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Synthesis, Characterization and Reduction of *p*-Nitrobenzoyl Hydroxypropyl Cellulose

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Synthesis and structural characterizations of *p*-nitrobenzoyl and *p*-aminobenzoyl hydroxypropyl cellulose were reported in this work. Nitrobenzoyl-hydroxypropyl cellulose was synthesized in good yield *via* esterification reaction between *p*-nitrobenzoyl chloride and hydroxyl groups of hydroxypropyl cellulose (Mw 80,000 and 100,000) in dried dichloromethane using pyridine as a catalyst. *p*-Nitrobenzoylhydroxypropyl cellulose was then attempted many times for its reduction to *p*-aminobenzoylhydroxypropyl cellulose by using three different reducing agents like sodium dithionite, tin(II) chloride dihydrate and palladium on activated charcoal. The resulting *p*-nitrobenzoyl and *p*-aminobenzoyl hydroxypropyl cellulose were characterized by FT-IR and ^{1}H NMR.

Keywords: Hydroxypropyl cellulose, *p*-Nitrobenzoylhydroxypropylcellulose, *p*-Aminobenzoylhydroxypropyl cellulose.

INTRODUCTION

The purpose of the work described in this paper was the synthesis of hydroxypropyl cellulose (HPC) containing primary aromatic amino groups. In the synthesis of heterocyclic compounds the aromatic amines play a major role. Usually such type of aromatic amines are achieved by the reduction of polymer-supported nitro derivatives[1]. Cellulose derivatives with aromatic NH_2 groups can be used to immobilize enzyme or immunoprotiens *via* diazo coupling in bio-chemical sensor technology[2]. On diazotization NH_2-functionalized cellulose derivatives can couple to many aromatic hydroxyl and aromatic amines that can play a vital role in pharmaceutical and textile sectors[3]. However, the synthesis pathways are frequently very complex for achieving this type of a target[4].

In solution phase chemistry, the reduction of aromatic nitro compounds is not a difficult task as compared to heterogeneous phase[5]. Recently, many novel reduction methods have been reported in the literature for small nitro compounds and polymer-supported aromatic nitro groups. The reducing agents that are routinely used are zinc, iron, or tin, in the presence of an acid, catalytic hydrogenation using Ni or Pd/C and other reagents like sodium dithionite *etc*[6]. However, the reduction of aromatic nitro groups on solid supports is still challengeable. The reduction of polymers having aromatic nitro groups through esterification or etherification reactions is unpredictable. The major challenges in this area are solubility issue, cleanly and completely conversion of all aromatic nitro groups, sensitivity of other functional groups, purification and to find the optimum conditions for large scale.

The goal of the present study was to develop *p*-aminobenzoylhydroxypropyl cellulose (HPC-NH_2) in a two-step process. During the first step, hydroxypropyl cellulose was esterified with *p*-nitro-benzoyl chloride and in the second step the aromatic nitro group was subjected to the reduction process to give primary amino group. The comparative reducing effects of sodium dithionite, tin(II) chloride dihydrate and catalytic hydrogenation using Pd/C were observed in this study. This finding will contribute to the development of a novel polyaromatic polyamine macromolecular carrier.

EXPERIMENTAL

Hydroxypropyl cellulose (Mw 100,000 and 80,000) was purchased from Sigma Aldrich (USA) and dried at 50 °C under vacuum for 3 days before use. *p*-Nitrobenzoyl chloride and palladium on activated charcoal (10 %) was purchased from Fluka (Switzerland). Rest of the chemicals and solvents were of analytical grade. IR spectra were recorded on a Perkin-Elmer FT-IR model spectrum one spectrophotometer. Catalytic hydrogenation was completed by hydrogenation apparatus (Parr® Low Pressure, USA). ^{1}H NMR spectra were recorded by the Varian Nuclear Magnetic Resonance Spectrometer (500 MHz). ^{1}H NMR spectra of all the products (10 mg sample/mL) were measured in dimethyl sulfoxide (DMSO-d_6) at 60 °C.

