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Efficient Perfacial Derivatization of Cyclodextrins at the Primary Face

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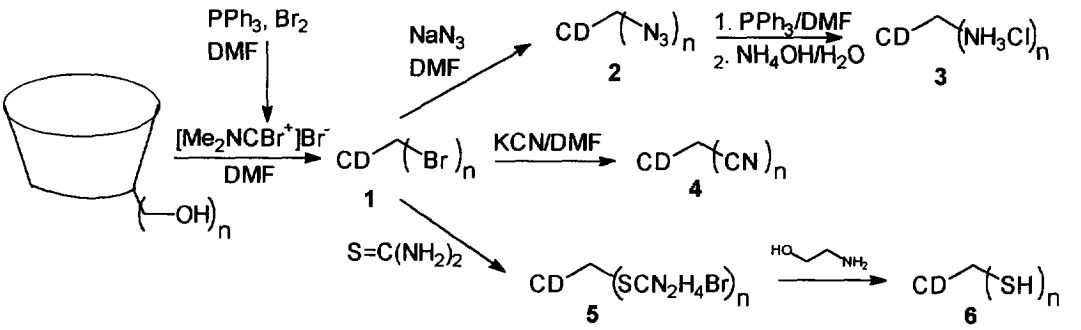
Abstract: Synthesis of thirteen cyclodextrin (CD) derivatives via the per-6-bromo-6-deoxy-CD is reported in order to demonstrate the efficiency and ease of perfacial functionalization of α, β and γCD employing a Vilsmeier-Haack reagent. Copyright © 1996 Elsevier Science Ltd

The cyclodextrins, αCD, βCD and γCD are naturally occurring cyclomaltooligosaccharides containing 6, 7 and 8 α-D-glucopyranosyl rings respectively.[1] Although the primary interest in CDs has been associated with their ability to form inclusion complexes with organic molecules, increasing interest is arising in the use of CDs as molecular scaffolds utilizing the primary and secondary hydroxyl groups as points of functionalization.[2] Herein, we report improved procedures for synthesis of the per-6-deoxy-6-bromo- derivatives of αCD, βCD and γCD and efficient conversion to a variety of perfacially substituted analogues including perazido, peramino, percyano, permercapto and perthioureido CD derivatives.

Despite recent advances, several obstacles remain to regioselective CD derivatization. The most significant problems involve the peculiar difficulties in separation and purification, in particular using chromatography, which are amplified in charged CD derivatives. Low yields, often reported in synthesis of CD derivatives exacerbate these problems. Early attempts at perfacial bromination of α and βCD were not entirely satisfactory. Defaye and co-workers published a perfacial bromination procedure using Br_2/PPh_3 in DMF.[3] However, Stoddart and co-workers have reported difficulties with the work-up presented in this and a further paper.[4] In its place, these workers employ selective precipitation and exhaustive Soxhlet extraction to remove impurities and by-products, in particular, residual triphenylphosphine oxide.[2b] We have been using an alternative procedure in which the Vilsmeier-Haack reagent $[(CH_3)_2NCHBr]^+Br^-$ is prepared and subsequently reacted with unprotected CD.[5] This method is ideally suited to CD synthesis since (a) it avoids significant purification problems; and (b) the isolated yields are extremely high.

Having efficiently prepared the per-6-bromo derivatives, further functionalization is facile employing reagents designed to minimize the complexity of purification procedures (Scheme 1). As examples, we report synthesis of: (i) the per-6-amino derivatives via reduction of the per-6-azido derivatives; (ii) the per-6-cyano derivatives using direct reaction with potassium cyanide; and (iii) the per-6-mercapto derivatives via *in situ*

alcoholysis of the per-6-thioureido derivatives. These procedures are general for αCD, βCD and γCD and efficiently yield compounds which are important synthons for further derivatization.



