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CONFORMATIONAL ANALYSIS OF METHYL TETROFURANOSIDES AND PENTOFURANOSIDES FROM $^1H, ^1H$ COUPLING CONSTANTS

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SUMMARY: *The coupling constant ($^3J_{HH}$) between a pair of vicinal protons of an oxygen containing five membered ring was expressed as a function of the prseudorotation parameters: the phase angle of pseudorotation (P) and the puckering amplitude (ϕ_m). The resulting equation, which also includes parameters for the adjustment of the ring geometry, was parametrized for the tetrahydrofuran as model compound, using molecular mechanics calculations. The resolution of the equation gave all the $^3J_{HH}$ values for the pseudorotation itinerary. The conformation of the α and β anomers of methyl tetrofuranosides and pentofuranosides was established from the best fit between calculated and experimental coupling constants.*

RESUMEN: *La constante de acoplamiento ($^3J_{HH}$) para cada par de protones vecinos de un anillo oxigenado de cinco miembros se expresó en función de los parámetros pseudorrotacionales: el ángulo de fase de pseudorrotación (P) y la amplitud de plegamiento (ϕ_m). La ecuación resultante, que incluye parámetros que definen la geometría del anillo, se parametrizó mediante cálculos de mecánica molecular realizados sobre un compuesto modelo, el tetrahidrofurano. Por resolución de dicha ecuación, se obtuvieron todos los valores de $^3J_{HH}$ a lo largo de todo el ciclo pseudorrotacional. La comparación de las constantes de acoplamiento experimentales con las calculadas permitió establecer la conformación más probable para los anómeros α y β de todos los metil tetrofuranósidos y pentofuranósidos.*

INTRODUCTION

The conformational properties of furanose rings have received considerable attention in recent years because of their influence in the structure, conformation and

dynamic of nucleic acids and other biopolymers. Thus, conformational preferences were assessed by means of molecular mechanics (1-3) and ab-initio MO-calculations (4,5) or by analysis of ^1H-^1H (1,6,7), ^1H-^{13}C and ^{13}C-^{13}C spin couplings (8,9), obtained from the NMR spectra of the furanoid compounds. As furanose rings may assume twist (T) or envelope (E) conformations, which are readily interconverted (i.e., with relatively low activation barriers) by the process of pseudorotation (6,8,10), the interpretation of NMR data is complicated since a time-averaged spectrum of all the pseudorotamers is obtained (8,10). However, taking into account that the spectral data of furanoses and furanosides are readily available (6,8), we have developed (11) a realiable procedure for the conformational assignments of furanose and thiofuranose derivatives from ^1H-^1H coupling constants ($^3J_{H,H}$). In this procedure, the conformational preferences of those rings may be established from the best fit between calculated and measured $^3J_{H,H}$ values. For a given compound all the $^3J_{H,H}$ couplings can be calculated for the full pseudorotation itinerary, using the following equation:

$$^3J = P_1\cos^2[ka+b\phi_m\cos(P + \text{phase})+c] + P_2\cos[ka+b\phi_m\cos(P + \text{phase})+c] + P_3 + \Sigma\Delta\chi_i \{P_4 + P_5\cos^2[\xi_i(ka+b\phi_m\cos(P + \text{phase})+c] + P_6|\Delta\chi_i|\}$$

$$\Delta\chi_i = \Delta\chi^{\alpha\text{-substituent}} - P_7\Sigma\Delta\chi_j^{\beta\text{-substituent}} \qquad (1)$$

Equation (1) gives $^3J_{H,H}$ as a function of the pseudorotation parameters: the phase angle of pseudorotation (P), and the puckering amplitude (ϕ_m). As eq. (1) is based on the Altona's generalization (12) of the Karplus equation, it includes corrections by the electronegativity ($\Delta\chi_i$) and relative orientation (ξ) of the substituents. The parameters P_1-P_7 were taken from Ref. 12 (sets E and D), and k values were fixed as zero for cis protons and ± 1 for trans protons.

RESULTS AND DISCUSSION

In order to express $^3J_{H,H}$ as a single function of P, the terms a, b, c and ϕ_m of eq. (1) were determined as previously described (11). The angle ϕ_m was calculated for a model compound: tetrahydrofuran (THF) by means of molecular mechanics calculations, using the PCMODEL program (from Serena Software, Bloomington, Indiana), which incorporates Allinger's MM2 force field (13). The value obtained for ϕ_m (40.3°) was in good agreement with those obtained from the X-ray diffraction data for other furanoid rings (14,15). The geometry of the ring was adjusted through the parameters a, b, and c in eq. (1), whose determined values (11) were a=122.4, b=1.11 and c=1.28.

