^{13}C NMR SPECTRA OF BIOLOGICALLY ACTIVE COMPOUNDS

XI. DIASTEREOMERIC EFFECTS IN C-GLYCOSIDES

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The ^{13}C NMR spectra of epimeric C—D-glucopyranosides with alkyl, aryl, and alkynyl substituents have been studied. The diastereomeric effects of the chemical shifts have been determined and assignments have been made to the 1α- and 1β- stereochemical series on the basis of HH COSY and CH HET CORR two-dimensional NMR spectra. The diastereomeric effects observed for the C-3 and C-5 carbon atoms are proposed as characteristic parameters for establishing the stereochemistry at the C-1 carbon atom.

The stereochemical analysis of O-glycosides using ^{13}C NMR spectroscopy is widely known [2]. In the case of C-glycosides, the most characteristic signals of the anomeric center are present in the same region of the field as the signals of the other carbinol atoms, which, to a certain degree, interferes with the unambiguous assignment. Information on the use of the direct carbon—proton constants $^1J_{C-H}$ of the anomeric center for carrying out stereochemical assignments has been given in [3]. However, a strongly bound proton system complicates the finding of spectral parameters directly from the spectrum, since it requires an accurate solution of a multispin system by iteration methods [4]. In view of this, an unambiguous assignment of the signals of the protons and of the carbon atoms in the spectra and the study of the correlation between the chemical shifts (CSs) in the structure of the molecules are of interest for finding characteristic parameters in the performance of stereochemical assignments.

Figure 1 gives a sketch of a correlation map of a homonuclear two-dimensional spectrum of one of the epimers of ethyl 2,3,4,6-tetra-O-benzyl-C-D-glucopyranoside (I) taken with the use of the HH COSY (45°) method [5]. Cross-peaks in the 1.73 and 3.93 ppm region unambiguously show the existence of a bond between the protons of the methylene group of the ethyl fragment and the proton of the C-1 anomeric center $^3J_{HH}$ = 7.6 Hz, found from the ^1H NMR spectrum). (See scheme on following page).

The magnitude of the vicinal constant (J_{HH} = 5.3 Hz) shows the α configuration of the ethyl group [2]. For the other epimer, having a shorter retention time under HPLC conditions, the contour map of a HH COSY experiment is shown in Fig. 2. According to the contour map, the diastereotopic protons of the methylene group, linked with one another by a geminal constant, interact with the proton giving the strongest-field signal at 3.18 ppm, which belongs to HC-1. In its turn, the HC-1 proton gives a cross-peak with the HC-2 proton having the relatively large coupling constant $^3J_{H-H}$ = 8.3 Hz, which shows the axial-axial arrangement of these protons or the equatorial-equatorial arrangement of the substituents, i.e., the trans for β (1S) configuration of the substituent in the preferred C1 conformation of the D-glucopyranose ring [2]. Analysis of the other cross-peaks enables an assignment to be made of the signals of all the protons of the rings of both the 1α- and the 1β- epimers.

For the epimers under investigation we carried out heteronuclear correlation spectroscopy experiments. Sketches of the correlation maps plotted by the use of the XH CORR procedure [6] for the 1α- and 1β- epimers are shown in Figs. 3 and 4, respectively. It can be seen from the spectrum of the 1α- epimer that the proton signal at 3.93 ppm is directly linked with the carbon signal at 75.49 ppm (the C-1 atom). The proton giving a signal at 3.75 ppm has a cross-peak with the carbon signal at 80.43 ppm belonging to C-2. Absorption in the carbon spectrum at 82.5 ppm relates to C-3. The corresponding signals for the 1β-

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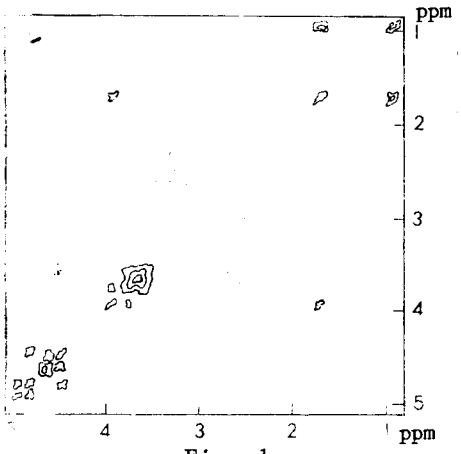


