

# Coupling Constants between Cisoidal Protons in Pentose Nucleosides. Limitations of Range of Application of Karplus Relation, and Solution Conformations of $\beta$ -Arabinofuranosyl and $\beta$ -Xylofuranosyl Nucleosides

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**Abstract:** The finite perturbation theory INDO SCF MO method has been employed to demonstrate that the Karplus relation is not unique for cisoidal proton-proton vicinal coupling constants in the pentose rings of nucleosides. The factors responsible for this were elucidated with the aid of the procedure of Barfield et al. as applied by Marshall et al. to norbornanes. Two model ring systems, cyclopentane and oxolane, were utilized for this purpose. Calculations for  $\beta$ -arabinofuranosyl nucleosides provided an interpretation for the large differences in the values of the experimental cisoidal coupling constants for the states N and S. For  $\beta$ -xylofuranosyl nucleosides the theoretical results led to formulation of the conformational state of these compounds as C(3')endo-C(4')exo.

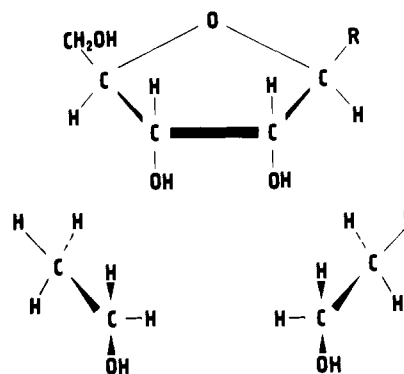
Considerable effort, both experimental and theoretical, is currently being devoted to elucidation of the solution conformation of nucleosides and nucleotides, as well as nucleotide coenzymes, and a variety of their analogues, many of which are of considerable biological significance, frequently as antimetabolites. An important element in the determination of the conformational parameters of such compounds is the sugar pentose ring, for which the appropriate parameters may be deduced with the aid of  $^1\text{H}$  NMR spectroscopy, using the Karplus relation<sup>2,3</sup> which links proton-proton vicinal coupling constants to the dihedral angles between these protons. It is also now generally accepted that, in solution, there is an equilibrium between two extreme conformational states of the pentose ring, viz., N (C(2')endo) and S (C(3')endo), the experimentally determined coupling constants being regarded as the time-average weighted means of the coupling constants for these two states.

Application to the conformation of the pentose ring of the concept of pseudorotation<sup>4,5</sup> has considerably simplified the description of the ring conformation. However, the procedure of Altona and Sundaralingam<sup>5</sup> for establishment of the pseudorotational parameters, and the conformer populations, is based on several assumptions of questionable validity, as formulated elsewhere.<sup>6</sup>

The uniqueness of the Karplus relation, which is of key importance in conformational studies, is considered in the present investigation. This relation was originally derived theoretically for the ethane molecule,<sup>2</sup> and its application to the conformation of sugar rings (including those of nucleosides) requires partition of the ring into several ethane-like fragments (see Scheme I), involving the inherent assumption that the influence of the remaining portions of the ring system is independent of the conformation.

Attention has already been directed to the absence of an accurate correlation between the dihedral angle and the corresponding vicinal coupling constant,<sup>7</sup> particularly marked for cisoidal couplings in nucleosides other than most frequently investigated ribosides (i.e., arabino, xylo, lyxo, and deoxy nucleosides). The purpose of the present study was to examine the uniqueness of the Karplus relation in such nucleosides, limiting ourselves to couplings between protons cis to each other. It will now be shown that available experimental data, and theoretical calculations, for the pentose rings of nucleosides

Scheme I



demonstrate the absence of a simple relationship between dihedral angles and cisoidal coupling constants. Furthermore, the effects of the errors, resulting from the poorly known orientation of the protons, are smaller for cis, relative to trans, protons.

As regards couplings between transoidal protons, our theoretical calculations contribute nothing new, in that in such instances they merely confirm the uniqueness of the Karplus relation, while the selection of experimental values for the parameters in the Karplus relation was found to furnish better results than the direct application of numerically calculated values.