Esterification of hydroxypropyl cellulose with *p*-nitrobenzoyl chloride: In the first step of the synthesis, 10 g (29.8 mmol) hydroxypropyl cellulose was dissolved in a 160 mL of dried dichloromethane in a two-necked round bottom flask with constant mechanical stirring at room temperature. Pyridine 12 mL (149 mmol) was added to the flask as an acid acceptor and *p*-nitrobenzoyl chloride 27.6 g (149 mmol) was added lastly by parts. The reaction mixture was heated at 25 °C overnight under nitrogen atmosphere. The solution that was obtained after the required time was clear and viscous with light yellow colour. The solution was evaporated for removing dichloromethane and re-dissolved in DMSO for transferring into the dialysis bag. The polymer product was purified by dialysis against distilled water (MWCO = 12,000-14,000 Da) for at least 3 days. The purified *p*-nitrobenzoylhydroxypropyl cellulose ester conjugate was obtained by lyophilization[7]. Yield: 85 % based on DS 2.52.

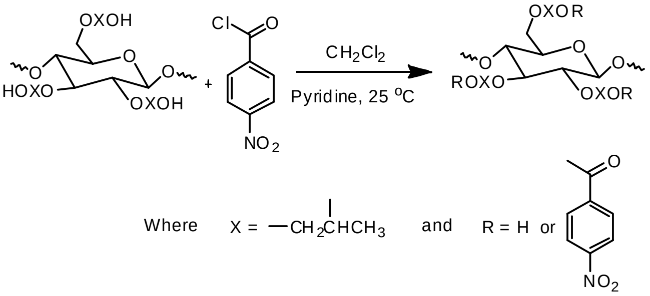
Reduction by hydrogenation: *p*-Nitrobenzoylhydroxypropyl cellulose ester conjugate was tried to reduce by catalytic hydrogenation using 10 % Pd/C as a catalyst. First of all, 40 mL dried THF was bubbled by nitrogen gas for few minutes and 10 % Pd/C (0.60 g) was added and activated by hydrogen gas for 10 min in the reaction flask. HPC-nitro (-NO_2) conjugate (2 g, 5.2 mmol) was then added and hydrogenated in a Parr Hydrogenator Apparatus by maintaining H_2 gas pressure at 25 (lbs/inch^2) for 12 h and the reaction mixture was then immediately filtered on a bed of celite to remove the catalyst. The dark yellow clear solution was then evaporated and dried in vacuum overnight[8].

Reduction by tin(II) chloride dihydrate: In this method, *p*-nitrobenzoylhydroxypropyl cellulose (2 g, 5.2 mmol) was dissolved in 30 mL DMF at 50 °C and 1 M tin(II) chloride dihydrate solution 30 mL prepared in DMF was added to the HPC-NO_2 solution slowly. The reaction mixture was homogeneous and stirred for 16 h at 50 °C. The resulting mixture was tried to purify by dialysis against distilled water (MWCO = 12,000-14,000 Da) for at least 3 days to remove excess tin and byproducts[5].

Reduction by sodium dithionite: *p*-Nitrobenzoylhydroxypropyl cellulose (2 g, 5.2 mmol) was dissolved in 30 mL DMF at 45 °C and sodium dithionite (24 g, 138 mmol) was dissolved in water and added dropwise to *p*-nitroben-zoylhydroxypropyl cellulose (HPC-NO_2) solution. The reaction medium was kept basic (pH 8-9) by $NaHCO_3$ and the reaction mixture was stirred at 45 °C for 24 h. The resulting product was purified by dialysis against distilled water (MWCO = 12,000-14,000 Da) for at least 24 h to remove excess sodium dithionite and byproducts. The product was obtained from the dialysis residue by lyophilization with 76 % yield[9].

