

A Novel Process to Prepare Chemoselectively Protected N-Phthaloyl-Chitosan without Drying of Solvent and Purging of Water Vapor

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ABSTRACT

A new process for preparing chemoselectively protected N-phthaloyl-chitosan microspheres, which was simple and practicable, was reported in this paper. Chitosan was phthaloylated using phthalic anhydride in dimethylformamide as solvent with addition of 5% water (v/v) as cosolvent and without drying of solvent to remove the contained water and without flowing of nitrogen to purge water vapor during reaction process. As comparison, the same condition reaction was also performed to prepare N-phthaloyl-chitosan but without addition of 5% water as cosolvent. The FTIR spectra showed that chemoselectively protected N-phthaloylation of chitosan can be prepared without pretreatment of solvent drying and without treatment of water vapor purging during the reaction.

Keywords: selective, protection, phthaloyl, chitosan.

1. INTRODUCTION

Chitin is the second most abundant natural polysaccharide, generally found in the composition of crustacean shells, insects, molluscan organs, and fungi. Chitosan is obtained from chitin by alkaline hydrolysis with inorganic base; the process essentially hydrolyzes N-acetyl groups at random within the polymer backbone (Fig. 1). Chitin and chitosan have gained tremendous interest due to their properties as non-toxic, biocompatible, and biodegradable polymers. Chitin is insoluble in water and almost all organic solvents while chitosan is soluble in dilute organic acid solutions such as acetic, formic, succinic, and lactic acids at pH below 6.5. Therefore, the applications of chitin and chitosan are limited due to less solubility in water and organic solvent. In order to improve the solubility and physicochemical and biological properties, several chemical modifications of chitosan have been reported (Sajomsang, 2010).

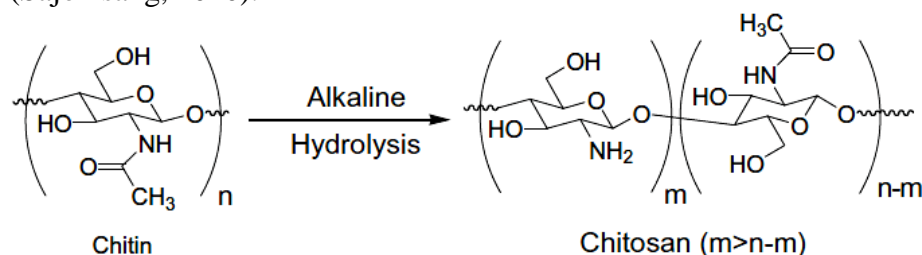


Fig. 1. Preparation of chitosan from chitin.

Phthaloylation can be a practical way for solubilization of chitosan in organic solvents, since the phthaloyl group is bulky and eliminates hydrogen from the amino group to prevent hydrogen bonding. In addition, phthaloylation can protect the amino functionalities of chitosan, and deprotection regenerates thee free of amino groups. Therefore, the N-phthaloyl group can be indispensable for both protection and solubilization. N-phthaloyl-chitosan has also proved to be most promising for conducting modification reaction with good facility and regioselectivity under mild conditions in solution (Kurita, 2001).

Phthaloylation of chitosan is usually performed in *N,N*-dimethylformamide (DMF) with excess phthalic anhydride at 120-130 °C for 8 h. Treatment of chitosan with phthalic anhydride, however, generally results in partial *O*-phthaloylation in addition to the *N*-substitution. With the phthaloylated product as a key intermediate, various modification reactions proceed smoothly in solution, but the *O*-phthaloyl group is an obstacle in most cases to quantitative and regioselective substitution (Nishimura *et al*, 1991). Kurita *et al* (2002) reported on a simple and reliable method to provide chemoselectively protected *N*-phthaloyl-chitosan in one step using DMF containing 5% water as a solvent. Interestingly, however, although Kurita *et al* (2002) using 5% water (v/v) as a cosolvent, he still use drying pretreatment to remove of water from the DMF as solvent and flowing nitrogen to purge of water vapor during reaction process. We report here a simple method to provide chemoselectively protected *N*-phthaloyl-chitosan using DMF containing 5% water as a solvent without pretreatment of drying of DMF and without flowing nitrogen to purge of water vapor during reaction process.

2. MATERIALS AND METHODS

2.1. Materials

Chitosan was obtained from deacetylated chitin that isolated from shrimp shells. *N,N*-dimethylformamide (DMF) and phthalic anhydride were obtained from Merck (Germany). All chemicals were used without further purification.

