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GLYCOSIDATION SHIFTS IN CARBON-13 NMR SPECTROSCOPY: CARBON-13 SIGNAL SHIFTS FROM AGLYCONE AND GLUCOSE TO GLUCOSIDE

Kazuo Tori,* Shujiro Seo, Yohko Yoshimura, Hitoshi Arita and Yutaka Tomita
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

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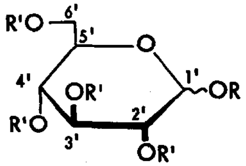
Lemieux and Koto[1] recently published a review on the conformational properties of glycosidic linkages, wherein ^{13}C chemical shifts around glycosidic linkages are shown to depend upon conformations thereabout by using some cyclohexyl glucosides. During our studies of structural determinations and ^{13}C FT NMR signal assignments of natural plant glycosides, we also found that ^{13}C signal shifts from aglycone and saccharide to glycoside, i.e., glycosidation shifts, are characteristic of chemical and steric environments of an OH group in which the glycosidation takes place, depending on the saccharide. This finding becomes important for determining the glycosidation position in an aglycone moiety and the kind(s) and sequence of sugar moiety in a natural glycoside without chemical degradation, because some glycosides are unstable against acid hydrolysis. We wish to report here a systematic study of the glycosidation shift using various α- and/or β-D-glucopyranosides (2-23) and their tetra-O-acetyl derivatives (2a-23a), which was prompted by a similar study by Tanaka and coworkers.[2]

^{13}C FT NMR spectra of various alcohols and their glucosides (2-23) were determined in pyridine-d_5, most natural glycosides being soluble in pyridine. The spectra of the alcohols and their acetates (2a-23a) were measured in $CDCl_3$. ^{13}C signals of the aglycone alcohols employed were already[3-6] or easily assigned by the usual procedure;[7] those of the methyl glucosides were known.[8] TABLE 1 lists the data obtained.

The glucosidation shifts were derived as $\Delta\delta_A = \delta(\text{R glucoside}) - \delta(\text{alcohol, RH})$ for aglycone moieties and $\Delta\delta_S = \delta(\text{R glucoside}) - \delta(\text{Me glucoside})$ for glucose moieties;[†] these values are also given in TABLE 1. The results with glucosidation shifts were examined and are summarized in TABLE 2. Simply speaking, the $\Delta\delta_S$(C-1') values change from -0.5—-1.5 via -2—-3 to -6—-8 ppm as the aglycones change from prim- via sec- to tert-alcohols, respectively. The $\Delta\delta_A$(C-α) and $\Delta\delta_A$(C-β) values are +6—+9 and -2—-5 (ca +0.5 for $\geqslant$C-) ppm, respectively. The $\Delta\delta_S$(C-2') and $\Delta\delta_A$(C-γ) values are small as -0.5—+0.5 ppm.

The data on 9, 9a, 23, and 23a (see TABLE 2) show that the steric hindrance between glucose and aglycone moieties markedly changes glucosidation shift values: in particular, the signals due to C-1' and C-α are strongly affected. In the



2-23 : R' = H
2a-23a: R' = Ac

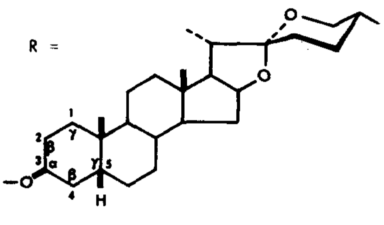
[†] We used methyl α- and β-D-glucosides as references to derive $\Delta\delta_S$ values. However, it may be better to use α- and β-D-glucoses for $\Delta\delta_S$ of free saponins. Therefore, we also include the data on glucoses in TABLE 1.

TABLE 1. ^{13}C Chemical Shifts of the Glucosides Examined[a] and Glucosidation Shifts, $\Delta\delta_S$ and $\Delta\delta_A$ in ppm[b]

