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Bromination of cellulose with tribromoimidazole, triphenylphosphine and imidazole under homogeneous conditions in LiBr-dimethylacetamide

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The bromination of microcrystalline cellulose with tribromoimidazole, triphenylphosphine and imidazole was studied under homogeneous conditions in LiBr-*N*,*N*-dimethylacetamide. Bromodeoxycellulose samples having ds values up to 1·6 were obtained at high molecular ratios of bromination reagents to the repeating unit of cellulose (5 or higher). Recoveries of high ds samples were below 50%. 3,6-Dibromo-3,6-dideoxyglucose units were present in the samples having high ds values together with 3,6-dibromo-3,6-dideoxyallose and 6-bromo-6-deoxyglucose units. The dibromoglucose units were formed from dibromoallose units by a nucleophilic substitution of bromine atoms at C-3 with bromide ions present in the system.

INTRODUCTION

We reported previously (Furuhata *et al.*, 1992*a*) the bromination of microcrystalline cellulose with *N*-bromosuccinimide (NBS) and triphenylphosphine (PPh_3) under homogeneous conditions in LiBr-*N*,*N*-dimethylacetamide (DMA). The ds value did not exceed 1 and only C-6 hydroxyl groups were replaced with bromine atoms. The chlorination with *N*-chlorosuccinimide and PPh_3 in LiCl-DMA (Furuhata *et al.*, 1992*b*) gave, on the other hand, chlorodeoxycellulose (Cell-Cl) samples having ds values with chlorine up to 1·9. In the samples having high ds values, C-3 hydroxyl groups were replaced with chlorine atoms with Walden inversion in addition to C-6 hydroxyl groups. Bromodeoxycellulose (Cell-Br) is expected to be more useful for the introduction of functional groups to cellulose by nucleophilic substitutions as compared with Cell-Cl because bromine is a better leaving group than chlorine. Cell-Br samples having high ds values will be advantageous to such reactions.

Krylova *et al.* (1990) obtained a Cell-Br sample containing 3-bromo-3-deoxyallose units (ds, 0·79) by the bromination of 6-*O*-tritylcellulose with tribroimidazole (Br_3Im), PPh_3 and imidazole (Im) in toluene followed by detritylation. The Br_3Im-PPh_3 reagent system is characteristic in that it replaces C-3 hydroxyl groups with bromine atoms in addition to C-6 hydroxyl groups of methyl α-D-glucoside (Classon *et al.*, 1981; Garegg *et al.*, 1982) and methyl β-D-glucoside (Me β-Glc) (Furuhata *et al.*, 1994*a*) but not C-4 hydroxyl groups. We have been studying the synthesis of Cell-Br samples having high ds values, and examined this reagent system for the bromination of cellulose.

In this paper, we describe the bromination of cellulose with the Br_3Im-PPh_3-Im reagent system under homogeneous conditions in LiBr-DMA. Cell-Br samples having ds values up to 1·6 were obtained under appropriate conditions. C-3 hydroxyl groups in high-ds samples were replaced with bromine atoms in addition to C-6 hydroxyl groups. 3,6-Dibromo-3,6-dideoxyglucose (3,6-Br_2-Glc) units were present in these samples together with 3,6-dibromo-3,6-dideoxyallose (3,6-Br_2-All) and 6-bromo-6-deoxyglucose (6-Br-Glc) units. The bromination of bead cellulose with this reagent system under heterogeneous conditions has been published in a separate paper (Aoki *et al.*, 1994).

MATERIALS AND METHODS

Reagents

Microcrystalline cellulose (Art. 2331, Merck) was dried under diminished pressure over silica gel in a desiccator. Br_3Im was synthesized according to the method of Stensiö *et al.* (1973). Other chemicals were purified using conventional methods (Furuhata *et al.*, 1992).

Bromination

Microcrystalline cellulose was dissolved in LiBr-DMA in a way reported previously (Furuhata *et al.*, 1992). The dissolution and consecutive bromination were performed under N_2. In a typical reaction, 1·0 g of cellulose was dissolved in 100 ml of DMA containing 24 g (0·276 mol) of LiBr, cooled with ice-water and prescribed amounts of Br_3Im, PPh_3 and Im were added, each as a DMA solution. The final volume was adjusted to 200 ml. The solution was then held at a prescribed temperature for a predetermined period with stirring. After the reaction, the solution was poured into 2 l of acetone. Precipitates formed were separated, washed with acetone and methanol, and treated with a sodium carbonate solution (pH 11·5) for longer than 12 h. They were then dialysed against distilled water and dried under diminished pressure over silica gel in a desiccator.

