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An Improved Synthesis of 6-Deoxyhalo Cyclodextrins via Halomethylenemorpholinium Halides Vilsmeier-Haack Type Reagents

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Abstract: *Per*(6-bromo-6-deoxy)cyclomalto-hexaose, -heptaose, and -octaose and the corresponding *per*(6-chloro-6-deoxy) derivatives were prepared in high yield by reaction of bromomethylenemorpholinium bromide or chloromethylenemorpholinium chloride, respectively, with cyclomaltohexaose, cyclomaltoheptaose and cyclomaltooctaose in dimethylformamide.
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Keywords: Cyclodextrins; cyclomaltooligosaccharides; bromomethylenemorpholinium bromide; chloromethylenemorpholinium chloride; *per*(6-deoxyhalo) cyclodextrins.

Per(6-bromodeoxy) cyclodextrins, of interest as precursors for the selective modification at the primary hydroxyl rim of cyclodextrins, have been initially prepared by reaction of cyclodextrins with methanesulfonyl bromide in dimethylformamide followed by a deformylation step with sodium methoxide;[1] however, simultaneous formation of sulfonated side products took place during the reaction.[2] More convenient was the use of the triphenylphosphine-halide system in dimethylformamide[3,4] resulting in 6-bromo-6-deoxy and 6-deoxy-6-iodo derivatives with, however, the impediment that a large amount of triphenylphosphine oxide had to be removed from the reaction medium.[5] Prior isolation of the Vilsmeier-Haack reagent, bromomethylenedimethylammonium bromide, has been recently proposed in order to circumvent this problem for the preparation of *per*(6-bromo-6-deoxy) cyclodextrins.[6] Various sulfonyl chlorides and imidazole in dimethylformamide have also been used in the preparation of heptakis(6-chloro-6-deoxy)cyclomaltoheptaose.[7]

The Vilsmeier-Haack reagent chloromethylenemorpholinium chloride (**1**) has been recently prepared and used for the cyclization of *N*-acylanthranilic acids.[8] It was found more reactive and easier to handle as compared to chloromethylenedimethylammonium chloride and was therefore an obvious candidate for the C-6 chlorination of cyclodextrins.

Treatment of cyclomaltohexaose, cyclomaltoheptaose, and cyclomaltooctaose with a small excess of **1** in dimethylformamide at 60 °C for 20 h, followed by deformylation with sodium methoxide in methanol, resulted in the corresponding *per*(6-chloro-6-deoxy) derivatives **3-5** in 80-98% yields.[9] The ^{13}C NMR spectra showed

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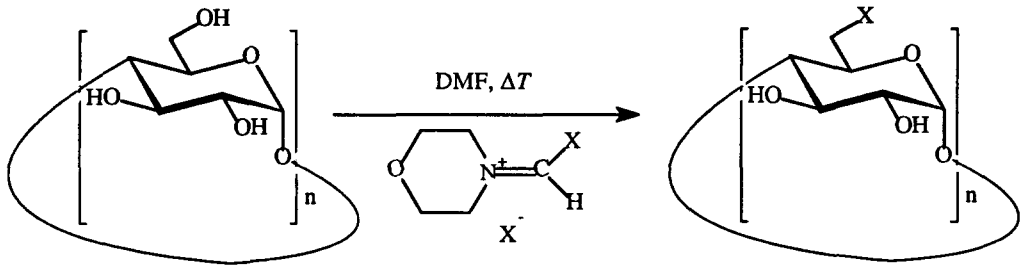
clearly the complete substitution in each case with a set of six signals, C-6 being shifted to $\delta \sim 45$ ppm. Data for the cyclomaltoheptaose derivative **4** were in full agreement with the literature.[7]

Since it was of interest to obtain, by the same approach, the more reactive *per*(6-bromo-6-deoxy) cyclodextrins, bromomethylenemorpholinium bromide (**2**) was needed as reagent. It was smoothly obtained as a crystalline material in almost quantitative yield[10,11] by treatment of stoechiometric proportions of *N*-formylmorpholine with oxalyl bromide in dichloromethane.

Reaction of cyclomaltohexaose and cyclomaltoheptaose with **2** in dimethylformamide at 45 °C gave the known[3,4] 6-bromo-6-deoxy derivatives **6** and **7**. Heating at 55 °C was needed for the cyclomaltooctaose derivative **8**.[12]



n = 6, 7, 8

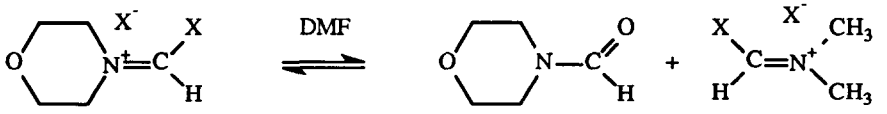
X = Cl **1**

X = Br **2**

n =	X = Cl	X = Br
6	**3**	**6**
7	**4**	**7**
8	**5**	**8**

Scheme 1

Involvement of halodimethylammonium halides **9**, **10** in these reactions, which could result from the equilibrium in Scheme 2, was ruled out since halomethylenemorpholinium halide reagents **1** and **2**, reacted with cyclomaltoheptaose in other dipolar aprotic solvents such as *N*-methyl-2-pyrrolidinone, *N*-dimethylacetamide, *N,N'*-dimethylpropyleneurea, and pyridine, affording **4** and **7** although in variable yields (Table 1).



