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Effect of a phosphorus atom upon vicinal ^{1}H–^{1}H coupling constants in pyranose derivatives having a C–P bond: Additivity rule for the effect of phosphorus substituents

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Abstract

Additivity constants for phosphorus were estimated for the prediction of vicinal ^{1}H–^{1}H coupling constants by means of an additivity rule in a series of pyranose analogs having phosphorus as the ring heteroatom. The experimental J values were well reproduced by employing the proposed additivity constants with a small overall root-mean-square difference of 0.32 Hz. The prediction of coupling constants was employed for the investigation of conformational equilibria of pyranose analogs having a phosphinyl group in the ring or on the ring-carbon.

Keywords: Phosphosugar; Pyranose analogs having a C–P bond; Vicinal coupling constants; Additivity rule for substituents

1. Introduction

We have prepared various sugar analogs in which the hemiacetal ring-oxygen is replaced by phosphorus (‘phosphosugars’) [1] [1,2]. Representative 5-deoxy-5-phosphinylpyranoses are analogs of D-xylo- [3–6], D-gluco- [6–10], D-manno- [11,12], or 6-deoxy-L-galactopyranoses [13,14]. These sugars are of interest in view of their structural and physical properties as well as their biological activity.

Introduction of a phosphinyl group causes a considerable change in the vicinal coupling constants between α and β protons. For example, when the hemiacetal ring-oxygen of β-D-glucopyranose is replaced by phosphorus, the magnitudes of $J_{1,2}$ and $J_{4,5}$ increase by 3.0 and 2.0 Hz, respectively [6–10].

Altona and Haasnoot [15] have reported that the prediction of vicinal coupling constants in pyranose chair conformations can be made by means of a simple additivity rule. They investigated the effect of the relative orientation and electronegativity [16] of substituents on the magnitude of ^{3}J(aa), ^{3}J(ae), and ^{3}J(ee), and estimated additivity constants ΔJ(X) for substituents X (see Table 1).

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[1] Sugar analogs, in which the ring oxygen is replaced by C, N, or S, are correctly termed carba, imino, or thio sugars, respectively, by the 1996 IUPAC–IUBMB recommendations. The term phosphosugar was used in this paper for sugar analogs having phosphorus, instead of oxygen, in the ring.

Table 1
Additivity constants $\Delta J(X)$ (Hz) for a substituent X

X	Vicinal *gauche* coupling[a]		Vicinal *anti* coupling[b,c]	
	$\Delta J(anti)(X)$	$\Delta J(gauche)(X)$	$J(gauche)(X)$	Ref.
H,C	0.0	0.0	0.0	[10]
N	-1.1	$+0.3$	-0.65	[10]
O	-1.8	$+0.5$	-1.45[d]	[10]
P	$+0.4$	-0.4	$+0.55$[e,f] $+1.5$[g]	present work

[a] The reference value: $J^0(\mathrm{ae}) = 4.4$, $J^0(\mathrm{ee}) = 2.6$ Hz.
[b] $J^0(\mathrm{aa}) = 12.2$ (in CHCH fragments), 12.9 Hz (in $\mathrm{CHCH_2}$ fragments).
[c] An increment of 0.5 Hz is added for each β-interaction.
[d] An increment of 0.4 Hz is added for β-interaction of *anti* 6-oxygen.
[e] An increment of 0.25 Hz is added for β-interaction of *anti* 6-oxygen.
[f] In the case of absence of oxygen on the α-carbon of phosphorus.
[g] In the case of presence of oxygen on the α-carbon of phosphorus.

