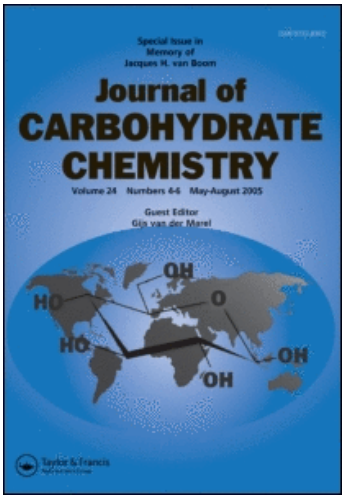

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A NOVEL CYCLIC CARBAMATE FROM THE ACID-CATALYZED REACTION OF D-GLUCOSE AND UREA

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ABSTRACT

The acid-catalyzed reaction of D-glucose with urea in a phenol-water solution has provided α-D-glucopyranosylamine 1,2-(cyclic carbamate) (1). The use of ^{1}H-^{13}C correlated NMR spectroscopy involving indirectly-bonded hydrogens and carbons proved to be indispensable in determining the structure.

INTRODUCTION

Carbohydrates have shown promise for replacing a significant amount of the phenol currently used by the forest products industry in adhesive formulations.[2,3] In order to understand and eventually predict the properties of these new adhesives, we have been investigating the chemistry of carbohydrate-based resin synthesis.[4] During the high-temperature (135 °C) phase of the reaction of D-glucose with urea in acidified phenol-water, urea decomposition provided a novel carbohydrate which has been identified as α-D-glucopyranosylamine 1,2-(cyclic carbamate) (1). The isolation and properties of this material and its perbenzoylated derivative (2) are the subject of this report.

RESULTS AND DISCUSSION

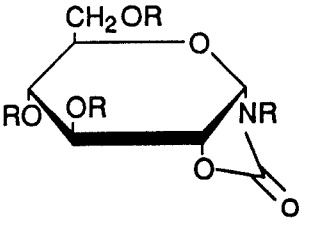
The preparation of the acid-stage carbohydrate-based resin has been described elsewhere.[4] Ion-exchange chromatography of the carbohydrate fraction gave 1 which crystallized from water. Periodate oxidation[5] of 1 resulted in one mole of periodate consumed per mole of substrate. FAB-MS indicated a molecular weight of 205 (*m/z* 206 $(M + H)^+$). This, along with the intense carbonyl peak at 1749 cm^{-1} in the FT IR spectrum, suggested the presence of a carbamate moiety.

The structure of 1 was determined by ^1H-^{13}C correlated NMR spectroscopy involving indirectly-bonded hydrogens and carbons[6] (Fig. 1). Protons H-1 and H-2 are coupled to the carbonyl carbon, and H-1 has a long-range coupling with C-5 through the ring oxygen. These correlations, in addition to the data from a standard COSY experiment, provide proof of a glucopyranosyl moiety with a 1,2-linked cyclic carbamate. The α-configuration was assigned due to the small proton $J_{1,2}$ value (5.3 Hz) in combination with the spectroscopic data of the *trans*-fused carbamate which has recently been synthesized ($J_{1,2}$ = 8.6 Hz).[7]

Benzoylation of 1 with benzoic anhydride using 4-dimethylamino-pyridine as catalyst[8] provided a tetrabenzoate as indicated by FAB-MS (*m/z* 622 $(M + H)^+$) and the absence of an N-H proton in the ^1H NMR of 2. This is in contrast to acetamidodeoxyhexoses[8] and glucosylureas[4] which do not undergo N-benzoylation under similar conditions.

Selected spectral data for compounds 1 and 2 are shown in Table 1. The $J_{2,3}$ and $J_{3,4}$ values for 1 and 2 were quite small and not resolved with the experimental conditions used. There were however correlations between H-2 and H-3, and H-3 and H-4 in the COSY spectra of 1. The structural rigidity imparted by the five-membered oxazolidine ring limits the energetically favorable conformations of cyclic carbamates.[9] The apparently small coupling constants for both 1 and 2 suggest $^{0,3}B$ boat conformations for both molecules.

