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Trimethylsilylation of cyclodextrins with *N*-(trimethylsilyl)acetamide in *N,N*-dimethylformamide

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Abstract

Trimethylsilylation of α- and β-cyclodextrin with *N*-(trimethylsilyl)acetamide in *N,N*-dimethylformamide gives the per-2,6-*O*-trimethylsilyl derivatives with high yield and selectivity.

Keywords: Trimethylsilylation; Cyclomaltohexaose (α-cyclodextrin); Cyclomaltoheptaose (β-cyclodextrin)

1. Introduction

Silylations of cyclodextrins (CDs) have been used in the preparation of chiral stationary phases [1], for purification of cyclodextrin derivatives [2], and for the preparation of starting materials for further chemical modifications [3–5]. Although the *t*-butyldimethylsilyl derivatives of CDs have generally been used for this purpose, we reported in a communication that per-2,6-di-*O*-trimethylsilyl-β-CD (**2a**), despite its relatively labile nature, could be converted selectively into per-2-*O*-substituted-6-*O*-trimethylsilyl-β-CDs in a reaction with sodium hydride in *N,N*-dimethylformamide followed by alkylation [6]. When our work was in progress, it was reported that the corresponding per-2,6-di-*O*-*tert*-butyldimethylsilyl-β-CD (2,6-TBDMS-β-CD) in a similar reaction run in tetrahydrofuran were transformed into per-3,6-di-*O*-*tert*-butyldimethylsilyl-2-*O*-substituted CDs [4,5]. The different behaviour of these closely related silyl derivatives and the fact that **2a** was obtained by the silylation with *N*-(trimethylsilyl)acetamide instead of usually used chlorosilanes, prompted us to investigate the trimethylsilylation reaction and characterise its products in some detail. The results of our research are presented in this paper.

2. Results and discussion

Birkofer et al. found that trimethylsilylation of glucose with *N*-(trimethylsilyl)acetamide occurred selectively giving tetrakis(1,2,3,4-*O*-trimethylsilyl)-glucose [7]. However, no selectivity was observed when we applied this procedure to β-CD, as the reaction resulted in the formation of several silyl derivatives. A reaction involving reflux of β-CD with an excess of *N*-(trimethylsilyl)acetamide in

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pyridine gave selectively **2a**, although contaminated by some minor side-products with R_f values larger and smaller than that for **2a**. The ^{1}H NMR spectra of the fraction of the products with the higher R_f values showed, apart from the main signals due to the trimethylsilyl groups at O-2 and O-6, some additional resonances owing to these groups at O-3. We obtained a similar result using the literature procedure involving trimethylsilylation of β-CD with *N*-(trimethylsilyl)-imidazole in dimethyl sulphoxide [8]. We found that the best result could be achieved by trimethylsilylation of β-CD with *N*-(trimethylsilyl)-acetamide in *N,N*-dimethylformamide. The product **2a** was sparingly soluble in this solvent and precipitated in the form of a fine crystalline solid as the reaction proceeded. The separation of this material gave heptakis(2,6-di-*O*-trimethylsilyl)cyclomaltoheptaose (**2a**) with some acetamide. The latter was removed by heating under vacuum. The product was purified by dissolving it in hexane and some solid was separated. Removal of the solvent and drying gave the product of mp 247–251 °C (yield 92%), which consisted almost exclusively of **2a** (NMR and TLC). This product was sufficiently pure for further reactions. Trimethylsilylation of α-CD under the same conditions gave **2c** (yield 93%). In contrast to the corresponding *tert*-butyldimethylsilyl derivatives of CDs, the analytical samples of the compounds **2a** and **2c** could be obtained by simple crystallisation from hexane or heptane.

