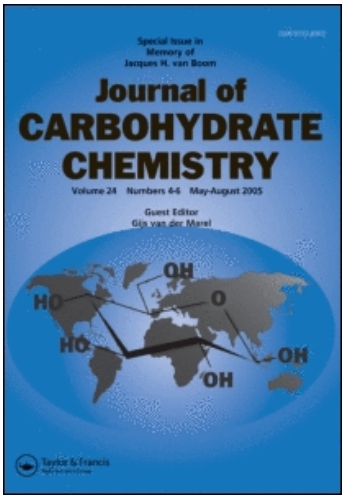


Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Iodination of α-Cyclodextrin with *N*-Iodosuccinimide and Triphenylphosphine in *N, N*-Dimethylformamide

Makoto Ando[a]; Hiroyoshi Kuzuhara[a]
[a] The Institute of Physical and Chemical Research, Wako-shi, Saitama, Japan

To cite this Article Ando, Makoto and Kuzuhara, Hiroyoshi(1984) 'Iodination of α-Cyclodextrin with *N*-Iodosuccinimide and Triphenylphosphine in *N, N*-Dimethylformamide', Journal of Carbohydrate Chemistry, 3: 2, 279 — 286
To link to this Article: DOI: 10.1080/07328308408058821
URL: http://dx.doi.org/10.1080/07328308408058821

J. CARBOHYDRATE CHEMISTRY, 3(2), 279-286 (1984)

IODINATION OF α-CYCLODEXTRIN WITH N-IODOSUCCINIMIDE AND TRIPHENYLPHOSPHINE IN N,N-DIMETHYLFORMAMIDE

Makoto Ando and Hiroyoshi Kuzuhara*

The Institute of Physical and Chemical Research,
Wako-shi, Saitama 351, Japan

Received December 26, 1983

ABSTRACT

α-Cyclodextrin mainly underwent monoiodo substitution on treatment with N-iodosuccinimide and triphenylphosphine in DMF, giving 6-monodeoxy-6-monoiodo-α-cyclodextrin. A small amount of 6,6'-dideoxy-6,6'-diiodo-α-cyclodextrin was also obtained as a by-product. The structures of these compounds were elucidated from their elemental analyses and ^{13}C NMR spectra.

INTRODUCTION

Development of the procedure for the selective modification of oligosaccharides seems to be of great value because some oligosaccharides such as maltose and cyclodextrins with high purity have been abundantly obtainable as the products of enzymztic treatment of natural polysaccharides. We have reported in a series of papers[1-5] the selective chemical modification of maltose. Now, we wish to describe a simple way for monoiodination at 6-position of α-cyclodextrin, which can be regarded as a key step for the versatile transformations of that oligosaccharide.

 0732-8303/84/0302-0279$3.50/0

RESULTS AND DISCUSSION

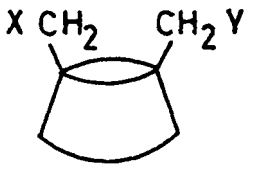
α-Cyclodextrin (1) is a cyclic (1→4)-α-D-glucan constituted of six D-glucopyranosyl moieties, indicating that six primary hydroxyl groups are present in almost the same situation within one molecule of the oligosaccharide. Consequently, "overreaction" will be apt to take place even if an equimolar reagent is used in order to prepare monosubstituted or monoacylated α-cyclodextrin.

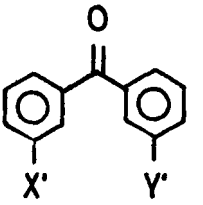
6-Monodeoxy-6-monoiodo-α-cyclodextrin (2) has been prepared from 1 through two steps of the reactions, monotosylation and the subsequent substitution of the resulting tosylate (3) with iodide ion.[6] However, the yield of the initial monotosylation is not so high and the isolation of the product is rather laborious. This prompted us to develop a better and simpler procedure for the preparation of 2 than the known one.

Modification of the two-step method was first attempted. Recently, Tabushi et al. reported that a "capped cyclodextrin," prepared from β-cyclodextrin and benzophenone-m,m'-disulfonyl chloride (4), was converted into 6,6'-dideoxy-6,6'-diiodo-β-cyclodextrin in high yield.[7] An α-cyclodextrin derivative capped with m-(m-chlorosulfonylbenzoyl)benzoyl chloride (5) might be a good candidate convertible into 2.