Thus, ^3J values are calculated by use of the following equation:

$$^3J = {}^3J^0 + \sum_{1}^{4} \Delta J(X)$$

where $^3J^0$ represents the reference value [$J^0(\mathrm{ae}) = 4.4$, $J^0(\mathrm{ee}) = 2.6$, and $J^0(\mathrm{aa}) = 12.2$ Hz] [15]. For example, the following equation is employed for the $J_{1,2}$ value (Hz) of α-D-glucopyranose derivatives:

$$\begin{aligned} J_{1,2} &= J^0(\mathrm{ae}) + \Delta J(gauche)(O) + \Delta J(anti)(C) \\ &\quad + \Delta J(gauche)(O) + \Delta J(anti)(O) \\ &= 4.4 + 0.5 + 0 + 0.5 - 1.8 = 3.6 \end{aligned}$$

The calculated value agrees well with the observed value [15,17].

This additivity rule appears to be quite reliable for the prediction of vicinal coupling constants of pyranoses in their chair forms. Although a number of additivity constants were reported for pyranoses having heteroatom substituents (X = O, N, S, halogens), no such constants seem, to the best of our knowledge, to have been systematically estimated for phosphorus. We have attempted herein to estimate additivity constants for phosphorus by the use of $J_{1,2}$ and $J_{4,5}$ values for pyranose-sugar analogs having phosphorus as the heteroatom in order to evaluate the substituent effect of phosphorus.

2. Results and discussion

The materials adopted for our data collection are shown in Fig. 1: α,β-D-xylo- (**1**) [3–6], α,β-D-gluco- (**2**) [6–10,18], α,β-L-ido- (**3**) [18,19], [2] β-D-manno- (**4**) [11,12], β-L-gulo- (**5**) [11], α,β-D-altro- (**6**) [13], α,β-L-galacto- (**7**) [13,14], α-D-fructo- (**8a**) [20], β-D-fructopyranose (**8b**) [20] analogs. All of these compounds exist in a pure conformational state (approximately 100% $^4C_1$ or $^1C_4$). Some such sugars, which exist as a conformational mixture, were not used (for instance, an α-D-mannopyranose analog [11,12]). Although compound classes **1** and **2** bear various types of ring-phosphorus (namely, phosphine oxide, phosphinate, phosphine sulfide, and phosphine), the mean values of $J_{1,2}$ and $J_{4,5}$ for each compound class show no significant differences. In addition, the difference in the configuration of the ring-phosphorus atom is negligible.

From pyranose analogs **1–8**, we collected a total of 219 different values of coupling constants $J_{1,2}$ and $J_{4,5}$ ($J_{5,6}$ for **8a,b**) obtained by 500- or 400- MHz ^{1}H NMR spectroscopy. These data were then classified into three groups, as illustrated in Fig. 2: **a**, axial–equatorial couplings with *anti P* (23 couplings); **b**, axial–equatorial couplings with *gauche P* (92 couplings); and **c**, axial–axial couplings with *gauche P* (104 couplings). This was made to estimate the additivity constants $\Delta J(anti)(P)$ and $\Delta J(gauche)(P)$ for *gauche* couplings, and $\Delta J(gauche)(P)$ for *anti* couplings. The reference values J^0 and the additivity