tert-Butyldimethylsilylation of β-CD with one equivalent of *tert*-butyldimethylsilyl chloride in pyridine gave selectively per-6-*O*-*tert*-butyldimethylsilyl-β-CD [9]. All our attempts to obtain per-6-*O*-trimethylsilyl-β-CD in a reaction of β-CD with one equivalent of *N*-(trimethylsilyl)acetamide both in *N,N*-dimethylformamide and in pyridine failed, resulting in a multitude of trimethylsilyl derivatives (NMR and TLC). Similarly, we found that silylation of β-CD with *N*-(*tert*-butyldimethylsilyl)acetamide was not selective irrespective of whether run in *N,N*-dimethylformamide or in pyridine, with excess or one equivalent of the reagent. For example, the reaction of β-CD with an excess of *N*-(*tert*-butyldimethylsilyl)acetamide in *N,N*-dimethylformamide run for 72 h at 50 °C gave a product whose NMR spectra and TLC revealed a multiplicity of silyl derivatives with R_f values ranging from 0.2 to 0.4 and no per-2,6-*O*-(*tert*-butyldimethylsilyl)-β-CD (R_f 0.61, silicagel 60, 30:2:1 heptane–ethyl acetate–pyridine). Evidently, steric transition state requirements are prohibitively high for *tert*-butyldimethylsilylation as compared with those for trimethylsilylation. These results are in accord with that reported in the literature where a reaction of β-CD with *N*-(*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide also resulted in randomly silylated CDs [1]. However, trimethylsilylation of per-6-*O*-(*tert*-butyldimethylsilyl)-β-CD with *N*-(trimethylsilyl)acetamide in *N,N*-dimethylformamide gave per-2-*O*-trimethylsilyl-6-*O*-(*tert*-butyldimethylsilyl)-β-CD (**2b**) in good yield (Experimental).

Although the ^{1}H NMR spectrum of **2a** was reported as early as in 1981, to our knowledge no detailed analyses of ^{1}H and ^{13}C NMR spectra were presented. The spectra of **2a–c** were initially recorded in $CDCl_3$, but extensive broadening of resonances and some additional signals were observed on prolonged standing. In C_6D_6 the spectra of these compounds did not change. Another advantage of using C_6D_6 was that the resonances of the trimethylsilyl derivatives **2a** and **2c** were better dispersed than those in $CDCl_3$. This phenomenon was not observed for the *tert*-butyldimethylsilyl derivatives **2b** and per-2,6-(*tert*-butyldimethylsilyl)-β-CD; as a matter of fact some resonances of these derivatives were even more overlapped in the spectra taken in C_6D_6 than in those recorded in $CDCl_3$.

The spectra of the silyl derivatives in both solvents with six signals for the sugar skeleton carbons point to the 7-fold symmetry for **2a–b** and the six-fold symmetry for **2c**. The resonances of **2a–c** at positions 1, 4 and 6 were assigned with the aid of the wealth of NMR data for CD derivatives [3–5,10,11]. The unequivocal assignment of the remaining resonances (C-2,3,5) were made by means of the ^{1}H-^{1}H COSY and HETCOR spectra. The glucopyranose residue carbon resonances of **2a–c** are very close to those for the corresponding *tert*-butyldimethylsilyl derivatives [5]. The change of solvent from $CDCl_3$ to C_6D_6 leads to downfield shifts of the carbon resonances by 0.6–1.1 ppm. These downfield shifts are a little smaller in the case of the α-CD derivative (**2c**) (Table 1).

The presence of two signals in the silyl region proved that only two sets of hydroxyl groups in the CDs were silylated. The cross-peaks between the signal of the free hydroxyl group and the H-3 proton observed in the ^{1}H-^{1}H COSY spectra of all the silyl derivatives in both solvents supported the 2,6-substitution. The trimethylsilyl resonances of **2a–c** were distinguished on the basis of the assignments

Table 1
^{13}C NMR data of silyl derivatives of α- and β-cyclodextrin (**2a–2c**)[a]

