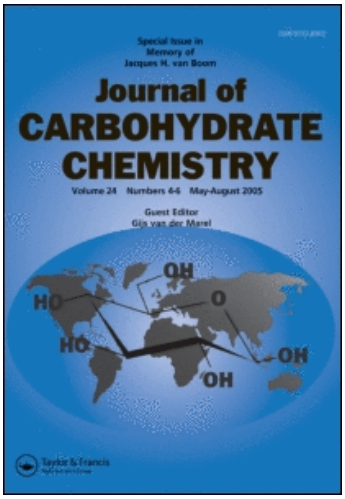

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^{1}H NMR CHEMICAL SHIFT INFORMATION ON THE CONFORMATION OF THE GLYCOSIDIC BOND IN DISACCHARIDES

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ABSTRACT

Experimental ^{1}H NMR chemical shifts were related to results obtained from theoretical calculations, in this case the HSEA approach, in order to obtain information about conformational equilibria about the glycosidic bond of disaccharides. Assuming the existence of the exo-anomeric effect, it was shown that the sign of torsion angle ψ can be obtained tentatively from the ^{1}H NMR chemical shifts.

INTRODUCTION

Understanding the conformational features of the glycosidic bond in disaccharides has been a challenge for more than fifteen years. In this respect, the pioneering work of R.U. Lemieux and coworkers[1-6] cannot be overestimated.

In order to gather information about the magnitude and sign of torsion angles constituting the glycosidic bond, the theoretical work of Rees and coworkers[7-9] with Monte Carlo calculations, the HSEA (hard sphere exo anomeric effect) calculations introduced by

Lemieux[1,4] and successfully applied by Bock[10] and Kenne[11-13], as well as the calculations of Tvaroska[14] were fundamental.

Theoretical work is always in need of experimental support. Experimental approaches such as ^{13}C NMR chemical shift studies by Lemieux,[1] Kochetkov,[15] and Perlin,[16,17] NOE studies by Lemieux,[1] and studies on the $^{13}C,^{1}H$ heteronuclear coupling constants by Perlin,[18] also gave insight into the values of φ and ψ.

Recent publications of Kenne[11-13] applied the knowledge of almost 15 years of research on the glycosidic bond to the methyl glycosides of disaccharides derived from aldohexopyranoses. He used HSEA calculations in order to obtain the minimum energy conformations about the glycosidic bond, to study the proximity of protons and substituents α and β to the glycosidic bond, and to correlate his findings with the ^{1}H and ^{13}C NMR chemical shifts of the compounds studied.

We believe that the ^{1}H NMR data contain more information than has been used so far. The ^{1}H NMR chemical shifts that we published[19-21] have certainly not been fully evaluated. With the present study it was not our goal to present new experimental data but to seek for useful generalizations based on the mass of previously published data.

We have directed our attention to ^{1}H NMR chemical shifts and not to ^{13}C NMR chemical shifts for two reasons. Kochetkov and coworkers[15] have already systematically investigated the effects of all possible linkages on ^{13}C NMR chemical shifts and thus have opened the way for the identification of the absolute configuration of the carbons of the aglycon on which the linkage occurs. Also, Lemieux and coworkers[2] have proved that ^{13}C NMR chemical shifts are unreliable for evaluation of the torsion angles ϕ and ψ because of their sensitivity to small changes in the valence angle τ of the oxygen of the glycosidic bond.

We had another reason. In 1975 we published for the first time a complete set of ^{1}H NMR data (chemical shifts and coupling constants) on a systematic series of disaccharides.[19-21] We found that when the chemical shifts of the ring protons were compared with the corresponding values in the basic sugars (e.g., α– and β–D-

glucopyranose) H–1', H–n as well as H–(n+1) (where n indicates the number of the linkage carbon in the aglycon) showed a downfield shift of +0.10/+0.30 ppm. Earlier, Usui and coworkers[22] published the ^{13}C NMR chemical shifts of the series of glucobioses. They showed that δC–n showed a downfield shift of ~8 ppm, while both δC–n±1 showed an upfield shift of ~2 ppm. The complementary information of both studies was very important in order to assign the location of the linkage in unknown disaccharides, and consequently to obtain information on the primary structure of unknown oligosaccharides.

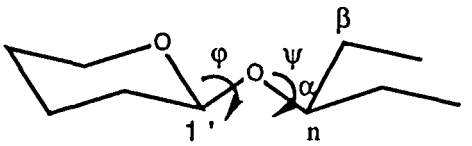
In our ^{1}H NMR study on glucobioses,[19] we suggested that the magnitude of the increments caused by the features of the glycosidic bond can be explained in terms of β and γ effects. Although such effects had been recognized ten years earlier in hexopyranose systems by Lemieux and coworkers,[23,24] at that time little was known about the nature of the increments (it seemed that the same increments extracted from different classes of compounds were not compatible), and too little information had been published about the torsion angle of the glycosidic bond. Therefore we did not proceed with the study at that time. Now that more data is available[11-13], we can evaluate our ideas carefully.