Fig. 1

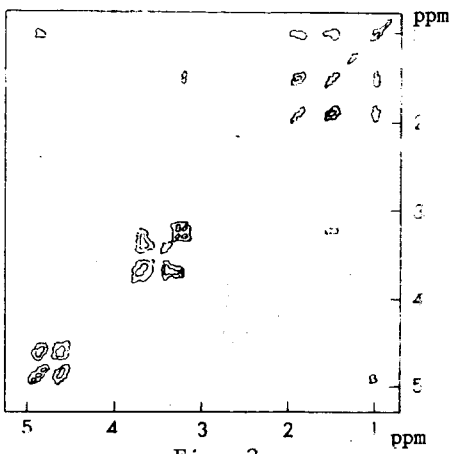
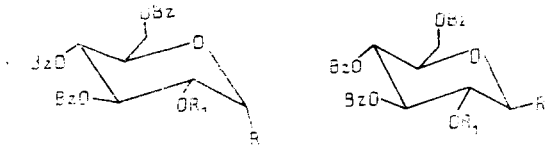


Fig. 2

Fig. 1. Contour map of a HH COSY (45°) two-dimensional homonuclear NMR spectrum of ethyl 2,3,4,6-tetra-O-benzyl-C-α-D-glucopyranoside (Iα).

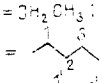
Fig. 2. Contour map of a HH COSY (45°) two-dimensional homonuclear NMR spectrum of ethyl 2,3,4,6-tetra-O-benzyl-C-β-D-glucopyranoside (Iβ).



α -epimer β -epimer

Bz = $-CH_2Ph$

R = CH_2CH_3; R_1 = Bz (I) (α-, β-)

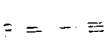
R =  R_1 = Bz (II) (α-, β-)

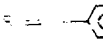
R =  R_1 = Bz (III) (α-, β-)

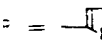
R =  R_1 = Bz (IV) (α-, β-)

R =  R_1 = Bz (V) (α-, β-)

R = $-C\equiv C-SiMe_3$; R_1 = Bz (VI) (α-, β-)

R =  R_1 = Bz (VII) (α-, β-)

R =  R_1 = Bz (VIII) (α-, β-)

R =  R_1 = Bz (IX) (α-, β-)

R = H; R_1 = Bz (X)

R = CH_2CH_3; R_1 = H (XI) (α-)

R =  R_1 = H (XII) (α-)

Scheme 1

epimer are located in weaker fields by from 2 to 4.8 pm, which is connected with 1,2-cis interactions in the 1α-epimer. The maximum diastereomeric effect [1] is observed for the C-5 signal (Table 1). A characteristic change of 6.79 ppm is observed in the screening of the α-carbon atom of the ethyl substituent.

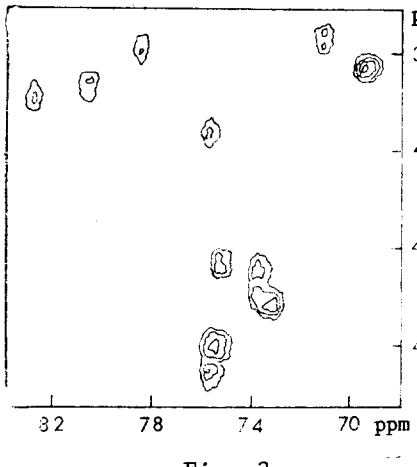


Fig. 3

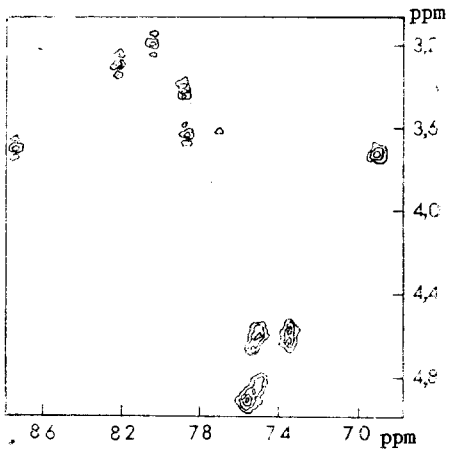


Fig. 4

Fig. 3. Contour map of a HC CORR two-dimensional heteronuclear NMR spectrum of ethyl 2,3,4,6-tetra-O-benzyl-C-α-D-glucopyranoside (Iα).

Fig. 4. Contour map of a HC CORR (45°) two-dimensional heteronuclear NMR spectrum of the tetrabenzyl ether of ethyl-C-β-glucopyranoside.