Analyses

NMR spectra were recorded on JNM-A500 and JNM-FX90Q spectrometers (JEOL, Ltd) in *N,N*-dimethylformamide (DMF)-d_7. The assignments were based on ^1H homonuclear and ^1H-^{13}C heteronuclear two-dimensional spectra except for Me β-Glc, whose peaks were assigned based on the results of two-dimensional measurements in D_2O (Furuhata *et al.*, 1994*b*). GLC and GLC-MS analyses of the hydrolysates of samples (as *O*-trifluoroacetyl derivatives) were carried out under the same conditions as described in the previous paper (Furuhata *et al.*, 1992). Silicone SE-30 (3% on Gas Chrom Q, 100–120 mesh) was used as a stationary phase. GPC analysis was carried out with a JASCO HPLC BIP-I chromatograph (JASCO Ltd.) equipped with Shodex/GPC AD80M/S columns and RI detectors. The elution solvent was 0·01% LiBr-DMF and monodispersed polystyrene standards were used for molecular weight calibration. Solution viscosities of Cell-Br samples were measured at 40°C in 2 M LiBr-DMA using an Ubbelohde viscometer.

RESULTS AND DISCUSSION

Effect of reaction conditions on ds with bromine

High reaction temperatures were sometimes adopted for the bromination of carbohydrates with the Br_3Im-PPh_3 system, for example, 75°C for 1 h and then 110°C for 4 h in the bromination of methyl α-D-glucoside to methyl 3,6-dibromo-3,6-dideoxy-α-D-alloside (yield over 70%) (Classon *et al.*, 1981; Garegg *et al.*, 1982). In the bromination of bead cellulose with Br_3Im-PPh_3-Im under heterogeneous conditions (Aoki *et al.*, 1994), the ds values attained at 90°C were not significantly higher than those attained at 70°C. The recoveries of the products, on the other hand, were much lower at 90°C because the degradation of beads occurred. In this study, therefore, the reaction temperature was fixed at 70°C and the effect of the molar ratios of reagents to the repeating unit of cellulose (AGU) was examined.

Figure 1 shows the ds and recovery values of products obtained by precipitation as a function of bromination time at three levels of the molar ratios of reagents. The bromination proceeds after an induction period of about 1 h. The ds value remains at a low level at the molar ratios ([Br_3Im]:[PPh_3]:[Im]:[AGU]) of 3:3:3:1 while it exceeds 1·4 in 6–12 h at 5:5:5:1 and 10:10:10:1. In the bromination of microcrystalline cellulose with NBS-PPh_3 under homogeneous conditions in LiBr-DMA (Furuhata *et al.*, 1992), no induction period was observed and the bromination proceeded rapidly. The ds value levelled off in about 1 h and did not exceed 1.

The recovery (based on the number of repeating units) of the product obtained by precipitation decreases remarkably at longer reaction times for the bromination at higher molar ratios of reagents. The ds value of the

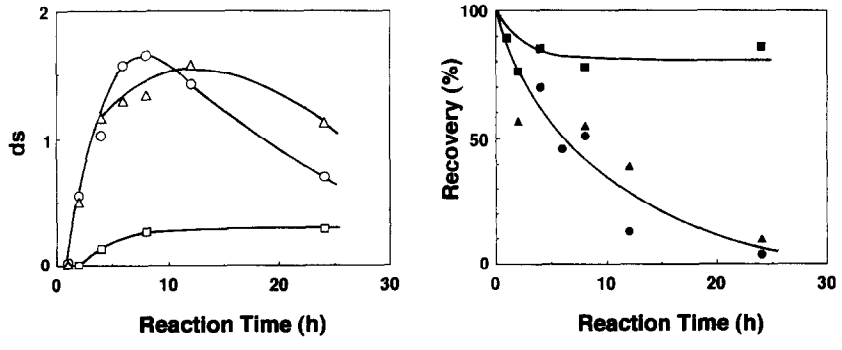

Fig. 1. ds and recovery of Cell-Br as a function of reaction time at 70°C. [Br_3Im]:[PPh_3]:[Im]:[AGU]: □ & ■, 3:3:3:1; ○ & ●, 5:5:5:1; △ & ▲, 10:10:10:1.

recovered sample also decreases at the later stages of the bromination. The reason for this decrease in the ds value is not clear at present. A tentative explanation is that high ds portions are susceptible to decomposition during the bromination and lost in the isolative treatment.