In this article, we try to answer the question : "assuming that the exoanomeric effect determines the sign and magnitude of φ,[25] what information do the ^{1}H NMR chemical shifts of the protons α and β to the glycosidic bond contain about the magnitude and sign of the torsion angle ψ ?".

RESULTS AND DISCUSSION

For this article we only consider 1,α → n and 1,β → n linked disaccharides, with n = 2, 3 and 4. We use the IUPAC recommendations[26,27] for defining the torsion angles constituting the glycosidic bonds, i.e., those around C–1'–O (φ) and O–C–n (ψ). φ is zero when, in the fragment H–1'–C–1'–O–C–n, the bonds H–1'–C–1' and O–C–n are eclipsed. ψ is zero when, in the fragment C–1'–O–C–n–H–n, C–1'–O and C–n–H–n are eclipsed. A clockwise rotation for φ viewed from

C–1' to the linkage oxygen is positive, and so is a rotation of ψ when viewed from the linkage oxygen to C–n (see Scheme 1). The terms α and β are used in two ways: 1) to indicate the anomeric form and 2) to indicate the site of substitution on the aglycon.



Scheme 1

It must be stressed that ^{1}H NMR spectroscopy provides only time-averaged conformational data. The values for the torsion angles used here are the most probable within a range of values.[2,6]

With respect to the use of ^{1}H NMR chemical shifts in order to gather information on features of the glycosidic bond, through space effects of nearby substituents have been correlated with changes in the chemical shifts by Lemieux and coworkers.[2,26] Consideration of this effect allows explanation of differences in the torsion angles of the glycosidic bond in closely related compounds. In this respect, Lemieux could explain small differences in the glycosidic bond of the Lewis human blood group determinants,[2] or e.g., a relationship between ^{1}H NMR signals of the X hapten and that of the H type 2 and Y hapten.[28] The chemical shift of H–5', which is only sensitive to effects operating through space, and its correlation with torsion angle ψ of the glycosidic bond was studied by Kenne.[11-13]

Although consideration of effects through space are sometimes very useful, care should be taken when studying such effects on protons in the β and γ positions to the substituent causing the effect. This problem did not occur in the compounds studied by Lemieux, since he studied the effect of a substituent of one moiety on a proton of another. However, in the present study this pitfall must indeed be considered.

Let us design the problem. Lemieux[5,29] has suggested that electrostatic interaction between a substituent (oxygen of one unit)

and a proton on another causes deshielding. He has applied his proposal succesfully in trisaccharides.[5] However, when such substituent effects are operating on a proton in the same ring, the observation of Lemieux elaborated for effects between different rings does not necessarily hold. Compare the effect of an axial hydroxyl group in cyclohexanol with the theoretical expected values in cyclohexane.[30] On a *synaxial* proton, a downfield shift (deshielding) of +0.46 ppm is seen, but on the *syn* proton in the β-position, no effect is seen. From the point of view of through-space electrostatic interactions, no explanation can be found for the effect caused on the β-*antiperiplanar* proton (+0.23 ppm) and the γ-*trans* proton (-0.27 ppm). These data show that when β and γ increments are studied, we first must know the basic values of the effects operating over bonds before considering effects operative through space. Therefore, although the effect of H–1' and H–n coming closer to a pseudo-*synaxial* position is reflected in an upfield shift on H–1', it is dangerous to say that an interaction through space between these protons explains the upfield shift found.

How can we measure the magnitude of β and γ effects operating over bonds ? Since the same effect in different systems (e.g., cyclohexanes, dioxanes, pyranose systems) does not seem to give consistent values of increments,[31] we have chosen to derive generalizations from the series of the glucobioses whose torsion angles are well known. We have then checked their application to other disaccharides whose geometries are well known. We will give one example.

In this study, we will use the ^{1}H NMR chemical shifts of the glucobioses published by us in 1975[19] (see Table 1). These values are in good correspondence with those published by Kenne[11-13] for the corresponding methyl glycosides. This correspondence has to be checked, because, in the cases of the sophoroses and the kojibioses, the effect of the methyl group can depend on the conformation of the C–OMe bond. Some of the NMR data on disaccharides published by us has been remeasured at higher fields by Morris and Hall.[32,33] The chemical shifts assigned by them with 2–D NMR techniques were in fair to good agreement with ours.