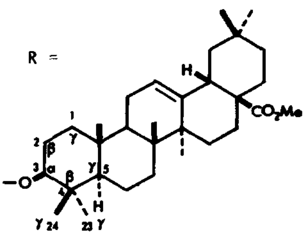
No.	R	Glc		Aglycone (in pyridine-d_5)			Glc		Aglycone (in CDCl$_3$)		
		$\delta_{C\text{-}1'}$ ($\Delta\delta_S$)	$\delta_{C\text{-}2'}$ ($\Delta\delta_S$)	$\delta_{C\text{-}\alpha}$ ($\Delta\delta_A$)	$\delta_{C\text{-}\beta}$ ($\Delta\delta_A$)	$\delta_{C\text{-}\gamma}$ ($\Delta\delta_A$)	$\delta_{C\text{-}1'}$ ($\Delta\delta_S$)	$\delta_{C\text{-}2'}$ ($\Delta\delta_S$)	$\delta_{C\text{-}\alpha}$ ($\Delta\delta_A$)	$\delta_{C\text{-}\beta}$ ($\Delta\delta_A$)	$\delta_{C\text{-}\gamma}$ ($\Delta\delta_A$)
		R α-D-Glucopyranosides					R Tetra-O-acetyl-α-D-glucopyranosides				
1	H	93.8 (-7.4)	74.0 (+0.3)	--			--		--		
2	Methyl	101.2 (0.0)	73.7 (0.0)	55.0 (+6.0)			97.1 (0.0)	71.7 (0.0)	55.5 (+5.5)		
3	n-Butyl	100.0 (-1.2)	73.6 (-0.1)	67.7 (+6.0)	31.9 (-3.9)	19.6 (0.0)	95.8 (-1.3)	71.1 (-0.6)	68.4 (+5.8)	31.4 (-3.5)	19.3 (+0.3)
4	iso-Propyl	98.3 (-2.9)	73.5 (-0.2)	69.7 (+6.5)	23.6 (-2.4) 21.6 (-4.4)		94.3 (-2.8)	71.1 (-0.6)	71.5 (+7.6)	23.1 (-2.2) 21.6 (-3.7)	
5	tert-Butyl	94.6 (-6.6)	73.6 (-0.1)	74.8 (+7.2)	28.9 (-2.9)		90.2 (-6.9)	71.2 (-0.5)	76.1 (+7.0)	28.3 (-2.9)	
6	p-Chloro-phenyl	99.7 (-1.5)	73.1 (-0.6)	156.8 (-1.0)	119.2 (+1.5)	129.6 (-0.1)	94.6 (-2.5)	70.4 (-1.3)	154.8 (+0.6)	118.2 (+1.3)	129.6 (0.0)
7	Cholesteryl[c]	98.6 (-2.6)	73.8 (+0.1)	78.2(C-3) (+7.1)	28.5(C-2) (-4.0) 40.8(C-4) (-2.5)	37.6(C-1) (-0.2) 141.5(C-5) (-0.4)	94.6 (-2.5)	71.5 (-0.2)	79.2(C-3) (+7.8)	28.2(C-2) (-3.4) 40.1(C-4) (-2.2)	37.3(C-1) (0.0) 140.7(C-5) (-0.1)
8	Smilagenin[d]	98.7 (-2.5)	73.9 (+0.2)	73.7(C-3) (+7.7)	24.9(C-2) (-3.7) 32.8(C-4) (-1.6)	31.2(C-1) (+0.6) 37.9(C-5) (+0.8)	93.8 (-3.3)	71.5 (-0.2)	73.5(C-3) (+6.5)	24.0(C-2) (-3.8) 32.0(C-4) (-1.6)	30.2(C-1) (+0.5) 37.4(C-5) (+0.8)
9	Methyl oleanolate[e]	97.4 (-3.8)	73.8 (+0.1)	84.6(C-3) (+8.5)	23.8(C-2) (-4.3) 40.1(C-4) (+0.4)	38.8(C-1) (-0.2) 56.3(C-5) (+0.5) 29.1(C-23) (+0.3) 17.0(C-24) (+0.5)	93.7 (-3.4)	71.6 (-0.1)	86.1(C-3) (+7.4)	23.8(C-2) (-3.3) 38.8(C-4) (+0.1)	38.5(C-1) (0.0) 56.0(C-5) (+0.8) 28.9(C-23) (+0.8) 16.5(C-24) (+0.9)