The effect of the composition of the reagent system was briefly studied. Figure 2 shows that both the doubling of the amount of PPh_3 and the exclusion of Im lower the highest attainable ds value of the products.

Structures of repeating units in Cell-Br

Figure 3 shows the ^{13}C NMR spectrum in DMF-d_7 of a Cell-Br sample of low molecular weight (ds, 1·37) whose GPC analysis will be described later. In the isolative treatment, the sample remained in the supernatant solution and was recovered by dialysis of the solution (recovery, 16%). A part of the sample remained undissolved in DMF and the soluble part was used for the NMR measurement. The assignment of absorptions was based on the ^{13}C chemical shifts in DMF-d_7 of Me β-Glc, methyl 6-bromo-6-deoxy-β-D-glucoside (Me 6-Br-Glc)

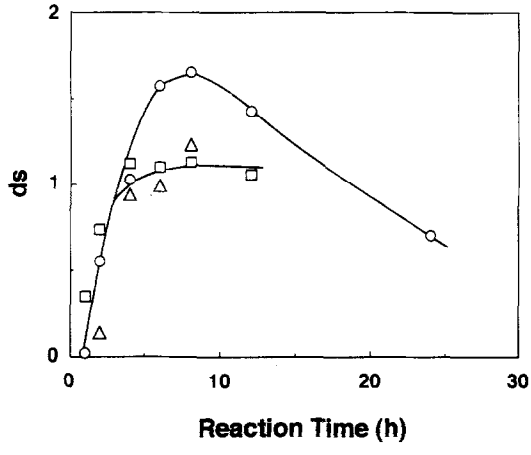

Fig. 2. ds of Cell-Br as a function of reaction time at 70°C. $[Br_3Im]$:$[PPh_3]$:[Im]:[AGU]: □, 5:5:0:1; ○, 5:5:5:1; △, 5:10:5:1.

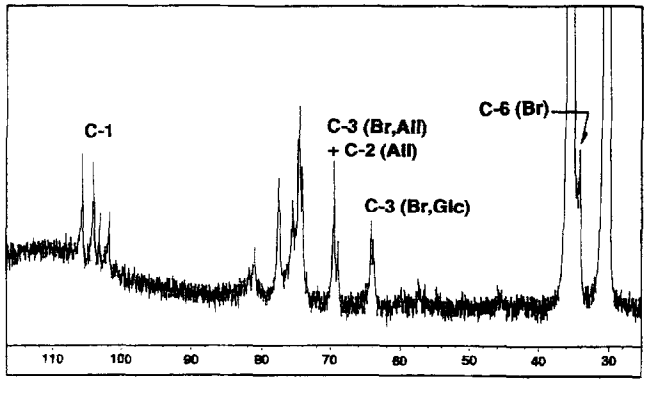

Fig. 3. ^{13}C NMR spectrum of a Cell-Br sample recovered by dialysis. The spectrum was measured in DMF-d_7. Large peaks at about 31 and 46 ppm are solvent absorptions.

(Hanessian & Plessas, 1969), methyl 3,6-dibromo-3,6-dideoxy-β-D-glucoside (Me Br_2-Glc) and -alloside (Me Br_2-All) (Furuhata *et al.*, 1994*a*) summarized in Table 1. Both the C-6 carbon of the Me β-Glc and the C-3 carbon of Me Br_3-Glc appear near 62·5 ppm. Since the amount of unmodified glucose units in this sample is very small as revealed by the GLC analysis of its hydrolysate, the absorptions around 64 ppm are ascribed to the C-3 carbons of 3,6-Br_2-Glc units. Only the C-2, C-3 and C-4 carbons of Me Br_2-All appear in the region of 66–70 ppm. The C-4 carbons of cellulose appeared at 79·1 ppm in LiCl-DMA (El-Kafrawy, 1982). Krylova *et al.* (1990) showed that C-4 carbons of 3-bromo-3-deoxyallose units in Cell-Br (ds, 0·69) appeared around 74 ppm in dimethyl sulfoxide-d_6. For the present sample, the C-4 carbons in the repeating units of various structures are considered to appear in the region of 75–82 ppm. The absorptions around 69 ppm of the sample can therefore be ascribed to the C-2 and C-3 carbons of 3,6-Br_2-All units. The C-1 carbons appear at several positions reflecting the presence of repeating units of different structures. The C-1 carbons of the Cell-Br sample reported by Krylova *et al.* (1990) also gave four peaks.

