Gluconate salts, methylene blue, docusate, heterogeneous catalyst, redox system.

1. Introduction

Gluconates are natural substances. In mammalian organisms both D-gluconic acid and its 1,5-lactone are important intermediates in the carbohydrate metabolism. Gluconates are readily biodegradable both in aerobic and anaerobic conditions [1]. As the sequestering tendency of gluconates decreases rapidly upon dilution or lowering pH, their chelated metal complexes are destroyed effectively and quickly by biological waste water treatment as well.

Gluconic acid, its salts of sodium, potassium and calcium are all characterized by a low vapour pressure [2] as well as low n-octanol/water partition coefficient (estimated as -5.99 for the sodium salt, -7.51 for the calcium salt, -5.99 for the potassium salt, -1.87 for the free acid).

Most of these compounds are listed as permitted food additives, which may be added to all foodstuffsas long as no special regulations restrict their use [3]. The manufacturing of gluconic acid is based on a fermentation process [4]. Estimation of the worldwide industrial production per year for all the derivatives of gluconate salts is around 100,000 tones.

Gluconic acid can be produced from glucose through a dehydrogenation reaction catalyzed by glucose oxidase [5]. Oxidation of the aldehyde group on the C-1 of D-glucose to a carboxylgroup results in the production of glucono-d-lactone and hydrogen peroxide [6]. Production of gluconicacid using the enzyme has the potential advantage that no product purification steps are required if the enzyme is immobilized [7]. However, this approach is not yet common in the industry.

Current commercial production of sodium gluconateuses submerged fermentation involving the

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use of glucose feedings andsodium hydroxide as neutralizing agent [8] (pH is held at 6.0-6.5 and the temperature at about 34 °C).

The properties of sodium gluconateare attractive in particular this high sequestering power. It is agood chelator at alkaline pH and in general better than ethylene diamine tetraacetic acid (EDTA), nitrilotriacetic acid (NTA) and other commercial available chelators [9]. Aqueoussolutions of sodium gluconate are resistant to oxidation and reduction at high temperatures. Another relevant characteristic of sodium gluconate are related with this biodegradability and the possibility to use as efficient plasticizer and inhibiting bitterness in foodstuffs [10]. In recent years, gluconic acid and its salts have been used in the formulation of food, pharmaceutical and hygienic products [11].

Sodium salt of gluconic acid has the outstanding property to chelate calcium and other di- and trivalent metal ions. It is used in the bottle washing preparations, allowing the prevention of scale formation and its removal from glass. 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 [12], where it prevents the deposition of iron and for desizing polyester and polyamide fabrics. It is also used in metallurgy for alkaline derusting, as well as in the washing of painted walls and removal of metal carbonate precipitates without causing corrosion [13]. This also finds application as an additive to cement, controlling the setting time and increasing the strength and water resistance of the cement.

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, etc.. Sodium gluconate is manufactured by fermentation process in large commercial scale. For fermentation process, it produces wastewater and environment problem. In recent years, alternative processes including catalytic methods [14] have been studied.

For noble metal catalyst process [15], which was a green chemical process, catalyst deactivation and short lifetime of catalyst also cause problems for production. A lot of research work has been done to improve effectiveness of catalyst and prevent catalyst deactivation by promoter such as lead, bismuth etc. Lead and Bismuth are the most common promoters but many others including Cd, Tl, Ag, Te, Se, Co, Ce and Sn have been proposed [14]. When used alone, these elements are inactive for the concerned oxidation reactions, but when associated with the noble metal, they considerably increased the overall catalytic performances (activity, selectivity and the lifetime of the catalysts.)

Bian et al. [16] reported the use of Bi-Pd/C catalyst as a very promising and effective catalyst for industrial production of sodium gluconatefrom glucose with the advantage of simple and green chemical process compared with enzymatic process. For industrial applications, cost effective and lifetime oroutput for per kilogram catalyst is a crucial point.

