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Selective Protection of the Secondary Side of β-Cyclodextrin

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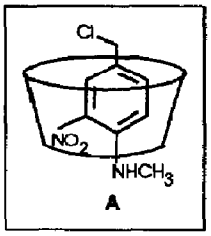
Abstract: Selective protection of the secondary side of β-cyclodextrin by reaction with *t*-butyldimethylsilyl chloride in the presence of NaH in dry DMF, is reported. Although, all the hydroxyl groups are not silylated in this reaction, these groups offer steric protection and direct the incoming electrophile to the primary side of the molecule.

Selective modifications of cyclodextrins,[1] although important in fields of enzyme mimics, complex formations, catalysis,[2] molecular recognition and self assembly,[3] are difficult to control[4] because this molecule can operate under rules of normal nucleophilicity[5] or rules of complex formation in which the orientation of the complex with the reagent dictates the regioselectivity.[6] For example, we reported[7] a reversal of nucleophilicity between primary and secondary hydroxyl groups by deprotonation of the hydroxyl group at the 2-position using NaH. Under these conditions, β-cyclodextrin reacts with *N*-methyl-4-chloromethyl-2-nitroaniline (**3**) to give the corresponding 2-substituted product. However, this electrophile does not exclusively afford the 6-substituted product under conditions where the normal nucleophilicity would be retained[8] but always gives a mixture of both the 2- and 6-substituted products. We can explain this only by suggesting that it forms a complex with **2** such that the chloromethyl group of the reagent is oriented towards the secondary side of the host as shown below as **A**.



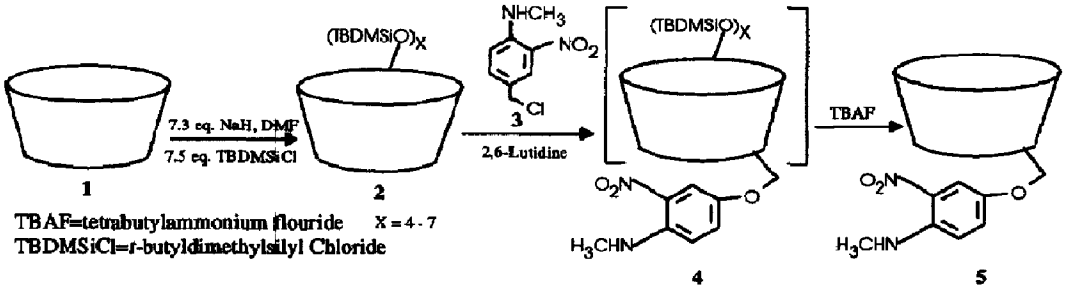
A

A recently reported[9] method for protection of the primary side overcomes complications due to complex formation as well as nucleophilicity and allows modification of the secondary side of cyclodextrin.[10] This method has revolutionized cyclodextrin chemistry[11] and has stimulated studies leading to several secondary side modifications.[12] However, a similar strategy for selective reactions on the primary side of cyclodextrin is not available. We now report our attempts to produce a method for selective protection of cyclodextrins on the secondary side which allows modifications of its primary side.

Our strategy, as shown in scheme 1, involves reaction of cyclodextrins with *t*-butyldimethylsilyl chloride, using NaH as a base, in dry DMF. The TBDMS group is expected to react with the hydroxyl groups on the secondary side because we have shown[7] that under similar conditions, only these hydroxyl groups are sulfonated.

Once the hydroxyl groups on the secondary side are thus protected, chemical manipulations on the primary side should be less complicated.

Scheme 1



β-cyclodextrin[13] (**1**) (5.0 g, 4.41 mmol) is stirred with 7.3 eq. of NaH (1.29 g of 60% dispersion in oil, 31.5 mmol) in 250 mL dry DMF under argon atmosphere until a gel is formed (48 hours). *t*-Butyldimethylsilyl chloride (4.99 g, 33.1 mmol, 7.5 eq.) in 50 mL dry DMF is added to the above gel drop wise for 4 hours.[14] The reaction mixture is cooled to room temperature and approximately two thirds of the DMF is removed by a rotavap. The residue is poured into 500 ml ice-water, the precipitate is filtered, washed with water and dried in a vacuum oven at 90° C overnight to give 6.7 gms (79% yield[15]) of the final product. The TLC of the product suggests that it is a mixture of products with varying degrees of substitution and its ^1H and ^{13}C NMR spectra indicate that the silylation has predominantly taken place on the secondary side. From a closer examination of the data it can be estimated that on an average[16] six out of the seven hydroxyl groups are hydroxylated.

Although this is not an ideal situation, it can be rationalized that the complete silylation on the secondary side is prevented presumably because of the steric hinderance caused by the presence of bulky *t*-butyldimethylsilyl groups. If this assumptions is correct, then it stands to reason that any further electrophilic reaction on the secondary side would be inhibited and this would enhance the possibility of selective chemical modifications on the primary side. This assumption can be tested by reacting the protected β-cyclodextrin **2** with the electrophile **3** which as described earlier fails to give exclusively 6-substituted product. A solution of **3** (121 mg, 0.6 mmol) in 40 mL 2,6-lutidine is stirred at 120 °C for 2 hours under an argon atmosphere and cooled to room temperature. The compound **2** (1 g, 0.52 mmol) is added to the reaction mixture in one portion and refluxed for 8 hours.[17] The deprotection step is carried out, without isolation[18] of the intermediate **4**, by addition of excess tetrabutylammonium fluoride (4 mL, 1N). The reaction mixture is allowed to react at 80°C overnight, cooled to 0°C and maintained at that temperature for one hour when the product crystallizes out. The product is filtered and its TLC analysis[19] indicates that it consists of the desired product **5** (R_f = 0.49), β–cyclodextrin (R_f = 0.32) and its higher substituted derivatives (R_f = 0.61). Product in which the secondary side of β-cyclodextrin is modified (R_f = 0.53) is not observed. The product is purified by ion exchange followed by Sephadex chromatography (G-15) to give 201 mg (23.8% yield from cyclodextrin) of the desired product.[20]