SCHEME 1

The Vilsmeier-Haack reagent was prepared by addition of Br_2 dropwise to triphenylphosphine in DMF. The reaction mixture was cooled to 0°C and allowed to stand forming a precipitate, which was filtered to isolate the imminium reagent as a white crystalline solid. After washing with cold DMF, the solid was dissolved in DMF and the CD (freshly dried) added to the solution. The mixture was heated for 18 hr at 80°C with a drying tube, allowed to cool and an aliquot of 3M sodium methoxide solution added. Solvent was removed at reduced pressure to yield the product as a syrup. Water was added and after stirring the precipitate was filtered and washed with water to yield the per-6-bromoCD product in 95-98% yield.

The per-6-cyanoCD was formed from reaction of per-6-bromoCD with KCN (1.3n eq.; n=6,7,8) in DMF with heating at 80°C for 24hr. After evaporation of solvent, water was added, yielding an off-white precipitate which was filtered. Thorough washing with water and methanol was responsible for isolation of the nitrile product in the somewhat reduced yield of 70%.

Reaction of per-6-bromoCD with thiourea (1.1n eq.) in DMF at 65°C for 15hr yielded the per-6-thiouronium salt, which was isolated by precipitation in acetone, filtration and washing with acetone in 95-98% yield. Per-6-mercaptoCD derivatives are easily obtained from the corresponding per-6-thioureidoCD without isolation of the thiouronium salts. Ethanolamine (2n eq.) was added directly to the reaction mixture, which was heated for a further 2hr at 65°C. After cooling, the reaction mixture was poured into water and the precipitate filtered and washed thoroughly with water and methanol to yield the per-6-mercaptoCD in 85-90% yield.

Per-6-azidoCD was obtained from reaction of the per-6-bromoCD with sodium azide (1.3n eq.) in DMF at 65°C for 24hr. Solvent was evaporated and the residue added to water. The precipitate was filtered and washed with acetone to give product in 94-98% yield. The corresponding per-6-ammonium salts are easily obtained by reduction of the azide with triphenylphosphine (3n eq.) in DMF with stirring at room temperature for 1.5hr followed by dropwise addition of concentrated ammonium hydroxide solution to the reaction mixture and stirring continued for 15hr. Solvent was evaporated and ethanol added to the residue. The resulting

precipitate was filtered, washed with ethanol and added to a small volume of water. Careful acidification with dil. HCl to pH 4 gave a solution of the water-soluble CD-ammonium chloride salt from which contaminants were removed by filtration. The product was isolated by reduction of the resulting filtrate under vacuum and subsequent drying in an isolated yield of 87-92%.

The synthetic strategies reported, yield CD derivatives, homogeneous by ^{1}H and ^{13}C NMR spectroscopy (Table 1), without recourse to chromatography nor protection of the secondary face, by relying on efficient synthetic methodology. ^{13}C NMR spectra for the per-6-thioureidoCDs are shown as representative examples (Fig. 1). FAB-MS (Cs^{+} ion source) provided molecular ions for all uncharged CDs synthesized (Table 1). Synthesis of **3β** from the per-6-azido derivative has recently been reported using a similar procedure to that above.[2b] The per-6-cyano-CDs represent interesting molecular hosts, the per-6-amino and per-6-thioureido-CDs useful cationic receptors. Both per-6-amino and per-6-mercapto CDs represent important synthons, elaboration of which is in progress.