Table 1. ^{1}H NMR Chemical Shifts of Disaccharides[a]

	H-1'	H-2'	H-3'	H-4'	H-5'	H-6A'	H-6B'	H-1	H-2	H-3	H-4	H-5	H-6A	H-6B
α-kojibiose	5.10	3.56	3.80	3.47	3.86	3.85	3.78	5.45	3.64	3.83	3.47	4.03	3.85	3.76
β-kojibiose	5.41	3.55	3.80	3.47	3.86	3.85	3.78	4.81	3.39	3.59	-	-	3.90	3.56
α-nigerose	5.38	3.56	3.77	3.47	4.02	3.82	3.82	5.24	3.63	3.86	3.67	-	-	-
β-nigerose	5.36	3.57	3.76	3.45	4.02	3.82	3.82	4.67	3.36	3.64	3.64	3.48	-	-
α-maltose	5.41	3.59	3.68	3.42	3.72	3.85	3.74	5.23	3.58	3.97	3.64	3.93	3.82	3.82
β-maltose	5.41	3.58	3.69	3.42	3.74	3.86	3.77	4.66	3.28	3.77	3.62	3.60	3.92	3.77
α-sophorose	4.63	3.37	3.52	3.42	3.46	3.91	3.75	5.45	3.65	3.87	3.47	3.87	3.84	3.77
α-laminaribiose	4.73	3.37	3.54	3.42	3.49	3.93	3.73	5.23	3.73	3.92	3.52	3.88	3.85	3.79
β-laminaribiose	4.63	3.37	3.54	3.42	3.49	3.93	3.73	4.74	3.44	3.74	3.49	3.49	3.90	3.74
β-cellobiose	4.51	3.32	3.52	3.42	3.50	3.92	3.75	4.67	3.29	3.60	3.65	3.58	3.97	3.82
								H-1A	H-1B	H-3	H-4	H-5	H-6A	H-6B
leucrose[b]	5.19	3.54	3.79	3.42	3.95	3.86	3.76	3.71	3.57	3.95	4.91	4.03	3.98	3.98

a. taken from reference 19
b. taken from reference 20

Table 2 shows the increments measured in the spectra of the glucobioses and the methyl glucobiosides, as well as the signs of φ and ψ calculated by the HSEA method. The increments are obtained by comparing the value of the chemical shift of a certain proton in a glucobiose with its value in the parent monosaccharide. Of the ^{1}H NMR chemical shifts of the six protons that can contain information about the conformation of the glycosidic bond, only those of four were found to provide useful information. Let us examine the information that each of them contains.

In order to design symbolism to represent each type of effect, we follow the pathway of the torsion angles from the group causing the effect (OH, CH_3) to the proton experiencing the effect. For example for a *synaxial* interaction between a proton and a hydroxyl space group, we write γOH (g^+g^-)H. Effects operating through space are also represented by the pathway over the bonds between the substituent operative on a proton and the substituent name. When the effect originates from a part of the skeleton of the disaccharide, the γ bond is explicitly indicated (e.g., γCO(ag)H).

H–2' of the glycosyl moiety

φ is ~60° if we have a 1,αD→n linkage and ~+55° for a 1,βD→n linkage[1]. As changes in the chemical shift of H–2' depend on changes in the torsion angle φ of the glycosidic bond, except when effects through space occur, we expect for both cases a set of very closely related values. We have measured the magnitudes of the chemical shifts of H–2' from the series of glucobioses and their methyl glycosides and compared them to the corresponding values from α and β–D–glucopyranose (see Table 2). In the methyl glycosides of the 1,αD→n linked glucobioses, increments of +0.02/+0.05 ppm are observed, in the 1,βD→n linked analogues the increments are +0.08/+0.12 ppm. In the glucobioses, the increments for both cases overlap. The increments are +0.05/+0.08 ppm if there is a 1,αD→n linkage, but +0.05/+0.10 ppm for a 1,βD→n linkage. Consequently, the increment for a γCO(aa)H effect is +0.02/+0.08 ppm, while for a γCO(ag)H effect it is +0.05/+0.13 ppm. The increment values outside

Table 2. Increments Measured on the Strategic Protons[a]

A. Glucobioses[b]	sign φ/ψ[c]	H-1'	H-2'	H-5'	H-(n-1)	H-n	H-(n+1)
α-kojibiose	-/-	-0.13	+0.06	+0.04	+0.22	+0.14	+0.12
β-kojibiose	-/-	+0.18	+0.05	+0.04	+0.18	+0.12	+0.14
α-nigerose	-/-	+0.15	+0.06	+0.20	+0.13	+0.15	+0.31
β-nigerose		+0.13	+0.07	+0.20	+0.09	+0.19	+0.29
β-maltose		+0.18	+0.08	-0.10	+0.32	+0.32	+0.18
α-sophorose		-0.02	+0.10	-	+0.22	+0.15	+0.16
α-laminaribiose		+0.08	+0.10	+0.07	+0.23	+0.21	+0.16
β-laminaribiose		+0.09	+0.10	+0.07	+0.17	+0.29	+0.14
β-cellobiose		-0.14	+0.05	+0.08	+0.15	+0.30	+0.16
leucrose[d]		-0.04		+0.13	+0.02		+0.27 (eq) +0.05 (ax)

(continued)

