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Regioselective silylation of C-2 hydroxyl group of α-cyclodextrin dependent on reaction temperature

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Abstract—Silylations of the C-2 hydroxyl group of α-cyclodextrin were carried out using *t*-butyldimethylsilyl imidazole in the presence of 4 Å molecular sieves in *N*,*N*-dimethylformamide. A unique aspect of this silylation method is the temperature dependence of the regioselectivity; silylation at 0°C regioselectively favored the C-6 position to afford mono-6-*O*-*t*-butyldimethylsilyl-α-cyclodextrin, whereas silylation at 140°C exhibited high regioselectivity on the C-2 hydroxyl group.

Cyclodextrins are cyclic α-1,4-linked-oligosaccharides with an optically active and hydrophobic cavity within their bucket-like structures, and hydroxyl groups, consisting of primary hydroxyl groups at the C-6 and secondary hydroxyl groups at the C-2 and C-3 positions, at the rim of the structures.[1] Cyclodextrins and their derivatives have been extensively investigated and have been utilized as molecular receptors towards a wide variety of guest substrates,[2] and as building blocks in supramolecular chemistry.[3] During the last few decades, these cyclodextrins have been extensively modified in an attempt to increase their functions. However, selective modifications have remained elusive due to the large number of the hydroxyl groups and steric factors;[4] in particular, regioselective modifications of the secondary hydroxyl groups have proved to be a challenge.

In the field of organic synthesis, silylations of hydroxyl groups have been widely utilized as a protection technique,[5] and accordingly silylation of cyclodextrins, especially using a *t*-butyldimethylsilyl (TBDMSi) group,[6] has been employed. Following the report by Michalski et al. describing the preparation of hexakis(2,6-di-*O*-TBDMSi)-α-cyclodextrin,[7] several silylations have been utilized for the purification of cyclodextrin derivatives,[8] or for the protection of the C-6 and/or the C-2 hydroxyl groups of cyclodextrins,[9] and subsequently, these protected cyclodextrins have been manipulated with further modifications.[10] In these silylations, except for the methods described by D'Souza et al.[9d] and by Bukowska et al.,[9g] the cyclodextrins were silylated using TBDMSi chloride, either with imidazole in *N*,*N*-dimethylformamide (DMF) or without imidazole in pyridine, resulting in a highly regioselective production of 6-*O*-TBDMSi-cyclodextrins or 2,6-di-*O*-TBDMSi-cyclodextrins. The preceding investigations have demonstrated that the reactivities of the hydroxyl groups of cyclodextrins toward silylation increase in the order as follow: OH-6 ≫ OH-2 ≫ OH-3. The Bukowska method involved the trimethylsilylation of α- and β-cyclodextrins with *N*-(trimethylsilyl)acetamide in DMF resulting in a highly effective production of per-2,6-*O*-trimethylsilyl cyclodextrins; however, regioselectivity between the C-2 and C-6 hydroxyl groups were not observed.[9g] As a unique method for the direct regioselective silylation of the secondary hydroxyl groups of β-cyclodextrin, D'Souza et al. have reported on the silylation of β-cyclodextrin with TBDMSi chloride using NaH as a base in DMF.[9d] However, an average degree of the silylation was approximately six, moreover it was unclear whether the silylation occurred at the C-2 or C-3 position. Furthermore, this D'Souza's method for α-cyclodextrin resulted in silylation of the primary hydroxyl group. Thus, direct regioselective silylation of the C-2 hydroxyl group(s) of unprotected cyclodextrins has been a challenge within cyclodextrin chemistry. Herein we report a highly regioselective mono-silylation of the C-2 hydroxyl group of unprotected α-cyclodextrin.

Keywords: cyclodextrin; regioselective silylation.

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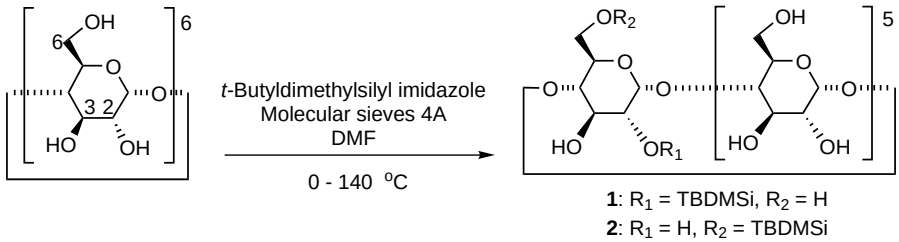
Recently, sulfonylations of cyclodextrins using sulfonyl imidazole reagents in the presence of molecular sieves in DMF have been reported for the exclusive regioselective sulfonylation of the C-2 hydroxyl groups.[11] Although the mechanism of this sulfonylation remains unclear, we have undertaken a similar strategy for the regioselective mono-silylation of the mono C-2 hydroxyl group by reacting α-cyclodextrin with TBDMSi imidazole in the presence of molecular sieves in DMF (Scheme 1). Initially, a mixture of α-cyclodextrin and freshly activated powdered 4 Å molecular sieves in anhydrous DMF was stirred at 20°C for 2 h under an argon atmosphere. After maintaining the reaction mixture for 10 min at temperatures as listed in Table 1, TBDMSi imidazole was added, and the reaction mixture was stirred at the indicated temperatures. The reaction was monitored using silica gel TLC (6:3:1, $MeCN/H_2O$/28% aqueous NH_3[12]). After the reaction was deemed as complete, the molecular sieves were removed by filtration, and the filtrate was concentrated under reduced pressure, then dissolved in a mixture of DMF and H_2O (1:50, v/v). The solution was readily purified using a simple open reverse-phase column chromatography (15×150 mm, Fuji Silisia Chroma-