In order to exclude the influence of the concentration and temperature dependences of the diasteromeric effects, we recorded the spectrum of an equimolar mixture of the α and β epimers of (I). Analysis of the results of the experiment which are given in Table 1 in parentheses shows that the maximum change in the diastereoisomeric effects does not exceed 0.2 ppm (C-2), i.e., less than 10% of the absolute magnitude of the effects. The effects observed were repeated almost completely for hexyl and butyl tetra-O-benzyl-C-D-glucopyranosides ((II) and (III), respectively) for which, on the basis of the C-1, C-3, and C-5 diastereomeric effects an unambiguous assignment of the stereoisomers to the 1α- and 1β-stereochemical series has been made.

In the case of an isobutyl substituent (compound (IV)) some weakening of the diastereomeric effect for C-1 was observed. The effects for the C-3 and C-5, and also the C-1', carbon atoms were more stable. For the sterically hindered structure (IVα) diastereotopic differences in the signals of the methyl groups arose (0.3 ppm).

The greatest difficulties appeared in the assignment of the carbon signals of the stereoisomers of compound (V) with a heptyne substituent. In the region of carbonyl carbon atoms the signals of a triple bond appeared which were distinguished by their intensity and multiplicity. The signals of the C-1 carbon atoms were assigned with allowance for the anisotropic influence of the triple bond, and an assignment of the isomers to the corresponding stereochemical series was made from the diastereomeric effects observed for the C-1—C-3 and C-5 carbon atoms.

To confirm this assignment, HH COSY homonuclear 2-dimensional NMR spectra were taken, and in these the HC-3—triple bond—HC1 chain of bonds was traced and the vicinal SSCC was determined for HC-1, which was 9.8 Hz in the case of the IVβ epimer.

The structure was shown and stereochemical assignments were made in the following epimeric pairs (VI-VIII) similarly. For compound (VIII) with a phenyl group at C-1 the β-epimer was isolated in the individual form, while the α- epimer was characterized in a 1:1 mixture of the α- and β- epimers. In the ^{13}C NMR spectrum of this mixture a set of signals corresponding to both the β- and α- epimers with retention of the characteristic differences of the CSs for the C-3 and C-5 atoms was ambiguously isolated.

The epimers of the C-glycoside (VII) with a phenylacetylene group were characterized from an equimolar mixture with practically diastereomeric effects as in the case of the epimeric pair (V).

The relationships obtained permit the identification of stereoisomers from a mixture of compounds and also a search for the signals of a minor component. For example, in the case of compound (IX), consisting of a mixture of epimers with α:β = 1:10, a complete assignment of all the signals of the carbon atoms with the α- and β- epimers was made.

TABLE 1. Parameters of the ^{13}C NMR Spectra of the Stereoisomers of a Series of C-Glycosides (I-IV) ($CDCl_3$, δ, ppm, 75 MHz; the Values for an Equimolar Mixture of the Isomers (Iα) and (Iβ) are Given in Parentheses.

C_i	I α	I β	Δδ, ppm	II α	II β	Δδ, ppm	III α	III β
C-1	75,49 (75,49)	80,36 (80,36)	4,87 (4,87)	74,04	79,30	5,26	74,06	79,35
C-2	80,43 (80,43)	82,39 (82,15)	1,96 (1,76)	80,42	82,48	2,06	80,46	82,50
C-3	82,59 (82,59)	87,38 (87,37)	4,79 (4,78)	82,63	87,43	4,80	82,65	87,43
C-4	78,35 (78,35)	78,98 (78,99)	0,53 (0,54)	78,36	79,00	1,64	78,39	78,99
C-5	70,92 (70,92)	78,78 (78,79)	7,86 (7,87)	71,00	78,80	7,80	71,00	78,78
C-6	69,25 (69,26)	69,16 (69,18)	−0,09 (−0,07)	69,24	69,21	−0,03	69,25	69,16
C-1′	17,89 (17,89)	24,68 (24,68)	6,79 (6,79)	27,58 25,89	31,46	3,88	24,60	31,84
C-2′	9,86 (9,86)	9,91 (9,86)	0,05 (0,00)	25,58 27,58	27,72		25,30	25,49
C-3′				24,29	22,73		29,09	29,35
C-4′				14,07	14,07			
C-5′							31,81	31,77
C-6′							22,62	22,65
							14,09	14,15

C_i	Δδ, ppm	IV α	IV β	Δδ, ppm	V α	V β	Δδ, ppm
C-1	5,29	72,06	74,44	2,36	68,82	70,22	3,40
C-2	2,04	80,35	83,07	2,72	79,35	82,60	3,24
C-3	4,78	82,60	87,44	4,84	83,16	86,06	2,90
C-4	0,60	78,28	79,03	0,75	77,75	78,92	1,07
C-5	7,78	71,07	78,76	7,69	72,57	77,81	5,24
C-6	−0,03	69,03	69,24	+0,21	68,89	68,89	0,00
C-1′	7,24	33,01	40,86	7,86	74,70	76,65	1,95
C-2′	0,19	24,02	24,56	0,54	90,44	87,04	−3,40
C-3′	0,24	21,37	21,74	0,37	18,92	18,90	−0,02
C-4′	−0,04	23,78	23,82	0,04	28,29	28,08	−0,21
C-5′	+0,03				31,04	31,11	−0,07
C-6′	0,06				22,17	22,15	−0,02
					13,94	13,88	−0,05

