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Selective Modification at the 3-Position of β-Cyclodextrin

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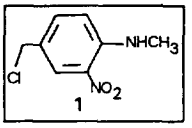
Abstract: Heptakis(6-*O*-*tert*-butyldimethylsilyl)β-cyclodextrin reacts with *N*-methyl-4-chloromethyl-2-nitroaniline to produce the 3-modified cyclodextrin after the necessary deprotection step. Complete NMR assignment and its comparison with cyclodextrin derivatives modified by the same group at the 2- and 6-position is reported. Copyright © 1996 Elsevier Science Ltd

Methods for selective modification of cyclodextrins have gained prominence in recent years[1] because they provide tools to overcome its structural and functional straightjacket[2] and access molecules with valuable properties in a variety of fields like enzyme mimics,[3] complex formation,[4] catalysis,[5] molecular recognition[6] and self assembly.[7] However, this process is complicated[8] because these methods follow rules of either normal reactivity or modified reactivity due to formation of a complex with its reagent (Scheme 1). Since rules of normal nucleophilicity dictate the hydroxyl groups at the 6-position to be most reactive, most of the modifications have taken place at this site[9] (A in Scheme 1). Earlier, we introduced[10] a method to reverse this reactivity [demonstrated using *N*-methyl-4-chloromethyl-2-nitroaniline (**1**) as the electrophile] by deprotonating the most acidic hydroxyl group of β-cyclodextrin (**2**) at the 2-position and thereby enabling modifications at the normally least basic hydroxyl group (B in Scheme 1). However, when the same electrophile under conditions of normal reactivity failed to give a product modified exclusively at the 6-position,(C in Scheme 1) we introduced a method[11] to protect the undesired 2-position and exclusively yield the desired 6-modified cyclodextrins(D. in Scheme 1). 3-Modified cyclodextrins are not easily accessible and so far, only one such derivative obtained in 18% yield by a reaction of β-naphthalene sulfonyl chloride with **1** has been reported.[12]

Scheme 1

CYCLODEXTRIN

A. Normal reactivity: weak base (e.g. pyridine) and a non-complexing electrophile →	6-modified CD
B. Reversed reactivity: strong base (deprotonate) and a non-complexing electrophile →	2-modified CD
C. Reaction via complex formation, use a complexing electrophile →	2-, 3- or 6-modified CD or a mixture of the three
D. Protect 2-position, any baseand any electrophile →	6-modified CD
E. Protect 6-position, weak base (e.g. lutidine) and any electrophile →	3-modied CD or 2-modified CD ?



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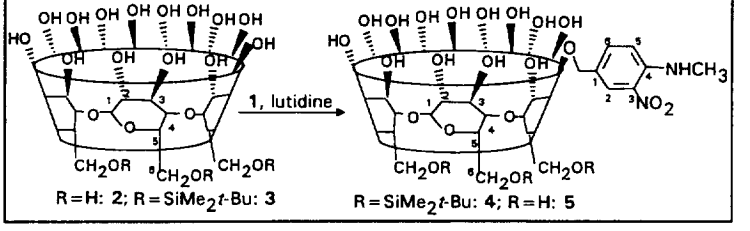
We now report the synthesis of another 3-modified cyclodextrin derivative in which reagent **1** (which is known to react preferentially at the 2-position) is reacted with the readily accessible heptakis(6-*O*-*tert*-butyldimethylsilyl)β-cyclodextrin (**3**). A solution of **1** (80.0 mg, 0.40 mmol) in lutidine (25 ml) was refluxed under argon for 2 hours, cooled to 80°C, **3** (1.0 g, 0.52 mmol) was added to it in one portion and the reaction mixture was refluxed for additional 2 hours. The product **4** was deprotected without isolation of the intermediate with excess TBAF (2 ml, 1.0 *N* in THF) at 80°C for 3 hours. Solvent was rotavaped, residue dissolved in 100 ml water, washed with ethyl acetate twice, concentrated to dryness and dried under vacuum overnight to afford 0.73 g of the crude product **5**. The product (200 mg) was purified with Sephadex G25-100 column in which the second yellow band collected between 600-720 ml of eluent contained the major product (Rf = 0.45). The eluent was concentrated to dryness and further dried under vacuum (0.2 mm Hg) for overnight to afford **5** as the major product (40 mg, 28.1% calculated from **1**). The sample was further purified with HPLC to yield **5** (28.5mg, 20.0%) whose elemental analysis and NMR spectral data are consistent with the proposed structure.[13] Although this method involves two extra steps and the yield is comparable to the previous[12] one, it provides a route to access 3-substituted derivatives with reagents which would normally not produce these compounds.

