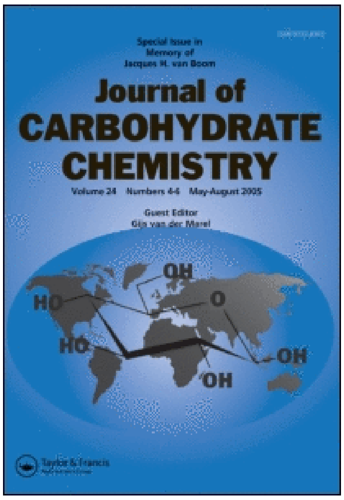

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COMMUNICATION

DESULFATION OF SULFATED CARBOHYDRATES MEDIATED BY SILYLATING REAGENTS

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Efficient methods of desulfation are often required in carbohydrate chemistry and biochemistry. In addition to conventional desulfation methods,[1,2] we recently reported a novel desulfation method employing a silylating reagent, *N,O*-bis(trimethylsilyl)-acetamide.[3,4] With this reagent, the 6-*O*-sulfoxyl groups of the sugar moiety are regioselectively removed and newly formed hydroxyl groups are further converted by silylation into trimethylsilyloxyl groups. The desulfated carbohydrates are easily recovered after desilylation with water or aqueous methanol. Although the mechanism for this reaction remains unclear, silylating reagents can be considered as potential reagents for desulfation reaction. In the present paper, we examined various silylating reagents to find effective and new desulfation reagents for carbohydrate sulfates.

The pyridinium salt of methyl α-D-galactopyranoside 3- or 6-sulfate was treated with a large excess of the silylating reagents in pyridine at 40 °C. Since the sulfoxyl group is substituted by a trimethylsilyloxyl group when desulfation occurs by the treatment with the silylating reagent, the degree of desulfation can be estimated by the amount of pertrimethylsilylated galactoside using GLC. Since reactivity of several reagents for silylating the hydroxyl group was found to be insufficient for the GLC analysis, the degree of desulfation with each reagent was estimated by GLC after further treatment with *N*-(trimethylsilyl)imidazole, a reagent that can completely silylate hydroxyl groups but not catalyze desulfation.[3] Since a large excess of the reagent was present in the system, the reaction was a pseudo first-order reaction, the rate constant for each reagent thus being estimated from the degree of desulfation. By comparison with the rate constant for the solvolytic reaction that proceeds under similar conditions except for absence of silylating reagent,[5] the silylating reagents used could be classified into three groups based on their rate constant k_{sil} relative to that for solvolytic reaction k_{sol} (TABLE 1). The group **A** reagents are incapable of desulfation, the group **B** reagents accelerate 6-*O*-desulfation but are ineffective for 3-*O*-desulfation, and the group **C** reagents non-specifically remove sulfate groups.

A pyridinium salt of a carbohydrate sulfate can be solvolyzed when treated in pyridine.[5] A small amount of water has been reported to facilitate the solvolytic desulfation when carried out in DMSO.[6,7] Accordingly, the silylating reagents were expected to prevent the solvolytic reaction since they can remove residual moisture from the system. The group **A** reagents thus caused a decrease in the rate of desulfation, whereas group **B** and **C** reagents show different effects from those observed in the group **A** reagents.

In the reaction with the group **B** reagents, preferential desulfation at O-6 may involve a mechanism other than solvolytic desulfation. The group **C** reagents are also likely to catalyze the desulfation in a mechanism different from the solvolytic desulfation.

Among the silylating reagents belonging to the group **B**, *N*-methyl-*N*-(trimethylsilyl)acetamide and *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide appear to be new reagents for effective 6-*O*-specific desulfation. Although the efficiency of the group **C** reagents was lower than these reagents, they would be potential desulfation reagents for sulfate groups at both primary and secondary hydroxyl groups, since a high degree (minimum 80%) of desulfation was achieved by a reaction at 80 °C (data not shown). The reagent *N,O*-bis(trimethylsilyl)acetamide belonging to the group **B** has already been successfully empolyed for desulfation of sulfated mono- and polysaccharides.[3,4] Treatment with the silylating reagents observed in the present report is thus a convenient method for the preparation of desulfated carbohydrates and constitutes an alternative method to solvolytic desulfation, since the procedure is simple and the introduced trimethylsilyl groups can be easily deprotected. An appropriate choice of the silylating reagent would be helpful for preparing suitably desulfated carbohydrates, as the position and the degree of the desulfation vary depending on the reagents employed.