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	$Si(R^1)_2R^2$-2	$Si(R^1)_2R^2$-6
2a	C_6D_6	103.8	75.2	73.1	83.9	72.4	62.0	$R^1=R^2=$Me; 0.37	$R^1=R^2=$Me; 0.0
2a	$CDCl_3$	102.8	74.4	72.3	82.8	71.7	61.3	$R^1=R^2=$Me; 0.22	$R^1=R^2=$Me; −0.23
2b	C_6D_6	103.5	75.3	73.0	83.3	72.5	62.5	$R^1=R^2=$Me; 0.35	$R^1=$Me; −4.82, −4.71 $R^2=$Bu^t C; 18.7, Me; 26.2
2b	$CDCl_3$	102.5	74.5	72.2	82.2	71.8	61.9	$R^1=R^2=$Me; 0.14	$R^1=$Me; −5.1, −5.2 $R^2=$Bu^t C; 18.3, Me; 25.9
2c	C_6D_6	103.1	74.7	73.5	83.4	72.4	62.0	$R^1=R^2=$Me; 0.40	$R^1=R^2=$Me; −0.08
2c	$CDCl_3$	102.6	74.0	72.9	82.9	71.5	61.4	$R^1=R^2=$Me; 0.28	$R^1=R^2=$Me; −0.31
3[b]	C_6D_6	103.5	75.6	72.7	83.0	72.7	62.6	$R^1=$Me; −4.2 $R^2=$Bu^t C 19.2, Me; 26.6	$R^1=$Me; −4.7, −4.2 $R^2=$Bu^t C; 18.7, Me; 26.2
3[b]	$CDCl_3$	102.6	75.0	71.9	82.0	72.2	62.0	$R^1=$Me; −4.6, −4.5 $R^2=$Bu^t C; 18.9, Me; 26.3	$R^1=$Me; −5.3, −5.0 $R^2=$Bu^t C; 18.3, Me; 25.9

[a] The spectra were recorded at 50.28 MHz.
[b] Compound **3** (per-2,6-TBDMS-β-CD) was prepared according to the literature procedure [9]; mp 308–310 °C; $[\alpha]_D^{20}$ +60.7° (*c* 1.3, $CHCl_3$).

made by Stoddart et al. for per-2,6-di-*O*-*tert*-butyldimethylsilyl-α-CD with the aid of NOE difference spectroscopy and selective heteronuclear decoupling experiments [3]. The result, somewhat expected on the steric grounds [12], proved that both carbon and proton resonances of the silyl groups at position 2 were shifted downfield relative to those at position 6.

Whereas the silyl singlets were narrow ($\Delta_{1/2}$ 0.4–0.6 Hz), the signals of the glucosidic proton resonances were definitely broader ($\Delta_{1/2}$ 0.8–2 Hz). The resonance patterns for the particular protons were the same throughout all the ^1H NMR spectra of **2a–c**. Namely, the characteristic H-1 resonance appeared as a doublet at ca. 5 ppm with a coupling constant of *ca.* 3 Hz, the H-2 resonance as a doublet of doublets, and the H-3 and H-4 resonances as apparent triplets. The H-6a, H-6b and H-5 resonances formed an ABC or ABX pattern (in Table 2 these resonances are indicated as multiplets.). The assignments of the resonances to the particular protons were made with the aid of the ^1H-^1H COSY spectra for **2a–c**. All the ^1H NMR spectra were dispersed and resolved well enough to obtain the approximate values of chemical shifts and coupling constants except those for coupling constants $J_{5,6a}$. The latter were generally observed with an unusually large broadening of the two lines for the H-6a proton, forming the part A of the ABC subspectrum. Even in the 500 MHz spectrum of **2c** these lines were observed as broad, largely overlapping doublets. No essentially better resolution was observed when the spectra were recorded at 50 °C. The approximate values of the NMR parameters for the glucosidic protons taken from the spectra of **2a–c** were numerically analysed as a seven spin system using the LAOCOON programme. Final differences between experimental and calculated line positions were less than 0.3 Hz. The calculation gave the values of the chemical shifts and coupling constants with an average error less than 0.03 Hz (Table 2). The results are in accord with the C_7 symmetry for **2a** and **2b**, and the C_6 symmetry for **2c** in both solvents. The change of solvent only slightly affects the coupling constants indicating that this change does not influence a chair conformation of the glucopyranose unit. Similarly like the carbon resonances, all the proton resonances are shifted downfield when going from $CDCl_3$ to C_6D_6 solutions. The solvent shift differences are larger for the β- (**2a–b**) than for the α-silyl derivatives (**2c**), particularly for H-3 and H-5. On the other hand, the shift solvent differences for H-6a, H-6b and the silyl protons are very close in both **2a–b** and **2c** (Table 2).

