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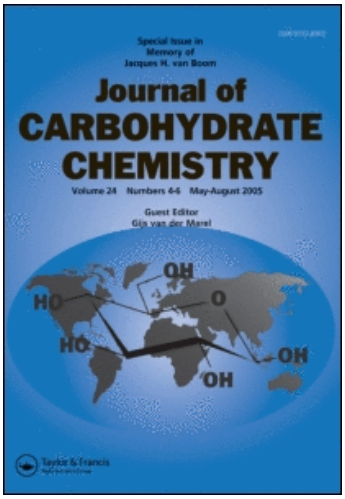

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THE REACTION OF D-GLUCOSE WITH SUBSTITUTED ANILINES: INVESTIGATION BY CARBON-13 NMR SPECTROSCOPY

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ABSTRACT

Carbon-13 NMR data are provided for a series of N-glycosyl amines and Amadori rearrangement products that were prepared by reaction of D-glucose with substituted anilines. These data demonstrate that ^{13}C NMR is a useful method for characterizing the products isolated from reactions of D-glucose with amines.

INTRODUCTION

D-Glucose, like other reducing sugars, reacts readily with primary amines such as ammonia, aliphatic and aromatic amines and amino acids. The reaction proceeds in stepwise fashion as outlined in Figure 1. A glucopyranosylamine is formed reversibly in the first step. In the presence of acid catalysts, this product rearranges to a 1-amino-1-deoxy-D-fructose derivative, the Amadori compound.[1]

Reaction conditions have been defined that are presumed to yield selectively either the glycosylamine or the Amadori rear-

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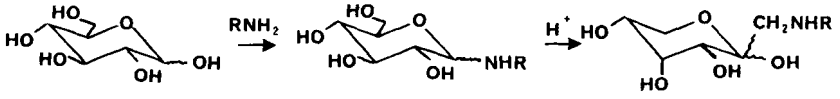

FIG. I. Stepwise Reaction of D-Glucose With Amines

rangement product.[1] To obtain the glycosylamines, the reaction of glucose and amine is carried out at room temperature in alcohol solution, to which may be added 0.001 N sulfuric acid.[1,2] In contrast, the Amadori rearrangement product is obtained when an aqueous solution of D-glucose and amine containing 2N acetic acid is heated on a steam bath.[1,2]

However, a method for monitoring the course of the reaction and for characterizing the structures of isolated products is not readily available. Such qualitative tests as reaction with Tillmans' reagent[3] or methylene blue[4] may not be sufficiently reliable for differentiating between a glycosylamine and an Amadori compound or for identifying product mixtures.

Because of the sensitivity of the chemical shift to structural and electronic effects, NMR is an excellent method for monitoring both reaction and products. Use of this technique is further supported by several recent literature reports that describe data of this type. For example, Mester and his colleagues characterized the products of reactions of poly-L-lysine with reducing sugars by ^{13}C NMR and reported that the C-1 carbon signal for the Amadori compounds is located at 53-54 ppm, whereas that for the N-glycosides is at 90-91 ppm.[5] Similarly, Gross and co-workers, who used ^{13}C NMR to characterize the products of reactions of D-glucose with four amino acids, reported distinctive upfield shifts for C-1 of the Amadori products, although the spectra were too complex to permit complete structural analyses.[6] A report by Funcke and Klemer describes the variation in ^{13}C chemical shift with mutarotatory structure in D-fructose and 1-amino-1-deoxy-D-fructose derivatives.[7] This study has been further elaborated by Roeper, Roeper and Heyns, who de-

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scribed the mutarotation of N-(1-deoxy-D-fructos-1-yl)-L-amino acids in D_2O as determined from the ^{13}C NMR spectra.[8]

This paper reports a ^{13}C NMR study of the products of the reaction of D-glucose with a series of meta- and para-substituted anilines. Chemical shifts are assigned to the products of these reactions as well as to the acetylated derivatives.

RESULTS AND DISCUSSION

Successful use of NMR in structural analysis is dependent on the availability of a data base that correlates chemical shift and structural features. Tables 1-3 summarize selected literature data for some aniline derivatives, the hexoses and hexose pentaacetates.

Results collected in this laboratory are summarized in Tables 4-6.