The possibility to develop alternative methods for the production of gluconate salts using non-enzymatic and non-metal catalysts are very attractive research field in terms of academic research as well as industrial point of view.

In this context, methylene blue [17] is a heterocyclic aromatic chemical compound which can be used asa potent cationic dye with maximum absorption of light around 670 nm. The specifics of absorption depend on a number of factors, including protonation, adsorption to other materials, and the possibility of formation of the dimers and higher-order aggregates depending on concentration and other interactions.

The applications of methylene blue (MB) have been described for several fields including biology, medicine and chemistry [18]. In biology MB is used as a dye for a number of different staining procedures as well as in order to examine ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) under the microscope or

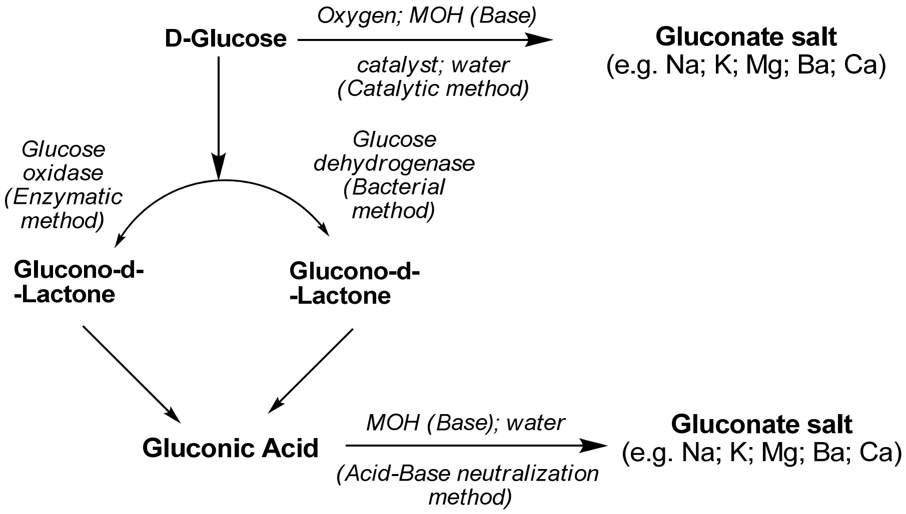

Fig. 1 Methods for the preparation of gluconic acid and gluconate salts.

in a gel [19]. It can also be used as an indicator to determine if a cell such as yeast is alive or not. The blue indicator turns colorless indicating living cells. In medical applications MB is a monoamine oxidase inhibitor (MAOI) [20] and is also structurally similar to the chlorpromazine and the typical antipsychotics. Other medical applications include their use as urinary analgesic/anti-infective/anti-spasmodic as well as for treatment of malaria and recent investigation for the photodynamic treatment of cancer [21].

In chemistry, MB has been studied for different applications in particular their useas photosensitizer in order to create singlet oxygen when exposed to both oxygen and light (production of organic peroxides by a Diels-Alder reaction which is spin forbidden with normal atmospheric triplet oxygen [22].

Methylene blue is widely used as a redox indicator in analytical chemistry. Solutions of this substance are blue when in an oxidizing environment, but will turn colorless if exposed to a reducing agent. The redox properties can be seen in a classical demonstration of chemical kinetics in general chemistry, the “blue bottle” experiment. Typically, a solution is made of glucose (dextrose), methylene blue, and sodium hydroxide. Upon shaking the bottle, oxygen oxidizes methylene blue, and the solution turns blue. The dextrose will gradually reduce the methylene blue to its colorless, reduced form. Hence, when the dissolved dextrose is entirely consumed, the solution will turn blue again.

2. Experiments

General remarks: commercially available reagents were purchased from Aldrich, BDH and Solchemar and then used as received. The solvents were purchased from Valente &Ribeiro and distilled before used. ^1H spectra in CD_3OD (from Euriso-Top) were performed on a Brucker AMX400 spectrometer at room temperature. Chemical shifts are reported downfield in parts per million (ppm). Fourier transform infrared spectroscopy (FTIR) spectra were carried out on a Perkin Elmer 683.

