Trimethylsilylated Chitosan: A Convenient Precursor for Chemical Modifications

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Trimethylsilylation of chitosan was attained efficiently with hexamethyldisilazane and chlorotrimethylsilane. The resulting silylated derivative was characterized by remarkable reactivity as well as improved solubility and proved to be a convenient precursor for modification reactions.

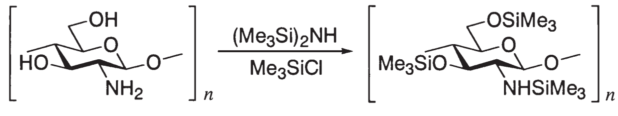
Chitin is a naturally abundant β-(1→4) glucan composed of *N*-acetyl-D-glucosamine and deacetylated to give chitosan. Despite the easy accessibility and distinctive biological activities,[1] these polysaccharides are being used only in a negligible amount owing primarily to their inherent intractable nature. Appropriate modifications of the molecular structures are expected to give rise to novel types of functional biomaterials useful in various fields.[2] Because of the free amino functionality, chitosan is considered to have a much higher possibility than chitin for developing advanced functions as well as for diversifying the structure. The lack in solubility in organic solvents has, however, caused difficulty in structural manipulations to give well-defined derivatives and hence in discussing the structure–property relationship.

Of some reactions of chitosan reported thus far, phthaloylation is particularly important; it improves solubility in organic solvents[3] and has enabled regioselective modifications such as branching.[4] Trimethylsilylation may be another potential method to solubilize chitosan as implied by the marked solubility of trimethylsilylated chitin[5] and cellulose.[6] Furthermore, trimethylsilylated chitosan would show a considerable reactivity to undergo controlled modification reactions in organic solvents. Here we report preliminary results of trimethylsilylation of chitosan and some notable properties of the product.

In order to discuss the trimethylsilylation behavior and to seek optimum conditions, two types of fully deacetylated chitosans (chitosan (α) and chitosan (β) prepared from shrimp α-chitin and squid β-chitin) were used. Deacetylation of α-chitin was effected with 40% sodium hydroxide at 110 °C, but β-chitin was deacetylated at a lower temperature of 80 °C to avoid discoloration.[7]

Trimethylsilylation of chitosan was performed with a mixture of hexamethyldisilazane and chlorotrimethylsilane in pyridine as suggested by the procedure for chitin,[5] and the product was isolated in acetone (Scheme 1). The reaction at room temperature was slow, and the degree of silylation (ds) was around 1.0 with chitosan (β) and 0.5 with chitosan (α) after 96 h as shown in Figure 1, supporting a higher reactivity of chitosan (β).

The reaction was still slow at 70 °C, a temperature for full trimethylsilylation of chitin,[5] but facile at 100 °C as evidenced in Figure 1. Although the difference in reactivity between the two types of chitosans became small at 100 °C, chitosan (β) still gave somewhat higher ds values in general. 4-Dimethylaminopyridine (DMAP) was effective as a catalyst and raised the ds as listed in Table 1. The ds reached 2.8 at 100 °C, but further improvement seemed difficult at reflux. Quinoline was also used as a solvent, which allowed the reaction to proceed at 120 °C, but pyridine was confirmed to be superior, judging from the ds value. The results in Table 1 indicate that the reaction in pyridine at 100 °C for 48 h was suitable for affording a trimethylsilylated derivative.



Scheme 1.

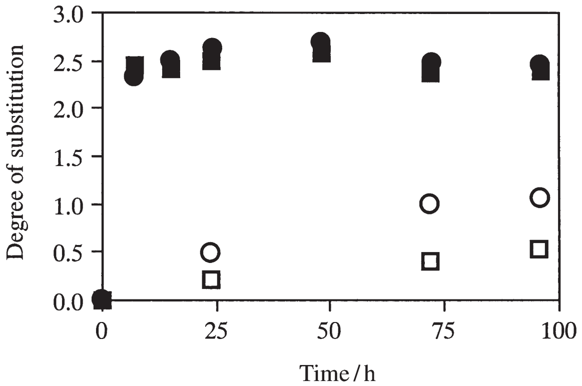


Figure 1. Trimethylsilylation of chitosans with a mixture of hexamethyldisilazane and chlorotrimethylsilane (10 equivalents each to pyranose) in pyridine: □, chitosan (α) at rt; ○, chitosan (β) at rt; ■, chitosan (α) at 100 °C; ●, chitosan (β) at 100 °C.

In the IR spectra of the resulting chitosan derivatives, a broad band at 3400 cm^{-1} due to the OH and NH_2 of chitosan became weak on silylation, while the C–H bands at 2880–2960 cm^{-1} became pronounced. Strong bands appeared at 1254 and 843 cm^{-1}, characteristic of the Si–CH_3 bonds. Elemental analysis data also supported the structure.[8]

A qualitative solubility test of the silylated products re-

Table 1. Trimethylsilylation of chitosans[a]

Chitosan	DMAP/ Pyranose[b]	Temp /°C	Time /h	Degree of silylation[c]
Chitosan (α)	—	100	24	2.50
Chitosan (β)	—	100	24	2.64
Chitosan (β)	—	100	48	2.69
Chitosan (β)	5	100	48	2.82
Chitosan (β)	5	Reflux	48	2.57

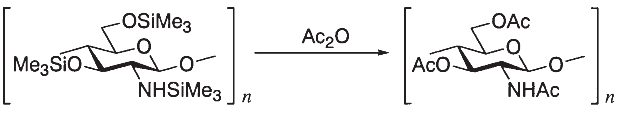
[a]Chitosan, 0.10 g; pyridine, 10 mL; silylating agents (hexamethyldisilazane and chlorotrimethylsilane), 10 equivalents each to pyranose. [b]Mole ratio. [c]Calculated from the C/N value of elemental analysis.

vealed that trimethylsilylation improved the affinity for organic solvents markedly, especially with an increase in the extent of substitution, and the derivative with a ds above 2.6 was almost soluble in pyridine leaving a small amount of highly swollen gels. It was partially soluble and/or swelled considerably in aprotic polar solvents such as dimethyl sulfoxide. Even common low-boiling solvents such as chloroform swelled the derivative moderately. In contrast, chitosan neither dissolved nor swelled apparently in all these solvents.