		R β-D-Glucopyranosides					R Tetra-O-acetyl-β-D-glucopyranosides				
10	H	98.4 (-7.0)	76.5 (+1.7)	--			--		--		
11	Methyl	105.4 (0.0)	74.8 (0.0)	56.7 (+7.7)			101.5 (0.0)	71.3 (0.0)	56.8 (+6.8)		
12	n-Butyl	104.5 (-0.9)	75.1 (+0.3)	69.4 (+7.7)	32.2 (-3.6)	19.4 (-0.2)	100.9 (-0.6)	71.4 (+0.1)	69.9 (+7.3)	31.4 (-3.5)	19.0 (0.0)
13	Benzyl	103.8 (-1.6)	75.1 (+0.3)	70.8 (+6.5)	138.8 (-4.8)	128.5 (+1.4)	99.3 (-2.2)	71.3 (0.0)	70.7 (+5.8)	136.7 (-4.2)	128.4 (+1.4)
14	iso-Propyl	102.4 (-3.0)	75.0 (+0.2)	70.8 (+7.6)	23.8 (-2.2) 22.0 (-4.0)		99.6 (-1.9)	71.6 (+0.3)	73.0 (+9.1)	23.3 (-2.0) 22.0 (-3.2)	
15	Cyclohexyl	102.4 (-3.0)	75.1 (+0.3)	76.5 (+7.1)	34.1 (-2.3) 32.2 (-4.2)	24.3 (-0.3) 24.1 (-0.5)	99.4 (-2.1)	71.6 (+0.3)	77.9 (+7.9)	33.2 (-2.4) 31.6 (-4.0)	23.6 (-0.9)
16	tert-Butyl	98.9 (-6.5)	75.2 (+0.4)	75.2 (+7.6)	29.0 (-2.8)		95.5 (-6.0)	71.6 (+0.3)	76.4 (+7.3)	28.4 (-2.8)	
17	Adamantan-1-yl	97.2 (-8.2)	75.1 (+0.3)	74.4 (+6.3)	43.0 (-3.2)	36.5 (-0.1)	94.0 (-7.5)	71.6 (+0.3)	75.5 (+8.7)	42.5 (-2.9)	36.3 (+0.1)
18	Phenyl	102.0 (-3.4)	74.8 (0.0)	158.6 (-0.1)	116.9 (+0.7)	129.8 (-0.2)	99.2 (-2.3)	71.3 (0.0)	156.9 (+2.1)	117.0 (+1.6)	129.6 (-0.1)
19	5α-Cholestan-3α-yl[f]	102.7 (-2.7)	75.1 (+0.3)	73.8(C-3) (+8.2)	26.0(C-2) (-3.8) 35.1(C-4) (-1.8)	33.1(C-1) (+0.2) 39.8(C-5) (+0.4)	99.3 (-2.2)	72.1 (+0.8)	74.6(C-3) (+8.0)	25.7(C-2) (-3.5) 34.5(C-4) (-2.3)	32.7(C-1) (+0.4) 39.5(C-5) (+0.2)
20	5α-Cholestan-3β-yl[f]	102.4 (-3.0)	75.2 (+0.4)	78.0(C-3) (+7.5)	30.1(C-2) (-2.3) 35.2(C-4) (-3.9)	37.5(C-1) (-0.1) 45.2(C-5) (-0.1)	99.6 (-1.9)	71.8 (+0.5)	79.7(C-3) (+8.6)	29.3(C-2) (-2.1) 34.7(C-4) (-3.4)	37.1(C-1) (0.0) 44.9(C-5) (-0.1)
21	Cholesteryl[c]	102.7 (-2.7)	75.2 (+0.4)	78.7(C-3) (+7.6)	30.4(C-2) (-2.1) 40.3(C-4) (-3.0)	37.8(C-1) (0.0) 141.4(C-5) (-0.5)	99.7 (-1.8)	71.8 (+0.5)	80.0(C-3) (+8.6)	29.5(C-2) (-2.1) 39.8(C-4) (-2.5)	37.3(C-1) (0.0) 140.4(C-5) (-0.4)

