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APPLICATION OF VICINAL CARBON-PROTON COUPLING CONSTANTS AND MOLECULAR MECHANICS CALCULATIONS IN THE CONFORMATIONAL ANALYSIS OF DIOXOLANE RINGS

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Abstract – *The conformation of the dioxolane ring of several bicyclic carbohydrate derivatives has been analyzed. The simultaneous use of vicinal carbon-proton coupling constants and molecular mechanics calculations has demonstrated to be useful in the conformational study of such a type of compounds.*

The conformation of five-membered rings has been a subject of interest for years[1-5] specially due to the potential influence of the conformation of the furanose ring in nucleic acid structure. Other five-membered rings, such as dioxolane rings, are frequently encountered in organic molecules. The conformational analysis of these five-membered rings has been performed using different approaches.[6] The conformation of furanose rings has been studied using ^1H-^1H couplings and it has been improved by using ^{13}C-^1H and ^{13}C-^{13}C couplings.[7,8] The conformation of dioxolane rings can not be elucidated by measuring ^1H-^1H couplings since the flipping of the ring at C-2' can not be estimated from these parameters. We are interested in the conformational analysis of 1,2-*O*-alkylidene pyranoses and we have determined the solution conformation of the pyranoid ring of a series of these molecules (compounds **1**-**26**) using ^1H-NMR spectroscopy.[9-16] We now report on the application of vicinal ^{13}C-^1H coupling constants and molecular mechanics calculations to the study of the conformation of the dioxolane rings.

Our previous work on the hexopyranose derivatives (**1**-**18**) have shown[9-12] that the pyranoid ring of these compounds can adopt $^OS_2$ (compounds **1**, **3**, **5**, **7**, **8**, and **15**-**18**) or $^4C_1$ (compounds **2**, **4**, **6**, and **9**-**14**) conformations.[16] The conformation of the pyranoid ring in the pentopyranose series[13-15] (compounds **19**-**26**) can be described as $^OS_2$ (compounds **19** and **25**), $^1C_4$ with small contribution of $^OS_2$ (compounds **20** and **26**), and equilibria between $^4C_1$ and $^OS_2$ (compounds **23** and **24**) or between $^4C_1$ and $^1C_4$ (compounds **21** and **22**) (*see Table I*). This knowledge of the conformation of the pyranoid ring may greatly facilitate the study of the conformation of the dioxolane rings since the 1,2-*cis* fusion of both rings considerably reduce the number of conformers and the torsion angle O1-C1-C2-O2 can be approximately estimated.

It is known that vicinal ^{13}C-^1H coupling constants depend on the torsion angle between the coupled nuclei.[17,18] The influence of the electronegativity and orientation of the substituents in this Karplus-like dependence is not exactly known[19-21] but we have recently shown[22] that for structurally related compounds the ^{13}C-^1H coupling constants can be safely related to the corresponding torsion angles when the coupling occurs along similar coupling paths.

The coupling constant between C-2' and the bridge-head protons, H1 and H2, of compounds **1**-**26** have been measured using both the selective heteronuclear 2D-*J* resolved experiment of Bax and Freeman[23] and the selective proton decoupling technique.[24] The fully coupled carbon spectra were finally calculated using a PANIC program with X-approximation. The values of $^3J_{C,H}$ for compounds **1**-**26** are given in Table II. The analysis of the allowed conformations of the dioxolane rings was performed using molecular mechanics calculations (*Tables III*-*VI*). The output of the MM2 program[25] provided a description of the

TABLE I

Major conformation in solution and in the solid state for the pyranoid ring of compounds **1** - **26**