Scheme 1.

Table 1. Silylation of α-cyclodextrin with *t*-butyldimethylsilyl (TBDMSi) imidazole in the presence or absence of 4 Å molecular sieves (4 Å MS) in DMF[a]

Entry	Equiv. of TBDMSi imidazole	4 Å MS	Temp. (°C)	Time (h)	Yield (%)[b]		Value of [**1**/**1**+**2**][c]
					1	**2**	
1	1	Added	0	24	2.5	26	0.088
2	1	Added	20	24	4.6	19	0.19
3	1	Added	50	5	11	8.2	0.57
4	1	Added	80	5	16	4.0	0.80
5	1	Added	110	2	16	1.3	0.92
6	1	Added	140	1	15	0.79	0.95
7[d]	1	Added	20+110	24+2	4.5	19	0.19
8[e]	1	Added	20+140	24+1	4.3	18	0.19
9[f]	1	Added	110+20	2+24	16	1.3	0.92
10	1	Not	20	24	0	Trace[g]	–
11	5	Not	20	24	0	Trace[g]	–
12	5	Not	80	5	0	Trace[g]	–
13	2	Added	110	2	20	2.9	0.87
14	3	Added	110	2	19	4.5	0.81
15	2	Added	140	1	17	1.3	0.93
16	3	Added	140	1	15	2.2	0.87
17[h]	1	Added	110	2	13	2.8	0.82
18[i]	1	Added	110	2	13	4.4	0.75
19[h]	1	Added	20	24	2.4	26	0.085
20[i]	1	Added	20	24	1.4	28	0.048
21[j]	1	Added	20+20	24+24	4.4	19	0.19
22[k]	1	Added	20+110	24+2	4.3	18	0.19

[a] Reactions were carried out using α-cyclodextrin (1.0 mmol), *t*-butyldimethylsilyl imidazole (listed amount), powdered activated 4 Å molecular sieves (2.0 g, in case of addition), and DMF (22 mL) unless otherwise specified.
[b] Isolated yield.
[c] Value of [(yield of **1**)/(combined yield of **1** and **2**)].
[d] Reaction was carried out at 20°C for 24 h and then at 110°C for 2 h.
[e] Reaction was carried out at 20°C for 24 h and then at 140°C for 1 h.
[f] Reaction was carried out at 110°C for 2 h and then at 20°C for 24 h.
[g] Product was detected only on silica gel TLC.
[h] Reaction was carried out in the presence of imidazole (1.0 mmol).
[i] Reaction was carried out in the presence of imidazole (2.0 mmol).
[j] Reaction was carried out at 20°C for 24 h and then in the presence of imidazole (2.0 mmol) at 20°C for 24 h.
[k] Reaction was carried out at 20°C for 24 h and then in the presence of imidazole (2.0 mmol) at 110°C for 2 h.

torex-ODS DM1020T gel, 0–50% aqueous MeOH) to afford, in order: unreacted α-cyclodextrin, mono-2-*O*-TBDMSi-α-cyclodextrin (**1**; R_f=0.67; 6:3:1, MeCN/H_2O/28% aqueous NH_3), mono-6-*O*-TBDMSi-α-cyclodextrin (**2**; R_f=0.56; 6:3:1, MeCN/H_2O/28% aqueous NH_3), and multi-*O*-TBDMSi-α-cyclodextrins. Mono-3-*O*-TBDMSi-α-cyclodextrin was not detected in any of the silylation reactions listed in Table 1. Mono-TBDMSi-α-cyclodextrins **1** and **2** were fully characterized by using FAB mass spectrometry (molecular ions $[M+H]^+$ at m/z 1087) and by ^1H and ^{13}C NMR spectroscopy (shown in Fig. 1).[13] Peak integrations of the ^1H NMR spectra and the FAB mass spectra indicated the mono-silylations. Spectral assignments of **1** and **2** were performed using ^1H–^1H COSY, ^1H–^{13}C COSY, and DEPT experiments. From the ^1H NMR spectra, significant downfield-shifts were observed for the H-2 proton of one glucose moiety of **1** and for the H-6 proton of one glucose moiety of **2**; signals for remaining protons of **1** and **2** exhibited chemical shifts similar to those of the native α-cyclodextrin. From the ^{13}C NMR spectra using ^1H–^{13}C COSY and DEPT experiments, downfield-shifts were observed for the C-2 carbon of the corresponding glucose moiety of **1** and for the C-6 carbon of the corresponding glucose moiety of **2**. The combined data of ^1H and ^{13}C NMR indicate that the silyl groups are attached to the C-2 oxygen of **1** and C-6 oxygen of **2**.