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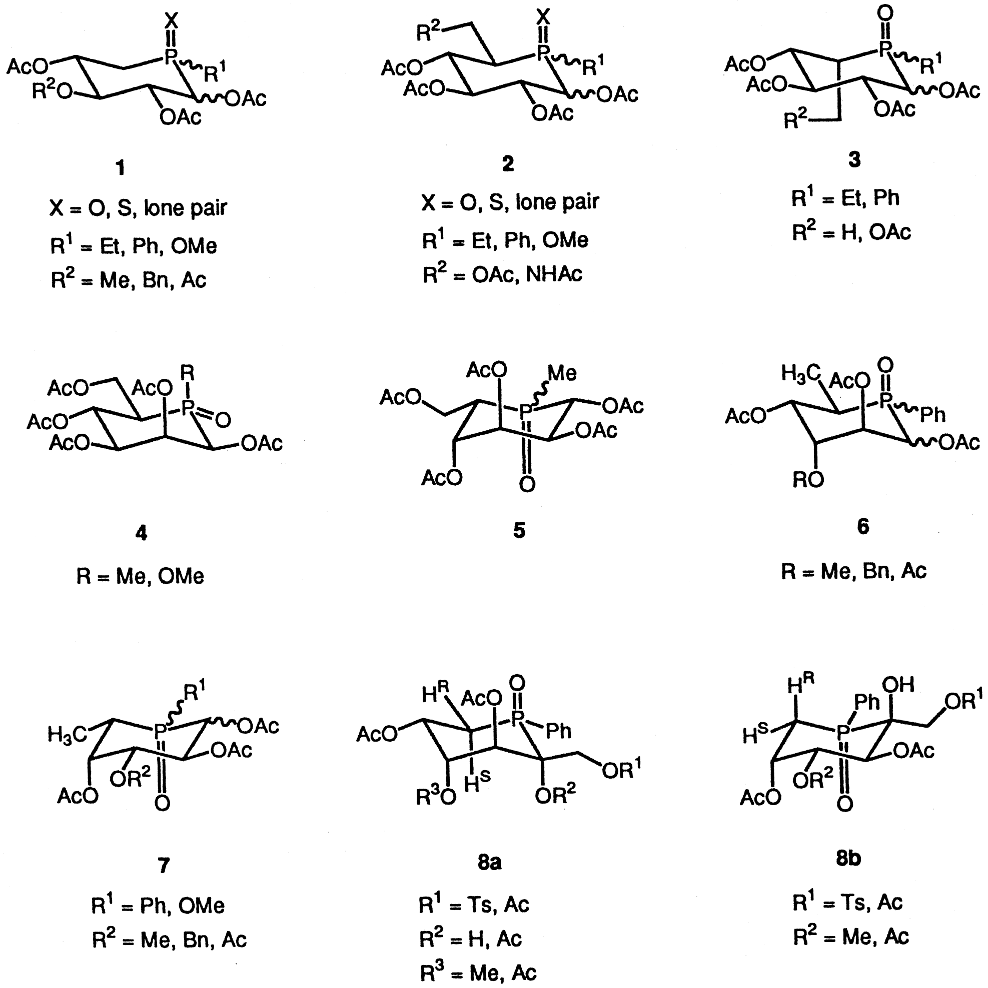
[2] ^{1}H NMR data for 1,2,3-,4-tetra-*O*-acetyl-5,6-dideoxy-5-[(*RS*)-methoxyphosphinyl]α,β-L-idopyranoses: (*R*)-*P*-α-isomer, $J_{1,2} = 10.9$, $J_{4,5} = 4.6$ Hz; (*R*)-*P*-β isomer, $J_{1,2} = 3.2$, $J_{4,5} = 5.1$ Hz; (*S*)-*P*-α-isomer, $J_{1,2} = 10.7$, $J_{4,5} = 4.9$ Hz; (*S*)-*P*-β-isomer, $J_{1,2} = 3.1$, $J_{4,5} = 5.2$ Hz; T. Hanaya and H. Yamamoto, unpublished results.



1

X = O, S, lone pair

R^1 = Et, Ph, OMe

R^2 = Me, Bn, Ac

2

X = O, S, lone pair

R^1 = Et, Ph, OMe

R^2 = OAc, NHAc

3

R^1 = Et, Ph

R^2 = H, OAc

4

R = Me, OMe

5

6

R = Me, Bn, Ac

7

R^1 = Ph, OMe

R^2 = Me, Bn, Ac

8a

R^1 = Ts, Ac

R^2 = H, Ac

R^3 = Me, Ac

8b

R^1 = Ts, Ac

R^2 = Me, Ac

Fig. 1. Phosphosugars adopted for data collection.

constants reported by Altona and Haasnoot [15] were employed for our calculation.