Compound	Conformation	
	Solution	Solid state
1	$^{O}S_{2}$	-
2	$^{4}C_{1}$	-
3[9]	$^{O}S_{2}$	$^{O}S_{2}$
4[11]	$^{4}C_{1}$	$^{4}C_{1}$
5	$^{O}S_{2}$	-
6	$^{4}C_{1}$	-
7[10]	$^{O}S_{2}$	$^{O}S_{2}$
8	$^{O}S_{2}$	-
9	$^{4}C_{1}$	-
10[11]	$^{4}C_{1}$	$^{4}C_{1}$
11	$^{4}C_{1}$	-
12	$^{4}C_{1}$	-
13[10]	$^{4}C_{1}$	$^{4}C_{1}$
14[16]	$^{4}C_{1}$	$^{4}C_{1}$
15[10]	$^{O}S_{2}$	$^{O}S_{2}$
16[12]	$^{O}S_{2}$	$^{O}S_{2}$
17	$^{O}S_{2}$	-
18	$^{O}S_{2}$	-
19[15]	$^{O}S_{2}$	$^{1}C_{4}$
20[15]	$^{1}C_{4}$	$^{1}C_{4}$
21	$^{4}C_{1} \rightleftarrows {}^{1}C_{4}$	-
22	$^{4}C_{1} \rightleftarrows {}^{1}C_{4}$	-
23[13]	$^{1}C_{4} \rightleftarrows {}^{O}S_{2}$	$^{1}C_{4}$
24	$^{1}C_{4} \rightleftarrows {}^{O}S_{2}$	-
25[14]	$^{O}S_{2}$	$^{O}S_{2}$
26[14]	$^{1}C_{4} \rightleftarrows {}^{O}S_{2}$	$^{1}C_{4}$

TABLE II

Vicinal carbon-proton coupling constants for compounds **1** - **26**

Compound	^{J}C2',H1	^{J}C2',H2
1	3.1	0.0
2	3.4	4.4
3	3.0	0.0
4	3.3	4.3
5	3.1	0.0
6	2.3	3.1
7	2.7	0.0
8	3.4	0.0
9	1.2	3.3
10	3.3	5.3
11	1.2	3.1
12	1.9	5.2
13	1.2	3.3
14	2.0	3.8
15	3.1	0.0
16	4.4	1.6
17	2.9	0.0
18	3.4	0.0
19	4.0	0.0
20	7.5	1.3
21	3.7	1.8
22	5.6	3.1
23	5.6	1.0
24	5.3	0.0
25	3.7	0.0
26	7.2	0.0

TABLE III

Relative steric energy values for the preferred conformations of the dioxolane ring according to MM2 calculations for compounds **1**, **15**, and **16** ($^{O}S_{2}$ for the pyranoid ring)

Torsion angle	Compound **1**			Compound **15**			Compound **16**				
O1-C1-C2-O2	-10	-20	-30	-14	-20	-30	-34	-30	-20	0	-10
C1-C2-O2-C2'	31	36	39	33	36	39	28	26	30	20	27
C2-O2-C2'-O1	-42	-41	-47	-42	-41	-31	-12	-14	-32	-34	-37
O2-C2'-O1-C1	35	27	17	32	27	17	-10	-6	18	34	29
C2'-O1-C1-C2	-15	-4	8	-11	-4	8	27	22	1	-20	-11
C2'-O1-C1-H1	108	117	129	112	117	129	148	144	125	100	112
C2'-O2-C2-H2	-86	-82	-79	-84	-82	-79	-90	-90	-87	-90	-90
Relative steric energy (kcal/mol)	0.00	0.03	0.70	0.00	0.08	0.78	0.00	0.09	0.26	0.28	0.48

TABLE IV

Relative steric energy values for the preferred conformations of the dioxolane ring, according to MM2 calculations, for compounds **2**, **9**, **10**, and **14** ($^4C_1$ for the pyranoid ring)

Torsion angle	Compound **2**						Compound **9**				
O1-C1-C2-O2	42	45	38	50	30	32	40	40	33	30	40
C1-C2-O2-C2'	-28	-35	-31	-38	-16	-25	-20	-22	-16	-9	-27
C2-O2-C2'-O1	5	15	15	15	-4	10	-7	-3	-7	-15	6
O2-C2'-O1-C1	23	15	10	20	24	10	34	30	29	36	20
C2'-O1-C1-C2	-40	-36	-30	-42	-33	-26	-45	-42	-38	-40	-37
C2'-O1-C1-H1	79	82	87	78	82	89	81	76	80	76	81
C2'-O2-C2-H2	-147	-153	-151	-155	-138	-146	-132	-135	-129	-131	-134
Relative steric energy (kcal/mol)	0.00	0.32	0.65	0.94	1.44	1.54	0.00	0.10	0.16	0.90	1.16