B. Methyl Glucobiosides[c]	sign φ/ψ	H-1'	H-2'	H-5'	H-(n-1)	H-n	H-(n+1)
Me α-kojibioside	-/-	-0.16	+0.02	+0.08	+0.22	+0.12	+0.06
Me β-kojibioside	-/-	+0.05	0.00	+0.16	+0.17	+0.15	+0.10
Me α-nigeroside	-/-	+0.09	+0.04	+0.13	+0.12	+0.10	+0.24
Me β-nigeroside	-/-	+0.09	+0.04	+0.14	+0.17	+0.15	+0.23
Me α-maltoside	-/-	+0.13	+0.05	-0.09	+0.25	+0.21	+0.11
Me β-maltoside	-/-	+0.13	+0.04	-0.09	+0.28	+0.20	+0.12
Me α-sophoroside	+/-	-0.02	+0.12	-0.03	+0.18	+0.11	+0.16
Me β-sophoroside	+/+	+0.12	+0.09	-0.05	+0.11	+0.28	+0.20
Me α-laminaribioside	+/+	+0.04	+0.12	+0.04	+0.21	+0.15	+0.10
Me β-laminaribioside	+/+	+0.07	+0.13	+0.03	+0.23	+0.24	+0.09
Me α-cellolubioside	+/-	-0.12	+0.08	+0.04	+0.12	+0.21	+0.12
Me β-cellolubioside	+/-	-0.11	+0.09	+0.05	+0.13	+0.20	+0.14
Me α-L-fucopyranosyl (1→2)α-D-glucopyranoside[f]		-0.13	+0.02	+0.10	+0.09	-0.02	+0.13

a. Increments are with respect to the values for α-D-glucopyranose : δ 5.23 for H-1, δ 3.50 for H-2, δ 3.71 for H-3, δ 3.36 for H-4 and δ 3.82 for H-5; and for β-D-glucopyranose : δ 4.67 for H-1, δ 3.27 for H-2, δ 3.45 for H-3, δ 3.35 for H-4 and δ 3.42 for H-5.
b. taken from reference 19
c. taken from reference 4
d. taken from reference 20
e. all data taken from reference 11 and 13
f. taken from reference 13

the overlapping range differ so little that it is dangerous to draw configurational conclusions about the anomeric form.

H–5' of the glycosyl moiety

In his evaluation of the chemical shifts of the methyl glycosides of disaccharides Kenne[11-13] was mainly interested in the chemical shifts of H–5', for which chemical shift changes can only be caused by effects operating through space. He consequently applied an earlier proposal of Lemieux. For the 1,αD→n glucobioses, he was able to explain the downfield shift increment of H–5' for the methyl kojibiosides and the methyl nigerosides as well as the upfield shift increment in the methyl maltosides. He also explained why, in the 1,βD→n glucobioses, a downfield increment is seen for the methyl laminaribiosides and the methyl cellobiosides, but an upfield increment in methyl α–sophoroside. For his interpretation, Kenne used the minimum energy conformations from HSEA calculations. From the point of view of the present study, the increment for H-5' will be considered as a confirmation of the conclusions drawn from the increments measured for H–1' and H–(n±1).

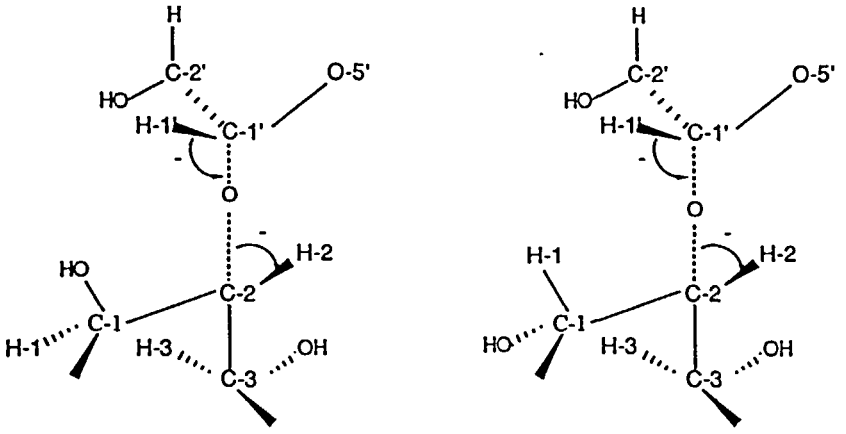
H–(n±1) of the aglycon

Except when effects through space are operative, the magnitude of the chemical shift of H–(n±1) is determined by γ–increments, which depend on ψ, i.e., the conformation about the O–C–n bond. Let us first examine disaccharides that have aglycons in the $^4C_1$(D) chair conformation and have only equatorial substituents on C–n and C–(n±1). To obtain basic information, we have studied the relevant chemical shifts in the glucobioses and their methyl glycosides except α–kojibiose and α–sophorose. The HSEA calculations of Lemieux[1] and Kenne[11-13] show that ψ mainly varies in the range ± (5°-50°). We use as visual working models Newman projections with torsion angles of 60°, but we know that deviation from these hypothetical angles are included in the increment value measured (see Schemes). We will first evaluate whether the present chemical shift data allows us to assign the sign of ψ in a disaccharide. If this is possible, we will then try to obtain the magnitude of the torsion angle.