These data confirm that reaction of D-glucose and an aniline at room temperature, i.e., the conditions defined by Honeyman,[1] selectively yields the glycosylamine. Only one anomer of each derivative was isolated in this laboratory, and the sugar C-1 chemical shift, which is consistently about 85 ppm, has been assigned to the β-D-glucopyranosylamine. (We would predict the chemical shift of C-1 of the α-anomer to be approximately 82 ppm.)

The chemical shifts of the peracetate derivatives support this assignment. As expected, on acetylation the absorptions of sugar carbons 2, 3, and 6 are characteristically shifted. However, that for C-1 of the sugar is seen at 85 ppm, a shift that we have assigned to the β-anomer.

Under the more strenuous reaction conditions described to promote Amadori rearrangement, 1-amino-1-deoxy-D-fructose derivatives were isolated only from reactions of D-glucose with p-toluidine, p-anisidine, and p-ethylaniline. In these examples, one anomer predominated. We have identified this on the

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TABLE 1

^{13}C Chemical shifts (in ppm) of Anilines[9]

	C-1	C-2	C-3	C-4	C-5	C-6	Other
Aniline	148.7	114.4	129.1	116.3	129.1	114.4	-
p-Anisidine	140.5	116.3	114.9	152.7	114.9	116.3	CH_3O 55.6
p-Bromoaniline	144.5	115.9	131.0	109.1	131.0	115.9	-
m-Chloroaniline	148.0	114.8	134.7	118.2	130.5	113.3	-
p-Chloroaniline	144.9	115.9	128.7	122.6	128.7	115.9	-

TABLE 2

^{13}C Chemical Shifts (in ppm) of D-Hexoses

	C-1	C-2	C-3	C-4	C-5	C-6	Ref
α-D-glucopyranose	92.9	72.5	73.8	70.6	72.3	61.6	10
β-D-glucopyranose	96.7	75.1	76.7	70.6	76.8	61.7	10
α-D-fructofuranose	64.5	105.7	83.4	77.9	83.0	62.7	11
β-D-fructofuranose	64.7	102.8	77.5	76.3	82.1	63.7	11
α-D-fructopyranose	63.2	99.0	71.8	72.1	66.2	62.2	11
β-D-fructopyranose	65.6	99.1	69.3	71.1	70.4	64.6	11

TABLE 3

^{13}C Chemical Shifts (in ppm) of D-Hexose Pentaacetates[12,13]

Peracetate	C-1	C-2	C-3	C-4	C-5	C-6	Other
α-D-glucopyranose	89.2	69.4	70.0	68.1	70.0	61.6	
β-D-glucopyranose	91.8	70.5	72.9	68.0	72.9	61.6	

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TABLE 4
^{13}C Chemical Shifts (in ppm) of β-D-Glucosylamines

Aniline Derivative	C-1 (C-1')	C-2 (C-2')	C-3 (C-3')	C-4 (C-4')	C-5 (C-5')	C-6 (C-6')	Other
m-Br	148.8 (84.9)	115.7 (72.8)	112.1 (77.0)	122.1 (70.1)	130.3 (77.4)	119.6 (61.0)	
p-Br	146.4 (85.0)	115.2 (72.9)	131.2 (77.0)	108.2 (70.2)	131.2 (77.5)	115.2 (61.0)	- -
m-Cl	148.6 (84.9)	112.8 (72.8)	133.7 (76.9)	116.7 (70.2)	129.9 (77.4)	111.8 (61.0)	
p-Cl	145.8 (85.1)	114.5 (72.8)	128.3 (76.9)	120.9 (70.2)	128.3 (77.4)	114.5 (61.0)	- -
p-MeO	141.2 (86.4)	114.5 (73.1)	114.5 (77.1)	151.9 (70.4)	114.5 (77.6)	114.5 (61.2)	55.4 CH_3O -