Scheme 2



The reaction of a electrophile with 6-protected cyclodextrin to give a 3-modified derivative **5** raises an interesting question in cyclodextrin chemistry. Since the basicity of hydroxyl groups are in the order of 6>3>2, (6- and 2- are known to be most basic and acidic respectively)[14] if those at the 6-position are protected, which of the two remaining groups is more nucleophilic? (E in scheme 1). We reacted several electrophilic reagents with **2** in the presence of a weak base and observed no reaction with unactivated benzyl halides and reactions at the 2-hydroxyl groups with sulfonyl halides which is consistent with other reports.[15] These results suggest that the hydroxyl group at the 2-position is more nucleophilic and sulfonyl halides react with **3** without the formation of a complex to give 2-substituted products. The formation of a 3-substituted product with **1** can be explained by its complex formation with **3** in which the orientation of reactive group is towards the hydroxyl group at the 3-position.

Since 3-modified cyclodextrins are rare, a series of experiments were carried out to determine the complete NMR assignments of **5**. The homonuclear two-dimensional correlation experiments (COSY, TOCSY and ROESY) did not give enough data to make unambiguous assignments because more than 70% of the skeleton proton signals are concentrated in a small region between 3.5-4.3 ppm. Since the chemical shift dispersion of the carbon spectrum was better, heteronuclear correlation experiments are used to make these

Table 1: $^{1}H(^{13}C)$ Chemical Shifts for 5[a]

Atom#→ Glucose#↓	1	2	3	4	5	6[b]
A	5.18(104.43)	4.05(75.81)	4.00(75.91)	3.77(80.82)	3.84(73.99)	4.09-3.86(61.49)
B	5.12(103.37)	3.70(73.99)	3.85(75.26)	3.65(83.49)	3.79(73.52)	"
C	5.21(103.92)	3.84(73.40)	4.08(74.76)	3.72(83.28)	3.90(73.45)	"
D	5.22(103.80)	3.83(73.74)	4.11(75.12)	3.75(82.82)	3.98(73.60)	"
E	5.22(103.69)	3.83(73.81)	4.12(74.69)	3.76(82.90)	3.97(73.54)	"
F	5.23(103.76)	3.84(73.60)	4.09(74.69)	3.75(82.97)	3.94(73.66)	"
G	5.24(103.69)	3.82(73.66)	4.11(74.75)	3.72(83.40)	3.90(73.44)	"
β-CD	4.99(103.13)	3.56(73.33)	3.88(74.33)	3.50(82.38)	3.78(73.08)	3.76(61.50)
Aromatic	-(123.69)	8.33(130.19)	-(131.82)	-(148.52)	7.21(116.15)	7.83(141.00)
	$N\text{-}CH_3$ - 3.25(30.89)		$Ar\text{-}CH_2$ - 5.28, 4.98(73.24)			

[a] Chemical shifts reported are in ppm and the glucose units are labeled in anti-clockwise direction starting from the modified sugar. [b] Since there is no separation for C6 resonances for carbohydrate region, only the chemical shift region is determined for ^{1}H.

assignments. The key experiment, proton detected heteronuclear long-range correlation (HMBC),[16] shows a three-bond correlation between the benzyl CH_2 protons and the third carbon of the substituted ring. At the same time, this experiment is also used to find correlations between the anomeric protons and the C4 atoms in the neighboring sugar rings. Since the broadening effect[17] of the homonuclear couplings on the indirectly detected carbon signal in the HMQC spectrum[18] makes the signals unassignable when the carbon spectrum is crowded, the HSQC method[19] was chosen to get the heteronuclear correlation spectrum. The carbon signals of the HSQC spectra are not affected by the proton-proton couplings and both one-bond and long-range correlation experiment can be set up. The third experiment was the HSQC-TOCSY using the previously assigned H1 and H4 chemical shifts as starting points. A TOCSY sequence (inserted after the basic HSQC sequence so that the TOCSY subspectra were separated by the carbon chemical shift) transferred the proton magnetization inside the glucose spin-systems. The resolution of the second dimension was increased by an extensive folding[20] in case of HSQC and HSQC-TOCSY. The assignment for both ^{1}H and ^{13}C resonances obtained by this series of experiments are summarized in Table 1.

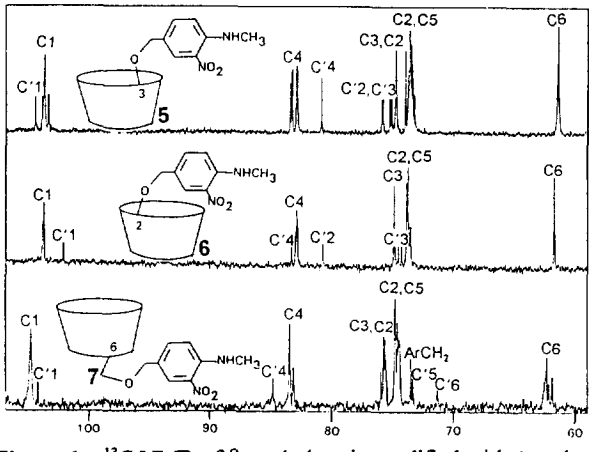


Figure 1: ^{13}C NMR of β-cyclodextrin modified with **1** at the 3-, 2- and 6- positions.