RESULTS AND DISCUSSION

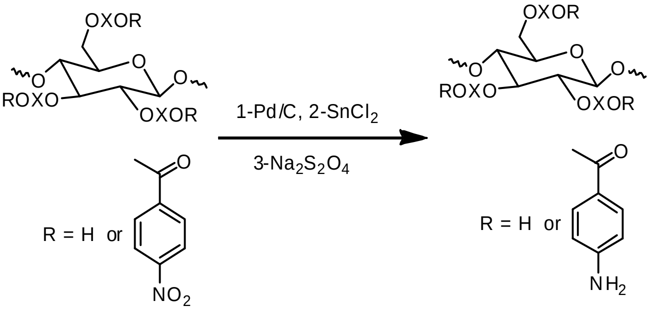
Hydroxypropyl cellulose with molecular weight 80,000 and 100,000 was selected as a backbone for the attachment of *p*-nitrobenzoyl chloride due to its properties like safety, pH insensitivity and solubility both in water and polar organic solvents. Hydroxypropyl cellulose is low-cost and biocompatible pharmaceutical excipient with three hydroxyl groups per anhydroglucose unit. In this study, these hydroxyl groups were esterified with *p*-nitrobenzoyl chloride under homogeneous reaction conditions in dry dichloromethane as a solvent and pyridine as bases to capture the released hydrogen chloride according to the synthesis given in **Scheme-I**. The product hydroxypropyl cellulose-NO_2 was easily purified by dialysis against distilled water because the impurity pyridinium chloride was soluble in water.



Scheme-I: Reaction between hydroxypropyl cellulose and *p*-nitrobenzoyl chloride

Hydroxypropyl cellulose was reacted with different molar ratios of *p*-nitrobenzoyl chloride but the maximum nitration was achieved with five fold excess of *p*-nitrobenzoyl chloride. The native hydroxypropyl cellulose was soluble in water but after the incorporation of aromatic nitro groups it could not preserve its water solubility property. Hydroxypropyl cellulose-NO_2 has solubility in organic solvents like dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), dimethyl acetamide (DMA), tetrahydrofuran (THF), *etc*,

The reduction of the aromatic nitro group to its respective amine can be completed by different ways. The reduction of HPC-NO_2 was carried out by using three different reducing agents *i.e.* sodium dithionite, tin(II) chloride dihydrate and catalytic hydrogenation using Pd/C according to the synthesis given in **Scheme-II**.



Scheme-II: Reduction of *p*-nitrobenzoylhydroxypropyl cellulose (HPC-NO_2) by Pd/C, $SnCl_2$ and $Na_2S_2O_4$

The complete and clean conversion of polymer supported aromatic nitro groups to primary amino groups is a high value task in organic synthesis. The reduction of aromatic nitro groups is readily accomplished in solution phase chemistry as compared to the solid phase. The major challenge is insolubility issue and in this situation the reducing agent has not complete access to -NO_2 groups. The reducing agent can reduce only outer surface of the polymer supported aromatic nitro groups but it cannot approach to the aromatic nitro groups that are present on the inner surface. *p*-Nitrobenzoylhydroxypropyl cellulose (HPC-NO_2) product has not capability to swell in an aqueous environment but it has good solubility in organic solvents. We conducted a comparison study of three different reducing agents for the reduction of HPC-NO_2.

The catalytic hydrogenation method was used in this study because it is the cleanest and simplest. In the first attempt we used dried methanol as a solvent but HPC-NO_2 could not soluble in this solvent. THF was selected as a solvent of choice after examination of many solvents for this reaction. *p*-Nitrobenzoylhydroxypropyl cellulose (HPC-NO_2) has solubility in THF and it can evaporate easily after completion of the reaction. The reaction was carried out in heterogeneous phase because HPC-NO_2 was in solution phase but on the other hand palladium on activated charcoal was in solid phase. The reaction was run for different time intervals and at different pressures and finally H_2 gas pressure at 25 (lbs/inch^2) and reaction time of 12 h were selected. The result demonstrated that most of the nitro groups on the polymers have been reduced to give HPC-NH_2. Some of the nitro groups remained may be due to the heterogeneous reduction conditions. About 60 % of the product yield (calculated by weight) was obtained. Some of the product was lost during the filtration process through celite.