2.1 Methylene Blue Chloride, [MB]Cl

The starting dye material was used from commercial available compound in 98% of purity.

FTIR (KBr): 3,434, 1,602, 1,494, 1,446, 1,420, 1,393, 1,356, 1,339, 1,255, 1,216, 1,184, 1,160, 1,062, 1,039, 947, 887, 855, 816, 789, 667 cm^{-1}. Mp > 200 °C (decomposition).

2.2 Preparation of Methylene BlueDocusate, [MB][AOT]

Sodium Docusate (0.8350 g, 1.88 mmol) was dissolved in methanol (5 mL). Methylene blue (0.5 g, 1.57 mmol) was also dissolved in methanol (15 mL) and added to the previous solution. The mixture was stirred at room temperature for 24 h. After the solvent evaporation, the residue was redissolved in acetone to precipitate the undesired inorganic salts. Then, the product was filtered, evaporated and dried in vacuofor 24 h. The desired product was obtained as a dark blue powder (0.823 g, 75%). Mp 163 ºC; ^{1}H-NMR (400.13 MHz, CD_3OD) δ = 7.93 (2H, d, J = 8.00 Hz); 7.47-7.44 (2H, dd, J = 4.00 Hz), 7.33 (2H, d, J = 4.00 Hz), 4.07-3.97 (8H, m), 3.38 (6H, s), 3.60-3.53 (4H, m), 3.42-3.29 (26H, m), 0.88 (12H, t, J = 9.20 Hz), FTIR (KBr): 3,445, 2,962, 2,934, 2,872, 2,863, 2,359, 2,346, 1,734, 1,609, 1,541, 1,495, 1,464, 1,402, 1,357, 1,348, 1,253, 1,220, 1,096, 1,046, 950, 890, 833, 803, 726, 668 cm^{-1}.

2.3 Preparation of Methylene Blue Trifluoromethanesulfonate, [MB][TfO]

Sodium trifluoromethanesulfonate (0.3230 g, 1.88 mmol) was dissolved in methanol (5 mL). Methylene blue (0.5 g, 1.57mmol) was dissolved in methanol (15 mL) and added to the previous solution. The mixture was stirred at room temperature for 24 h. After the solvent evaporation, the residue was redissolved in acetone to precipitate the undesired inorganic salts. Then, the product was filtered, evaporated and dried in vacuo for 24 h. The desired product was obtained as a dark blue powder (0.560 g, 83%). Mp 195 °C; ^{1}H-NMR (400.13 MHz, CD_3OD) δ = 7.86 (2H, br s); 7.43-7.39 (2H, dd, J = 2.80 Hz); 7.27 (2H, s), 3.36 (12H, s), FTIR (KBr): 3,502, 2,360, 2,341, 1,600, 1,533, 1,490, 1,441, 1,396, 1,356, 1,339, 1,266, 1,226, 1,182, 1,153, 1,067, 1,031, 950, 839, 827, 668, 638 cm^{-1}.

2.4 Preparation of Sodium Gluconateusing Methylene Blue Derivatives as Catalysts

An aqueous solution (30 mL) in a flask was used in combination with sodium hydroxide (0.6 g) and glucose (1 g). For each reaction flask was added a catalytic amount of methylene blue salt derivatives as catalysts (2 mol% of each, [MB]Cl and [MB][TfO] as homogeneous system while [MB][AOT] as heterogeneous catalyst) The reactions were carried out at room temperature in the presence of air flux. After 3h of reaction the product (combined with catalyst) was isolated in the case of homogeneous system ([MB]Cl and [MB][TfO]) or was separated from the heterogeneous system ([MB][AOT]) and then isolated. [MB][AOT] can be recovered from reaction media and re-used again. NMR spectra allowed to proof about the final product and their purity.

3. Experimental Results

3.1 Preparation of Methylene Blue Salts Derivatives

Synthetic methods were optimized in order to prepare novel methylene Blue salts in particular using trifluoromethanesulfonate (Triflate) and docusate (AOT) as organic anions (Fig。 2).