The resulting trimethylsilylated chitosan is expected to be a precursor suitable for chemical modifications because of the high affinity for organic solvents. To evaluate the silylated chitosan as a precursor, acetylation was examined as a typical example of modification reactions in comparison with that of the original chitosan (Scheme 2). Trimethylsilylated chitosan and chitosan were thus treated with acetic anhydride in pyridine at room temperature, and the acetylated products were isolated in water.

When chitosan (α) was acetylated for 48 h in the presence of DMAP, the degree of acetylation (da) was 1.5 as shown in Table 2. Trimethylsilylated chitosan exhibited a much higher reactivity to give a da 2.0 even in the absence of the catalyst, and the da reached 2.5 in the 72 h reaction. On addition of DMAP, the da increased noticeably to as high as 2.8 in 6 h. The da values achieved by the reactions for 16 h or above were 3.0 within the experimental errors, indicating quantitative substitution under such mild conditions. The structures of the resulting acetylated products were established by IR spectroscopy; strong ester and amide bands were observed at 1746, 1670, and 1545 cm^{-1}. Elemental analysis also gave structural proofs.[9]

The results in Table 2 demonstrate the significant reactivity of trimethylsilylated chitosan, which will therefore be promising as a versatile precursor to conduct chemical modifications in organic solvents.



Scheme 2.

Table 2. Acetylation of trimethylsilylated chitosan[a]

Chitosan	DMAP/ Pyranose[b]	Time /h	Degree of acetylation[c]
Chitosan (α)	1.5	48	1.53
TMS-chitosan	—	48	2.08
TMS-chitosan	—	72	2.55
TMS-chitosan	1.5	6	2.85
TMS-chitosan	1.5	16	3.03
TMS-chitosan	1.5	48	3.05

[a] TMS-chitosan (trimethylsilylated chitosan, ds 2.6–2.8), 0.10 g; pyridine, 10 mL; acetic anhydride, 100 equivalents to pyranose; temperature, rt. [b] Mole ratio. [c] Calculated from the C/N value of elemental analysis.

Consequently, trimethylsilylation of chitosan proceeded efficiently in pyridine with a mixture of hexamethyldisilazane and chlorotrimethylsilane, the ds of the product depending on the reaction conditions. The resulting silylated chitosan proved to be a convenient precursor for chemical modifications because of the enhanced solubility and substantial reactivity in organic solvents. It would therefore make possible facile preparation of chitosan derivatives with well-defined structures under mild reaction conditions.

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References and Notes

1 a) R. A. A. Muzzarelli, "Chitin," Pergamon Press, Oxford (1977). b) G. A. F. Roberts, "Chitin Chemistry," Macmillan, London (1992). c) "Applications of Chitin and Chitosan," ed. by M. F. A. Goosen, Technomic Publishing, Lancaster, PA (1997).

2 a) K. Kurita, in "Desk Reference of Functional Polymers: Synthesis and Applications," ed. by R. Arshady, American Chemical Society, Washington, DC (1997), pp 239–259. b) K. Kurita, *Prog. Polym. Sci.*, **26**, 1921 (2001).

3 a) S. Nishimura, O. Kohgo, K. Kurita, and H. Kuzuhara, *Macromolecules*, **24**, 4745 (1991). b) K. Kurita, H. Ikeda, Y. Yoshida, M. Shimojoh, and M. Harata, *Biomacromolecules*, **3**, 1 (2002).

4 For example: a) K. Kurita, K. Shimada, Y. Nishiyama, M. Shimojoh, and S. Nishimura, *Macromolecules*, **31**, 4764 (1998). b) K. Kurita, T. Kojima, Y. Nishiyama, and M. Shimojoh, *Macromolecules*, **33**, 4711 (2000). c) K. Kurita, H. Akao, J. Yang, and M. Shimojoh, *Biomacromolecules*, in press.

5 K. Kurita, M. Hirakawa, and Y. Nishiyama, *Chem. Lett.*, **1999**, 771.

6 R. E. Harmon, K. K. De, and S. K. Gupta, *Carbohydr. Res.*, **31**, 407 (1973).

7 K. Kurita, K. Tomita, T. Tada, S. Ishii, S. Nishimura, and K. Shimoda, *J. Polym. Sci., Part A: Polym. Chem.*, **31**, 485 (1993).

8 For example: trimethylsilylated chitosan with ds 2.82; Calcd for $(C_{12}H_{27}NO_4Si_2)_{0.18}(C_{15}H_{35}NO_4Si_3)_{0.82}\cdot 0.3H_2O$: C, 46.92; H, 9.30; N, 3.78%. Found: C, 46.99; H, 9.23; N, 3.79%.

9 For example: acetylated chitosan with da 2.85; Calcd for $(C_{10}H_{15}NO_6)_{0.15}(C_{12}H_{17}NO_7)_{0.85}\cdot 0.6H_2O$: C, 48.16; H, 6.18; N, 4.80%. Found: C, 48.02; H, 6.01; N, 4.79%.

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