Table 3. γ-Increment Values for H-(n→1)

	H-n facing	H-(n±1) facing		increment (in ppm)
γCO(ag)H γCO(g$^+$g$^+$)H	O-5'	OH-2'	short distance	+0.17/+0.31
γCO(ag)H γCO(g$^+$g$^+$)H	O-5'	OH-2'	long distance	+0.06/+0.15
γCO(ag)H γCO(g$^+$g$^+$)H	OH-2'	O-5'	short distance	+0.13/+0.16
γCO(ag)H γCO(g$^+$g$^+$)H	OH-2'	OH-2'	long distance	+0.12/+0.15 (+0.20 Me α-sophoroside)
γCO(g$^+$g$^-$)H	O-5'	OH-2'	short distance	+0.22
γCO(g$^+$g$^-$)H	OH-2'	O-5'	short distance	+0.18/+0.22

For the cases studied in this section (substituents on C–n and C–(n±1) equatorial) it seems that for both 1,αD→n and 1,βD→n linkages, only two γ increments must be considered when evaluating the value of the chemical shift of H–(n±1), namely γCO(ag)H and γCO(g$^+$g$^+$)H (or γCO(g$^-$g$^-$)H). In Table 3 is the data that we have gathered. To illustrate how the data in Table 3 was compiled, let us consider the case of β–kojibiose (see Scheme 2a). From the HSEA calculations, we know that here φ and ψ are both negative. H–2 faces 0–5', H–3 faces OH–2'. H–3 has a basic γCO(ag)H effect over the bonds and undergoes further an εOH(gaag)H effect through space, which must, because of the distance, be minimal. We find an increment of +0.14 ppm. H–1 is subjected to a basic γCO(g$^+$g$^+$)H effect. It also faces OH–2' and is much closer to this group. This time, an εOH(gagg)H effect over a short distance is operative through space. Its increment is +0.18 ppm. In the column "increments" of Table 3, we have listed the lowest and highest value found for a certain increment.



Scheme 2

In our convention, we symbolize an effect through space by following the pathway from the group causing the effect to the proton being affected. In this respect, we see that in β–sophorose (Scheme 3), OH-2' causes an εHO(gagg)H effect through space on H-3, and an εHO(gaag)H effect on H–1. Consequently, it is the follow-up of two *antiperiplanar* relationships between OH–2' and the proton being affected that determines a "long distance". O–5' causes a δ effect. From Table 3 it follows that for both γ increments, two ranges of values are found, namely +0.06/+0.15 ppm and +0.17/+0.31 ppm.

These two ranges are now considered with respect to the geometries of the minimum energy models calculated by HSEA calculations and represented in the studies of Kenne.[11-13] The protons facing OH–2' but far away from this group (so that effects through space are minimal) have chemical shift increments within the range +0.06/+0.15 ppm. We consider this range as having the basic values for these γ increments. When the proton having such a γ effect faces OH–2' and is close to it, the second range in which a further downfield effect through space of up to 0.1 ppm is obtained.

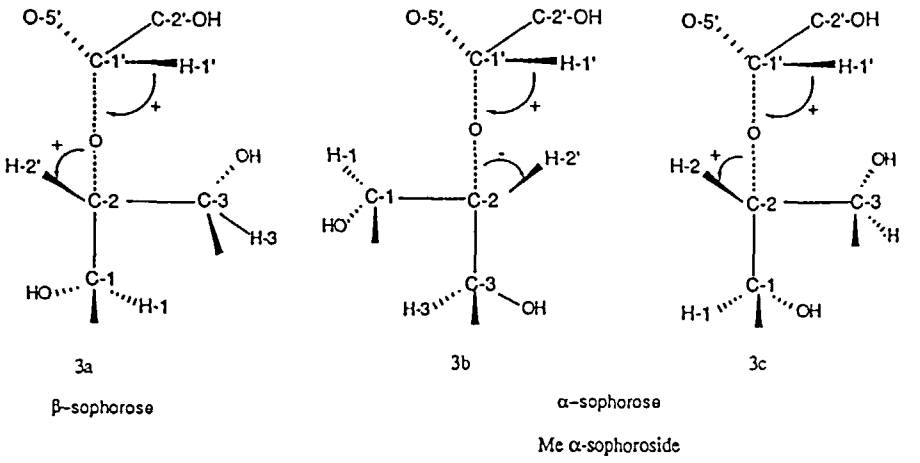
This observation is in agreement with the postulate of Lemieux[2] that a proton in one moiety is shifted downfield when it approaches an OH from another moiety.