The preparation of 5 was attained through chlorosulfonation of m-benzoylbenzoic acid (6)[8] and the subsequent rechlorination of the product that was needed since the chlorocarbonyl group was partially hydrolyzed during the work-up for the former treatment. Unfortunately, the expected coupling reaction of 5 with 1 failed, giving no "capped α-cyclodextrin." This would be probably because the unstable chlorocarbonyl group in 5 was readily hydrolyzed during the reaction.

Our attention was next directed towards the direct iodination of 1. It has been reported that the primary hydroxyl group in carbohydrates molecules can be selectively halogenated with carbon tetrahalide and triphenylphosphine (TPP) when pyridine is employed as the solvent.[9] Although this method was applied to the iodination of 1, no reaction took place in this case. Finally, the





	X	Y
1	OH	OH
2	I	OH
3	OTs	OH
7	I	I

	X'	Y'
4	SO_2Cl	SO_2Cl
5	SO_2Cl	COCl
6	H	COOH

Hanessian's selective halogenation procedure using N-halogenosuccinimide and TPP in DMF[10] was successfully applied to 1.

Treatment of the dried 1 with N-iodosuccinimide — TPP in excess in DMF gave essentially one main product, being accompanied with a small amount of by-product. Also, a moderate amount of the unreacted 1 was recovered. Complete dehydration of 1 prior to use was mandatory since commercially available 1 contained various amounts of water that strikingly lowered the yield of the products. Replacement of TPP with the polymer-supported TPP[11] in the reaction in expectation of increasing the selectivity did not seem to bring any improvement.

Separation of the reaction mixture was performed with silica gel column chromatography and each raw product was further purified by recrystallization from water.

The structure of these products was elucidated on the basis of the results of elemental analyses and ^{13}C NMR spectra. Results of elemental analyses suggested that the major product was monodeoxy-monoiodo-α-cyclodextrin, whereas the minor was dideoxy-diiodo-α-cyclodextrin. Fig. 1 shows ^{13}C NMR spectrum of the major product. In addition to the signals of ordinary α-cyclodextrin