In case of tin(II) chloride dihydrate the reduction of HPC-NO_2 was carried out homogeneously in DMF. HPC-NO_2 has good solubility in DMF along with tin(II) chloride dihydrate and that is why all the aromatic nitro groups were completely and cleanly converted to amino groups. The HPC-NH_2 was obtained from the dialysis residue by lyophilization and the percentage yield of HPC-NH_2 (calculated by weight) was up to 140 %. Despite the advantages of tin reduction, we observed that substantial quantities of tin by-products remain inside the dialysis bag due to insolubility in distilled water.

Sodium dithionite was investigated as an alternative to tin due to inexpensive, non-toxic, neutral and specific to the reduction of nitro compounds in the presence of other functionalities. We carried out an examination of HPC-NO_2 reduction by sodium dithionite. Optimum conditions for the reduction of HPC-NO_2 involving, type of solvent (water, organic solvents *e.g.* DMA, DMF, DMSO, THF, cosolvents, *etc.*), quantity of reducing agent (nitro product : reducing agent, 1:4, 1:6, 1:8, 1:10 and 1:12 by weight), reaction time (8, 12, 16, 20 and 24 h), reaction temperature (room temperature, 45, 60 and 85 °C) and dialysis time (12, 18 and 24 h) were monitored. The optimum conditions for the reduction of HPC-NO_2 were determined as following : In water, sodium dithionite was readily soluble but HPC-NO_2 was not soluble. To solve this issue we first prepared the homogeneous solution HPC-NO_2 in DMF and then added aqueous solution of sodium dithionite slowly. The pH was maintained at 8 to 9 since it is known that the best reduction condition using sodium dithioniteas a reducing agent should be performed in basic condition[10] and its consumption was determined such as 1 g of the HPC-NO_2 require almost 12 g of sodium dithionite, with 24 h reaction time at 45 °C and dialysis time was 24 h. Sodium dithionite did not give any reduction in organic solvents alone like DMA, DMF, DMSO, THF, *etc.* due to the insolubility in these solvents.

In FT-IR spectra (Fig. 1) and data of the native hydroxypropyl cellulose (A), the OH group stretching of native hydroxypropyl cellulose appeared in the range of 3600-3200 cm^{-1} and OH bending appeared near ~1020 cm^{-1}. In case of HPC-NO_2 (B) the strong absorption bands appeared at 1527 and 1348 cm^{-1} correspond to NO_2 asymmetric and symmetric stretch, respectively. The absorption band at 1276 cm^{-1} correspond to C-N stretching and an absorption band appeared at 1722 cm^{-1} due to carbonyl stretching. These FT-IR results confirmed the esterification reaction between hydroxypropyl cellulose and *p*-nitrobenzoyl chloride. Catalytic hydrogenation using 10 % Pd/C as a catalyst (C) reduced maximum NO_2 to NH_2 as in FT-IR results N-H stretching absorption bands appeared at 3460 and 3364 cm^{-1} but on the other hand small peaks of NO_2 are still present at 1527 and 1348 cm^{-1}. In case of using tin(II) chloride dihydrate (D) and sodium dithionite (E) as the reducing agents,the NO_2 peaks were completely disappeared but no bands assigned to N-H stretching and bending in the range of 3500-3000 and 1640-1560 cm^{-1}, respectively. This may be due to the overlapping of OH stretching band of unreacted hydroxyl groups, in the range of 3600-3000 cm^{-1} and the bending of adsorbed water molecules at approximately 1650 cm^{-1} because HPC-NH_2 was purified by dialysis process against distilled water. The aromatic sharp peak was observed at 1607 cm^{-1} in all the cases except native hydroxypropyl cellulose.