Additional evidence for the presence of 3,6-Br_2-Glc units, in addition to 3,6-Br_2-All and 6-Br-Glc units, in the Cell-Br samples having high ds values was obtained by the GLC and GLC-MS analyses of the hydrolysates as *O*-trifluoroacetyl derivatives. The hydrolysates of Me Br_2-All and Me Br_2-Glc were used as the reference samples for the determination of peak materials of the hydrolysates of Cell-Br samples by comparing GLC retention parameters and mass spectra. The samples having high ds values were resistant to acid hydrolysis due to halogen substitution (Ishii *et al.*, 1976; Furuhata *et al.*, 1992), and relative peak areas of glucose, 6-Br-Glc and dibrominated aldohexoses do not correspond to the relative amounts, in the Cell-Br samples before hydrolysis, of these saccharides with differing extents of bromine substitution.

Figure 4 shows GLC chromatograms of the hydrolysates of Cell-Br samples having different ds values. A maximum of four peaks will appear for an aldohexose

Table 1. ^{13}C NMR chemical shifts for methyl β-glycosides[a]

Compound	^{13}C Chemical shift (ppm)						
	1	2	3	4	5	6	OCH_3
Me β-Glc	104·79	74·41	77·66[b]	71·14	77·55[b]	62·26	56·46
Me 6-Br-Glc	104·78	74·38	77·32	72·96	75·74	34·83	56·48
Me Br_2-Glc	105·09	75·19	62·34	73·77	77·04	34·60	56·78
Me Br_2-All	103·07	69·58	66·04	68·74	74·74	34·83	56·48

[a]Spectra were measured in DMF-d_7.
[b]Assignments may be reversed.
Me β-Glc, methyl β-glucoside; Me 6-Br-Glc, methyl 6-bromo-6-deoxy-β-glucoside; Me Br_2-Glc, methyl 3,6-dibromo-3,6-dideoxy-β-glucoside; Me Br_2-All, methyl 3,6-dibromo-3,6-dideoxy-β-alloside.

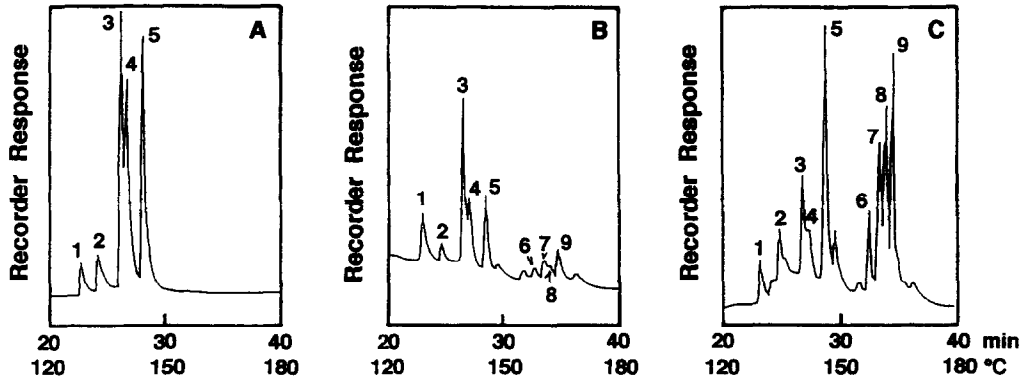

Fig. 4. GLC chromatograms of the hydrolysates of Cell-Br samples obtained at $[Br_3Im]:[PPh_3]:[Im]:[AGU]$ of 5:5:5:1. ds value: A, 0·82; B, 1·03; C, 1·57. (1), *a*-Glc*p*; (2), *β*-Glc*p*; (3), 3,6-anhydroglucose; (4) & (5), 6-Br-Glc*p*; (6) & (8), 3,6-Br_2-Glc*p*; (7), 3,6-Br_2-All*p*; (9), unknown.

due to α and *β*-anomers of pyranose and furanose forms. 3,6-Anhydroglucose is an artifact derived from 6-Br-Glc during acid hydrolysis and subsequent neutralization (Furuhata *et al.*, 1992). The unknown peak also appeared on the chromatograms of the hydrolysates of Me Br_2-All and Me Br_2-Glc. It is clear from the figure that only glucose and 6-Br-Glc units are present in the Cell-Br sample having ds of 0·82.The total area of peaks of 3,6-Br_2-Glc and 3,6-Br_2-All relatively increases as the ds of the sample increases. 3,6-Br_2-Glc units and 3,6-Br_2-All units are present in a ratio of about 2:1.