2.2. Synthesis of *N*-phthaloyl-chitosan

To a solution of 0.83 g (5.6 mmol) of phthalic anhydride in 6 mL of *N,N*-dimethylformamide (DMF) containing 5% (v/v) water was added 0.300 g of chitosan, and the mixture was heated at 90 °C with stirring. After 8 h of reaction, the resulting pale tan mixture was cooled to room temperature and poured into ice water. The precipitate was collected on a filter, washed with 150 mL of methanol at room temperature for 1 h, and dried to give the product as a pale tan powdery material. As comparison, the same condition reaction was also performed to prepare *N*-phthaloyl-chitosan but without addition of 5% water (v/v) as cosolvent. The products were characterized by recording the FTIR spectrum on a Shimadzu FTIR (IRPrestige-21).

3. RESULTS AND DISCUSSION

Protection of the functional groups of chitosan is crucial for conducting modification reactions in a well-controlled manner, and introduction of the phthaloyl group at the amine functionality is ideal not only for the protection but also for improving solubility.

Phthaloylation of chitosan is usually performed in DMF with excess phthalic anhydride at 120-130 °C for 8 h. Interestingly, however, the *ds* (degree of substitution) decreased to some extent on prolonged reaction. This implies the possibility of hydrolytic cleavage of the once formed ester linkages with the water produced by *N*-phthaloylation. Kurita *et al* (2002) reported on a simple and reliable method to provide chemoselectively protected *N*-phthaloyl-chitosan in one-step using DMF containing 5% water as a solvent. It is interesting to examine the preparation of chemoselectively protected *N*-phthaloyl-chitosan using DMF containing 5% water as a solvent without pretreatment of drying of DMF and without flowing of nitrogen to purge of water vapor during reaction process.

The structures of both products were confirmed by the characteristic peaks of phthalimido group (1774, 1712 cm^{-1} (C=O anhydride)), and aromatic ring (721 cm^{-1}), as shown in Fig. 2. The product prepared in DMF showed weak bands at 2600-2700 cm^{-1} (free carboxyl) and sharp ones at 1288 and 1265 cm^{-1} (ester) in the FTIR spectrum that suggests incomplete cyclization at the amino group and/or partial *O*-phthaloylation (Scheme 1). The product obtained in the mixed solvent (DMF and 5% water) showed very weak bands at 1288

and 1265 cm^{-1} and no appreciable bands due to ester carbonyl at about $2600\text{--}2700\text{ cm}^{-1}$. This result is in accordance with the previous result (Kurita *et al*, 2002) that used DMF and 5% water as a mixed solvent and with pretreatment of drying water on DMF and by flowing nitrogen to purge of water vapor during the reaction.