Although a single value of $^3J_{H,H}$ can correspond to several different pseudorotamers, a set of three or four coupling constants for pentoses or tetroses, respectively, allows conformational assigments for the furanose ring. Thus, the resolution of eq. (1) for

methyl α-D-erythrofuranoside gives the correlation of $J_{1,2}$, $J_{2,3}$, $J_{3,4}$ and $J_{3,4'}$ with P, along the pseudorotation itinerary (table I). As shown in table I, a single segment of the pseudorotation cycle (P= 144-180) which matches the calculated with the observed J values (table II) can be identified. For all the compounds studied, the calculated couplings for the given segment of the itinerary have been directly averaged (table II), i.e. assuming equal population of all the conformers of the region, in order to determine the trends in coupling constant values. However, the estimation of the conformational composition within the region, on the basis of calculated couplings, is not recommended as serious distortion may be obtained. The averaged J values calculated for methyl α-D-erythrofuranoside ($J_{1,2}$ 4.7, $J_{2,3}$ 4.8, $J_{3,4}$ 5.3 and $J_{3,4'}$ 1.8 Hz) are in good agreement with the experimental data (table II), indicating a $^2T_1 \rightleftarrows {}^2E \rightleftarrows {}^2T_3$ conformational equilibrium for the compound.

Besides of a good correlation between the calculated and experimental J values (table II), the following criteria of stability for a substituted furanoid ring (6,8) were considered in orden to assess its conformation: a) the anomeric substituent will prefer a quasi-axial orientation (anomeric effect), b) the bulky side chain will tend to take up a quasi-equatorial disposition, and c) ring substituents will locate in staggered orientation. Thus, the pseudorotamers of methyl α-D-erythrofuranoside in the $^2T_1$-$^2T_3$ region satisfy the anomeric effect, and are essentially free of eclipsing or paralell interactions. For the compound, Serianni and Barker (8) and Angyal (6), proposed approximately the same preferred conformation.

For methyl β-D-erythrofuranoside, a single region of the pseudorotation itinerary, which matches with the experimental J values, was not found. This fact would suggest that the compound is conformationally unstable, and therefore the observed couplings are averaged in a complex fashion. Accordingly, Serianni and Barker (8) have found poor complementarity for J values, and they were not able of performing conformational assignments. Angyal (6) suggested that the conformation of methyl β-D-erythrofuranoside can be described as a mixture of $^2T_3$ and $^3T_2$ forms, which occupy opposite sides in the pseudorotation cycle. However, we have observed that the best correlation between calculated and experimental J values result from the average of the ^1E and $^4T_3$ conformers. These appear to be rather stable conformations, as they satisfy the anomeric effect, and HO-2 and HO-3 lie in a staggered disposition.

The procedure here described when applied to methyl α-D-threofuranoside and its β anomer dictates preferred $^0T_1$-$^2T_3$ and $^3T_0$-$^1T_2$ conformations, respectively, in good agreement with the results obtained by considering $J_{H,H}$ and $J_{13C,H}$ couplings (8).

The conformation of methyl α-D-ribofuranoside on the basis of the $J_{H,H}$ couplings was, according to Angyal (6), difficult to assign. However, our calculated coplings fit with those measured for the $^0T_1$-^2E segment (table II), which should be the most populated. The pseudorotamers in this region are stabilized by the axial orientation of the anomeric substituent. Serianni and Barker (8) have found a similar conformation (E_1-^2E) for methyl α-D-ribofuranoside.

Methyl β-D-ribofuranoside is conformationally located in the $^1T_2$-$^3T_2$ segment. In spite of the strong preference for the $^3T_2$ conformation proposed (6), our calculations indicate a substantial contribution of the ^2E and $^1T_2$ conformers to the equilibrium. Their presence accounts for the increment of $J_{2,3}$ and the decrease of $J_{3,4'}$, with respect to the expected values for the $^3T_2$ form. The other furanosides that, as methyl β-D-ribofuranoside, have the anomeric substituent and the side chain an C-4 cis oriented, satisfy the

foregoing mentioned stability criteria for the ${}^1T_2$-${}^3T_2$ segment. Accordingly, calculated and experimental ${}^3J_{H,H}$ values for methyl β-D-arabinofuranoside, methyl β-D-xylofuranoside, and methyl β-D-lyxofuranoside fit the ${}^1T_2$-${}^3T_2$ region.