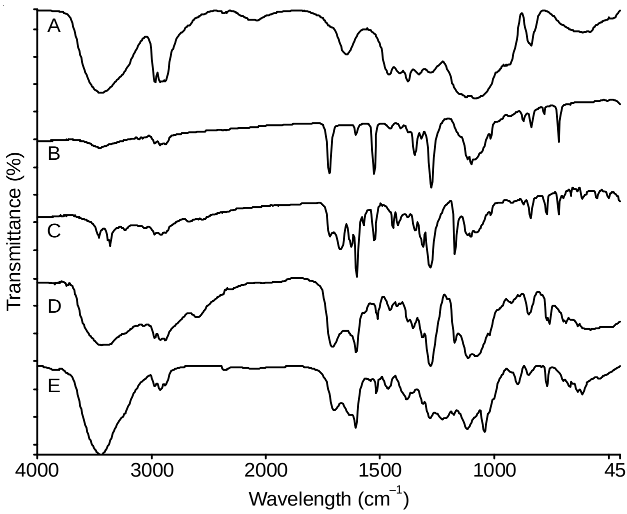


Fig. 1. FTIR spectra of: (A) HPC, (B) H.PC-NO_2, (C) HPC-NH_2 by Pd/C, (D) HPC-NH_2 by tin(II) chloride dihydrate, (E) HPC-NH_2 by sodium dithionite

^{1}H NMR spectrum (not shown) further confirmed the synthesis of HPC-NO_2 and HPC-NH_2 as the multiplet signals of protons of aromatic moiety appeared from 6.7 to 8.2 ppm. In case of HPC-NH_2 the aromatic amines was simply tested and confirmed by diazotization reaction.

Conclusion

p-Nitrobenzoylhydroxypropyl cellulose was synthesized by homogeneous reaction in dried dichloromethane in combination with *p*-nitrobenzoyl chloride and characterized successfully. Light yellow HPC-NO_2 was organo soluble and a comparison study of its reduction was conducted by using three different reducing agents. According to the reduction results sodium dithionite was found to be the better choice for nitroreduction because it is safer and low cost as compared to tin(II) chloride dihydrate and palladium on activated charcoal. Both the molecular weights of hydroxypropyl cellulose (Mw 80,000 and 100,000) behave similarly in case of esterification and reduction. Further studies are planned with the help of sodium dithionite by finding a suitable phase-transfer catalyst and solvent system to minimize its consumption during reduction process.

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REFERENCES

1. R. Kaplanek and V. Krchnak, *Tetrahedron Lett*., **54**, 2600 (2013).
2. P. Berlin D. Klemm A. Jung H. Liebegott R. Rieseler J. Tiller. P. Berlin, D. Klemm, A. Jung, H. Liebegott, R. Rieseler and J. Tiller, *Cellulose*, **10**, 343 (2003).
3. S. Chang, B. Condon and J.V. Edwards, *Fibers and Polymers*, **11**, 1101 (2010).
4. R.R. Mclaughlin and D.B. Mutton, *Can. J. Chem*., **33**, 646 (1955).
5. R.A. Scheuerman and D. Tumelty, *Tetrahedron Lett*., **41**, 6531 (2000).
6. P.S. Kumar and K.M. Lokanatha Rai, *Chem. Papers*, **66**, 772 (2012).
7. J. Zhang, J. Wu, Y. Cao, S. Sang, J. Zhang and J. He, *Cellulose*, **16**, 299 (2009).
8. T.F. Conceicao, J.R. Bertolino, G.M.O. Barra, S.L. Mireski, A.C. Joussef and A.T.N. Pires, *J. Braz. Chem. Soc*., **19**, 111 (2008).
9. D.H. Campbell, E. Luescher and L.S. Lerman, *Proc. Natl. Acad. Sci. USA*, **37**, 575 (1951).
10. J.G. De Vries and R.M. Kellogg, *J. Org. Chem*., **45**, 4126 (1980).