Torsion angle	Compound **10**					Compound **14**				
O1-C1-C2-O2	43	41	37	33	30	40	40	30	39	50
C1-C2-O2-C2'	-29	-31	-27	-25	-15	-22	-27	-13	-29	-31
C2-O2-C2'-O1	6	12	9	9	-5	-2	6	-8	10	3
O2-C2'-O1-C1	23	15	15	12	26	29	20	28	16	30
C2'-O1-C1-C2	-40	-34	-32	-28	-34	-42	-37	-36	-34	-48
C2'-O1-C1-H1	79	83	85	87	81	77	81	80	84	74
C2'-O2-C2-H2	-148	-150	-148	-147	-137	-142	-145	-135	-146	-148
Relative steric energy (kcal/mol)	0.00	0.30	0.58	1.29	1.45	0.00	0.56	0.85	1.25	1.25

TABLE V

Relative steric energy values for the preferred conformations of the dioxolane ring, according to MM2 calculations for compound **20** ($^1C_4$ for the pyranoid ring)

Torsion angle	Compound **20**						
O1-C1-C2-O2	-44	-44	-43	-45	-42	-45	-45
C1-C2-O2-C2'	27	24	21	29	19	32	35
C2-O2-C2'-O1	-1	3	7	-5	11	-9	-13
O2-C2'-O1-C1	-29	-33	-36	-25	-39	-21	-16
C2'-O1-C1-C2	44	46	47	42	48	40	37
C2'-O1-C1-H1	157	159	161	156	162	154	152
C2'-O2-C2-H2	-91	-92	-95	-90	-97	-88	-86
Relative steric energy (kcal/mol)	0.00	0.01	0.17	0.30	0.59	0.67	1.16

geometry of each conformer and the torsion angles between C-2' and the bridge head protons of these calculated geometries were compared to those to be expected from the vicinal ^{13}C-^1H couplings.

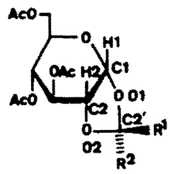
The values shown in Table II for the hexopyranose derivatives having the pyranoid ring in a $^OS_2$

TABLE VI

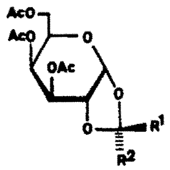
Relative steric energy values for the preferred conformations of the dioxolane ring, according to MM2 calculations for compound **19** ($^{O}S_{2}$ for the pyranoid ring)

Torsion angle	Compound **19**		
O1-C1-C2-O2	-19	-10	-30
C1-C2-O2-C2'	34	32	38
C2-O2-C2'-O1	-38	-42	-34
O2-C2'-O1-C1	26	34	18
C2'-O1-C1-C2	-4	-14	8
C2'-O1-C1-H1	115	109	128
C2'-O2-C2-H2	-83	-87	-78
Relative steric energy (kcal/mol)	0.00	0.02	0.91