TABLE 5
^{13}C Chemical Shifts (in ppm) of β-D-Glycosylamine Peracetates

Aniline Derivative	C-1 (C-1')	C-2 (C-2')	C-3 (C-3')	C-4 (C-4')	C-5 (C-5')	C-6 (C-6')	Other
m-Br	145.9 (84.0)	116.9 (71.2)	123.1 (72.8)	122.8 (68.9)	130.5 (72.5)	113.3 (62.2)	171.2, 170.7, 170.0, 169.6 20.6, 20.5
p-Br	143.6 (84.3)	115.9 (71.2)	132.1 (72.8)	111.9 (68.8)	132.1 (72.5)	115.9 (62.1)	171.1, 170.6, 170.0, 169.5 20.5, 20.4
m-Cl	145.8 (84.0)	114.0 (71.2)	135.0 (72.8)	119.8 (68.9)	130.2 (72.5)	112.8 (62.2)	171.1, 170.6, 169.9, 169.9 20.6, 20.5
p-Cl	143.4 (84.5)	115.7 (71.4)	129.3 (72.6)	124.8 (69.1)	129.3 (73.1)	115.7 (62.3)	171.1, 170.6, 170.1, 169.7 20.5, 20.4
p-MeO	138.3 (85.3)	115.9 (71.2)	114.8 (72.3)	153.8 (68.9)	114.8 (73.0)	115.9 (62.1)	170.9, 170.6, 170.0, 169.5 55.6, 20.6, 20.5, 20.4
p-CH_3	142.1 (84.8)	114.4 (71.2)	129.2 (72.3)	129.7 (68.9)	129.2 (73.1)	114.4 (62.2)	171.0, 170.6, 170.0, 169.5 20.5, 20.4, 20.3
p-Et	142.3 (84.7)	114.6 (71.2)	128.6 (73.1)	135.6 (69.0)	128.6 (72.3)	114.4 (62.2)	171.1, 170.6, 170.1, 169.6 20.6, 20.5, 27.9, 15.7

TABLE 6
^{13}C Chemical Shifts (in ppm) of 1-Amino-1-deoxy-D-fructose Derivatives

Aniline Derivative	C-1 (C-1')	C-2 (C-2')	C-3 (C-3')	C-4 (C-4')	C-5 (C-5')	C-6 (C-6')	Other
p-Me	146.7 (49.8)	112.6 (97.9)	124.5 (69.0)	129.2 (70.2)	124.5 (69.2)	112.6 (63.2)	20.0 (CH_3)
p-MeO	143.2 (50.4)	114.4 (97.8)	113.6 (69.1)	151.0 (70.1)	113.6 (69.1)	114.4 (63.1)	55.2 (CH_3O)
p-Et[a]	146.8 (49.7) (48.9)	112.5 (97.8) (101.8)	127.9 (69.0) (76.6)	131.4 (70.1?) (75.2)	127.9 (69.1) (82.1)	112.5 (63.1)[b] (62.3)[c]	27.3 (CH_2), 15.8 (CH_3)

[a] Absorptions assigned to glycosylamine also seen.
[b] Major component. Assigned as β-D-fructopyranose derivative.
[c] Lesser component. Assigned as β-D-fructofuranose derivative.

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basis of chemical shifts as the 1-amino-1-deoxy-β-D-fructopyranose. Large changes in the position of absorption of sugar carbons 1 and 2 to approximately 50 and 98 ppm, respectively, were observed.

In the case of p-ethylaniline, a product mixture was isolated under Amadori conditions. Analysis of the spectrum suggested that the β-D-fructopyranose is the major product, with the α- and β-D-fructofuranoses as minor components in the product mixture. In addition, a weak absorption at 85 ppm is seen. If this reflects the presence of the β-D-glucopyranosylamine, rearrangement was incomplete.

Attempts to isolate crystalline peracetates of the Amadori compounds were unsuccessful.

In summary, the ^{13}C chemical shifts of the sugar moiety can be used diagnostically to identify the anomeric D-glucosylamine and 1-amino-1-deoxy-D-fructose derivatives from reactions of D-glucose with amines.

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EXPERIMENTAL METHODS

All chemicals used in this study were reagent grade. If discolored, aniline derivatives were suitably purified before use. The reaction conditions are those described by Honeyman.[1] Products were further purified by column chromatography on silica gel (EM Reagents). Peracetate derivatives were prepared by reaction of the amino sugar derivatives with acetic anhydride in pyridine. Further purification was effected by recrystallization.

Melting points were obtained using a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, IL.

^{13}C NMR spectra were recorded at 20.1 MHz with an IBM Model NR80 spectrometer. Deuterochloroform or perdeuterated chloroform/DMSO was used as the solvent and TMS served as an internal reference. The spectra were proton decoupled.

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