C_i	VI α	VI β	Δδ, ppm	VII α+VII β=1:1 VII α	VII β	Δδ, ppm	VIII α+VIII β=1:1 VIII α	VIII β
C-1	67,06	70,31	3,25	67,05	70,36	3,31	78,39	81,76
C-2	79,18	82,35	3,17	79,20	82,33	3,13	81,22	84,18
C-3	82,85	86,05	3,20	82,98	86,37	3,39	81,91	86,74
C-4	79,18	79,18	0,00	77,62	79,20	1,58	78,33	78,40
C-5	72,48	77,69	5,21	72,51	77,43	4,89	72,29	79,41
C-6	68,38	68,78	0,40	68,66	68,54	−0,08	69,01	69,19
C-1′	82,85	91,28	8,23	83,87	85,93	2,06		
C-2′	100,27	102,60	2,33	89,33	85,96	−3,37		
C-3′								
C-4′								
C-5′								
C-6′								

C_i	Δδ, ppm	IX α+IX β=1:10 IX α	IX β	Δδ, ppm	X	XI α	XII α
C-1	3,43	73,40	76,37	2,97	68,17	73,30	72,07
C-2	3,26	80,91	83,07	2,16	75,07	68,47	68,32
C-3	4,83	82,85	86,83	3,98	86,38	75,42	75,48
C-4	0,07	78,46	78,46	0,00	79,35	78,35	78,56
C-5	7,12	71,38	79,35	7,97	73,24	73,23	73,56
C-6	0,18	69,25	69,25	0,00	69,05	69,60	69,93
C-1′						21,18	27,81
C-2′						9,89	25,42
C-3′							29,22
C-4′							31,80
C-5′							22,60
C-6′							14,09

The dead-end chain of proton bonds observed in the HH COSY two-dimensional NMR spectrum of compound (X) and the geminal protons connected with the protons at C-2 that were present showed the absence of substituents at the C-1 atom.

For compound (XI) with a C-1 ethyl radical the α configuration of the ethyl group was assigned on the basis of the position of the C-5 signal as the least subjected to perturbation. The chain of bonds for this compound in the HH COSY two-dimensional NMR spectrum showed the presence of H_2C1'—HC1—HC2—OH bond expressed by a doublet signal of the hydroxy group at 2.81 ppm.

The selected removal of protection also took place in the case of compound (XIIa). In this case, the hexyl radical was present in the α configuration according to the values of the C-5 and C-1 chemical shifts.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a AM 300 spectrometer with working frequencies of 300 and 75 MHz, respectively. The solvent was $CDCl_3$ and the internal standard TMS. The homonuclear HH COSY (45°) [5] and heteronuclear HC HET CORR [6] experiments were performed by the standard programs of the Bruker firm.

^1H NMR spectrum ($CDCl_3$, TMS, ppm for (Iα)): 0.95 t (CH_3, ^3J = 7.4 Hz), 1.72 q.d. (CH_2, ^3J = 7.4; ^3J = 7.6 Hz), 3.93 t.d. (HC-1, ^3J = 7.6; ^3J = 5.3 Hz), 3.75 m (HC-2), 3.80 m (HC-3), 3.58 m (HC-4), 3.55 m (HC-5), 3.66 m (2H, C-6), 4.62–4.93 m (8H, CH_2O), 7.20–7.40 m (2OH, Ph).

For (Iβ): 1.00 m (CH_3), 1.51 d.q.d (^1H, CH_2, ^2J = 15.0; ^3J = 7.3, ^3J = 8.5), 1.89 d.q.d. (H, CH_2, ^2J = 15.0; ^3J = 7.3; ^3J = 2.6 Hz), 3.18 d.d.d. (H C-1, ^3J = 8.3; ^3J = 8.5; ^3J = 2.6), 3.28 dd (HC-2, ^3J = 8.3; ^3J = 9.4), 3.71 m (HC-3), 3.41 m (HC-4), 3.61 m (HC-5), 3.71 m (2H C-6), 4.57–4.90 m (8H CH_2O), 7.20, 7.40 m (2OH, Ph).

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