The analysis performed on methyl α-D-arabinofuranoside indicated that the E_4-E_1 conformations would be preferred in accordance with previous reports (6,8). However, of all the furanosides studied, this compound showed the poorer complementarity between experimental and calculated couplings (table II) for the proposed pseudorotation segment. As furanosides having O-1 and the C-4 side chain in a trans disposition can not satisfy simultaneously all the criteria of stability, they are expected to populate different regions of the pseudorotation itinerary (6). Thus, the $J_{1,2}$ and $J_{2,3}$ values lower than the expected ones for the E_4-E_1 region, would suggest the contribution of other conformations for methyl α-D-arabinofuranoside. Similarly, the conformation of methyl α-D-xylofuranoside and methyl α-D-lyxofuranoside can be described as a mixture of ${}^2T_3$ and ${}^3T_2$ (or ${}^3E$) conformers. The ${}^3J_{H,H}$ values calculated, given in table II, correspond to mixtures having 50% of each form. The good agreement between calculated and experimental J values obtained suggests substantial contribution of pseudorotamers from opposite sides of the itinerary, in the conformational equilibrium of both compounds.

TABLE I

Calculated ${}^3J_{H,H}$ values (Hz) for methyl α-D-erythrofuranoside ($\phi_m = 40.3$)

Conform.	P(°)	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{3,4'}$	Conform.	P(°)	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{3,4'}$
${}^3T_2$	0	3.4	4.0	8.4	9.5	${}^2T$	180	5.1	4.3	3.6	1.3
${}^3E$	18	4.3	4.4	7.6	10.1	E_3	198	5.8	4.6	2.7	1.4
${}^3T_4$	36	5.4	5.2	7.3	10.2	${}^4T_3$	216	6.3	5.5	2.3	1.5
E_4	54	6.2	6.4	7.6	10.1	${}^4E$	234	6.2	6.6	2.7	1.4
${}^0T_4$	72	6.3	7.5	8.4	9.5	${}^4T_0$	252	5.4	7.7	3.6	1.2
${}^0E$	90	5.8	8.1	9.1	8.3	E_0	270	4.3	8.1	5.2	1.5
${}^0T_1$	108	5.1	7.7	9.4	6.4	${}^1T_0$	288	3.4	7.5	7.0	2.5
E_1	126	4.6	6.6	8.6	4.3	${}^1E$	306	2.7	6.4	8.6	4.3
${}^2T_1$	144	4.3	5.5	7.0	2.5	${}^1T_2$	324	2.5	5.2	9.4	6.4
${}^2E$	162	4.6	4.6	5.2	1.5	E_2	342	2.7	4.4	9.1	8.3

TABLE II

Experimental and calculated $^3J_{HH}$ values for methyl D-tetrofuranosides and methyl D-pentofuranosides, and their preferred conformations.

Compound	$^3J_{1,2}$		$^3J_{2,3}$		$^3J_{3,4}$		$^3J_{3,4'}$		Conformation		
	Exp.[a]	Calc.[b]	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.	Ref. 6	Ref. 8	This work
α-erythrofuranoside	4.6	4.7	5.6	4.8	4.9	5.3	2.2	1.8	^2E	$^0T_1$-$^2T_3$	$^2T_1$-$^2T_3$
β-erythrofuranoside	2.9	3.3	4.8	5.5	5.0	5.6	3.5	2.9	$^2T_3$, $^3T_2$		^1E, $^4T_3$
α-ribofuranoside	4.2	5.0	6.2	6.5	3.3	2.8				E_1-^2E	$^0T_1$-^2E
β-ribofuranoside	1.2	1.2	4.6	4.7	6.9	7.4			$^3T_2$	$^1T_2$-^3E	$^1T_2$-$^3T_2$
α-arabinofuranoside	1.7	1.4	3.3	2.6	5.9	6.5			^0E	$^0T_4$-E_1	E_2-E_1
β-arabinofuranoside	4.6	4.8	8.0	8.3	7.1	7.0				^1E-^2E	$^1T_2$-$^3T_2$
α-threofuranoside	0.5	1.3	1.2	1.1	5.8	6.6	3.3	3.2		^0E-^2E	$^0T_1$-$^2T_3$
β-threofuranoside	4.4	5.1	4.6	4.2	6.1	6.7	4.1	3.8		^4E-$^1T_2$	$^4T_0$-$^1T_2$
α-xylofuranoside	4.5	4.7	5.5	5.3	6.1	5.6			$^2T_3$, $^3T_2$		$^2T_3$, $^3T_2$
β-xylofuranoside	b.s.[d]	1.2	1.7	1.7	5.1	4.7			$^3T_2$		$^1T_2$-$^3T_2$
α-lyxofuranoside	3.6	3.3	4.8	4.7	4.3	5.0			^3E, $^2T_3$		$^2T_3$, ^3E
β-lyxofuranoside	4.8	5.0	5.0	5.2	4.6	4.9			$^3T_2$		$^1T_2$-$^3T_2$

[a]Exp.: observed J values from Ref. 8 (600 MHz, ^2H_2O).
[b]Calc.: caldulated J values from eq. (1) and averaged for the preferred regions of the pseudorotation itinerary (see the text). [d]b.s.: broad singlet.

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