## Methods

Calculations of coupling constants were based on the formulation of finite perturbation theory (FPT)<sup>8</sup> in the intermediate neglect of differential overlap (INDO)<sup>9</sup> approximation of self-consistent field (SCF) molecular orbital (MO) theory. Because of the difficulties involved in the delineation of the individual factors which influence the values of the coupling constants, the approach adopted was that of Barfield et al.,<sup>10</sup> which should be consulted for details. This procedure has proven quite successful in studies on long-range  $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ - $^{19}\text{F}$  coupling constants.<sup>10,11</sup> Its application to norbornanes<sup>12</sup> led to elucidation of the factors responsible for the nonequivalence of the exo-exo and endo-endo vicinal coupling constants and, in addition, gave results for cisoidal coupling constants in fairly good agreement with experimentally mea-

**Table I.** Calculated Cisoidal Coupling Constants  $^3J(1,2)$  for the Exo Protons of Oxolane and Cyclopentane

Conformation and phase angle of pseudorotation	$\theta,^a$ deg	$\phi,^b$ deg	Type of calculation <sup>c</sup>	Coupling constants, Hz		Conformation and phase angle of pseudorotation	$\theta,^a$ deg	$\phi,^b$ deg	Type of calculation <sup>c</sup>	Coupling constants, Hz	
				Oxolane	Cyclopentane					Oxolane	Cyclopentane
C(3)endo 18°	95	-24	U	9.02	9.92	C(3)exo 198	142	22	U	6.45	8.77
			M	9.20	10.10				M	8.32	10.89
C(4)exo 54°	118	-1	U	10.53	12.31	C(4)endo 234°	120	0	U	8.58	10.61
			M	11.01	12.77				M	11.60	13.68
O(1)endo 90°	141	23	U	8.16	9.92	O(1)exo 270°	97	-22	U	8.03	8.77
			M	8.31	10.10				M	10.26	10.89
C(1)exo 126°	155	37	U	5.26	6.81	C(1)endo 306°	82	-37	U	6.53	6.48
			M	5.21	6.86				M	7.27	7.18
C(2)endo 162°	155	36	U	4.67	6.48	C(2)exo 342°	81	-38	U	6.75	6.81
			M	5.16	7.18				M	6.78	6.86

<sup>a</sup>  $\theta$  is the dihedral angle O(1)-C(1)-C(2)-H(2) for oxolane. <sup>b</sup>  $\phi$  is the mean value of the dihedral angle H(1)-C(1)-C(2)-H(2) between the coupled protons in oxolane and cyclopentane; the difference between them is usually about 1°. <sup>c</sup> U, unmodified; M, modified calculations. See text.

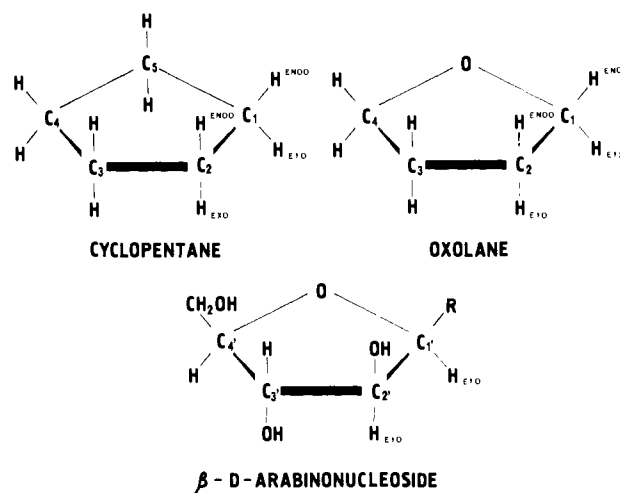
sured values. The five-membered rings were constructed according to the pseudorotational concept of Altona and Sundaralingam.<sup>4</sup> All calculations have been performed for  $\tau_m$  equal to 39°. Since the procedure of Saran et al.<sup>13</sup> frequently leads to incorrect results, a new method has been employed using the pseudorotational model for bond angles in five-membered rings and minimization of the differences between computed and crystallographic bond lengths, bond angles, and dihedral angles by means of the Simplex procedure.<sup>14</sup> For the exocyclic hydroxyl group, the average values of C-O bond lengths and C-C-O bond angles are from crystallographic data, while for O-H and C-H bonds, standard lengths were employed.<sup>15</sup> The value for C-O-H angles was also taken from the standard model of Pople and Gordon.<sup>15</sup> There are several criteria for the choice of the angles C-C-H and H-C-H, e.g., Altona and Sundaralingam,<sup>5</sup> Cremer and Pople.<sup>16</sup> The one adopted in this study is similar to that of Cremer and Pople.<sup>16</sup> As in their study, local  $C_{2v}$  symmetry is retained, but with the additional condition of equality of the angles C-C-H and H-C-H, the validity of which is supported by experiment<sup>17,18</sup> and ab initio calculations.<sup>19</sup> The results obtained with the aid of the criterion of Cremer and Pople are almost identical.