The β-effect [15,16] [an increase of 0.5 Hz for J(aa)] was taken into account in some cases: namely, $J_{1,2}$ for **5**, $J_{4,5}$ for **6**, and $J_{5,6S}$ values for **8a** (see Fig. 3a,b). The $J_{4,5}$ values for compounds **2** and **4** were expected to be influenced by the orientation of the 6-O group, as in the case of normal pyranoses [15], which normally exist as a mixture of the side-chain (C-5–C-6) rotamers [21,22]. The ratio of *anti* H–C-5–C-6–O rotamer (*gg*) was estimated by the following equations which are modified from those reported earlier (for example, see refs. [21,22]) using our results:

$$2.2\,gg + 5.3\,gt + 12.0\,tg = J_{5,6S}$$

$$3.0\,gg + 12.0\,gt + 4.5\,tg = J_{5,6R}$$

$$gg + gt + tg = 1$$

Thus the rotamer with the *anti* H–C-5–C-6–O conformation (**c**) was shown to exist to the extent of ~ 30–70% of the rotamer population. For the pur-

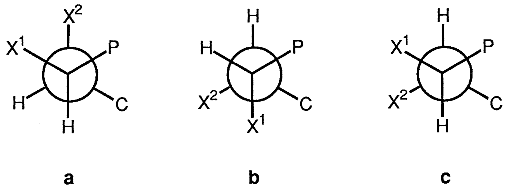


Fig. 2. Three orientations of vicinal protons (Newman projection along the C-1–C-2 or C-5–C-4 bond: X = O, C, H, and other substituents).

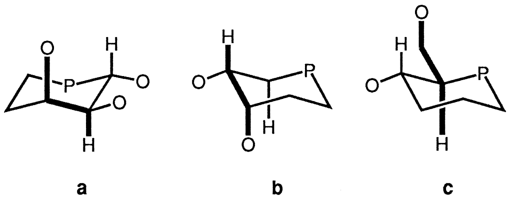


Fig. 3. Some cases where a β-effect is present.

Table 2
Observed and calculated coupling constants (Hz) in phosphopyranose systems[a]

Compd class	Anomer	$J_{1,2}$		$J_{4,5a}$		$J_{4,5e}$	
		Experimental	Calculated	Experimental	Calculated	Experimental	Calculated
1	α-D-xylo (18)	2.75	2.7	11.85	12.0	4.3	4.5
1	β-D-xylo (18)	10.75	10.8	11.95	12.0	4.3	4.5
2	α-D-gluco (8)	2.6	2.7	11.65	11.55	–	–
2	β-D-gluco (8)	10.8	10.8	11.6	11.55	–	–
3	α-L-ido (6)	10.75	10.8	–	–	4.95	4.5
3	β-L-ido (6)	3.1	2.7	–	–	4.8	4.5
4	β-D-manno (2)	3.45	3.5	11.4	11.55	–	–
5	β-L-gulo (2)	11.55	11.3	–	–	3.35	3.0
6	α-D-altro (3)	3.6[b]	4.0	12.0	11.8	–	–
6	β-D-altro (3)	3.5	3.5	12.1	11.8	–	–
7	α-L-galacto (7)	2.9	2.7	–	–	2.9	3.0
7	β-L-galacto (5)	10.9	10.8	–	–	2.8	3.0
8a	α-D-fructo (5)	–	–	12.65[c]	12.5	4.1[d]	4.5
8b	β-D-fructo (4)	–	–	4.4[b,c]	3.5	3.3[d]	3.0

[a] Experimental values signify the mean values for the observed coupling constants, of which the numbers are shown in parenthesis.

[b] Not used in the calculation of $\Delta J(P)$ values and the statistical evaluation of $J(\mathrm{obs}) - J(\mathrm{calc})$.

[c] $J_{5,6S}$.

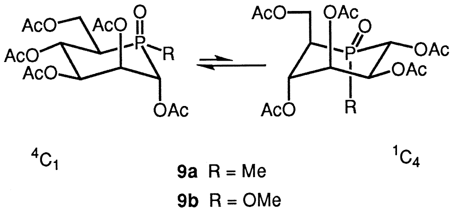
[d] $J_{5,6R}$.

pose of simplifying the present additivity rule, we adopted the mean population value (50%). The β-effect of the 6-O group of phosphosugars was then estimated to be a 0.25 Hz increase (as compared with a 0.4 Hz increase for normal pyranoses [15,16]).

