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A Silyl-α-cyclodextrin Intermediate. Preparation and Characterization of Dodeca-*t*-butyldimethylsilyl-hexahydroxy-α-cyclodextrin

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Abstract. The title compound (**II**) was prepared by treating dry, purified α-cyclodextrin with 20 equivalents of *t*-butyldimethylsilyl chloride 20 hr at 110° in DMF/pyridine. Work-up of the product mixture gave 60% **II**, which was identified by ^{1}H and ^{13}C NMR. Treatment of **II** with Bu_4NF 6 hr in refluxing dry THF efficiently removed the protecting groups.

Key words: α-cyclodextrin silylation, protection, deprotection, ^{1}H and ^{13}C NMR, butyldimethylsilyl α-cyclodextrin.

Cyclodextrins can serve as enzyme models because of their stereospecific binding followed by stereospecific reactions [1]. The synthesis of new polyprotected cyclodextrins and studies of the unique geometry of cyclodextrins as enzyme mimics are limited by the scarcity of well-characterized polysubstituted derivatives.

Several modifications of cyclodextrins, specifically of their primary and secondary hydroxyls as tosylates, methoxylates, allyl ethers and many others have been described [2]. None of the above methods, however, offer intermediates for further modification on the secondary side of α-cyclodextrin which are as soluble in nonpolar solvents, stable under ordinary conditions and easily deprotected as the *t*-butyldimethylsilyl derivatives [3].

We report here the preparation and characterization of $2^A,2^B,2^C,2^D,2^E,2^F$, $6^A,6^B,6^C,6^D,6^E,6^F$-dodeca-*tert*-butyldimethylsilyl-α-cyclodextrin **II**, a new synthetic intermediate. Since positions $3^A,3^B,3^C,3^D,3^E,3^F$ are not silylated in this compound, they are available for further modification.

The synthesis of **II** and a method for its deprotection are outlined in Figure 1. Dry purified cyclodextrin **I** was reacted with 20 equivalents of *tert*butyldimethyl-silyl chloride in DMF/Py 2 : 0 at 110° for 20 hours [4]. TLC on silica gel (hexane : benzene : methanol 20 : 4 : 1) of the reaction mixture indicated a multitude of products. Subsequent precipitation of the products by cooling yielded two major derivatives with R_f values 0.70 and 0.65, (**II**) and (**III**), in a ratio 4 : 1. The desired $2^A,2^B,2^C,2^D,2^E,2^F,6^A,6^B,6^C,6^D,6^E,6^F$ symmetrically substituted-silyl-α-cyclodextrin **II** (R_f–0.7) was isolated in 60% yield after column chromatography on silica gel eluting with hexane and increasing concentrations of ethyl acetate (from 1 to 5% v/v). **II** was identified by ^{1}H and ^{13}C NMR spectroscopy, IR, and elemental analysis [5].

The ^{13}C NMR spectrum (Figure 2) shows a single isomer with six-fold symmetry indicating a symmetric pattern of substitution on both sides of an α-cyclodextrin [6]. All predicted signals were seen: C-1 at 102.67, C-2 at 74.65, C-4 at 82.60, C-6 at 62.30 ppm. Carbons C-3

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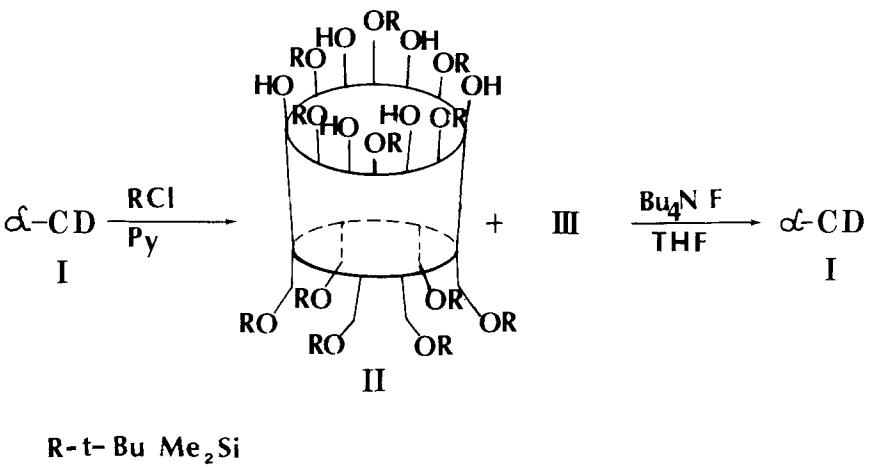

Fig. 1. Sililation and desililation of α-cyclodextrin.