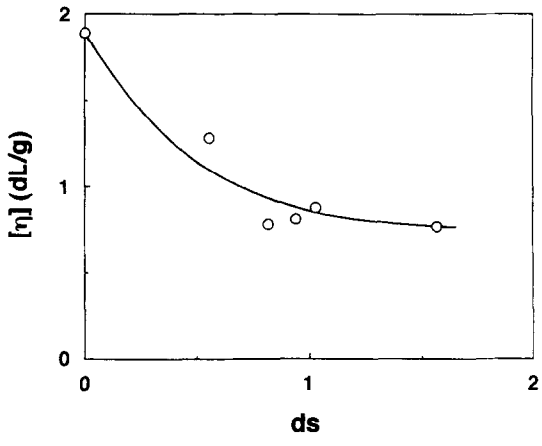

Fig. 5. Intrinsic viscosity as a function of ds. Viscosities were measured at 40°C in 2 M LiBr-DMA.

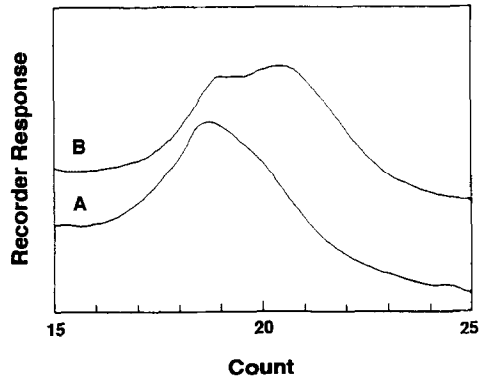

Fig. 6. GPC chromatograms of Cell-Br fractions. A, fraction recovered by precipitation (ds, 1·44; recovery, 20%); B, fraction recovered by dialysis (ds, 1·37; recovery, 16%). Eluent, 0·01% LiBr-DMF.

In the present bromination, it is obvious that 3,6-Br_2-All units are initially formed with Walden inversion at C-3 and converted quickly into 3,6-Br_2-Glc units with further Walden inversion in LiBr-DMA during the reaction. We showed (Furuhata *et al.*, 1994*a*) that Me Br_2-All was initially formed from Me *β*-Glc and Br_3Im-PPh_3 in toluene and converted quickly into Me Br_2-Glc with Walden inversion, and further that the equilibrium of the interconversion between Me Br_2-All and Me Br_2-Glc in LiBr-DMA was shifted to Me Br_2-Glc and the rate constants of the interconversion were much larger than those of the interconversion between methyl 3,6-dichloro-3,6-dideoxyalloside and -glucoside in LiCl-DMA (Furuhata *et al.*, 1994*b*).

Solution viscosity of Cell-Br

Figure 5 shows intrinsic viscosities in 2 M LiBr-DMA of the original microcrystalline cellulose and several Cell-Br samples recovered by precipitation after the bromination within 8 h. The figure shows that the [η] value decreases as the ds value increases from 0 to1·0 and then levels off. A similar result was observed for Cell-Br samples obtained with NBS-PPh_3 in LiBr-DMA (Furuhata *et al.*, 1992). The decrease in the [η] value of precipitated Cell-Br can be ascribed to the molecular chain scission during the bromination and/or the substitution of hydroxyl groups with bromine atoms resulting in a change in chemical structure, a decrease in hydrogen bonding or a change in conformation.

To clarify this, one batch of microcrystalline cellulose was brominated for 8 h and a fraction obtained by precipitation (ds, 1·44; recovery 20%) and that recov-

ered from the supernatant solution by dialysis (ds, 1·37; recovery, 16%) was analyzed by GPC in 0·01% LiBr-DMF. The chromatograms are shown in Figure 6. For the precipitated sample, DP_n of 330 and M_w/M_n of 3·5 were calculated. The DP_n value is considered quite similar to that of the original microcrystalline cellulose (Dalbe & Peguy, 1990; Hasegawa *et al.*, 1993). This finding suggests that the decrease in $[\eta]$ for the precipitated Cell-Br is due, at least in part, to the substitution of hydroxyl groups with bromine atoms. For the sample non-precipitated and recovered by dialysis, DP_n of 130 and M_w/M_n of 6·8 were obtained. These low DP_n and high M_w/M_n values of the non-precipitated sample clearly show that chain scission occurred during the bromination. The decrease in recovery of the precipitated sample can be explained in terms of the scission of cellulose molecular chains.

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