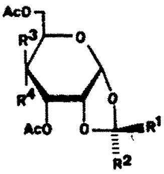
conformation (compounds **1**, **3**, **5**, **7**, **8**, and **15-18**) with the exception of **16** range between 2.7 and 3.4 Hz, in the case of $^{3}J_{C2',H1'}$ and are very close to zero, in the case of $^{3}J_{C2',H2}$. The MM2 calculations for **1** (D-glucopyranose series) and **15** (D-allopyranose series) indicate that, having the pyranoid ring in the $^{O}S_{2}$ conformation, there are two favoured conformations. E_{O2} and $^{C2'}T_{O2}$ of the dioxolane ring. The energy difference between the two conformations is 0.03 and 0.08 kcal/mol for **1** and **15**, respectively. The torsion angles associated to these forms are $\Phi_{C2',H1}$ 117° and $\Phi_{C2',H2}$ -82° for both compounds with the dioxolane ring in the E_{O2} conformation, and $\Phi_{C2',H1}$ 108° and 112°, and $\Phi_{C2',H2}$ -86° and -84° for compounds **1** and **15**, respectively, with the dioxolane ring in the $^{C2'}T_{O2}$ form. The $^{3}J_{C,H}$ values to be expected for these calculated angles are in good agreement with those observed and the results accord to previous studies on the conformation in the solid state of **3**[9], **7**[10], and **15**[10], the dioxolane ring of which was found to be in a conformation very close to E_{O2} (*Fig. 1a*). The observed couplings for **16** indicate a different conformation of the dioxolane ring. The molecular mechanics calculations for this compound predict several different conformers in an energy range of less than 0.5 kcal/mol. However, the large value of $J_{C2',H1}$ could be taken as an indication of a large torsion angle as should be expected for a ^{C2}E conformation somehow distorted towards a $^{C2}T_{C1}$ conformation similar to that determined in the solid state from X-ray diffraction data[12] (*Fig. 1b*). It is interesting to note that all those compounds in which the major conformation of the pyranoid ring has been determined to be $^{O}S_{2}$ (compounds **1**, **3**, **5**, **7**, **8**, and **15-18**) with the exception of **16**, present an *endo* methyl or phenyl group. The methyl group of **16** is in an *exo* orientation and all the above results are in agreement with previous findings that indicate a tendency of the alkyl groups to occupy pseudo-equatorial rather than pseudoaxial positions.[6]



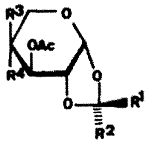
	R1	R2
1	H	Me
2	Me	H
3	CN	Me
4	Me	CN
5	H	Ph
6	Ph	H
7	OBu^{t}	Me
8	Me	Me



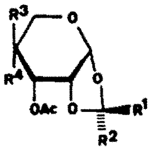
	R1	R2
9	CN	Me
10	Me	CN
11	H	Ph
12	Ph	H
13	OBu^{t}	Me
14	Me	Me