TABLE 1 (continued)

No.	R	Glc $\delta_{C\text{-}1'}$ ($\Delta\delta_S$)	Glc $\delta_{C\text{-}2'}$ ($\Delta\delta_S$)	Aglycone (in pyridine-d_5) $\delta_{C\text{-}\alpha}$ ($\Delta\delta_A$)	Aglycone (in pyridine-d_5) $\delta_{C\text{-}\beta}$ ($\Delta\delta_A$)	Aglycone (in pyridine-d_5) $\delta_{C\text{-}\gamma}$ ($\Delta\delta_A$)	Glc $\delta_{C\text{-}1'}$ ($\Delta\delta_S$)	Glc $\delta_{C\text{-}2'}$ ($\Delta\delta_S$)	Aglycone (in $CDCl_3$) $\delta_{C\text{-}\alpha}$ ($\Delta\delta_A$)	Aglycone (in $CDCl_3$) $\delta_{C\text{-}\beta}$ ($\Delta\delta_A$)	Aglycone (in $CDCl_3$) $\delta_{C\text{-}\gamma}$ ($\Delta\delta_A$)
22	Smilagenin[d]	103.1 (-2.3)	75.2 (+0.4)	74.7(C-3) (+8.7)	27.1(C-2) (-1.5) 31.0(C-4) (-3.4)	31.0(C-1) (+0.4) 37.2(C-5) (+0.2)	98.6 (-2.9)	71.5 (+0.2)	74.3(C-3) (+7.3)	26.6(C-2) (-1.2) 30.3(C-4) (-3.3)	29.8(C-1) (-0.1) 36.8(C-5) (+0.2)
23	Methyl oleanolate[e]	106.3 (+0.9)	75.6 (+0.8)	89.1(C-3) (+11.0)	26.5(C-2) (-1.6) 40.0(C-4) (+0.3)	39.0(C-1) (0.0) 56.2(C-5) (+0.4) 28.4(C-23) (-0.4) 17.3(C-24) (+0.8)	102.9 (+1.4)	71.8 (+0.9)	90.5(C-3) (+11.8)	25.9(C-2) (-1.2) 39.0(C-4) (+0.3)	38.7(C-1) (+0.2) 55.9(C-5) (+0.7) 27.9(C-23) (-0.2) 16.4(C-24) (+0.8)



8(α-Glc) ; 22(β-Glc)



9(α-Glc) ; 23(β-Glc)

[a] ^{13}C NMR spectra were measured on a Varian NV-14 FT NMR spectrometer at 15.087 MHz in pyridine-d_5 (1-6, 10-18 at 30°; 7-9, 19-23 at 100°) or $CDCl_3$ (1a-6a, 10a-18a at 30°; 7a-9a, 19a-23a at 80°) with TMS as an internal standard (δ_C 0) in 8-mm spinning tubes; concentrations were about 0.1-0.5 mmol/cm^3. FT measurement conditions were: spectral width, 3923 Hz; pulse flipping angle, 15-20°; acquisition time, 0.6 sec; number of data points, 4820. Glucosides 3-9, 3a-9a, 12-23, and 12a-23a were synthesized by the Koenigs—Knorr method; 8: mp. >300°, $[\alpha]_D^{24}$ +34.0° (c = 1.0 in pyridine); 8a: mp. 193°, $[\alpha]_D^{25}$ +44.8° (c = 0.8 in $CHCl_3$); 17: mp. 223-224°, $[\alpha]_D^{24.5}$ -26.2° (c = 1.0 in pyridine); 17a: mp. 157-158°, $[\alpha]_D^{23}$ -7.1° (c = 1.1 in $CHCl_3$); 22: mp. 243-244°, $[\alpha]_D^{23.5}$ -52.7° (c = 0.6 in pyridine); 22a: mp. 218°, $[\alpha]_D^{22.5}$ -53.7° (c = 1.0 in $CHCl_3$). [b] For definition, see text; the plus sign denotes a downfield shift. [c,d,e,f] For signal assignments of these aglycone alcohols, see refs 3-6, respectively.

glucosides, conformations around $\begin{matrix}-O\\-C(2')\end{matrix}\!>\!C(1')\text{-}O\text{-}C\!<\!\begin{matrix}CH_2(\beta)\text{-}\\CH_2(\beta')\text{-}\end{matrix}$ should be stable on an average, when the glucose C(1')-H and the sec-carbinyl C-H are syn to each other (see footnote d in TABLE 2). Thus, a substituent(s) on the CH_2(β or β') anti to the C(2') moiety (anti-substitution) shields C-1', whereas that on CH_2(β or β') syn to C(2') (syn-substitution) strongly deshields C-1' and also C-α, as suggested earlier.[1] It should also be noted that $\Delta\delta_S$(C-1') values for tert-alcohol glucosides are largely negative, as already pointed out.[2,9] However, the differences in $\Delta\delta_S$(C-1') and $\Delta\delta_A$(C-α) between 16 and 17 cannot be immediately explained.