The synthesis of **5** provides us with

an unique opportunity to compare the NMR spectra of cyclodextrins modified by the same group at three different positions (3-, 2- and 6-) as shown in Figure 1. It is interesting to note that the signal for the α-carbon of the modified glucose unit is 1.49, 7.36 and 11.97 ppm down field in **5**, **6** and **7** respectively from the corresponding signal of the native cyclodextrin. The calculated values[21] for these chemical shifts are 2.67, 4.0 and 10.67 ppm respectively down field from those of β-cyclodextrin which is consistent with the observed changes. The signals for β-carbons have shifted down field by 2.42 (C′2), -1.56 (C′4) for **5** (- sign indicates up field shift), -1.53 (C′1), -0.1 (C′3) for **6** and 0.23 (C′5) for **7** compared to signals of native cyclodextrin while the calculated values show a difference of -0.54 (C′2), -5.22 (C′4) for **5**, -2.46 (C′1), 0.27 (C′3) for **6** and -1.25 (C′5) for **7**. Both experimental and calculated results suggest that the chemical shift changes in the signals for the modified glucose vary when the substitutions take place at different positions of cyclodextrin.

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References

1. (a). Ashton, P. R.; Hartwell, E. Y.; Philp, D.; Specncer, N.; Stoddart, J. F. *J. Chem. Soc. Perkin Trans.* II **1995**, 1263. (b). Martin, K. A.; Mortellaro, M. A.; Sweger, R. W.; Fikes, L. E.; Winn, D. T.; Clary, S.; Jognson, M. P.; Czarnik, A. W. *J. Am. Chem. Soc.* **1995**, *117*, 10443.
2. Khan, A.; Barton, L.; D'Souza, V. *J. Chem. Soc., Chem Commun.*, **1992**, 1112.
3. (a). Breslow, R. *Pure & Appl. Chem.* **1994**, 66, 1573. (b). Breslow, R. *Acc. Chem. Res.* **1995**, 28, 146. (c). Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, 96, 721.
4. Szejtli, J. *Cyclodextrins and Their Inclusion Complexes*; Akadamiai Kiado: Budapest, Hungary, 1982.
5. Ye, H; Tong, W.; D'Souza, V. T. *J. Am. Chem. Soc.* **1992**, *114*, 5470.
6. Inoue, Y.; Dong, F.; Yamamoto, K.; Tong, L-H.; Tsuneishi, H.; Hakushi, T.; Tai, A. *J. Am. Chem. Soc.* **1995**, *117*, 11033.
7. (a). Parrot-Lopez, H.; Ling, C-C.; Zhang, P.; Baszkin, A.; Albrecht, G.; Rango, C.; Coleman, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 5479. (b). Khan, A. R.; Tong, W.; D'Souza, V. T. *Supramolelar Chem.* **1995**, *4*, 243.
8. Wenz, G. Angew. *Chem. Int. Ed. Engl.* **1994**, *33*, 803.
9. Croft, A. P.; Bartsch, R. A. *Tetrahedron* **1983**, *39*, 1417.
10. Rong, D.; D'Souza, V. T. *Tetrahedron Lett.* **1990**, 31, 4275
11. Tian. S.; D'Souza, V. T. *Tetrahedron Lett.* **1994**, *35*, 9339.
12. Fujita, K.; Tahara, T.; Imoto, T. and Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030.
13. Analysis: Calcd. for $C_{50}H_{78}N_2O_{37}3H_2O$: C, 44.38; H, 6.26; N, 2.07. found: C, 44.43; H, 6.18; N, 2.08.
14. Bender, Myron; Komiyama, M. *Cyclodextrin Chemistry* Springer-Verlag, New York, **1978**.
15. Coleman, A. W.; Shang, P.; Ling, C. C.; Manhutea, J.; Parrot-Lopez, H.; Miocque, M. *Supramolecular Chem.* **1992**, *1*, 11.
16. Bax, A. and Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.
17. a) Norwood, T. J.; Boyd, J.; Heritage, J. E.; Soffe, N.; Campbell, I. D. *J. Magn. Reson.* **1990**, *87*, 488. b) Bax, A.; Ikura, M.; Kay, L. E.; Torchia, D. A.; Tschudin, R. *J. Magn. Reson.* **1990**, *86*, 304.
18. Müller, L. *J. Am. Chem. Soc.*, **1979**, *101*, 4481.
19. Bodenhausen, G.; Ruben, D. J. *Chemical Physics Letters*, **1980**, *69*, 185.
20. Schmeider, P. ; Ippel, J. H.; van den Elst, H.; van den Marel, G. A.; van Boom, J. H.; Altona, C.; Kessler, H. M.*Nucleic Acid Research*, **1992**, *20*, 4747.
21. Calculated using the ^{13}CNMR spectrum calculation software "ACD/CNMR" ver 1.1, Adavanced Chemistry Development, Inc., Toronto, Canada, **1995**.

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