The basic values for γ CO(ag)H and γ CO(g^+g^+)H are in both cases –0.06/+0.15 ppm. H–4 (from the aglycon) in leucrose has a γCO(ga)H or γCO(aa)H increment, but it does not have an effect through space because of its orientation. Therefore, a basic value of +0.02 ppm is seen. Consequently, as follows from the case of leucrose, although a basic γ increment can be diagnostic, this is not the case for the glucobioses. Protons facing O–5' at a short distance (only protons at a short distance from O–5' are encountered in the present study) also have a basic increment value. The influence of a ring oxygen and hydroxyl oxygen on a proton of the other moiety is consequently different.

We find more diagnostic information in glucobioses where one of the H–(n±1) protons is equatorial. In this respect α–kojibiose and α–sophorose are interesting examples. We will first examine the data from α–kojibiose (see Scheme 2b). In both α– and β–kojibiose, φ and ψ have the same sign.[4] From the HSEA calculations, the two torsion angles are of comparable magnitude. The only cause of differences in chemical shifts is the anomeric configurations.

In β–kojibiose, H-3 has a γCO(ag)H increment and faces OH–2' over a long distance εHO(gaag)H. A value of +0.06/+0.15 ppm is found (+0.06 ppm in Me α–kojibioside and +0.12 ppm in α–kojibiose) for this relationship. H–1 is now *synaxial* with respect to the C–1'–O–2 bond, having a γCO(g^+g^-)H increment and faces OH–2' over a short distance with a value of +0.22 ppm. Because here an important through-space effect (from OH–2') must be operative, we expect that the value observed is ca. 0.1 ppm too positive in comparison to the basic value for this increment.

Let us now consider the sophoroses. In Me β–sophoroside, (see Scheme 3a) φ and ψ are positive. H–3 has a basic γCO(g^+g^+)H increment, (and it faces OH–2' over a short distance (a εOH(gagg)H increment). A value of +0.20 ppm is found. H–1 also faces OH–2' but over a long distance (namely, εOH(gaag)H) with a basic γCO(ag)H increment. A value of +0.11 ppm is observed.



Scheme 3

In Me α–sophoroside, (see Scheme 3b), φ and ψ have different signs. If ψ is negative, H-3, facing O-5' over a long distance (εOH(gaag)H), with a basic γCO(ag)H increment, shows a value of +0.16 ppm. For H–1, which faces O-5' over a short distance, a $\gamma CO(g^+g^-)H$ increment of +O.18/+0.22 ppm is observed.

The increment values for $\gamma CO(g^+g^-)H$ (*synaxial*) are very instructive. It appears that not only the groups directly causing an effect on a proton must be considered, but also the complete orientation of the aglycon, i.e., H-n facing OH-2' or O-5'. With the information in Table 3, we have a criterion for discrimination between the two possible signs of ψ. Let us by way of example again consider α–sophorose, and presume that φ and ψ have the same sign (+) (see Scheme 3c). Here, H-3 has a basic $\gamma CO(g^+g^+)H$ relation with C-1'-O, and as it faces OH-2' over a short distance, a value of +0.17/0.31 ppm is expected. We find +0.16 ppm. However, H-1 has a basic γCO(ag)H relation with respect to the C-1'-O bond, facing OH-2' over a long distance, and H-2 faces O-5'. Therefore, a small value is expected. This is not the case. Consequently, a positive value for ψ does not fit with the experimental chemical shifts.

Although this criterion is in certain cases a good method for estimating the sign of ψ, further confirmation of its validity is needed.

H–1' of the glycosyl moiety

Four effects operate on the ^{1}H NMR chemical shift of H–1'. The β effect is related to the torsion angle φ. Since the magnitude of φ is nearly the same in all of the 1,α D → n and 1,β D → n linked disaccharides, the size of this effect must also be nearly the same. There are two γ effects, whose value is dependent on ψ and both follow a similar pathway. In some cases, effects through space may occur. Three ranges of increment values for H–1' are discerned from the data for the glucobioses in Table 2 : a large negative value of ca. –0.15 ppm, a small negative increment and a positive increment of +0.05/+0.15 ppm. Let us investigate the origin of these differences.

The case of the two kojibioses is very interesting. In both cases, φ and ψ have the same sign, and the conformations are closely related (see Scheme 2). Anomerization of OH from equatorial to axial causes an upfield shift of -0.31 ppm and -0.21 ppm for the corresponding methyl glycoside on H-1'. Here, the basic value, i.e., the averaged value of the increment when no effects through space are operating, is ca. -0.15 ppm. In β-kojibiose, with an increment of +0.15 ppm for H-1' and +0.05 ppm for the corresponding methyl glycoside, OH-1 and H-1' are on the same side of the plane C-1'-O-n-C-n and OH-1' and H-1' are close together in space. We have outlined the features governing the increments of H-1' in Table 4.

