CHEMISTRY LETTERS, pp. 243-246, 1990.

Syntheses of Novel Chitosan Derivatives Soluble in Organic Solvents by Regioselective Chemical Modifications

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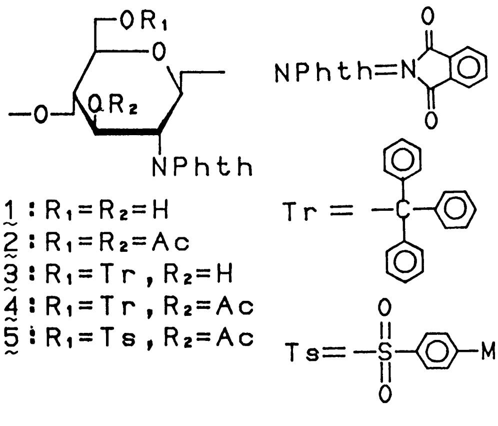
Regioselective chemical modifications of chitosan were successfully carried out in homogeneous solution under mild condition using phthalimido chitosan as a key starting material. Discrimination between the primary and secondary hydroxyl groups were also examined by O-tritylation or O-tosylation. As anticipated, the new chitosan derivatives exhibited a much improved solubility in common organic solvents.

Although several attempts[1-3)] have been reported to aid in obtaining functional derivatives of chitin and chitosan, only a few examples[4,5)] attained solubility in general organic solvents by chemical modifications. The enhancement of solubility of these compounds in organic solvents may become a key step for developing finely designed materials, since the intractability has delayed the modification study and moreover, made regioselective reactions difficult. This paper deals with a facile and reproducible procedure of phthalimido chitosan in homogeneous reaction systems without depolymerization.



1 : $R_1=R_2=H$
2 : $R_1=R_2=Ac$
3 : $R_1=Tr$, $R_2=H$
4 : $R_1=Tr$, $R_2=Ac$
5 : $R_1=Ts$, $R_2=Ac$

The protection of amino groups was successfully performed by employing phthalic anhydride/N,N-dimethylformamide (DMF) system. A mixture of chitosan

Table 1. Elemental analyses of some new chitosan derivatives

Compound	Yield %	Formula	Calcd % C	Calcd % H	Calcd % N	Found % C	Found % H	Found % N
1	95.8	$C_{14}H_{13}O_6N \cdot H_2O$	54.37	4.89	4.53	54.07	4.39	3.90
2	88.2	$C_{18}H_{17}O_8N \cdot 0.5H_2O$	56.25	4.72	3.64	56.36	4.51	3.68
3	99.0	$C_{33}H_{27}O_6N$	74.28	5.10	2.63	74.03	5.57	2.41
4	89.3	$C_{35}H_{29}O_7N \cdot 1.5H_2O$	69.76	5.53	2.32	69.63	4.96	2.73
5	77.4	$C_{23}H_{21}O_9NS \cdot 0.5H_2O$	55.64	4.34	2.87	55.14	4.16	3.27

(5.0 g, degree of deacetylation > 99%) and 3 fold excess phthalic anhydride (13.8 g) in DMF (100 mL) was heated with stirring at 130°C under a nitrogen atmosphere. After 5 to 7 h, the mixture became a clear and viscous solution. The precipitate obtained by pouring the solution into ice-water was successively washed with hot ethanol and ether, to give **1** (8.7 g, 95.8%). The characteristic absorptions due to phthalimido groups at 1770 cm^{-1} and 1710 cm^{-1} were observed in the IR spectrum (Fig.1, a), and analytical data (Table 1) suggested that the degree of substitution was estimated to be almost 1.0 per glucosamine residue. Compound **1** was soluble in pyridine, DMF, N,N-dimethylacetamide (DMAc) and dimethyl sulfoxide(DMSO). The improved solubility of **1** prompted us to examine following protections of the remaining hydroxyl groups.