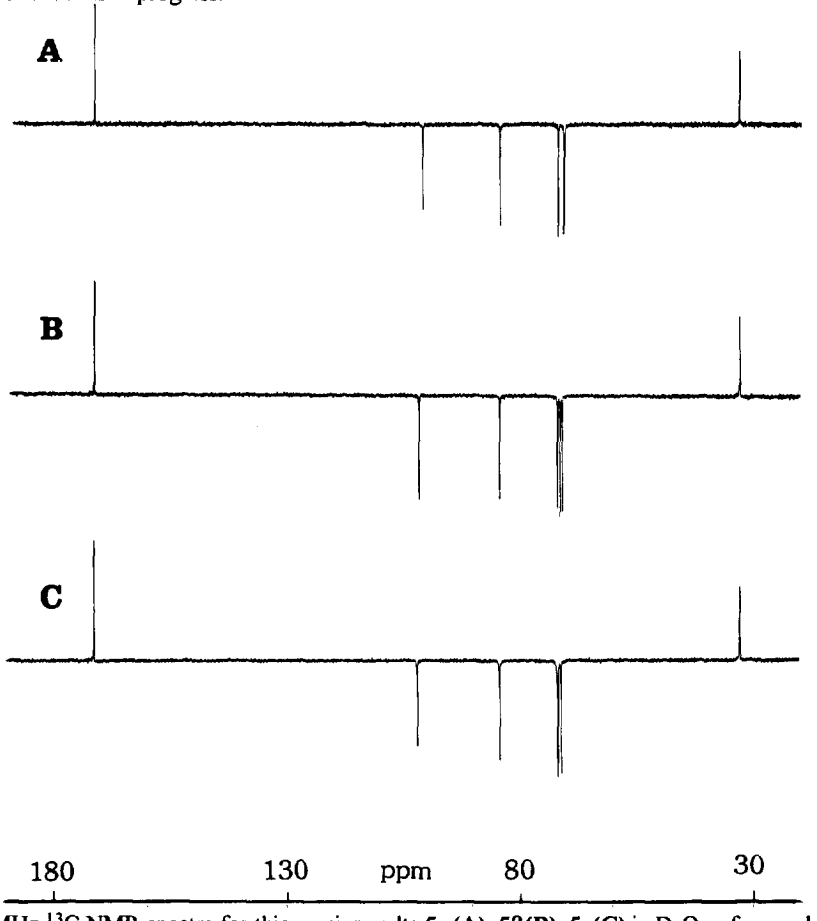


Fig. 1 100MHz ^{13}C NMR spectra for thiouronium salts **5α(A), 5β(B), 5γ(C)** in D_2O; referenced to external TMS.

Table 1 Spectroscopic data for CD derivatives

		^{13}C NMR shifts (ppm)							
	FAB-MS[a]	C1	C2	C3	C4	C5	C6	C(N)	solvent
1α	1351	101.84	71.62	72.49	84.70	70.66	34.76	-	DMSO
2α	1096[c] *1047*	101.81	71.61	72.76	83.44	70.45	51.40	-	DMSO
3α	967[b]	101.37	71.37	72.66	82.56	68.04	40.44	-	D_2O
5α	-	100.97	70.82	72.04	84.41	70.62	33.11	171.11	D_2O
6α	1070	101.84	71.50	72.78	85.04	71.86	26.10	-	DMSO
1β	1576	102.09	72.04	72.28	84.62	71.01	34.43	-	DMSO
2β	1333[c] *1284*	102.03	71.99	72.58	83.18	70.32	51.32	-	DMSO
3β	1128[b]	101.65	71.86	72.40	82.44	68.01	40.47	-	D_2O
4β	1198	102.13	71.86	72.18	85.34	67.03	20.66	118.13	DMSO
5β	-	101.53	71.30	71.88	84.24	70.83	32.83	170.96	D_2O
6β	1247	102.19	72.29	72.54	84.95	72.01	25.98	-	DMSO
1γ	1825[c]	102.02	72.18	72.26	84.05	71.02	34.38	-	DMSO
2γ	1521[c] *1472*	102.03	72.23	72.44	82.65	70.44	51.44	-	DMSO
3γ	1290[b]	100.67	71.86	72.07	81.03	67.78	40.46	-	D_2O
5γ	-	101.75	71.74	71.56	84.09	70.91	32.71	171.00	D_2O
6γ	1426	102.19	72.42	72.51	84.44	72.09	25.89	-	DMSO

a. Positive ion detection; Cs^+ ion source. Molecular ion peaks corresponding to the most intense isotopic m/z ratio are reported. Isotope distributions and ratios are compatible with structure assignment. Figures in italics refer to $(M - N_2 + 2H)^+$. b. Free amines used for MS analysis. c. $M+Na^+$ parent ion.

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References & Footnotes

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