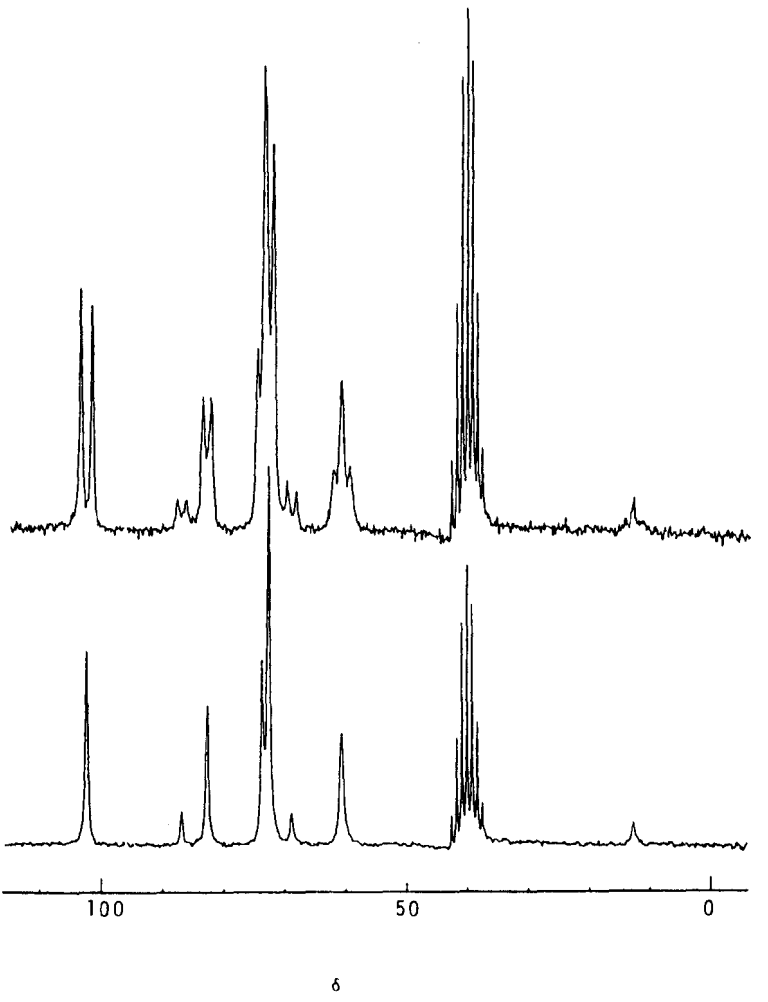


Fig. 1. ^{13}C NMR spectrum of 6-monodeoxy-6-monoiodo-α-cyclodextrin (2) (DMSO-d_6, 100 MHz). Upper: off-resonance decoupling, lower: complete decoupling.

at δ 60.0 (C-6), 72.0 (C-3 and C-5), 73.1 (C-2), 82.0 (C-4), and 101.9 (C-1),[12] there are small signals at δ 11.9, 68.2, and 86.2 ascribable to the monoiodinated glucose moiety. The signal appearing unusually upfield (δ 11.9) is assignable to the carbon bearing the iodine atom as a result of the heavy atom effect. This signal is observed as a triplet in off-resonance decoupling

spectrum, indicating that iodine atom is attached to the methylene group. Consequently, the major product was identified as 2 in spite of some discrepancy of physical constants between our product (mp 179 – 180 °C (dec), $[\alpha]_D^{28}$ +128°) and 2 reported in the literature[6] (mp 175 °C (dec), $[\alpha]_D^{22}$ +106°).

The ^{13}C NMR spectrum of the minor product (not shown here) showed essentially the same pattern as that of 2 except the relative intensities of the signals, i. e., the intensities of the signals ascribable to the glucopyranosyl moiety decreased whereas those to the 6-monodeoxy-6-monoiodo-glucopyranosyl moiety increased. These results supported that the minor product was 6,6'-dideoxy-6,6'-diiodo-α-cyclodextrin (7) although the relative orientation of the iodine atom in 7 was uncertain. Melting points of 7 (mp 176 – 177 °C (dec)) and of 2 are very close to each other and it was surprising to notice that the mixed melting point of 7 and 2 was not depressed. IR spectrum and specific rotation of 7 were also very similar to those of 2.

EXPERIMENTAL

General Procedures. Melting points are uncorrected. ^{13}C NMR spectra and IR spectra were recorded on a JOEL FX 100 and a Shimadzu IR-27 G instruments, respectively. Optical rotations were determined with a Perkin-Elmer 241 MC polarimeter. Thin layer chromatography was performed on precoated silica gel 60 F_{254} sheet (Merck No. 5554) with solvent system, isopropyl alcohol – water – concentrated aqueous ammonia (10 : 4 : 1 v/v) or precoated cellulose F_{254} sheet (Merck No. 5574) with solvent system, butyl alcohol – acetic acid – water (2 : 1 : 1 v/v).

m-(m-Chlorosulfonylbenzoyl)benzoyl Chloride (5). Solid m-benzoylbenzoic acid (6)[8] (57.5 g) was added in small portions to chlorosulfuric acid (250 mL) over the period of 1 h with stirring while the temperature of the mixture was kept below 30 °C. The mixture was kept at 30 °C for another 1 h and at 120 °C overnight, poured upon ice, and extracted with chloroform. After insoluble material had been filtered off with celite, the filtrate was

washed with water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure until a crystalline product was separated out. Cyclohexane was added to the mixture and the precipitates were collected. A mixture of the precipitates and thionyl chloride (200 mL) was kept at 75 °C for 2 h with stirring and the thionyl chloride was evaporated. The crystalline residue was dried over soda lime *in vacuo*, giving 5 (41.1 g, 47%). Because of the instability of 5, it was used in the next step without further purification; mp 117 – 118 °C. Anal. Calcd for $C_{14}H_8Cl_2O_4S$: C, 49.00; H, 2.35; Cl, 20.66; S, 9.34. Found: C, 48.62; H, 2.35; Cl, 20.44; S, 9.55.