## Results and Discussion

One of the starting points of the present investigation was the known nonequivalence of the exo-exo and endo-endo vicinal H-H coupling constants in norbornanes. With the aid of a series of model compounds, for which theoretical calculations of coupling constants were carried out and compared with experimentally measured values, Marshall et al.<sup>12</sup> demonstrated that the foregoing nonequivalence is due to interaction of the C(7) methylene bridge with the bonds of the C(2)-C(3) ethane bridge.

On the basis of the foregoing study, it was inferred that interaction of a C-C bond with a diametrically opposed methylene group could be one of the factors responsible for the differences in coupling constants of the "mirror image" conformations endo and exo of the pentose ring<sup>20</sup> (conformations for which there is a difference in pseudorotational parameters,  $P$ , of 180°). Two series of calculations were therefore carried out for the model compounds oxolane (tetrahydrofuran) and

Scheme II



cyclopentane (see Scheme II). The results are displayed in Table I. For each value of the pseudorotational parameter in the table, the upper value is the cisoidal vicinal coupling constant calculated without modifications, while the lower value is that obtained when the interaction with the methylene group was set to zero. The figures set against the vertical arrows represent the percentage decrease in coupling constant as a result of interaction with the methylene group. It will be noted that these values are strikingly similar for both model compounds.

A second factor which influences the coupling constants in the pentose ring is the ring oxygen, testified to by the results of a number of investigators.<sup>21</sup> It seems that the method of calculation herein employed quite accurately reflects the influence of the ring oxygen on the cisoidal coupling constants in six-membered rings (Table II).

Comparison of the values of the coupling constants for cyclopentane and oxolane (Scheme II) makes possible an evaluation of the effect of the ring oxygen on the coupling constants for various conformations of the latter, as shown in Table I by the figures beside the horizontal arrows, which denote the

**Table II.** Experimental and Calculated Values of Vicinal Cis Coupling Constants in Some Six-Membered Rings

Compd	Assignment	Coupling constants, Hz	
		Exptl	Calcd <sup>a</sup>
<i>tert</i> -Butylcyclohexane	3e4a	3.77 <sup>b</sup>	4.22
<i>trans</i> -4- <i>tert</i> -Butylcyclohexanol	1a2e	4.3 <sup>c</sup>	4.56 <sup>d</sup>
<i>cis</i> -4- <i>tert</i> -Butylcyclohexanol	1e2a	3.0 <sup>c</sup>	2.77 <sup>d</sup>
1,2- <i>cis</i> -Dihydroxycyclohexane	Mean <sup>e</sup> (2e3a ~ 2a3e)	3.8 <sup>f</sup>	3.8 <sup>g</sup>
1,2- <i>trans</i> -Dihydroxycyclohexane	2a3e	4.5 <sup>f</sup>	4.8 <sup>g</sup>
1,4-Dioxane	Mean <sup>e</sup> (2a3e ~ 2e3a)	2.8 <sup>h</sup>	2.96