Experimental results of the silylations are summarized in Table 1. Silylation at 0°C gave mono-TBDMSi-α-cyclodextrins **1** and **2** in 2.5 and 26% yields, respectively (entry 1), exhibiting unexpectedly high regioselectivity toward the C-6 hydroxyl group. Although at higher temperatures, the overall combined yields of **1** and **2** slightly were lower (entries 2–6), the regioselectivity towards the C-2 hydroxyl group was markedly increased. The reaction at 140°C (entry 6) exhibited the highest regioselective silylation of the C-2 hydroxyl group, with a relative value of 0.95 [(yield of **1**)/(combined yields of **1** and **2**)]. Silylation at 20°C for 24 h, followed by increasing the temperature to 110°C for 2 h (entry 7) or to 140°C for 1 h (entry 8) exhibited comparable results as that for 20°C for 24 h (entry 2), thus indicating that increasing the temperature after the initial silylation period does not result in either the decomposition of **1** and **2**, nor in the migration of silyl group from the C-6 to the C-2 oxygen. Conversely, silylation at 110°C for 2 h followed by reducing the temperature to 20°C for 24 h (entry 9) exhibited similar yields of **1** and **2** as for 110°C for 2 h (entry 5), indicating that decreasing the temperatures does not cause the migration of the silyl group from the C-2 to the C-6 oxygen. Based on these observations, the regioselectivities of the silylation of the C-2 and C-6 hydroxyl groups must be attributable to the transition state of the silylation adduct, which is dependent on the reaction temperature; reactivity of the C-6 hydroxyl group toward the silylation at the lower temperature is greater than that of the C-2 hydroxyl group, conversely reactivity of the C-2 hydroxyl group at the higher temperature is greater than that of the C-6 hydroxyl group. Interestingly, in the cases of the cyclodextrin sulfonylations, exclusive regioselective sulfonylation of the C-2 hydroxyl groups was independent of the reaction temperature,[14] suggesting that the mechanism of the silylation described herein may differ from that of the sulfonylation. Reactions without the molecular sieves afforded only trace amounts of mono-6-*O*-