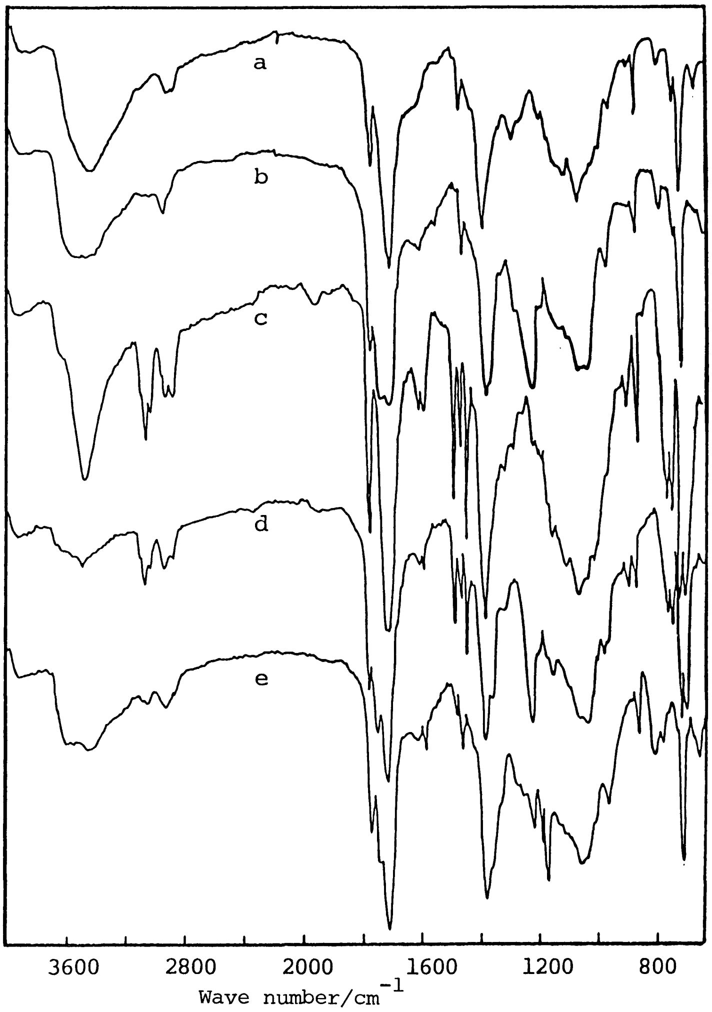


Fig. 1. IR spectra of chitosan derivatives
a) **1**, b) **2**, c) **3**, d) **4**, and e) **5**.

Complete O-acetylation of 1 was performed by treating with acetic anhydride-pyridine for 12 h at room temerature. The product was purified by chromatography on Sephadex LH-20 with 95:5 (v/v) chloroform-ethanol as eluant to give 2 in 88.2% yield. The structure was confirmed by the IR spectrum (Fig.1, b) and the satisfactory result of elemental analysis (Table 1). The presence of O-acetyl groups was shown by characteristic absorptions at 1745 cm^{-1} and 1230 cm^{-1}. A more definitive analysis of the structure was made with carbon and proton nuclear magnetic resonance spectroscopies. The presence of phthalimido and acetyl groups was shown in the 67.8 MHz ^{13}C-NMR spectrum of 2 in $CDCl_3$ (Fig. 2). The ratio of methyl protons (1.70-1.95 ppm) and aromatic protons (7.6-7.9 ppm), as calculated by integration in 270 MHz ^{1}H-NMR spectrum, suggested that the degree of acetylatyion was 2.0 per monosaccharide residue.

6-O-Tritylation of 1 was attempted in pyridine to discriminate two hydroxyl groups based on the steric hinderance of this bulky potective group and the higher reactivity of the primary hydroxyl groups. To a solution of 1 (5.0 g) in pyridine (75 mL) was added 3 fold excess triphenylmethyl chloride, and the solution was stirred for 24 h at 80°C under a nitrogen atmosphere. The mixture was poured into ethanol. The precipitate was successively washed with ethanol and ether, and dried over P_2O_5 to give 3 (9.1 g, 99%). The structural elucidation of 3 was made with the satisfactory result of elemental analyses (Table 1) and IR spectrum (Fig.1, c). Characteristic absorptions at 690 cm^{-1}, 710 cm^{-1}, and 750 cm^{-1} due to mono-substituted phenyl groups were observed in the spectrum. Subsequent modification at C-3 position of 3 was preliminarily demonstrated by acetylation with acetic anhydride-pyridine at room temperature. The precipitate obtained by pouring the mixture into ice-water was collected and washed with ethanol and