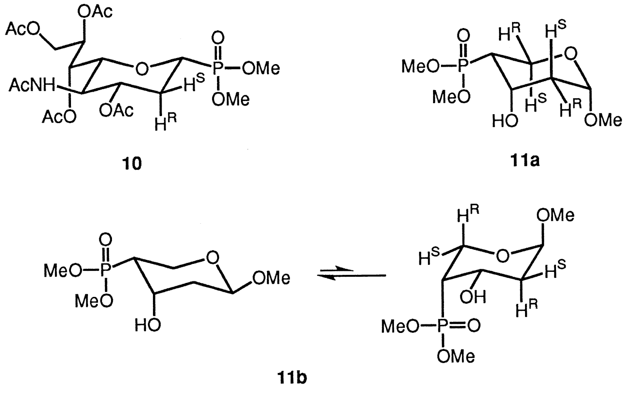
The additivity constants $\Delta J(anti)(P)$ and $\Delta J(gauche)(P)$ for *gauche* couplings derived from $J_{1,2}$ values were found to be almost the same as the respective constants deduced from $J_{4,5}$ values. On adopting the mean of both values, $\Delta J(anti)(P)$ and $\Delta J(gauche)(P)$ values were estimated to be +0.4 Hz and −0.4 Hz, respectively, for *gauche* couplings, whereas in the case of $\Delta J(gauche)(P)$ for *anti* couplings the additivity constant (+1.5 Hz) deduced from $J_{1,2}$ values turned out to differ appreciably from that (+0.55 Hz) obtained from $J_{4,5}$ values (Table 1). Therefore, the last two values have to be employed separately in the following situations: $\Delta J(gauche)(P) = +1.5$ [in the case where an oxygen atom exists at the geminal position of phosphorus, **c** ($X^1 = O$), in Scheme 2] and +0.55 (in other cases).

It should be noted that the signs of $\Delta J(P)$ are opposite to those of the other series (X = N, O) (see Table 1). It is well established that oxygen and nitrogen are more electronegative than carbon, whereas phosphorus is more electropositive than carbon [23–25]. This indicates that phosphorus substituents are expected to exert an opposite effect on vicinal coupling constants in comparison with other substituents: then, *gauche* phosphorus increases the magnitude of *anti* vicinal coupling, while the corresponding oxygen analog decreases it.

The observed and calculated coupling constants ($J_{1,2}$ and $J_{4,5}$) for phosphopyranoses **1–8** are listed in



Scheme 1.



Scheme 2.

Table 3
Observed and calculated coupling constants (Hz) of phospho-α-D-mannopyranoses (**9a,b**)

Compound and conformation	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
9a,b calculated for $^4C_1$ form	4.0	3.1	9.8	11.55
9a,b calculated for $^1C_4$ form	11.3	3.1	3.6	3.5
9a[a] observed	6.8	2.8	8.5	9.2
calculated for a 69:31 mixture	6.3	3.1	7.9	9.05
9b[b] observed	6.4	2.8	8.6	9.9
calculated for a 76:24 mixture	5.75	3.1	8.3	9.6

[a] Ref. [11].
[b] Ref. [12].

Table 2. J(ee) values (7 samples) were eliminated from the statistical treatment because they showed an irregular discrepancy and could not be used in the calculation of $\Delta J(anti)(P)$. Such a discrepancy appears to arise from local variations in the geometry of the pyranose ring and is related to variations in the substitution pattern. The X-ray crystallographic analyses on some phosphopyranoses [7,26–29] have confirmed such local distortions which may be ascribed to characteristic torsion angles and bond lengths around a phosphorus atom in comparison with those of normal pyranoses.