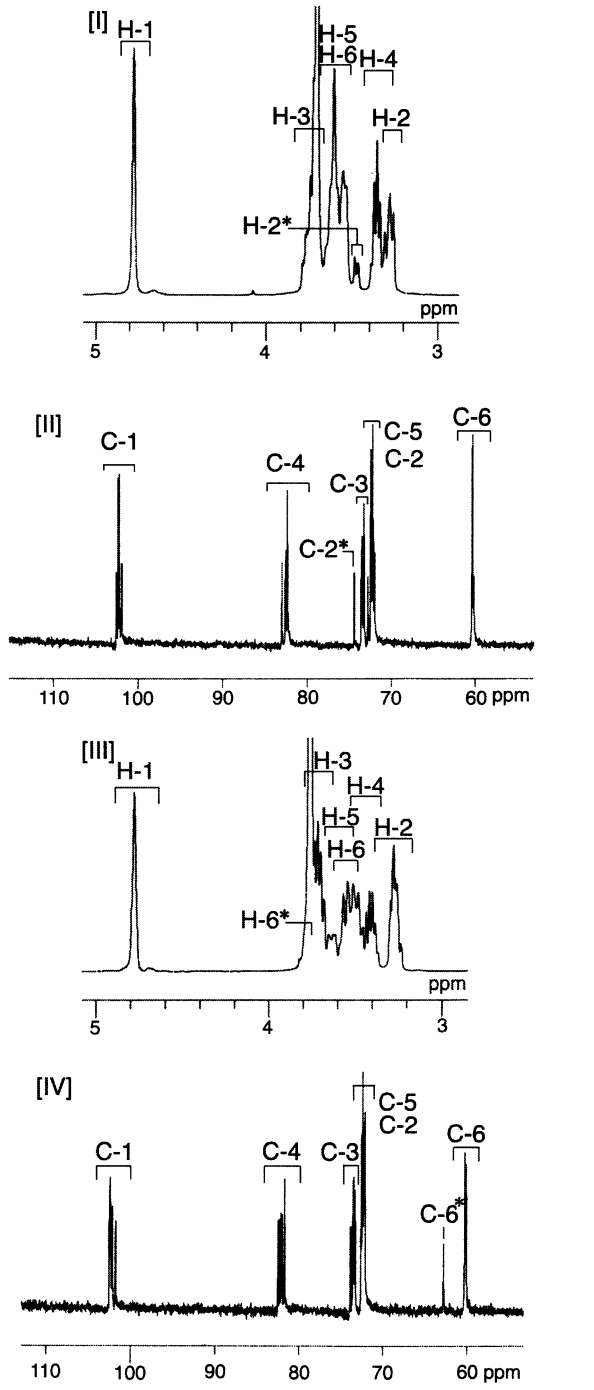


Figure 1. Partial ^1H and ^{13}C NMR spectra of **1** and **2** (26°C, DMSO-d_6 containing 5% D_2O, ref., DMSO: δ 2.49 for ^1H and 39.5 for ^{13}C). The assigned signals are numbered according to the usual convention shown in Scheme 1, and the symbol * for **1** and **2** refers to the silylated glucose moieties. [I] ^1H NMR of **1**; [II] ^{13}C NMR of **1**; [III] ^1H NMR of **2**; [IV] ^{13}C NMR of **2**.

TBDMSi-α-cyclodextrin (**2**) without any mono-2-*O*-TBDMSi-α-cyclodextrin (**1**) (entries 10–12), indicating that 4 Å molecular sieves are necessary in the silylations of both C-2 and C-6 hydroxyl groups.

In an attempt to improve the yield of **1**, two- or three-molar TBDMSi imidazole was used, as multi-silylation can generally occur due to the large number of hydroxyl groups of cyclodextrin, resulting in a successful increase of the yield of **1** (entries 13–16). It should be noted that in the cases with an excess amount of TBDMSi imidazole, the regioselectivity of the silylation of the C-2 hydroxyl group actually decreased. When the silylations were carried out in the presence of one or two-molar imidazole at 110 or 20°C (entries 17–20), the regioselectivities of the silylation of the C-2 hydroxyl group were significantly lower. However, addition of two-molar imidazole at 20 or 110°C (entries 21 and 22, respectively), following the initial silylation at 20°C, resulted in yields that were similar to that without the addition of imidazole (entry 2). Therefore, although imidazole must play a role such as activation of the C-6 hydroxyl group and/or inactivation of the C-2 hydroxyl group toward the silylation, it does not appear that imidazole causes the decomposition of the mono-TBDMSi-α-cyclodextrins (**1** and **2**) or the migration of silyl group. With regard to the cases of using two- or three-molar TBDMSi imidazole as described earlier, a greater amount of free imidazole should be present in these reaction systems, as compared to the one-molar TBDMSi imidazole, and this increase may cause the decrease of the regioselectivity of the silylation of the C-2 hydroxyl group. If the presence of imidazole in the silylation system using TBDMSi imidazole can be lowered, or if the imidazole can be excluded from the system, regioselectivity of the silylation toward the C-2 hydroxyl group could perhaps be increased.

In conclusion, we have discovered a temperature-dependent regioselective mono-silylation of the C-2 hydroxyl group of α-cyclodextrin using TBDMSi imidazole in the presence of molecular sieves in DMF; the silylation at the higher temperature exhibited the greater regioselectivity on the C-2 hydroxyl group. This silylation method can be highly useful since the C-2 hydroxyl group can be directly silylated without the protection of the C-6 hydroxyl groups. We are currently investigating the reaction mechanism for this silylation, subsequent manipulations using mono-2-*O*-TBDMSi-α-cyclodextrin (**1**), and applications of this method toward other cyclodextrins.

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13. Data of ^{1}H and ^{13}C NMR omitted in Fig. 1 (26°C, DMSO-d_6 containing 5% D_2O, ref., DMSO: δ 2.49 for ^{1}H and 39.5 for ^{13}C); ^{1}H NMR for **1**: 0.07 (3H, s, SiCH_3), 0.10 (3H, s, SiCH_3), 0.86 (9H, s, SiC(CH_3)$_3$), ^{13}C NMR for **1**: −4.13 (SiCH$_3$), −4.08 (SiCH$_3$), 18.82 (SiC(CH$_3$)$_3$), 26.47 (SiC(CH$_3$)$_3$), ^{1}H NMR for **2**: −0.03 (3H, s, SiCH_3), −0.02 (3H, s, SiCH_3), 0.78 (9H, s, SiC(CH_3)$_3$), ^{13}C NMR for **2**: −4.98 (SiCH$_3$), −4.70 (SiCH$_3$), 18.43 (SiC(CH$_3$)$_3$), 26.21 (SiC(CH$_3$)$_3$).
14. Unpublished data.