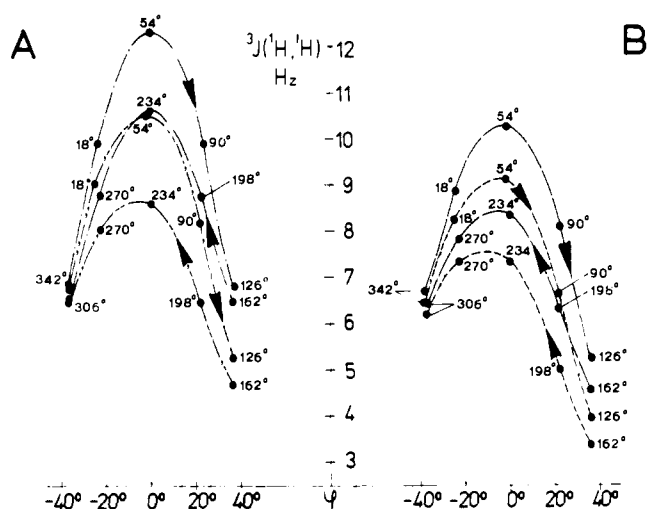
<sup>a</sup> Geometrical parameters for the rings from M. Davis and O. Hassel, *Acta Chem. Scand.*, **17**, 1181 (1963). Standard values for bond lengths with substituents from ref 15; bond angles are as described in text. <sup>b</sup> J. D. Remijnse, H. van Bekkum, and B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **90**, 779 (1971). <sup>c</sup> F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962). <sup>d</sup> Mean value for the two low-energy conformations of the hydroxyl group. The conformation with the hydroxyl above the ring possesses an energy about 2.5 kcal higher, so that its contribution to the mean value of the coupling constant is negligible. <sup>e</sup> Average for couplings of two equivalent conformers in rapid equilibrium with each other, with equal populations. <sup>f</sup> R. V. Lemieux and J. W. Lown, *Tetrahedron Lett.*, 1229 (1963). <sup>g</sup> Average weighted value for the four possible orientations of the two hydroxyls. As in footnote *d*, the high-energy conformations were excluded. The differences between these results and those of Maciel et al. (Table V in ref 24) are due to the use of different geometrical parameters for the rings. <sup>h</sup> J. B. Lambert, *J. Am. Chem. Soc.*, **89**, 1836 (1967).

decreases in coupling constants resulting from the presence of the ring oxygen. In particular, it should be noted that these values are similar for both the modified and unmodified calculations.

Puckered rings for which the difference in the pseudorotational parameter is 180° exhibit closely similar absolute values of dihedral angles. The small differences existing, <3°, result from the use of the criterion for the orientations of the C-H bonds. Despite this, there are appreciable differences in the values of the calculated coupling constants, with a larger value for the cisoidal coupling constant frequently corresponding to a larger dihedral angle. Careful examination of the data in Table I indicates that the differences in the values of the coupling constants are due to a superposition of the two factors referred to above. The methylene group diametrically opposite to the C(1)-C(2) bond interacts most strongly with the exo protons on this bond when it is above the plane of the four remaining ring atoms, leading to strong interaction of the rear lobes of the C-H bonds linking the protons in question with the carbons of the methylene group at C(4). The influence of the ring oxygen on the coupling constants between these protons is, in turn, most pronounced when the oxygen is in the extreme trans position<sup>21</sup> relative to one of the C(2) protons, i.e., with the conformation C(2) endo for exo protons.

The resultant of these two effects is a decrease in the cisoidal coupling constants between the exo protons at C(1) and C(2) of over 28% for the conformation C(3)exo relative to C(3)endo, and 31% for C(2)endo relative to C(2)exo. It is worthy of note that, in both instances, the higher values of the cisoidal coupling constants parallel the higher absolute value of the dihedral angle, despite the predictions of the classical Karplus relation. This shows that the investigated effect is at least an order of magnitude greater than the changes resulting from the maximal possible error in the geometrical parameters.

Performance of the modified calculations for the cyclo-



**Figure 1.** Dependence of the cisoidal coupling constants for the exo protons of the C(1)-C(2) bond on dihedral angle. The figures beside the dots denote corresponding values for the pseudorotational parameter, P: (A) — · — ·, cyclopentane; - - - -, oxolane; (B) — · — ·, oxolane (with geometry of arabinose ring); - - - -, arabinose ring.

pentane ring leads to values of the coupling constants, for symmetrical conformations, closely similar to each other. The minor differences (<8%) in the results are probably due to the influence of the methylene groups adjacent to a given bond, which must be taken into account in the calculations.