	R1	R2	R3	R4
15	H	Me	H	OAc
16	Me	H	H	OAc
17	CN	Me	H	OAc
18	H	Me	OAc	H

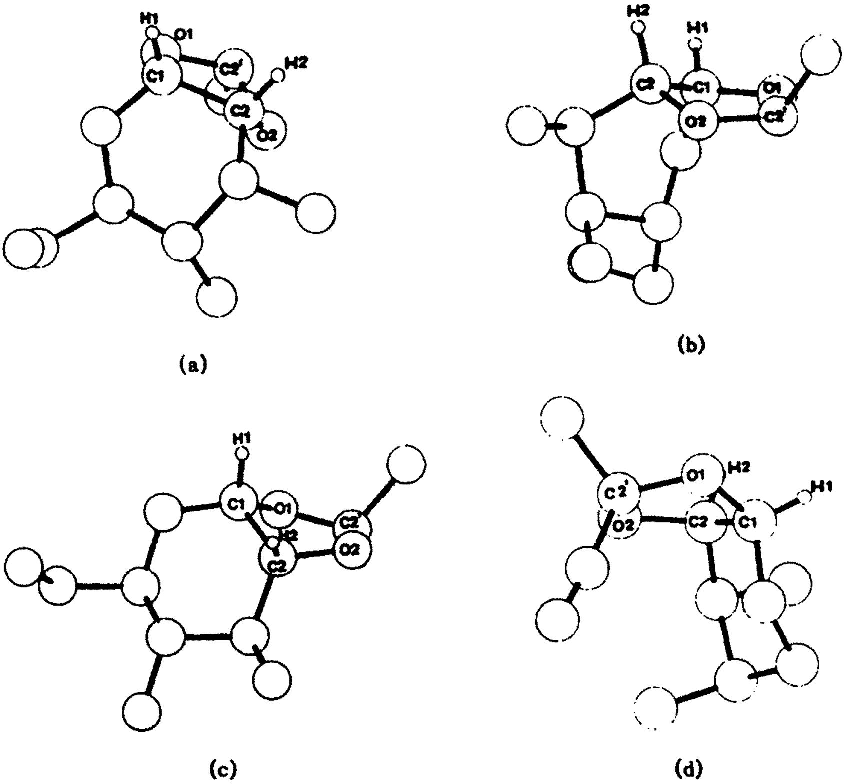


	R1	R2	R3	R4
19	CN	Me	H	OAc
20	Me	CN	H	OAc
21	CN	Me	OAc	H
22	Me	CN	OAc	H



	R1	R2	R3	R4
23	CN	Me	H	OAc
24	H	Me	H	OAc
25	CN	Me	OAc	H
26	Me	CN	OAc	H

The values shown in Table II for the hexopyranose derivatives having the pyranoid ring in a $^{4}C_{1}$ conformation (compounds **2**, **4**, **6**, and **9-14**) can be gathered into three different groups corresponding to compounds **2**, **4**, and **10** ($J_{C2,H1}$ between 3.3 and 3.4 Hz, $J_{C2',H2}$ between 4.3 and 5.3 Hz), compounds **9**, **11**, and **13** ($J_{C2',H1}$ 1.2 Hz, $J_{C2',H2}$ between 3.1 and 3.3 Hz), and compounds **6**, **12**, and **14** showing



Figures caption.- Fig. 1: Plots showing the more stable minima of the dioxolane rings for **(a)** E_{O2} from **15**, **(b)** ${}^{C2}E$ from **16**, **(c)** distorted ${}^{C1}E$ from **2**, and **(d)** E_{C1} from **20**. Acetyl groups are omitted for simplicity.

couplings in between the above. Molecular mechanics calculations (*Table IV*) indicate that the favoured conformation of the dioxolane ring of compounds **2**, **9**, **10**, and **14** would be ${}^{C1}E$ (compound **14**) somehow distorted towards ${}^{C1}T_{C2}$ (compounds **2** and **10**) or ${}^{C1}T_{O1}$ (compound **9** and these results also account for the observed ${}^3J_{C,H}$ values (*Fig. 1c*). Thus, the torsion angles to be expected for the ${}^{C1}T_{C2}$ are larger than for the ${}^{C1}T_{O1}$ conformation, and therefore the conformation of the dioxolane ring of the compounds showing larger couplings (**2**, **4** and **10**) may be described as an equilibrium between ${}^{C1}E$ and ${}^{C1}T_{C2}$ forms with higher contribution of the latter in the case of compound **10**. Similarly, for **9**, **11**, and **13**, a conformational equilibrium between ${}^{C1}E$ and ${}^{C1}T_{C1}$ could account for the observed couplings while for **6** and **14** the values can be explained by a pure ${}^{C1}E$ form. All these results are also in agreement with previous work which demonstrated that the conformation in the solid state of the dioxolane ring of **4** and **10**[11] is ${}^{C1}T_{C2'}$, and these of **13**[10] and **14**[10], ${}^{C1}E$ distorted towards ${}^{C1}T_{O1}$ and ${}^{C1}E$, respectively. The larger value of $J_{C2',H2}$ for **12** could indicate a distortion of the envelope towards the ${}^{C1}T_{C2}$ form, although the value of $J_{C2',H1}$ should be higher and similar to those for **2**, **4**, and **10**. According to the calculations, the dioxolane rings in these compounds having the pyranoid ring in ${}^4C_1$ conformation (**2**, **4**,**6**, and **9**-**14**) are more flexible than those in the compounds with the pyranoid ring in the ${}^OS_2$ conformation (**1**, **3**, **5**, **7**, **8**, and **15**-**18**) and small variations in the torsion angles may result in noticeable changes of the value of the couplings. As above, the molecules having the methyl group in an *exo*-orientation show larger couplings.

