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Regioselective Silylations of C-2 Hydroxyl Groups of Cyclodextrins Dependent on Reaction Temperature

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Abstract

Silylations of the C-2 hydroxyl group of cyclodextrins were carried out using *t*-butyldimethylsilyl imidazole in the presence of 4A 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*-butyldimehylsilyl-cyclodextrins, whereas silylation at 140 °C exhibited high regioselectivity on the C-2 hydroxyl group.

Introduction

In the field of organic synthesis, silylations of hydroxyl groups have been widely utilized as a protection technique [1], and accordingly silylation of cyclodextrins, especially using a *t*-butyldimethylsilyl (TBDMSi) group [2], has been employed. Following the report by Michalski *et al.* describing the preparation of hexakis(2,6-di-*O*-TBDMSi)-α-CD [3], several silylations have been utilized for the purification of CD derivatives [4], or for the protection of the C-6 and/or the C-2 hydroxyl groups of cyclodextrins [5], and subsequently, these protected CDs have been manipulated with further modifications. In these silylations, except for the methods described by D'Souza *et al.* [5(d)] and by Bukowska *et al.* [5(g)], the CDs 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-CDs or 2,6-di-*O*-TBDMSi-CDs. The preceding investigations have demonstrated that the reactivities of the hydroxyl groups of CDs toward silylation increase in the order as follows: OH-6 $\gg$ OH-2 $\gg$ OH-3. The Bukowska method involved the trimethylsilylation of α- and β-CDs with *N*-(trimethylsilyl)acetamide in DMF resulting in a highly effective production of per-2,6-*O*-trimethylsilyl CDs; however, regioselectivity between the C-2 and C-6 hydroxyl groups were not observed [5(g)]. As a unique method for the direct regioselective silylation of the secondary hydroxyl groups of β-CD, D'Souza *et al.* have reported on the silylation of β-CD with TBDMSi chloride using NaH as a base in DMF [5(d)]. 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-CD resulted in silylation of the primary hydroxyl group. Thus, direct regioselective silylation of the C-2 hydroxyl geroup(s) of unprotected CDs has been a challenge within cyclodextrin chemistry. Herein we report a highly regioselective monosilylation of the C-2 hydroxyl group of unprotected α-, β-, and γ-CDs.

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Materials and method

Materials

Powdered 4A molecular sieves, DMF, and imidazole were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Powdered 4A molecular sieves were heated at 250–300 °C for 2 h. α-, β-, and γ-CDs were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and dried under vacuum at 120 °C for 12 h. TBDMSi imidazole was purchased from Tokyo Chemical Industry Co., Ltd. DMSO-d_6 was purchased from Aldrich Chemical Co. (St. Louis, MO, USA).

Characterization of CD compounds

^{1}H and ^{13}C NMR spectra were recorded using a JEOL JNM-A500 spectrometer in DMSO-d_6. ^{1}H and ^{13}C NMR chemical shifts were assigned on the basis of ^{1}H -^{1}H COSY, DEPT ^{13}C NMR, and ^{1}H–^{13}C COSY experiments. FAB mass spectra (positive) were measured using a JEOL DX-303 instrument with glycerol as a matrix.

General procedure for reactions of CDs with TBDMSi imidazole

A mixture of CD (1.0 mmol) and freshly activated powdered 4A molecular sieves (2 g) in DMF (22 ml) was stirred at 20 °C for 2 h. After maintaining the reaction mixture for 10 min at desired temperature, TBDMSi imidazole was added,

and the reaction mixture was stirred at the same temperatures. The reaction was monitored using silica gel TLC (6 : 3 : 1, MeCN/H_2O/28% aqueous NH_3 [6]). 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 Chromatorex-ODS DM1020T gel, 0–50% aqueous MeOH) to give pure silylated CDs.