and C-5 could not be distinguished due to their very close proximity (72.37 and 72.03 ppm). The carbon signals of the *tert*-butyldimethylsilyl groups were located as follows: $(CH_3)_3$ on C-2 at 26.25, $(CH_3)_3$ on C-6 at 25.95 ppm; quarternary carbons on C-2 and C-6 at 18.38 and

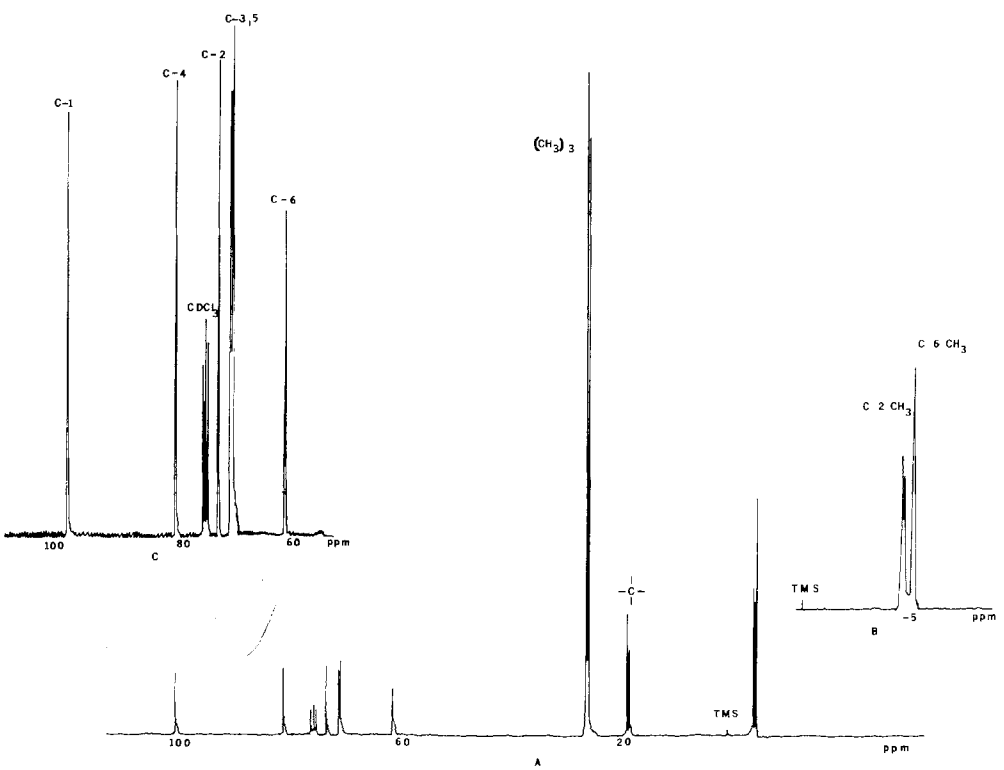

Fig. 2. (A) The ^{13}C NMR spectrum of **II** in $CDCl_3$; (B) Expansion of aliphatic region of II; (C) Expansion of carbohydrate region of **II**.

18.84 ppm, respectively. The carbons of the dimethyl groups on C-2 and C-6 were found respectively at −4.58, −4.66 and −5.12 ppm.

The ^{1}H NMR spectrum shows (Figure 3) the presence of a simple isomer with six-fold symmetry. Chemical shifts were assigned as follows:

δ0.039 (*s*, 6H, 6–O–Si*Me*$_2$); δ0.136, 0.149 (*d*, 6H, 2–O–Si*Me*$_2$);
δ0.881 (*s*, 9H, 6–O–Si–*tBu*); δ0.907 (*s*, 9H, 2–O–Si–*tBu*);
δ3.478 (*dd*(*t*), 1H, $J_{4,5}$-8,9 Hz, H-4); δ3.545 (*d*,*d*, 1H $J_{2,3}$-9,9 Hz, H-2);
δ3.673–3.744 (*m*, 2H, H-5, H-6^1); δ3.948 (*dd*, 1H, H-6);
δ3.989 (*dd*, 1H, $J_{3,2}$-9,9, H-3); δ4.373 (*s*, 1H, OH-3);
δ4.787 (*d*, 1H, $J_{1,2}$-2.8 Hz, H-1).

Integration confirmed the predicted numbers of protons. The assignments of the positions of protons were confirmed by decoupling experiments. The proton NMR spectrum follows a similar pattern to that which was observed for β-cyclodextrin substituted with *tert*-butyldimethylsilyl groups [3]. The ^{1}H and ^{13}C NMR show the nonequivalence of the methyl groups at C-2 in the *t*-butyldimethylsilyl moiety which suggests steric hindrance of the adjacent methyl groups.