Reaction of 5 (1.2 mole equivalents) with α-cyclodextrin (1) was performed in pyridine at room temperature and then at 60 °C. Thin layer chromatogram of the reaction mixture on cellulose showed no spots of capped derivatives that would move faster than 1.

6-Monodeoxy-6-monoiodo-α-cyclodextrin (2) *and 6,6'-Dideoxy-6,6'-diiodo-α-cyclodextrin* (7). To a stirred solution of α-cyclodextrin (1) (dried at 100 °C for several hours *in vacuo* over phosphorus(V) oxide) (4.8 g) and TPP (4.0 g) in DMF (100 mL) was added solid *N*-iodosuccinimide (2.0 g) in small portions over the period of 10 min. The resulting solution was kept at 50 °C for 3 h and cooled. After methanol (10 mL) had been added to the solution, the resulting mixture was heated at 50 °C for 1 h and concentrated *in vacuo*. The residue was extracted with water and the extract was washed with chloroform, concentrated, and chromatographed on silica gel (Merck No. 7734) with isopropyl alcohol – water – concentrated aqueous ammonia (70 : 24 : 6 v/v) as the eluent, giving two raw products and unreacted 1. Repeated recrystallization of each of the products a few times from water gave 2 (1.3 g, 24%) and 7 (0.2 g, 3%).

Compound 2: mp 179 – 180 °C (dec), $[\alpha]_D^{28}$ +128° (c 0.429, pyridine) (lit.[6] mp 175 °C (dec), $[\alpha]_D^{22}$ +106° (c 0.42, pyridine)). The data of ^{13}C NMR spectrum (DMSO-d_6, 100 MHz) were described above. Anal. Calcd for $C_{36}H_{59}IO_{29}$: C, 39.93; H, 5.49; I, 11.72. Found: C, 39.32; H, 5.45; I, 11.79.

Compound 7: mp 176 – 177 °C (dec), $[\alpha]_D^{22}$ +113° (c 0.392, pyridine), ^{13}C NMR (DMSO-d_6, 100 MHz) δ 11.9 (t, C-6'), 60.2, 68.7, 72.0, 73.2, 82.3, 84.6, and 102.0. Anal. Calcd for $C_{36}H_{58}I_2O_{28}$: C, 36.26; H, 4.90; I, 21.28. Found: C, 35.47; H, 4.82; I, 21.60.

ACKNOWLEDGMENT

The authors wish to express their gratitude to Dr. Jun Uzawa for recording ^{13}C NMR spectra and to Dr. Haruo Homma and his collaborators for performing elemental analyses.

REFERENCES AND FOOTNOTE

1. I. Fujimaki and H. Kuzuhara, Agric. Biol. Chem., 44, 2055 (1980).

2. F. Sugawara and H. Kuzuhara, Agric. Biol. Chem., 45, 301 (1981).

3. I. Fijimaki, Y. Ichikawa, and H. Kuzuhara, Carbohydr. Res., 101, 148 (1982).

4. I. Fujimaki and H. Kuzuhara, J. Carbohydr. Chem., 1, 145 (1982).

5. N. Sakairi, H. Murakami, and H. Kuzuhara, Carbohydr. Res., 114, 63 (1983).

6. L. D. Melton and K. N. Slessor, Carbohydr. Res., 18, 29 (1971).

7. I. Tabushi, Y. Kuroda, K. Yokota, and L. C. Yuan, J. Am. Chem. Soc., 103, 711 (1981).

8. M. E. Smith, J. Am. Chem. Soc., 43, 1920 (1921).

9. R. L. Whistler and A. K. Anisuzzaman, Methods Carbohydr. Chem., 8, 227 (1980).

10. S. Hanessian and P. Lavallee, Methods Carbohydr. Chem., 7, 49 (1976).

11. D. C. Sherrington, D. J. Craig, J. Dagleish, G. Domin, J. Taylor, and G. V. Meehan, Eur. Polym. J., 13, 73 (1973).

12. These δ values agreed with those calculated from the data given in ppm upfield from the external carbon disulfide

reference, which appeared in K. Takeo, K. Hirose, and T. Kuge, Chem. Lett., 1233 (1973).