With regard to the pentopyranose derivatives (**19**-**26**) these compounds having a ${}^1C_4$ major conformation of the pyranoid ring (**20**) and (**26**) show a large $J_{C2',H1}$ value, which corresponds to a very large $\Phi_{C2',H1}$ torsion angle, and, in the case of **20**, a $J_{C2',H2}$ value which corresponds to an angle around 90°. These angles are the expected for the dioxolane ring in the E_{C1} conformation (*Fig. 1d*) ($\Phi_{C2',H1} \simeq 160°$, $\Phi_{C2',H2} \simeq -90°$, according to calculations shown in Table V) and accord to previous X-ray diffraction data for **20**.[15] For **26**, the observed values of ${}^3J_{C,H}$ could be explained by a contribution of conformers having the pyranoid ring in the ${}^OS_2$ conformation. The D-xylopyranose and L-lyxopyranose derivatives having the methyl group at C-2' in an *endo* orientation (compounds **19** and **25**), both of them with a major ${}^OS_2$

conformation of the pyranoid ring show coupling values in agreement with a conformation of the dioxolane ring which could be described as an equilibrium between E_{O2} and $^{C2'}T_{O2}$ forms, as predicted by molecular mechanics calculations (*Table VI*). The higher value of $J_{C2',H1}$ may indicate a larger contribution of the E_{O2} form than that encountered in the hexopyranose series. The conformation of the pyranoid ring of all other pentopyranose derivatives (**21-24**) have been described as an ≈ 1:1 equilibrium between two major forms.[13,14] For all these compounds, the observed values of $^3J_{C,H}$ can be interpreted as corresponding to conformational equilibria between the different expected forms of the dioxolane ring according to the above findings: $E_{C1} \rightleftharpoons E_{O2} + {}^{C2'}T_{O2}$ for the D-ribopyranose derivatives **23** and **24** ($^1C_4 \rightleftharpoons {}^oS_2$ equilibria for the pyranoid ring) and $E_{C1} \rightleftharpoons {}^{C1}T_{C1}$ for the L-arabinopyranose derivatives **21** and **22** ($^1C_4 \rightleftharpoons {}^4C_1$ equilibria for the pyranoid ring).

In conclusion, the above results show that the combined use of vicinal carbon-proton coupling constants and molecular mechanics calculations provides a valuable information in the study of the conformation of dioxolane rings in solution.

EXPERIMENTAL

Materials.- The synthesis of compounds **1-26** has been reported previously.[10-16]

N.m.r. data.- The ^{13}C-n.m.r. spectra were recorded on a Varian XL-300 spectrometer. Long-range carbon-proton coupling constants were measured by two methods:

a) Selective Heteronuclear 2D-J resolved spectroscopy following the sequence proposed by Bax and Freeman.[23] The preparation period for establishment of n.O.e. was fixed to 5 s. The variable evolution period was incremented in 32 steps, giving a spectral width in the F1 dimension of ± 7.5 Hz. The proton-flip technique was used with decoupler pulse intensity $\gamma B_2/2\pi = 25$ Hz and 20 ms for the π pulse.

b) Selective pulse decoupling.[24] The pulse sequence contained a preparation time of 5 s for building up the n.O.e. followed by selective irradiation on a chosen proton signal with low power intensity (40 Hz) and recording the partially coupled spectrum.

Differences smaller than 0.3 Hz were found when comparing both methods. The measured coupling constants were used as input data for simulating the coupled carbon spectra using a PANIC program with X-approximation. The experimental and calculated spectra matched satisfactorily.

Molecular mechanics calculations.- The MM2 program[25] was modified for carbohydrates by using the acetal segment parameters proposed by Jeffrey and Taylor.[26] It was also necessary to provide two parameters for torsion angles not included in the program database, namely, C_{sp}-C_{sp3} and C_{sp}-C_{sp3}-O-LP (V1 = V2 = 0, V3 = 0.2) and one bending parameter for angle C_{sp}-C_{sp3}-O |K(B) = 0.98, THETA(O) = 108.5°|. The default value for the bulk dielectric constant (1.5 D) corresponding to the gas phase was substituted for a value (10 D), stated as a good efective ϵ for chloroform.[27] The starting coordinates for the different conformations were taken from the crystallographic values.[9-16] Driver option of the program was used in order to look for all the possible local minima. Tables III-VI gather the conformers with a relative steric energy under 2 kcal/mol.

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