With this information, the different increments for H-1' observed for methyl α- and β-sophoroside (see Scheme 3) can be rationalized. When φ and ψ are both positive (methyl β-sophoroside), and OH-3 is in a β equatorial position H-1' and OH-3 are on the same side of the plane of the glycosidic bond and are very close together in space. A positive value is expected and observed. When the signs of φ and ψ are different, as found for methyl α–sophoroside, OH-1 and OH-3 are far away from H-1', but H-1' and H-2 are *synaxial*. In such a case, an interaction between

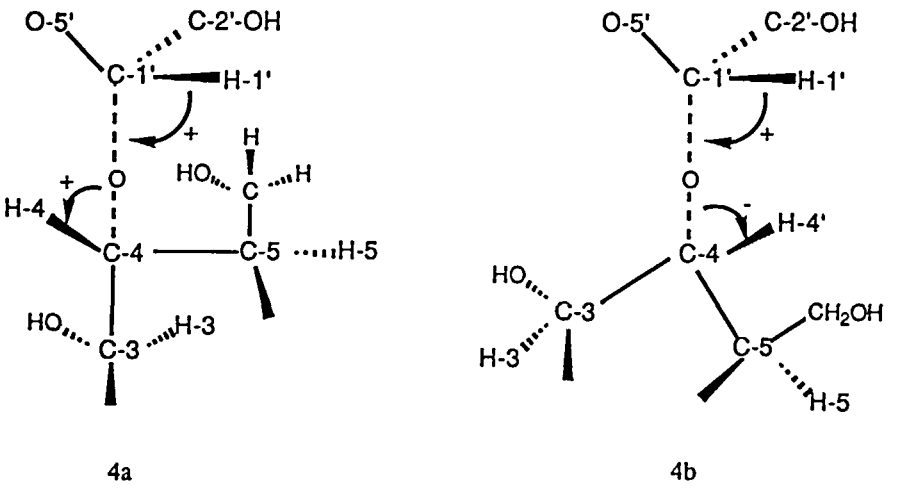
Table 4. Features Determining the Increment Value of H–1'

value	circumstances
(1) BV (basic value) = -0.15 ppm	both OH's on Cn±1 far away from H-1'
(2) BV + 0.10 ppm = slightly negative	(a) if H-1' and H-n are quasi-synaxial (b) H-1' and OH-(n±1) on different side of the plane of C-1'-O-C-n, but very close
(3) BV + 0.20/0.30 ppm = positive value	(a) OH on Cn±1 equatorial and close to H-1' (b) OH-(n±1) and H-1' on the same side of the C-1'-O-C-n plane and very close

H-1' and H-n is expected. Therefore, an upfield shift is predicted for H-1' with respect to the basic value, although the overall increment on H–1' remains slightly negative.

With this information, we can consider the conformation of the glycosidic bond in the cellobioses, where H-3 and H-5 both show increments of +0.12/+0.15 ppm and consequently no discrimination on the basis of the values of δH–(n±1) is possible.

Let us first consider the hypothetical situation where both φ and ψ are positive (see Scheme 4a). H-3 would undergo a basic γCO(ag)H increment and it would face OH-2' over a long distance (εOH(gaag)H). We would expect indeed a value of +0.12/+0.15 ppm. H–5 would have a basic $\gamma CO(g^+g^+)H$ increment, but would face OH-2' closely. A large increment value is expected, but not found. H-1' would be (taking into consideration the conformation around the C–5–C–6 bond) close to one of the protons of the hydroxymethylene



Scheme 4. Cellobiose

group, causing an upfield shift. From this set of three increments, the value observed for H–5 is not in agreement with the expected value.

When we considered the real situation[12] with φ positive and ψ negative (see Scheme 4b) both, the increments of H–3 and H–5 can be explained. Although H–1' and OH–3 (OH–3 is in a β equatorial position) are on different sides of the plane of the glycosidic bond, they are in close proximity to each other. H-1' and H-4 are in a *synaxial* relationship. For such an arrangement, a small upfield shift is seen for H-1'. Here the set of three increments (H-3, H-5 and H-1') agree with those expected.

Although the set values for H-1', H-(n+1) and H-(n-1) are useful to determine the conformation of the glycosidic bond in glucobioses, disaccharides with other configurations seem to offer even more diagnostic possibilities. Leucrose (α-D-glucopyranosyl-(1→5)–β-D-fructopyranose)[20] provides a good example. H-4 of the aglycon shows an increment of +0.02 ppm. H-4 has a γCO(ga)H or γCO(aa)H arrangement (dependent on the two possibilities for the sign of ψ). The value observed is 0.1 ppm to higher field than the basic values of the three γ increments encountered so far. In the