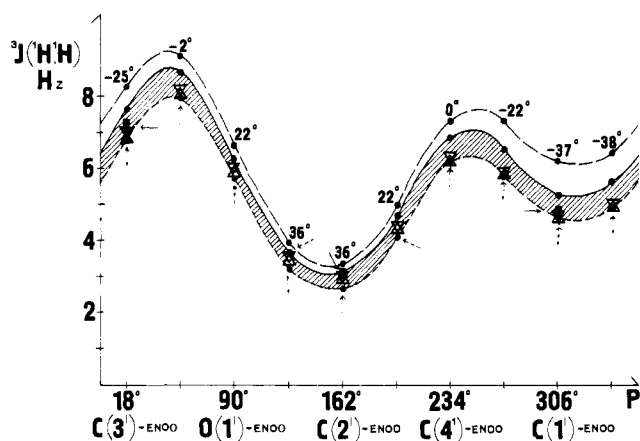
Figure 1A exhibits the dependence of the cisoidal coupling constants for the exo protons of the C(1)-C(2) bond on the dihedral angle, the dots referring to those points on the pseudorotational cycle for which calculations were performed. The arrows indicate the direction of increase of the pseudorotational parameter. It should be noted that, both for cyclopentane and oxolane, the dependence on the pseudorotational parameter and on the dihedral angle is similar in both instances.

In extending the calculations of coupling constants to the sugar pentose ring, account must be taken of the conformation-dependent influence of the exocyclic hydroxyl groups. The appreciable conformation-dependent influence of an electronegative substituent on vicinal coupling constants has, in fact, been demonstrated experimentally in a number of instances.<sup>21-23</sup> In addition, theoretical studies on simple molecules<sup>24</sup> have underlined the significance of this effect, particularly for cis protons.

Comparisons of the experimental and calculated (by the INDO FPT procedure) values of the coupling constants for cyclohexane derivatives of known conformation (Table II) show that the theoretical method is capable of evaluating the conformation-dependent effects of an -OH group on cisoidal coupling constants. A comparison of the values of  $^3J(1',2')$  for  $\beta$ -D-2'-deoxynucleosides, which exhibit a definite preference for the conformation C(2')endo, with the extreme values for the state S of arabinofuranosides demonstrates that the influence of the hydroxyl groups is also adequately accounted for by the theoretical procedure in the case of five-membered rings.

Rotation of the protons of the hydroxyl groups affects cisoidal coupling constants to only a minor extent. If we exclude the high-energy conformations (with a proton above the plane of the pentose ring), the effect is usually less than 3%. The negligible effect of the exocyclic carbinol group on  $^3J(1',2')$ , <1%, and of a heterocyclic base or amino group on  $^3J(3',4')$ , has also been confirmed.

The presence of hydroxyl groups affects the dependence of the coupling constants on the pseudorotational parameter (and



**Figure 2.** Dependence of the cisoidal  ${}^3J(1',2')$  on the pseudorotational parameter  $P$ : —, arabinose ring; the shaded region is for arabinosylamine for all possible angles of rotation about the glycosidic bond;  $\Delta$ ,  $\nabla$ , arabinofuranosyluracil with  $\chi$  equal to 20 and 50°, respectively;  $\blacksquare$ , arabinofuranosyluracil in syn conformation. Where symbols are not clear solid arrow indicates  $\blacksquare$ , broken arrow indicates  $\bullet$ .

on the dihedral angle, which is a function of the pseudorotational parameter), but does not essentially modify the character of this dependence in comparison with oxolane. This is evident from Figure 1B, which presents the curves for the dependence of the H(1)–H(2) and H(1')–H(2') exo vicinal coupling constants on dihedral angle for the oxolane ring (with the geometry of the arabinose ring) and the arabinose ring. A hydroxyl adjacent to a C–C bond appreciably decreases the value of  ${}^3J$  when the former is trans to one of the protons in question; e.g., for  ${}^3J(1',2')$  in arabino nucleosides this occurs for conformations close to C(2')endo.