3. Experimental

General methods.—Melting points were determined with a micro melting point apparatus and are uncorrected. Optical rotations were determined with a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. Elemental analyses were carried out on a Perkin–Elmer 240 analyser. LSIMS mass spectra were measured on an AMD INTECRA-604 mass spectrometer with NBA as the matrix. ^1H NMR spectra were recorded on a Varian XL-300 spectrometer. ^{13}C NMR, ^1H-^1H COSY and HETCOR spectra were recorded with a

Table 2
^{1}H NMR data of silyl derivatives of α- and β-cyclodextrin (**2a–2c**)[a]

Compound	Solvent	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	HO-3	$Si(R^1)_2R^2$-2	$Si(R^1)_2R^2$-6
		($J_{1,2}$ Hz)	($J_{2,3}$ Hz)	($J_{3,4}$ Hz)	($J_{4,5}$ Hz)	($J_{5,6a}$ Hz) ($J_{5,6b}$ Hz)	($J_{6a,6b}$ Hz)				
2a[b]	C_6D_6	5.05 (d) (3.4)	3.80 (dd) (9.4)	4.36 (t) (9.2)	3.78 (t) (8.7)	4.04 (m) (0.6) (3.1)	3.95 (m) (−11.0)	4.19 (m)	5.31 (s)	$R^1=R^2=$Me 0.30 (s)	$R^1=R^2=$Me 0.24 (s)
2a	$CDCl_3$	4.77 (d) (3.5)	3.57 (dd) (9.5)	3.80 (t) (9.5)	3.37 (t) (8.8)	3.65 (m) (0.8) (3.5)	3.69 (m) (−11.3)	3.88 (m)	4.89 (s)	$R^1=R^2=$Me 0.19 (s)	$R^1=R^2=$Me 0.11 (s)
2b	C_6D_6	5.12 (d) (3.6)	3.84 (dd) (9.4)	4.37 (t) (9.4)	3.82 (t) (9.6)	3.99 (m) (0.4) (2.7)	3.94 (m) (−11.3)	4.23 (m)	5.24 (s)	$R^1=R^2=$Me 0.33 (s)	$R^1=$Me 0.22, 0.24 (s) $R^2=Bu^t$; 1.04 (s)
2b	$CDCl_3$	4.78 (d) (3.5)	3.48 (dd) (9.7)	3.81 (t) (9.3)	3.41 (t) (9.7)	3.59 (m) (1.3) (2.7)	3.67 (m) (−11.2)	3.91 (m)	4.80 (s)	$R^1=R^2=$Me 0.18 (s)	$R^1=$Me 0.02, 0.03 (s) $R^2=Bu^t$; 0.87 (s)
2c[b]	C_6D_6	4.97 (d) (3.3)	3.78 (dd) (9.5)	4.28 (t) (8.9)	3.77 (t) (9.3)	3.98 (m) (1.2) (3.2)	3.95 (m) (−11.2)	4.17 (m)	5.09 (s)	$R^1=R^2=$Me 0.29 (s)	$R^1=R^2=$Me 0.26 (s)
2c[c]	$CDCl_3$	4.78 (d) (3.4)	3.61 (dd) (9.3)	3.95 (t) (9.1)	3.46 (t) (9.0)	3.78 (m) (1.2) (3.7)	3.73 (m) (−11.1)	3.88 (m)	4.81 (s)	$R^1=R^2=$Me 0.19 (s)	$R^1=R^2=$Me 0.12 (s)

[a] Chemical shifts (δ) and coupling constants (J) of the spectra recorded at 300 MHz unless stated otherwise. Symbols (d), (t) and (m) refer to doublet, apparent triplet and multiplet, respectively.
[b] Recorded at 200 MHz.
[c] Recorded at 500 MHz.