The reactions were performed by simple anion exchange reaction in methanol during 24 h at room

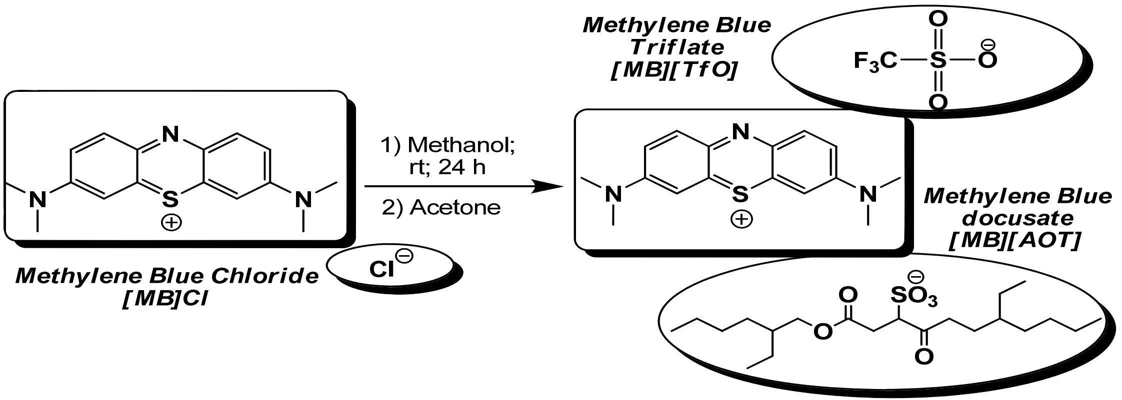

Fig. 2 Preparation of novel methylene blue salts.

temperature. The desired anion as sodium salt (Triflate and docusate) were used in excess (1.2 equivalents) in order to allow a complete exchange reaction.

This synthetic methodology have already been optimized for different other examples of functionalorganic salts including ionic liquids, molten salts and liquid crystals.

The further purification method is a crucial step for the reaction involving the adequate dissolution of the crude (after evaporation of methanol) in acetone in order to precipitate all the inorganic salt (NaCl and unreacted starting materials).

Table 1 summarizes some relevant parameters of the three methylene blue salts studied in this work.

The exchange of chloride to triflate and docusate allowed a reduction of the melting point (avoid the decomposition observed in the case of chloride salt). The desired methylene blue salts were obtained in moderate to high yields (75%to 83%) and high purity levels. Both synthetized salts were completely characterized by ^{1}H and ^{13}C NMR in order to identify the characteristic proton and carbon peaks from cation and anion as well as their final salt stability and purity. FTIR spectra were used as additional helpful spectroscopic technique in order to identify the selected anions (triflateand docusate). Another relevant observation in the case of novel methylene blue salts is related with their water solubility. [MB][TfO] is water soluble in the same line of the starting [MB]Cl while [MB][AOT] is an example of a water immiscible salt.

Complementary UV-Visible studies showed a similar absorption behavior in the UV region in the case of three salts (two characteristic peaks at 245 and 290 nm). In the visible region of the spectra a switch of the maximum wavelength was observed according the type of anion selected (644 nm for [MB]Cl; 639 nm for [MB][AOT] and 633 nm for [MB][TfO].

3.2 Application of Methylene Blue Salts as Heterogeneous Catalysts

All the methylene blue salts were tested as catalysts for preparation of gluconate salts.

Using the optimized “Blue Bottle reaction” is possible to compare the efficiency of three methylene blue salts. An appropriate mixture of glucose, sodium hydroxide and methylene blue salt (chloride, triflate and docusate) in aqueous solution were carried out. It’s already known that glucose in an alkaline solution is slowly oxidized by oxygen from the air in the bottle after a vigorous shake to form gluconic acid, which, in alkaline solution is in the sodium gluconate form. Methylene blue acts as a catalyst in order to facilitate a selective oxidation of glucose, and it is itself reduced to leucomethylene blue and becomes colorless.