Extension of the calculations to nucleosides must take account of the effect of the aglycone on the coupling constants of the pentose ring. Since calculations involving the entire base are excessively expensive, attempts were made to circumvent this by replacement of the base by an amino group. This should account for the influence of the electronegative nitrogen in an N–C glycosidic bond and the interactions through space of the nitrogen lone pair.

In the case of arabino nucleosides the calculations have been performed with the inclusion of the base (in this case uracil)<sup>25</sup> for ten conformations of the pentose ring with two different values of the glycosidic angle in the anti region ( $\chi = 20$  and 50°) and for three conformations of the pentose ring with two different syn positions of the base (Table III). The results fully confirm our assumption (see Figure 2).

The value of the glycosidic angle is only approximately known and assumes different values in the solid state. Consequently a series of calculations was performed for various values of the dihedral angle O(1')–C(1')–N(1)–H in arabinosylamine, providing minimal and maximal values of the coupling constants for each ring conformation.

The results for calculations of  ${}^3J(1',2')$  in arabino nucleosides are collected in Figure 2. Beside the values of the pseudorotation parameters, for which calculations were carried out, are given the values of the dihedral angles between the corresponding protons. The top dashed line embraces the results for the arabinose ring alone, while the shaded region includes the results for the arabinosylamine at various angles of rotation about the "glycosidic" bond. All values of the coupling constants for arabino nucleosides are found within the range of the limiting curves for different orientations of the amino group of the arabinosylamine. It will be noted that, for different values of the pseudorotation parameter  $P$ , there are large differences in the values of the coupling constants for the same dihedral angles; e.g., there are two minima localized in the

**Table III.** Calculated Cisoidal Coupling Constants  ${}^3J(1',2')$  in 1- $\beta$ -D-Arabinofuranosyluracil for Different Conformations of the Pentose Ring (Indicated by the Phase Angle of Pseudorotation,  $P$ ) and Glycosidic Angle ( $\chi$ )<sup>a</sup>

$P$ , deg	$\chi$			
	20°	50°	200°	230°
18	6.83	6.99	7.07	7.26
54	7.97	8.15		
90	5.88	6.03		
126	3.46	3.55		
162	2.92	3.00	3.04	3.13
198	4.29	4.41		
234	6.13	6.29		
270	5.73	5.87		
306	4.56	4.68	4.69	4.84
342	4.88	5.01		

<sup>a</sup> Definition of the glycosidic angle according to M. Sundaralingam, *Biopolymers*, 7, 821 (1969).

vicinity of C(2')endo and C(1')endo and, notwithstanding that the dihedral angles, are identical for these two cases, the coupling constants differ up to 45%. By contrast, very similar values of coupling constants were obtained for the neighboring conformations C(4')endo and O(1')exo, despite the fact that the dihedral angle for the former is 0° and for the latter 22°.

#### Application to Experimental Systems

The foregoing results were next applied to experimental data on  $\beta$ -D-arabino nucleosides. A statistical method<sup>26</sup> was employed to determine for a broad group of analogues the values of the coupling constants corresponding to the two extreme conformational states which are present in equilibrium in solution. For  $J(1',2')$ ,  $J(2',3')$ , and  $J(3',4')$  the values were 6.5–7, 8–10, and 8–10 Hz for the state N, and 3–4, 0–1.5, and 0.5–3 Hz for the state S. Somewhat unusual is the inordinately low value of the cisoidal  $J(1',2')$  for the state S, 3–4 Hz. On the basis of the classical Karplus relationship, such a low value for a cisoidal coupling constant can be accounted for only by an unusually large value of  $\tau_m$ , hitherto not observed in the solid state for a number of arabinoside nucleosides.<sup>27–35</sup> For example, an increase of  $\tau_m$  from 39 to 45° should lead to a decrease of the lowest value of the vicinal cisoidal coupling constant by less than 0.8 Hz. For the pentose ring of an arabino nucleoside,  ${}^3J(1',2')$  derived from the classical Karplus relation with such a high value of  $\tau_m$  is never less than 4.5 Hz at any point in the pseudorotational cycle. Perusal of the crystallographic data for arabino nucleosides<sup>27–35</sup> demonstrated that, on the basis of the criterion of Altona and Sundaralingam<sup>5</sup> for the orientation of the protons, there should be a decrease in the value of the dihedral angle  $\phi(1',2')$  for the conformational state S and, in line with this, an increase in the value of the cisoidal coupling constant predicted by the Karplus relation.