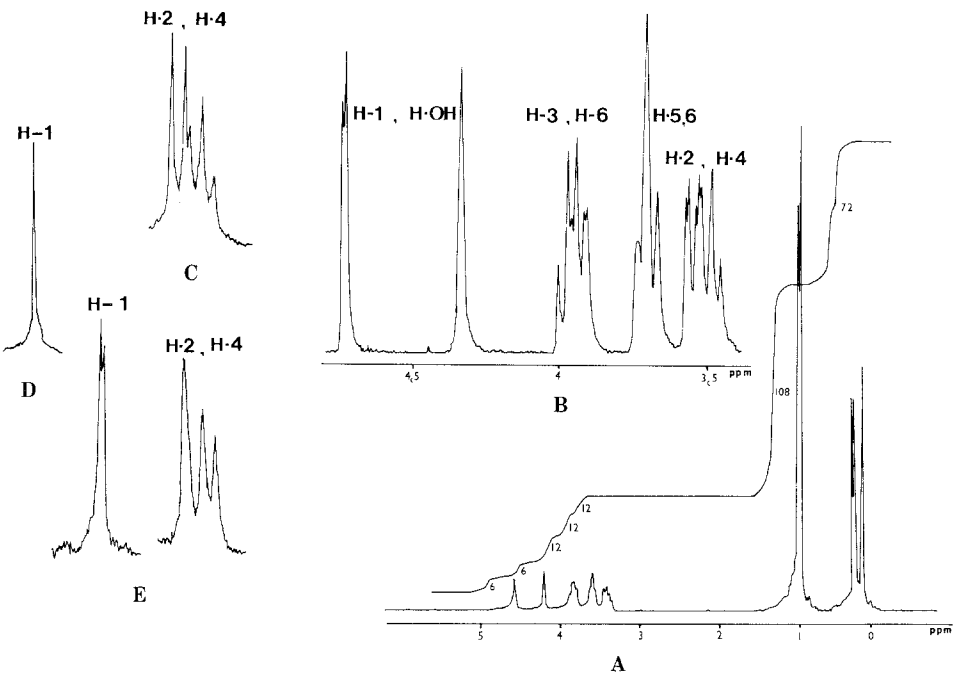

Fig. 3. (A) The ^{1}H NMR spectrum of **II** in $CDCl_3$; (B) Expansion of the carbohydrate region of **II**; (C) Protons H-2, H-4 after irradiation at proton H-1; (D) Proton H-1 after irradiation at proton H-2; (E) Proton H-1 and H-2, H-4 after irradiation at protons H-3.

The second product **III**, (R_f-0.65) after isolation in 23% yield appeared to be a mixture of four silyl-substituted α-cyclodextrins with an average degree of substitution of nine as determined by ^{1}H, and ^{13}NMR spectroscopy. Further treatment of **III** with a large excess *tert*-butylsilyl chloride led to a maximum of 50% of **III** converted to **II**, suggesting that certain

of the isomers of **III** are reactive precursors of **II** while others are unreactive to further silylation under the above conditions.

Removal of *tert*-butyldimethylsilyl protective groups from **II** and **III** and subsequent formation of α-cyclodextrin **I** was accomplished by treatment with tetrabutylammonium fluoride in dry THF under reflux for 6 hours [7] (See Figure 1). It is noteworthy that treatment of **II** with acetic acid : THF water (1 : 10 : 1) for 24 hours did not cause significant desilylation of **II**, indicating good stability of **II** even under acidic conditions.

Our current interest lies in the functionalization of the secondary side of cyclodextrin through modification of α-cyclodextrin silyl derivatives in order to improve its complexing properties.

Acknowledgement

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4. We have observed that pyridine as a catalyst gives a higher yield of **II** than does the more-frequently used imidazole.
5. IR : (υOH (stretch), 3440 cm^{-1}, υSi-$(CH_3)_3$ 1250 cm^{-1}), m.p. 274 °C (decomposition), ^1H, ^{13}C NMR: JEOL, JNM-FX270, multinuclear, $CDCl_3$-TMS. Elemental analysis: calculated for formula: $C_{108}H_{228}O_{30}Si_{12}$, C-55.34, H-9.81, O-20.48, Si-14.38. Found: C-55.39, H-9.97, O-19.35, Si-14.56.
6. Assignments for most of the signals in the ^{13}C NMR spectra were based upon data on cyclodextrins and other carbohydrates, e.g., P. Colson, H. J. Jennings, and J. C. P. Smith: *J. Am. Chem. Soc.* **96**, 8081 (1974); K. Takeo, K. Hirose, and T. Kluge: *Chem. Lett.* 1233 (1973); J. Boger, R. Corcoran, and J.-M. Lehn: *Helv. Chim. Acta* **61**, 2190 (1978).
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