For statistical evaluation, we calculated the root-mean-square (rms) differences of ΔJ [$=J$(obs) $-$ J(calc)] for 219 couplings. The rms differences were considerably constant over the various subsets: ΔJ(ae) for $J_{1,2}$ (44 couplings), 0.27 Hz; ΔJ(ae) for $J_{4,5}$ (and $J_{5,6}$) (71 couplings), 0.39 Hz; ΔJ(aa) for $J_{1,2}$ (39 couplings), 0.20 Hz; ΔJ(aa) for $J_{4,5}$ (and $J_{5,6}$) (65 couplings), 0.33 Hz. Furthermore, the overall rms difference for 219 couplings was only 0.32 Hz. Therefore these data indicate that the additivity rule for pyranose rings is also retained even when the ring oxygen is replaced with a phosphorus atom.

As an application of the present additivity rule, we estimated conformational purity of phosphosugars of the α-D-mannopyranose type (**9a,b**), which are considered to exist as mixtures of the $^4C_1$ and $^1C_4$ conformers [11,12] (Scheme 1). On the basis of the calculated coupling constants for the $^4C_1$ and $^1C_4$ conformers of **9a** and **9b**, the best-fitting populations of each conformer were respectively estimated to be 69:31 for **9a** and 76:24 for **9b** (see Table 3).

Furthermore, we also attempted to apply our results to a conformational study for compounds having a phosphinyl substituent on a ring-carbon. The 1-phosphinyl-octopyranose derivative (**10**) [30] was expected to be in the $^1C_4$ conformation, whereas 4-phosphinyl-α- and β-D-pentopyranosides (**11a,b**) [31] were expected to adopt the $^4C_1$ conformations (Scheme 2). Reinvestigation of the conformational populations of these compounds by employing the present additivity rule confirmed that **10** and **11a** exist in the pure $^1C_4$ and $^4C_1$ forms, respectively. However, **11b** was estimated to exist as a conformational mixture of 81% $^4C_1$ and 19% $^1C_4$ forms (Table 4).

In conclusion, the present additivity rule has been proved highly reliable also for pyranoses having a phosphinyl group in (or on) the ring when the newly established additivity constants for phosphorus are employed. Application of this rule to other types of phosphorus-containing sugars is under investigation.

3. Experimental

The ^{1}H NMR spectra for all compounds (except for **10** [30]) were recorded, for solutions in $CDCl_3$, using a Varian VXR-500 instrument (500 MHz, the SC-NMR Lab., Okayama Univ.) with a spectral width

Table 4
Observed and calculated coupling constants (Hz) for the 1- and 4-phosphinylpyranose derivatives (**10, 11a,b**)

Compound and conformation	$J_{1,2R}$	$J_{1,2S}$	$J_{2R,3}$	$J_{2S,3}$	$J_{3,4}$	$J_{4,5R}$	$J_{4,5S}$
10[a] observed	12.8	2.0	11.2	4.8	10.1	10.4[b]	
calculated for $^1C_4$	12.95	2.2	11.45	4.9	10.1	10.5[b]	
11a[c] observed	1.4	3.5	3.0	3.5	2.3	4.6	12.0
calculated for $^4C_1$	1.3	3.1	3.1	2.6	2.2	4.5	11.95
11b[c] observed	2.5	8.2	4.8	2.8	2.8	4.4	10.0
calculated for $^4C_1$	3.1	10.0	3.1	2.6	2.2	4.5	11.95
calculated for $^1C_4$	1.3	3.1	11.95	4.9	5.3	3.0	0.4
calculated for a 81:19 mixture	2.75	8.7	4.8	3.0	2.8	4.2	9.75

[a] Ref. [30].
[b] $J_{4,5}$.
[c] Ref. [31].

of 8000 Hz (normally 32 scans in 51,200 data points) at 21–23 °C. The experimental errors in the coupling constants are within 0.05 Hz.

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