Our calculations (Figure 2) indicate that the conformational range in which  ${}^3J(1',2') < 4$  Hz extends from C(1')exo, through C(2')endo to C(2')endo–C(3')exo. In solution, the S state of the pentose ring should be in this conformational region. This is in good accord with the results obtained from experimental values of transoidal vicinal coupling constants alone, i.e.,  ${}^3J(2',3')$  and  ${}^3J(3',4')$ .<sup>26</sup> For the N state, the transoidal coupling constants predict a C(3')endo conformation. An equilibrium between such N and S states is in accord with our results for the cisoidal coupling constant  ${}^3J(1',2')$ . The large observed difference in the values of this coupling constant between N and S states is well reproduced by our calculations, but not by the classical Karplus relation.

In the case of  $\beta$ -xylofuranosyl nucleosides an examination of the transoidal coupling constants  ${}^3J(1',2')$  and  ${}^3J(2',3')$  by

**Table IV.** Calculated cisoidal Coupling Constants  $^3J(3',4')$  (Hz) in Xylo Nucleosides for Different Conformations of the Pentose Ring ( $P$ ) and Exocyclic Carbinol Group

$P$ , deg	Conformation of exocyclic group		
	Gauche-gauche	Gauche-trans	Trans-gauche
18	3.64	3.62	3.62
54	4.34	4.31	4.31
90	7.68	7.73	7.66
126	11.18	11.40	11.18
162	10.70	11.12	10.78
198	8.55	9.04	8.71
234	8.22	8.59	8.28
270	9.37	9.66	9.38
306	8.84	9.03	8.84
342	5.64	5.67	5.61

the classical Karplus procedure led only to prediction of a strong preference for the N-type conformation.<sup>36</sup> The experimental value of the cis  $^3J(3',4')$  is 3–4.4 Hz. As for arabino nucleosides, above, application of the Karplus relation in this case would account for such a low value only on the assumption of an unusually large  $\tau_m$ . Calculations by our procedure showed that values of  $^3J(3',4')$  in this range are obtained only for the conformation C(3')endo–C(4')exo (Table IV). It should be clearly noted that, on the basis of the transoidal coupling constants alone, it would not be feasible in this instance to establish unequivocally the N-type conformational state.

### Concluding Remarks

The surprisingly good agreement between experimental findings and the results of quantum chemical calculations presented above may be partly fortuitous, and should not necessarily be interpreted as the principal result of the present investigation. To some extent we are dealing with a situation in which there is a canceling out of some errors; e.g., the somewhat high values obtained theoretically for the coupling constants in the oxolane and the cyclopentane rings are reduced by the abnormal decrease in these values on addition of the hydroxyl groups.

The principal result of this investigation is rather the demonstration that establishment of a conformation about an isolated bond on the basis of experimentally measured cisoidal coupling constants, without taking into account the influence of the remainder of the molecule, can lead to serious errors. Furthermore, the widely applied procedure of accounting for the effect of an electronegative substituent, by subtracting a constant value from the calculated classical coupling constant, or by multiplication of the coupling constant obtained from the classical Karplus relation by a factor dependent only on the electronegativity of the substituent, is incapable of providing correct results for a rather broad range of dihedral angles.

Finally, it should be emphasized once again that all of the foregoing calculations were based entirely on the standard parameters of Pople et al.<sup>8</sup> for the 1S hydrogen charge density on nuclei, and the standard parametrization of the INDO method.<sup>9</sup>

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