A review of the pertinent literature indicates that 1 was probably originally synthesized by Zemplén and coworkers.[10] The reaction of D-glucose with potassium thiocyanate in aqueous hydrochloric acid



1 R=H
2 R=Bz

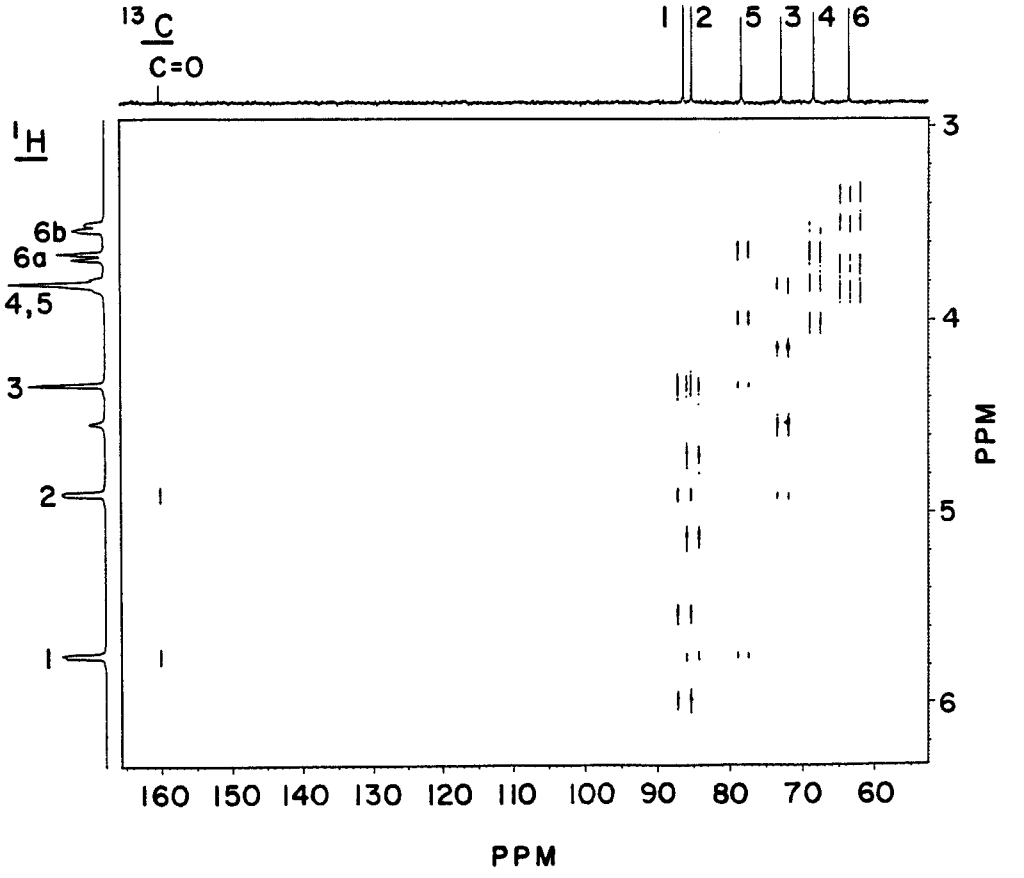


Fig. 1. Heteronuclear shift correlation spectrum of 1 with optimized delay times for polarization transfer through two- and three-bond ^{13}C-^{1}H couplings. The sample (40 mg) was exchanged three times in D_2O prior to the experiment.

TABLE 1. Selected NMR Spectral Data for Compounds 1 and 2.[a,b]

^{13}C NMR Chemical Shifts (ppm)

	C-1	C-2	C-3	C-4	C-5	C-6	C=O
1	86.4	85.3	72.9	68.5	78.4	63.6	160.3
2	88.2	81.4	75.9	69.4	77.3	64.4	152.4

^{1}H NMR Chemical Shifts (ppm)

	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b
1	5.74d	4.90d	4.33s	3.81bs	3.81bs	3.51q	3.66q
2	6.85d	5.45d	5.89d	5.31t	5.92m	4.70q	4.98q

^{1}H NMR Coupling Constants (Hz)

	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
1	5.3	<0.5	--[c]	--	4.7	2.1	-12.1
2	5.8	<0.5	3.3	9.0	5.1	2.5	-12.4

a. Chemical shifts are relative to tetramethylsilane (0 ppm).