If there is enough available oxygen, leucomethylene blue is re-oxidized and the blue color of solution restores.

This methodology was tested for the three methylene blue salts in order to prepare Sodium Gluconate as described in Fig. 3.

Similar behavior was observed between chloride and triflate from methylene blue catalysts. Both salts can be used as homogeneous catalysts due their high water solubility’s and produce sodium gluconate in moderate to high yields (higher than 75%) after 3 hours of reaction. The further purification as well as the catalyst recovering can be problematic related with their solubility behavior.

Table 1 Properties of novel methylene blue (MB) salts.

Compounds	Yield (dye purity)[a]	Melting point (°C)	Maximum wavelength absorption (nm)[c]	Water solubility
[MB]Cl	(98%)	> 200 °C (dec.)[b]	245, 290, 644	Miscible
[MB][TfO]	83% (99%)	195 °C	245, 290, 639	Miscible
[MB][AOT]	75% (98%)	163 °C	245, 290, 633	Immiscible

Legend:[a]Reaction Yield and Dye Purity of each compound estimated from ^{1}H NMR spectra (in brackets); [b]Decompositionof the compound before melting; [c]MaximumWavelength Absorption values from UV and visible region of absorption spectra of each compound solubilized in acetonitrile (1×10^{-5}M).

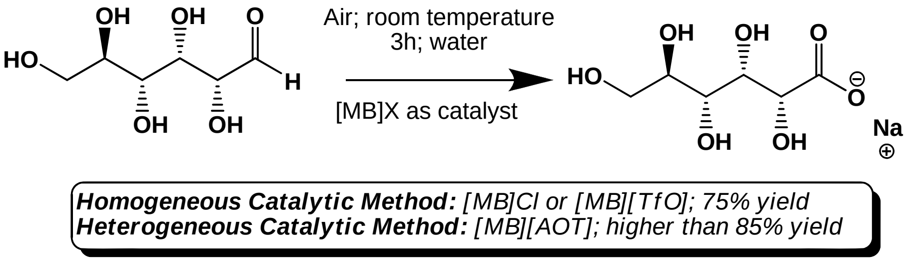

Fig. 3 Comparative catalytic studies for preparation of gluconate salts using methylene blue derivatives as heterogeneous catalyst.

In this context, docusate anion as non-toxic, hydrophobic and biocompatible anion should be an attractive alternative for methylene blue salts as well as the preparation of sodium gluconate. [MB][AOT] was tested as heterogeneous catalyst for synthesis of sodium gluconate using similar reaction conditions described for [MB]Cl and [MB][TfO] salts.

This novel salt showed higher efficiency in order to produce sodium gluconate (higher than 85%) after 3 hours of reaction. In this case the pure sodium gluconate can be removed after evaporation of water while the [MB][AOT] as catalyst can be recycled many times by simple phase separation.

The final sodium gluconate was identified by ^{1}H NMR in order to compare their desired structure and purity.

[MB][AOT] was also check by ^{1}H NMR after reaction in order to compare with initial salt.

4. Conclusions

In this paper, we demonstrated the possibility to develop alternative methylene blue salts using triflate and docusate as anions in order to apply for preparation of sodium gluconate.

Docusate as anion showed several advantages comparing to original chloride salt in particular related with its low toxicity, biocompatibility and water immiscibility. Methylene Blue Docusate is an interesting material in order to be used as efficient, versatile, recyclable heterogeneous catalyst for preparation of sodium gluconate. This sustainable synthetic process can avoid the use of long and expensive enzymatic or metal catalysis.

Other gluconate salts can be prepared using this method according the selection of adequate basic solution. In particular several examples such as potassium, lithium, calcium, barium and other transition metal salts can be considered.

Taking advantage of the properties of methylene blue the novel [MB][AOT] is a very attractive material for efficient catalytic and separation processes as well as for biology and medical approaches.

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