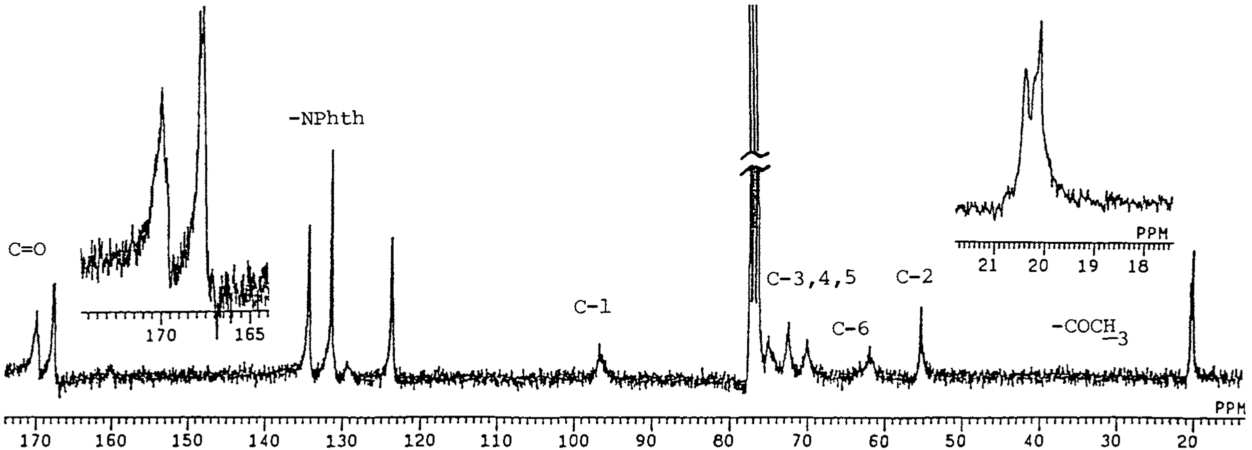


Fig. 2. ^{13}C-NMR spectrum of derivative 2 in $CDCl_3$.

Table 2. Solubility data of chitosan derivatives[a)]

Compound	DMF	DMAc	DMSO	pyridine	$CHCl_3$	CH_2Cl_2
1	+	+	+	+	-	-
2	+	+	+	+	+	+
3	+	+	+	+	±	+
4	+	+	+	+	+	+
5	±	±	±	+	-	-

a)(-): insoluble; (±): partially soluble or swelled; (+): soluble

ether, to give **4** (Fig. 1, d and Table 1).

6-O-Tosylated derivative **5** was also prepared from **1** with p-toluenesulfonyl chloride (10 fold excess) in pyridine at room temperature and then acetylated with acetic anhydride-pyridine. The IR spectrum of **5** showed a characteristic absorption at 1180 cm^{-1} due to tosyl groups in addition to the absorptions due to acetyl groups (1740 cm^{-1} and 1230 cm^{-1}).

Table 3. Specific rotations

Compound	$[\alpha]_D^{23}$/°	C/g·dL^{-1}	Solvent
1	+15.5	0.30	DMF
2	-8.4	0.30	$CHCl_3$
3	-2.9	0.30	DMF
4	-16.9	0.30	$CHCl_3$
5	-17.3	0.30	pyridine

Solubility data and specific rotations were listed in Tables 2 and 3, respectively. Some of these chitosan derivatives exhibited much improved solubility in general organic solvents and high probability of further selective manipulations.

This work was partly supported by The Foundation "Hattori Hokokai" and Grant-in-Aid for Scientific Research on Priority Areas, New Functionality Materials-Design, Preparations, and Control-, the Ministry of Education, Science, and Culture (#01604595).

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(Received November 14, 1989)