X = Cl **1**

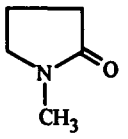
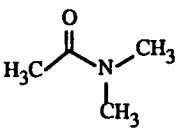
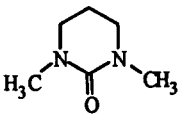
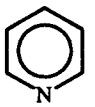
X = Br **2**

X = Cl **9**

X = Br **10**

Scheme 2

Table 1. Yields of Heptakis(6-chloro-6-deoxy)cyclomaltoheptaose (4) and Heptakis(6-bromo-6-deoxy)cyclomaltoheptaose (7) in Solvents Other than DMF.

SOLVENT				
4, η [%]	99	0	28	69
7, η [%]	48	97	-	0

Data in Table 1 indicate that halomethylenemorpholinium halides **1** and **2** are active species in the deoxyhalogenation reactions performed in solvents other than dimethylformamide.

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9. **3**: Yield 98%; mp 254 °C (dec.); $[\alpha]_D$ 116.5 (*c* 1, DMF); NMR, Me_2SO-d_6, ^1H: δ 5.70 (d, 1 H, OH), 5.54 (d, 1 H, OH), 4,91 (d, $J_{1,2}$ 2.8 Hz, 1 H, H-1) 4.20-3.20 (2 m, remaining H); ^{13}C: δ 101.64 (C-1), 83.54 (C-4), 72.58, 71.57, 70.80 (C-2,3,5), 45.17 (C-6), DEPT 135°: inverted signal at 45.17 (C-6);

Anal.Calc for $C_{36}H_{54}O_{24}Cl_6$: C, 39.89; H, 4.99; Cl, 19.67. Found: C, 40.19; H, 5.24; Cl 19.55; SIMS (+), glycerol, *m/z* 1084.0 $[M + H]^+$, 2168.9 $[2 M + H]^+$; {Isotope pattern 100%, 1082.9 $[M + H]^+$, 2167.8 $[2 M + H]^+$}.

4: Yield 92%; mp 245 °C (dec.); $[\alpha]_D$ 122.1 (*c* 1.02, DMF); ^1H and ^{13}C NMR identical to Ref. 7; *Anal*.Calc for $C_{42}H_{63}O_{28}Cl_7$: C, 39.89; H, 4.99; Cl, 19.67. Found: C, 40.40; H, 5.34; Cl 18.10; SIMS (+), glycerol, *m/z* 1266.2 $[M + H]^+$, 2529.7 $[2 M + H]^+$; {Isotope pattern 100%, 1265.0 $[M + H]^+$, 2529.2 $[2 M + H]^+$}.

5: Yield 80%; mp 238 °C (dec.); $[\alpha]_D$ 149.1 (*c* 1, DMF); NMR, Me_2SO-d_6, ^1H: δ 5.93 (s, 2 H, 2 x OH), 4.97 (d, $J_{1,2}$ 3.4 Hz, 1 H, H-1) 4.20-3.20 (2 m, remaining H); ^{13}C: δ 101.99 (C-1), 82.96 (C-4), 72.32 71.95, 71.11 (C-2,3,5), 44.95 (C-6), DEPT 135°: inversed signal at 44.95 (C-6); *Anal.* Calc for $C_{48}H_{72}O_{32}Cl_8$: C, 39.89; H, 4.99; Cl, 19.67. Found: C, 40.18; H, 5.24; Cl, 17.68; SIMS (+), NBA, *m/z* 1469.1 $[M + Na]^+$; {Isotope pattern 100%, 1467.1 $[M + Na]^+$}.

10. Bromomethylenemorpholinium bromide **2**, typical procedure: To a solution of *N*-formylmorpholine (3.2 mL, 32 mmol) in dry dichloromethane (25 mL) cooled in ice and with a reflux condenser, oxalyl bromide (6.0 g, 32.0 mmol) in the same solvent (8 mL) was added dropwise with vigorous stirring. The reaction mixture was kept in ice during 30 min, with continued stirring. Then, the precipitate was quickly filtered, dried and stored in a dessicator over P_2O_5. Yield 7.1 g (85%); mp 145 °C; NMR, Me_2SO-d_6, ^1H: δ 8.00 (s, 1 H, N=C-H), 3.60-3.45 (m, 4 H, O-CH_2), 3.40-3.30 (m, 4 H, N-CH_2), ^{13}C: δ 160.97 (HC=N), 66.75, 65.75 (O-CH_2), 45.12 (N-CH_2), a signal of one N-CH_2 was hidden under the Me_2SO multiplet; DEPT 135°: 160.97 (HC=N), opposite phase of the signals at 66.75, 65.75 (O-CH_2) and 45.12, 39.95 (N-CH_2).
11. The Vilsmeier salt **10**, prepared according to Ref. 6, underwent hydrolysis when stored under the same conditions as described for bromomethylenemorpholinium bromide (**2**).
12. **6**: Yield 91%, **7**: Yield 94%, **8**: Yield 86%; NMR and SIMS spectroscopic data were in agreement with the literature (Refs 3, 4, and 13).
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