Interestingly, the difference in $\Delta\delta_A$(C-β) values between the two β-CH_2 signals (about -2 and -4 ppm) always appears for sec-alcohol glucosides. In view of the glucoside conformation, the β- or β'-CH_2 syn to C(2') moiety can be concluded to have a larger $\Delta\delta_A$(C-β) value of about -4 ppm (see footnote d in TABLE 2), as suggested earlier.[1]

Marked exceptions of this rule are glucosides of phenol derivatives, as expected from literature data.[10] In this case, $\Delta\delta_S$(C-1') values are about -1.5 (α-Glc), -3 (β-Glc), and -2.5 (acetates) ppm, but $\Delta\delta_A$ values seem to depend on the aglycone structures.

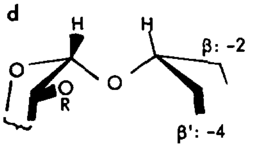
The present results should be useful for determining structures as well as assigning ^{13}C signals of natural glycosides. However, as pointed out earlier, glycosidation shifts also depend on the kind(s) of saccharides,

TABLE 2. Aspects of Glucosidation Shifts, $\Delta\delta_S$ and $\Delta\delta_A$ in ppm

		R Glucosides (in pyridine-d_5)			R Tetra-O-acetylglucosides (in $CDCl_3$)		
		$-CH_2OH$	>CHOH	≽COH	$-CH_2OH$	>CHOH	≽COH
$\Delta\delta_S$(C-1')	α-Glc steric(anti)^{a}	∼-1	-2.5 – -3^{c} increased upfield (3.8 in 9)	∼-6.5	∼-1.5	-2.5 – -3.5^{b} increased upfield (-3.4 in 9a)	∼-7
	β-Glc steric(syn)^{a}	-1 – -1.5	-2 – -3^{c} increased downfield (+0.9 in 23)	-6.5 – -8	∼-0.5	-2 – -3^{b} increased downfield (+1.4 in 23a)	-6 – -7.5
$\Delta\delta_S$(C-2')	α-Glc	∼0	∼0	∼0	∼-0.5	0.0 – -0.5	∼-0.5
	β-Glc steric(syn)^{a}	0 – +0.5	0 – +0.5 (+0.8 in 23)	0 – +0.5	∼0	0 – +0.5 (+0.9 in 23a)	∼+0.5
$\Delta\delta_A$(C-α)	α-Glc steric(anti)^{a}	∼+6	+6.5 – +8^{b} (+8.5 in 9)	∼+7	∼+6	+6.5 – +9^{c}	∼+7
	β-Glc steric(syn)^{a}	∼+8	+7 – +9^{b} increased downfield (+11.0 in 23)	+6.5 – +7.5	+6 – +7	+7 – +9^{c} increased downfield (+11.8 in 23a)	+7 – +9
$\Delta\delta_A$(C-β)	α- & β-Glc	-3.5 – -5	-2 – -5^{d} (+0.4)^{e}	∼-3^{f}	-3.5 – -4	-2 – -4^{d} (+0.3)^{e}	∼-3^{f}
$\Delta\delta_A$(C-γ)	α- & β-Glc steric^{a}	∼0	-0.5 – +0.5 (+0.8 in 8, 23)	∼0	∼0	-0.5 – +0.5 (+0.8 in 8a, 9a, 23a)	∼0

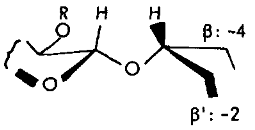
[a] In the presence of steric hindrance between glucose and aglycone (anti- or syn-substitution effect). [b] Larger in magnitude for an axial OH than for an equatorial OH. [c] Smaller in magnitude for an axial OH than for an equatorial OH.

[d]

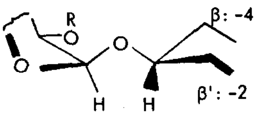


R = H, Ac

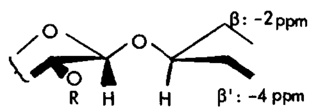
Predicted (α-Glc)



19, 19a (β-Glc)



7, 7a, 8, 8a (α-Glc)



20-22, 20a-22a (β-Glc)

[e] Values for quat-C. See ref 2 for values and discussion of methine-β-C. [f] For asymmetrical aglycones, see ref 2.

and thus more data should be accumulated before proposing a general rule.

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