TABLE 1. Ratio of rate constants for the reaction of methyl galactoside 3- and 6-sulfates in pyridine with (k_{sil}) and without (k_{sol}) silylating reagent. The k_{sol} values at 40 °C for 6- and 3-sulfates were estimated at 9.0×10^{-6} sec^{-1} and 1.8×10^{-6} sec^{-1}, respectively.

group	silylating reagent	k_{sil}/k_{sol} 6-sulfate	k_{sil}/k_{sol} 3-sulfate
A	*N*-(trimethylsilyl)imidazole	0	0
	1-(trimethylsilyl)-1,2,4-triazole	0.6	0.2
	N-(trimethylsilyl)acetamide	0.2	0.5
	3-(trimethylsilyl)-2-oxazolidinone	0.9	0.2
	nonamethyltrisilazane	0	0.2
	N,*N*-dimethylaminotrimethylsilane	0.5	0
	hexamethyldisiloxane	0.5	0.1
	isopropenoxytrimethylsilane	0	0
	1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene	0.1	0.2
	1-(trimethylsilyl)propyne	0.7	0.1
	bis(trimethylsilyl)acetylene	0.5	0
B	*N*,*O*-bis(trimethylsilyl)acetamide	21.6	0
	N-methyl-*N*-(trimethylsilyl)acetamide	14.9	0
	N-methyl-*N*-(trimethylsilyl)trifluoroacetamide	36.4	0
	hexamethyldisilazane	1.2	0.4
	heptamethyldisilazane	4.5	0
	N,*N*-diethylaminotrimethylsilane	1.4	0
	1-methoxy-1-(trimethylsilyloxy)-2-methyl-1-propene	1.1	0.2
C	trimethylsilyl azide	1.7	3.1
	trimethylsilyl isocyanate	2.4	3.8
	bis(trimethylsilyl)carbodiimide	2.1	7.8
	1-methoxy-2-(trimethylsilyloxy)propane	2.1	3.1
	trimethylethoxysilane	2.1	4.2
	4-(trimethylsilyloxy)-3-pentene-2-one	4.5	3.8
	trimethylsilyl acetate	1.5	3.8
	trimethylsilyl trifluoroacetate	2.3	2.0
	bis(trimethylsilyl) adipate	1.9	3.4
	trimethylchlorosilane	3.9	3.4

EXPERIMENTAL

General method. Ammonium salts of methyl α-D-galactopyranoside 3- and 6-sulfates were prepared as described elsewhere.[8] Pyridinium salts of these compounds were obtained by neutralization of the acidic form of sugar sulfate with pyridine after passing through a column of Amberlite IR 120 (H^+ form) resin. The silylating reagents employed were products of Petrarch systems, Tokyo Kasei, Aldrich, or Wako. Other reagents were purchased from Wako. GLC was carried out using a gas chromatograph (GC-8A, Shimadzu) equipped with FID and a WCOT column (OV-1 bonded, 0.3 mm x 25 m, GL-Science) at 180 °C. Nitrogen was used as the carrier gas; flow rate, 20 mL/min; split ratio, 20:1.

Reaction with silylating reagents. The pyridinium salt of methyl α-D-galactopyranoside 3- or 6- sulfate (100 µg) was dissolved in pyridine (100 µL) containing methyl α-D-glucopyranoside (50 µg) as internal standard. To the solution was added the silylating reagent (40 µL), and the mixture was heated to 40 °C. To the reaction mixture was added *N*-(trimethylsilyl)imidazole (40 µL), the solution was heated for 5 min at 80 °C and then analyzed by GLC. The degree of desulfation with each reagent was estimated based on peak area ratio of desulfated and silylated galactosides and the internal standard. As a control, the same mixture without the silylating reagent was heated with pyridine (100 µL) at 40 °C, the solution silylated with *N*-(trimethylsilyl)imidazole (40 µL), and then analyzed with GLC.

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