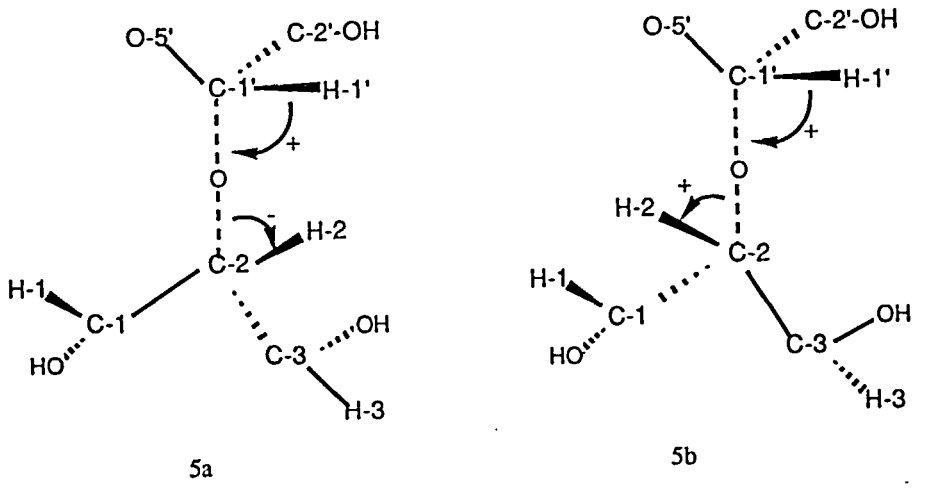
position β to the aglycon, there is a methylene function. To the best of our knowledge no HSEA calculations have been published either on such compounds or on the dialdopentopyranoses. The increments for the two protons of the methylene function may provide diagnostic information.

Notwithstanding the limits of the information gathered from the glucobioses, interesting applications are possible.

We will apply our findings to methyl α-L–fucopyranosyl (1→2)–α–D–glucopyranosde, and consider the two possibilities :

1) φ+ and ψ- (see Scheme 5a). H–1 shows a synaxial relationship with respect to the C-1'-O-n bond (γCO(g$^+$g$^-$)H) and closely faces O-5'. From the data for α-sophorose, we expect a value of +0.18/+0.22 ppm. However, in α-kojibiose, H–1 is far away from the hydroxymethylene group C-6', whereas in this case, H–1 is very close to the protons of C-6'. This latter conclusion takes into consideration the conformation of the C-5'-C-6' as deduced from the vicinal coupling constant $^3J_{5',6'}$. As pointed out by Kenne,[12] such an arrangement causes an upfield shift. H-3 has a basic γCO(ag)H increment. A small value is expected and +0.13 ppm was found. Since OH-1 and OH-3 are far away from H-1', a very negative value is expected for H-1' and -0.13 ppm was observed. Finally, H-5 is very close to H–1, a fact that must be reflected in a negative value. The value found was -0.10 ppm. All these observations agree with the experimental data.

2) φ+ and ψ+ (see Scheme 5b). H-2 is now *synaxial* with respect to the C-1'-O-5' bond, and consequently face O-5'. H-1 also points towards O-5' and undergoes a through space effect over a long distance δ(gag), and a basic γCO(ag)H effect. A small value is expected, found +0.09 ppm. H-3 has a basic γCO(g$^+$g$^+$)H increment and faces OH-2' over a long distance. Here also a small value is expected. OH-3 is β equatorial and very close to H-1' on the same side of the C-1'-O-C-n plane. We expected a large positive value, but observed a large negative value. H–5' is in this case far away from any group that can cause a through space effect. Certainly, a large negative increment (-0.10 ppm)



Scheme 5. Methyl α-L-fucopyranosyl (1→2) α-D-glucopyranoside

is not expected. These data are not in agreement with the experimental values.

Although the chemical shifts of H-(n±1) do not allow discrimination between the two possibilities in this case, the chemical shifts of H-1' and H-5' do. From this reasoning, it is clear that φ and ψ have a different sign. This conclusion was also reached by HSEA calculations.[11]

H–n of the aglycon

The increments of H-n are not found to be useful. They must be the result of a combination of four effects operating together. In contradiction to the β-effect operating on H–1', where because of the anomeric effect φ is ± 60, the β-effect operating on H–n is not so regular and may differ from case to case. The two γ-effects follow a different pathway (in one we encounter only carbons, in the other we have an oxygen at the end of the path) and can be different. Finally, sometimes effects through space may occur. There is no way to evaluate these four parameters separately.

CONCLUSION

In this article we have given an outline of how, by consideration of a combination of effects through bonds and through space, the ^{1}H NMR chemical shifts in a series of glucobioses and methyl glucobiosides yield generalizations related to the conformation of the glycosidic bond. These generalizations have been shown to be useful in predicting the conformations of other disaccharides. When the exo anomeric effect is assumed, it is possible to obtain the sign of the averaged torsion angle ψ. A qualitative estimate of its magnitude is not possible. This method seems to be promising for those disaccharides where the β-position in the aglycon is occupied by a methylene group.

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