Proton NMR of **5** (DMSO-d_6) δ 2.95 (3H, d, J=4.8Hz, -CH_3), 3.17 - 3.8 (42 H, m, carbohydrate region), 4.30 - 4.55 (8H, m, 6-OH, benzylic -CH_2), 4.80 (7H, d, J=2.7 Hz, anomeric H), 5.58 - 5.82 (14H, m, 14 OH), 6.98 (1H, d, $J_{2,3}$ = 9Hz), 7.51 (1H, dd, $J_{2,3}$ = 9Hz, $J_{5,6}$=1.9Hz), 7.99 (1H, d, $J_{5,6}$=1.9Hz), 8.14 (1H, m, NH). ^{13}C NMR (DMSO-d_6) of **5** (R_f = 0.49) showed peaks at δ 68.4 (C'-6), 70.2 (C'-5), 81.9 (C'-4) and 102.3 (C'-1) for the substituted glucose unit besides the normal six peaks for cyclodextrin clearly indicating that the substitution has taken place at the 6-position.

This method is superior to the earlier one[21] in which the protection of the secondary side of β-cyclodextrin is effected by first protection of the primary side, followed by protection of the secondary side with a different reagent and then finally deprotection of the primary side. The method described herein is appropriate for obtaining mono-substitutions on the primary side of β-cyclodextrins with reagents that form complexes and tend to react with its secondary side. However, our attempts to use this method to react all the hydroxyl groups on the primary side with any electrophile (e.g. tosyl chloride) gave a mixture of products with varying degrees of substitution on the primary side leading to the conclusion that some of the hydroxyl groups on the primary side react with TBDMSCl under these conditions. Although this has little effect on reactions attempting to produce mono-substituted β-cyclodextrin, its per-modification of the primary side is not possible by this method.

In an attempt to extend this method, α-cyclodextrin (5 g, 5.1 mmol) is stirred with 6 eq. NaH (1.24g 60% dispersion in oil, 30.8 mmol) in 250 mL anhydrous DMF in Argon atmosphere for 7 days. The gel that forms under similar conditions with β-cyclodextrin is not observed. TBDMSCl (7 eq, 4.66g, 38.3 mmol) in 50 mL dry DMF was added dropwise to the above mixture and allowed to react for 4 hours. Examination of the product by ^{13}C and ^{1}H NMR spectra after appropriate work up indicates that it is a mixture of products with silylation of the primary side as the major component. A reasonable explanation of this observation is that, given the smaller ring size of α-cyclodextrin, it is not possible to form six anions (which are probably solvated) and thus a gel like substance is not formed. When the electrophilic reagent is introduced, it reacts with its normal reactivity and primary hydroxyl groups are predominantly silylated.

In conclusion, selective protection of the secondary side of cyclodextrin is available for mono-functionalization of its primary side. This method is useful for reactions with reagents that form complexes with cyclodextrin and orient the reactive group towards its secondary side. This method has limitations and cannot be used for per functionalization or with the smaller sized α-cyclodextrin.

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8. Reaction conditions for these reactions include use a) pyridine or lutidine as solvent/base and b) silver oxide, silver carbonate or proton sponge as a catalyst in dry DMF
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13. Freshly dried in a drying pistol at 117°C (under *n*-butanol) under vacuum for 24 hours.
14. During the initial 2 hours of the addition, the temperature is raised from 25°C (rt) to 90°C.
15. Calculated assuming all seven hydroxyl groups are substituted.
16. We suggest that the substitution pattern is a range from 4-7 with an average of approximately six.
17. Under identical conditions, native cyclodextrin yields a mixture of 2- and 6-substituted cyclodextrins. This reaction presumably proceeds *via* formation of quaternary salt between the substituted benzyl chloride and lutidine which then reacts with the hydroxyl group of β-cyclodextrin
18. In a separate experiment, the intermediate **4** was isolated by rotary evaporation of the reaction mixture to remove most of the lutidine, poured into iced water, filtered, washed with water, and dried in the vacuum oven for overnight at 90°C. The ^{1}H and ^{13}NMR of the crude product indicate that the *N*-methyl-4-methyl-2-nitroaniline moiety is attached to the primary side of the cyclodextrin. Since this is a mixture of varying degrees of silylation on the secondary side of cyclodextrin as indicated by TLC , a complete characterization of this product is not possible. This intermediate, when refluxed with 8 equivalents of TBAF in THF overnight, gives the same final product after appropriate work up.
19. Solvent is *n*-butanol, 95% ethanol, water (5:4:3 by volume)
20. Elemental analysis: Calcd for $C_{56}H_{78}N_2O_{37}.6H_2O$: C, 42.68; H, 6.45; N, 1.99. Found: C, 42.72; H, 6.50; N, 1.87.
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