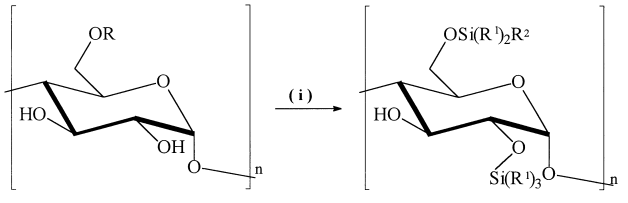
Varian Gemini 200 spectrometer. Chemical shifts were referenced to signals of residual H atoms in $CDCl_3$ (7.26 ppm) and C_6D_6 (7.15 ppm), and to $CDCl_3$ (77.0 ppm) and C_6D_6 (128.0 ppm) in the ^{1}H and ^{13}C NMR spectra, respectively. Reactions were monitored and the purity of products was checked on silica gel plates (Kieselgel 60 F_{254}, E. Merck), developed with 30:2:1 heptane–EtOAc–pyridine with detection by charring with 0.5% $KMnO_4$ in H_2SO_4.

General procedure.—A homogeneous solution of dry β-cyclodextrin (1 mmol) and *N*-(trimethylsilyl)-acetamide (24.5 mmol) in DMF (7 mL) was stirred for 48 h at 50 °C under Ar. A colourless solid began to precipitate within 1 h. After cooling to room temperature, the mixture was centrifuged and the crystalline solid was washed with a small amount of DMF. The remaining DMF and acetamide were removed by heating at 100 °C under reduced pressure to afford a colourless product. The product was purified by dissolving in hexane (20 mL) and some solid material separated. Removal of the solvent and drying at 100 °C under reduced pressure gave a colourless product, which consisted almost exclusively of **2**. (Scheme 1)

Heptakis(2,6-di-O-*trimethylsilyl)cyclomaltoheptaose* (**2a**).—A crude product (2.02 g, 94%; mp 247–251 °C) consisted mainly of **2a** as evidenced by its ^{1}H and ^{13}C NMR spectra (Tables 1 and 2). TLC: R_f 0.32; $[\alpha]_D^{20}$ +86.5^0 (*c* 1, $CHCl_3$); an analytical sample was obtained by crystallisation from hexane yielding **2a**; mp 262–263 °C; LSIMS: *m/z* 2167 for $[M+Na]^+$; Calcd for $C_{84}H_{182}O_{35}Si_{14}$: M = 2145. Anal. Calcd for $C_{84}H_{182}O_{35}Si_{14}$: C, 47.0; H, 8.55. Found: C, 47.05; H, 8.60.

Hexakis(2,6-di-O-*trimethylsilyl)cyclomaltohexaose* (**2c**).—A crude product (1.69 g, 92%; mp 251–254 °C) consisted mainly of **2c** (NMR, Tables 1 and 2). TLC: R_f 0.32; $[\alpha]_D^{20}$ +85.7^0 (*c* 0.9, $CHCl_3$); mp 258–260 °C (hexane); LSIMS: *m/z* 1861 for $[M+Na]^+$; Calcd for $C_{72}H_{156}O_{30}Si_{12}$: M = 1839.

Heptakis(6-O-tert-*butyldimethylsilyl-2*-O-*trimethylsilyl)cyclomaltoheptaose* (**2b**).—A mixture of heptakis(6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (**1b**) [9], *N*-(trimethylsilyl)acetamide and DMF was stirred for 72 h at 50 °C. The usual



1 **2**

(i) : TSA, DMF, 50 °C, 48 h.

1a : R = H **2a** : $R^1 = R^2$ = Me n = 7

1b : R = $SiBu^tMe_2$ **2b** : R^1 = Me; $R^2 = Bu^t$ n = 7

1c : R = H **2c** : $R^1 = R^2$ = Me n = 6

Scheme 1.

workup gave a colourless crude product (2.34 g, 96%; mp 280–284 °C). Although the ^{1}H and ^{13}C NMR spectra of this product were consistent with **2c**, its TLC revealed, apart from **2c** (R_f 0.4), a minor side product (R_f 0.16). An analytical sample was obtained by a short silica gel column (silica gel 60, 230–400 mesh, E. Merck; 100:1:1 hexane–EtOAc–pyridine); mp 290–292 °C; $[\alpha]_D^{20}$ +71.2° (*c* 0.9, $CHCl_3$); NMR (Tables 1 and 2); LSIMS: *m*/*z* 2462 for $[M+Na]^+$; Calcd for $C_{105}H_{224}O_{35}Si_{14}$: M = 2040.

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