b. Solvents for 1 and 2 were D_2O and acetone-d_6, respectively. Sample 1 was completely exchanged with D_2O prior to the NMR experiment.

c. The width of the H-3 signal at half-height was approximately 3-4 Hz.

provided a material which, upon treatment with hydrogen peroxide, gave a compound with an optical rotation ($[\alpha]_D$ +6.79°) similar to our result ($[\alpha]_D$ +6.1°). Later investigations[11] of this compound established a C-1 nitrogen in contrast to the 2-amino-2-deoxy-α-D-glucopyranosyl 2,1-(cyclic carbamate) structure originally proposed by Zemplén et al.[10]

The reaction pathway by which 1 is formed during the acid stage of resin synthesis has not been fully established. Significant amounts of the glucosylureas are present in the acid stage.[4] The current hypotheses are that 1 is produced late in the reaction either by an intramolecular attack of the C-2 hydroxyl at the urea carbonyl of

N-α-D-glucopyranosylurea with loss of ammonia, or by the formation of a transient isocyanate[12] and subsequent cyclization.

EXPERIMENTAL

General Procedures. Melting points are uncorrected. Evaporations were carried out under reduced pressure at 35 °C. Rotations were determined with a Perkin-Elmer 243 polarimeter (589 nm). FT IR spectra (KBr pellets) were recorded with a Nicolet 5-DXB instrument. NMR spectra were obtained with a Bruker AM-400 spectrometer. FAB-MS were obtained with a Kratos MS-50TC instrument. The extent of periodate oxidation[5] was monitored with a Shimadzu 265 UV spectrophotometer. Preparation of the acid-stage carbohydrate-based resin as well as the isolation of the resulting carbohydrate fraction has been described previously.[4]

α-D-glucopyranosylamine 1,2-(cyclic carbamate) (1). The carbohydrate fraction of the acid-stage resin (2.52 g) was applied to a gravity feed AG 50W-X4 (-400 mesh; BioRad) column (370 mL) and eluted with 43 mM formic acid. The fractions containing 1 were combined (344 mg, 90% purity) and rechromatographed to yield 1 (239 mg) which crystallized from water (150 mg). Analytical data: R_f 0.47 (silica gel TLC, BuOAc-HOAc-EtOH-H_2O, 3:2:1:1 v/v); mp 186-7 °C; $[\alpha]_D$ +6.1° (c 0.95, water); FT IR: (cm^{-1}) 3398, 3272, 1749, 1226, 1106, 1094, 1023, 961, and 942.

Anal. Calcd for $C_7H_{11}O_6N$: C, 41.0; H, 5.4; N, 6.8. Found: C, 40.8; H, 5.4; N, 6.7.

N-benzoyl-3,4,6-tri-O-benzoyl-α-D-glucopyranosylamine 1,2-(cyclic carbamate) (2). The carbohydrate fraction of the acid-stage resin (1.6 g) was perbenzoylated with benzoic anhydride (50 g) in pyridine (250 mL) using 4-dimethylaminopyridine (DMAP, 25 g) as catalyst.[6] Subsequent workup provided the carbohydrate perbenzoates (3.6 g). Silica gel chromatography (Kieselgel 60, Merck) of a portion of the carbohydrate perbenzoates (1.12 g) in 85:15 (v/v) toluene:ethyl acetate gave crude 2 (75% purity, 142 mg). Final purification was achieved with preparative C-8 reversed-phase HPLC in 85:15 acetonitrile:water resulting in 50 mg of 2. Analytical data: R_f 0.54 (silica gel TLC, toluene-EtOAc, 85:15 v/v); mp 78-84 °C; $[\alpha]_D$ +48.6° (c 0.93, acetone);

FT IR: (cm^{-1}) 3440, 1796, 1728, 1268, 1109, 1097, and 711; FAB-MS: *m/z* 622 $(M + H)^+$ and 500 $(M - BzOH + H)^+$.

Anal. Calcd for $C_{35}H_{27}O_{10}N$: C, 67.6; H, 4.4; N, 2.2. Found: C, 67.3; H, 4.3; N, 2.4.

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