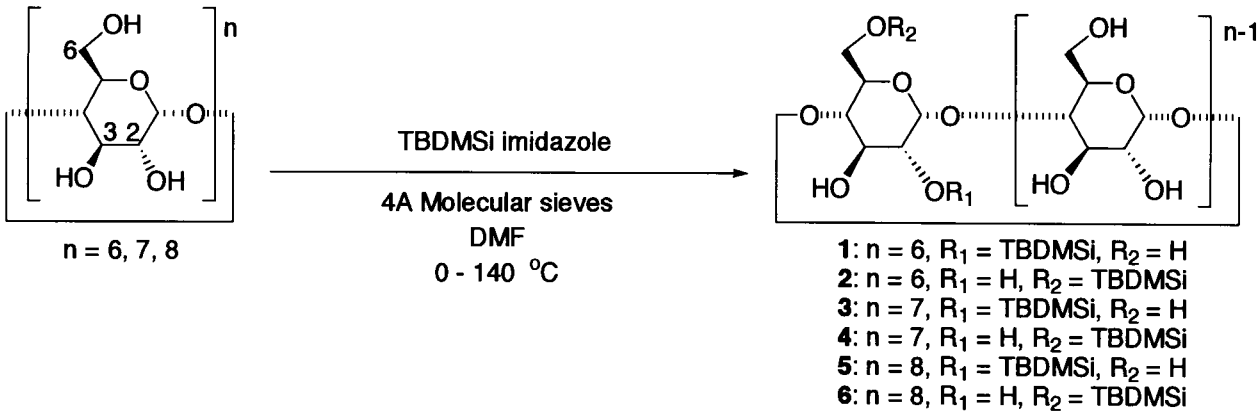
Results and discussion

Recently, sulfonylations of α-, β-, and γ-CDs 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 [7]. Although the mechanism of this sulfonylation remains unclear, we have undertaken a similar strategy for the regioselective monosilylation of the mono C-2 hydroxyl group by reacting α-, β-, and γ-CDs with TBDMSi imidazole in the presence of molecular sieves in DMF (Scheme 1). Initially, a mixture of CD and freshly activated powdered 4A molecular sieves in DMF was stirred at 20 °C for 2 h. 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. Mono-2-*O*-TBDMSi-CDs and mono-6-*O*-TBDMSi-CDs were isolated using a simple open reverse-phase column chromatography, but mono-3-*O*-TBDMSi- were not detected in any of the silylation reactions listed in Table 1.

Experimental results of the silylations of α-CD are summarized in Table 1. Silylation at 0 °C gave mono-2-*O*-TBDMSi-α-CD **1** and mono-6-*O*-TBDMSi-α-CD **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** were slightly 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 CD sulfonylations, exclusive regioselective sulfonylation of the C-2 hydroxyl groups was independent of the reaction temperature, 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 **2** without any mono-2-*O*-TBDMSi-α-CD (**1**) (entries 10-12), indicating that 4A molecular sieves is 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, since multi-silylation can generally occur due to the large number of hydroxyl groups of α-CD, 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 °C 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 °C 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-CDs (**1** and **2**) or the migration of silyl group. In 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.

Results of Silylations of β- and γ-CDs were summarized in Tables 2 and 3. Regioselectivity between C-2 and C-6 hydroxyl groups in these silylation was dependent on reaction temperature similar to that for α-CD; the silylation at the higher temperature exhibited the greater regioselectivity on the C-2 hydroxyl group. Interestingly, investigations demonstrated that the regioselectivity of the C-2 hydroxyl groups of α-, β-, and γ-CDs toward silylation increase in the order as follow: γ-CD > β-CD > α-CD. Relative values of [(yield of 2-*O*-TBDMSi-CD)/(combined yields of 2-*O*-TBDMSi-CD and 6-*O*-TBDMSi-CD)] at 20 °C for α-, β-, and γ-CDs are 0.19, 0.42, and 0.56, respectively, and the values at 110 °C are 0.92, 0.93, and 0.95, respectively. These results suggest that the regioselectivity between the C-2 and C-6 hydroxyl



Scheme 1. Silylation of α-, β-, and γ-CDs.

Table 1. Silylation of α-CD with TBDMSi imidazole in the presence or absence of 4A molecular sieves (MS 4A) in DMF[a]

Entry	Equiv. of TBDMSi imidazole	MS 4A	Temp. (°C)	Time (h)	Yield (%)[b] **1**	**2**	Value of [**1**/**1** + **2**][c]
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	non	20	24	0	trace[g]	–
11	5	non	20	24	0	trace[g]	–
12	5	non	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-CD (1.0 mmol), TBDMSi imidazole (listed amount), powdered activated 4A 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.

Table 2. Silylation of β-CD with TBDMSi imidazole in the presence of 4A molecular sieves in DMF[a]

Entry	Equiv. of TBDMSi imidazole	Temp. (°C)	Time (h)	Yield (%)[b] **3**	**4**	Value of [**3**/**3** + **4**][c]
1	1	0	24	4.0	16	0.20
2	1	20	24	6.1	8.4	0.42
3	1	50	5	9.0	4.7	0.66
4	1	80	5	13	2.1	0.86
5	1	110	2	15	1.2	0.93
6	1	140	1	12	0.49	0.96
7	2	110	2	28	3.7	0.88
8	3	110	2	32	4.9	0.87
9	2	140	1	28	1.8	0.94
10	3	140	1	26	2.0	0.93

[a] Reactions were carried out using β-CD (1.0 mmol), TBDMSi imidazole (listed amount), activated powdered 4A molecular sieves (2.0 g, in case of addition), and DMF (22 mL) unless otherwise specified.
[b] Isolated yield.
[c] Relative value of [(yield of **3**)/(combined yield of **3** and **4**)].

Table 3. Silylation of γ-CD with TBDMSi imidazole in the presence of 4A molecular sieves in DMF[a]

Entry	Equiv. of TBDMSi imidazole	Temp. (°C)	Time (h)	Yield (%)[b] **5**	**6**	Value of [**5**/**5** + **6**][c]
1	1	0	48	7.5	14	0.35
2	1	20	24	11	8.8	0.56
3	1	50	5	11	4.5	0.71
4	1	80	5	14	2.7	0.84
5	1	110	2	12	0.66	0.95
6	1	140	1	6.2	0.22	0.97
7	2	110	2	13	1.0	0.93
8	3	110	2	11	1.0	0.92

[a] Reactions were carried out using γ-CD (1.0 mmol), TBDMSi imidazole (listed amount), activated powdered 4A molecular sieves (2.0 g, in case of addition), and DMF (22 mL) unless otherwise specified.
[b] Isolated yield.
[c] Relative value of [(yield of **5**)/(combined yield of **5** and **6**)].

groups toward the silylation could be dependent on not only reaction temperature but also cyclic structure of CDs.

Conclusion

We have discovered a temperature-dependent regioselective mono-silylation of the C-2 hydroxyl group of α-, β-, and γ-CDs 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.

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