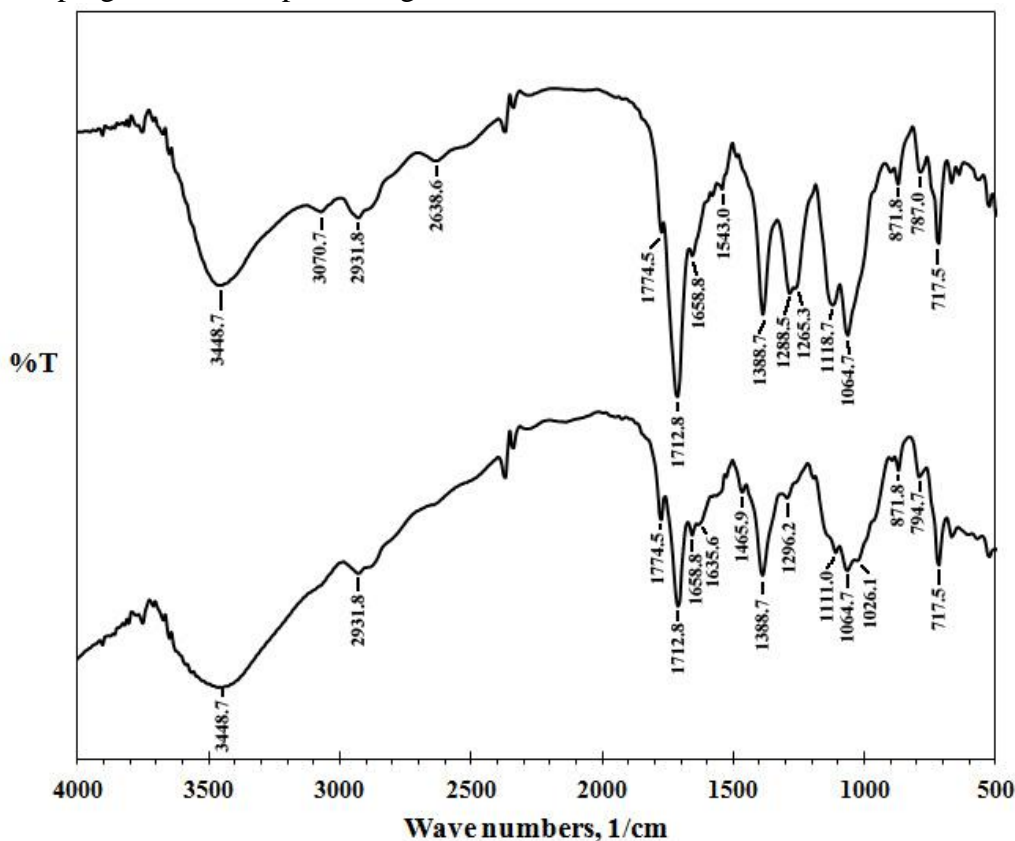
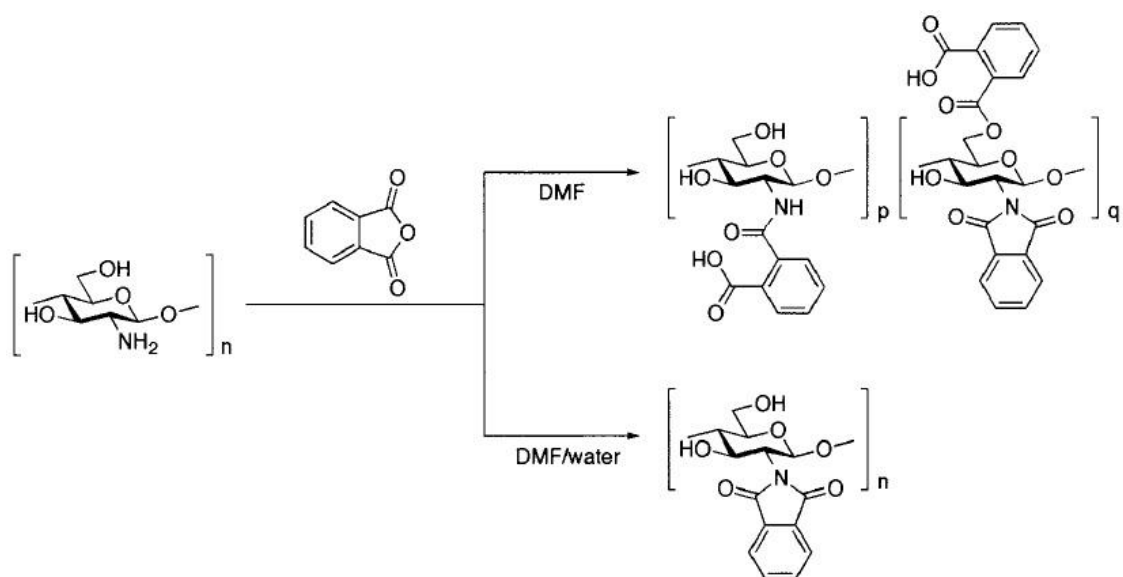


Fig. 2. FTIR spectra of phthaloylated chitosan prepared by the reaction at $90\text{ }^{\circ}\text{C}$ for 8 h in DMF without addition of water (top) and at $90\text{ }^{\circ}\text{C}$ for for 8 h in DMF/water (95:5) (bottom). Both products were obtained by reaction without pretreatment of drying of solvent and without purging of water vapor during reaction process.



Scheme 1

A qualitative solubility test indicated that the resulting *N*-phthaloyl-chitosan was soluble in organic solvent such as *N,N*-dimethylacetamide/8% LiCl. It swelled in more

common solvents such as DMF. Kurita *et al* (2002) have shown that the relatively low solubility of *N*-phthaloyl-chitosan may be partly attributable to some crystallinity as suggested by the X-ray diffractometry.

CONCLUSIONS

Chemoselective *N*-phthaloylation of chitosan could be accomplished successfully in one-step using DMF containing 5% water as a solvent without pretreatment of drying of DMF and without flowing nitrogen to purge of water vapor during reaction process. The *N*-phthaloyl-chitosan exhibited high affinity for organic solvents, although somewhat lower than that of the product having additional *O*-phthaloyl groups. The simple procedure established here enables facile preparation of *N*-phthaloyl-chitosan, a convenient precursor for the construction of sophisticated molecular architectures based on the specialty biopolymer chitosan.

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