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PSEUDOROTATIONAL ANALYSIS OF 4-THIOHEXOFURANOSE DERIVATIVES FROM ^{1}H-^{1}H COUPLING CONSTANTS

DANIEL CICERO AND OSCAR VARELA

Dep. Quím. Orgánica, Fac. Ciencias Exactas y Naturales, Univ. Buenos Aires,
Ciudad Universitaria, Pabellón II, 1428-Buenos Aires, Argentina.

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Abstract: On the basis of Altona's empirical generalization of the Karplus equation, an expression of $^3J_{H,H}$ as function of pseudorotation parameters for five-membered rings, was deduced. The resulting equation was parametrized by means of molecular mechanics calculations for tetrahydrofuran and tetrahydrothiophene. Estimation of $^3J_{H,H}$ for the full pseudorotational itinerary was made. From the best fit between calculated and measured $^3J_{H,H}$ values the preferred conformation of those rings may be established. The procedure was applied for the conformational analysis of 4-thiohexofuranose derivatives, having α and β, D-*galacto* and D-*manno*, and α-D-*talo* configurations.

In connection with our work on the synthesis of 4-thiofuranose derivatives,[1,2] we investigated the conformation of the sulfur containing five-membered ring of these compounds. The replacement of the ring oxygen atom by sulfur modifies the conformation of 5-thiopyranoses,[3] but the effect on a furanoid ring was not yet established. Furanoid ryng systems usually adopt twist (*T*) and envelope (*E*) conformations, which can readily interconvert by the process of pseudorotation.[4-6] Theoretical studies[7,8] and *ab-initio* MO-calculations[9] have been conducted to determine the conformation of furanoid derivatives, which was also investigated by NMR spectroscopy, from the analysis of vicinal ^{1}H-^{1}H spin couplings[4,5,10] or by considering ^{13}C-^{1}H and ^{13}C-^{13}C couplings.[6,11] The interpretation of the NMR data is complicated as a time-averaged spectrum of all the conformers is obtained due to pseudorotation,[4] and a single three bond coupling constant ($^3J_{H,H}$) value may correspond to several different pseudo rotamers.[6] From vicinal proton couplings of furanoid systems, Altona and co-workers[12] have developed a computer assisted pseudorotation analysis (PSEUROT program). For this type of analysis geometrical information obtained by X-ray crystallography seems to be indispensable.[13] Unfortunately, no X-ray or neutron-diffraction studies appear available for 4-thiofuranose derivatives. Therefore, we have employed an alternative procedure for calculation $^3J_{H,H}$ as a function of pseudorotational parameters, which allows, from the best fit between calculated and measured $^3J_{H,H}$ values, estimation of the conformation of the furanose and thiofuranose rings.

PROCEDURE

Vicinal $^1H-^1H$ coupling constants ($^3J_{H,H}$) are related with the $^1H-^1H$ torsion angles ($\phi_{H,H}$) by the empirical generalization[14] of the original Karplus equation. The torsion angle $\phi_{H,H}$ may be described as a function of the endocyclic torsion angles (ϕ_j) by the following relationship:

$$\phi_{H,H} = ka + b\,\phi_j + c \qquad (1)$$

where in the case of trigonal symmetry b=1, c=0°, a=120°, and k=0 for *cis* protons and k=±1 for *trans* protons. Furthermore, as for five-membered rings ϕ_j is related with the pseudorotation parameters P, the phase angle of pseudorotation and ϕ_m, the puckering amplitude,[15] $^3J_{H,H}$ may be expressed as a function of P and ϕ_m:

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

$$\Delta\chi_i = \Delta\chi^{\alpha\text{-substituent}} - P_7.\Sigma\Delta\chi_j^{\beta\text{-substituent}}$$

Equation (2) includes corrections by the electronegativity ($\Delta\chi_i$) and relative orientation (ξ) of the substituents. The parameters $P_1 - P_7$ were taken from the recommended[14] data set (E or B) for the H-C-C-H fragments. Altona and co-workers[12,13] have deduced a similar relationship for systems such as nucleosides, which are usually described by a two-state conformational equilibrium.

In order to express $^3J_{H,H}$ as a single function of P in eq. (2), the parameters a, b, c, and the puckering amplitude (ϕ_m) of the ring under study, must be determined. Thus, ϕ_m for a sulfur containing five-membered ring was estimated by means of molecular mechanics calculations on a chosen model compound, the tetrahydrotiophene (THT). The conformation of lower energy for THT was established by employing the Still's PCMODEL program (from Serena Software, Bloomington, Indiana), which incorporates Allinger's MM2 program.[16] From the structure of minimum energy the ϕ_j and hence the $\phi_{H,H}$ angles were measured. Starting at the C-2—C-3 bond (j=0) the values along the ring were: ϕ_0=-50.6°, ϕ_1=38.6°, ϕ_2=-14.3°, ϕ_3 =-13.7°, and ϕ_4 =38.2°. A phase angle of pseudorotation P and a puckering amplitude ϕ_m of 180.4° and 48.6°, respectively, were determined from the ϕ_j angles, using relationships previously described.[15]

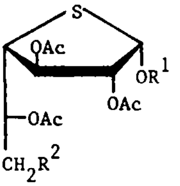
The calculated ϕ_m for THT (48.6°) is larger than the calculated by the same procedure, for tetrahydrofuran (THF), ϕ_m=40.3°. This latter value is in good agreement with those obtained by X-ray diffraction for other furanose rings,[13,17] and further supports the methodology employed for calculating ϕ_m.

We have assumed a fixed value of ϕ_m (48.6°) for THT and its derivatives, as this value was similar to that calculated for 1,2,3,5-tetra-*O*-acetyl-6-deoxy-4-thio-α-D-galactofuranose (2, ϕ_m =49.2°), by the PCMODEL from an energy local minimum, generated without taking into account stereoelectronic effects. Furthermore, the geometry of the ring may be adjusted through the parameters a, b, and c, in eq. (2), by correcting the deviations of bond angles from their ideal tetrahedral or trigonal projection values. Fitting eq. (1) to the torsion angles $\phi_{H,H}$, measured from the structure of lower energy of THT, twelve equations of $\phi_{H,H}$ as a function of a, b, and c, with P=180.4° and ϕ_m =48.6°, were obtained. From these equations the parameters a=119.5°, b=1.095, and c=-0.335° were calculated by the least square method extended to two variables. Those values allowed to estimate the torsion angles $\phi_{H,H}$, with a root-mean-square (rms) difference of 0.2°. Similarly, values of ϕ_m =40.3°, a=122.4°, b=1.11, and c=1.28° were obtained for the THF ring.

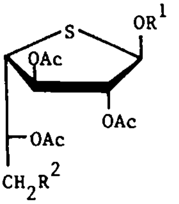
RESULTS AND DISCUSSION

Resolution of eq. (2) for a furanose gives the expected variation of $^3J_{H,H}$ for different conformations. Although a single value of $^3J_{H,H}$ may correspond to several different pseudorotamers, a set of three coupling constants ($J_{1,2}$, $J_{2,3}$, and $J_{3,4}$) may allow the assignment of conformational preferences for a furanoid ring, in accordance with the best fit between calculated and experimental J values. When a good correlation is obtained within a narrow region of the pseudorotational itinerary, this will be considered the preferred conformation for the analyzed system. To test the reliability of this procedure, we have calculated the conformation of conformationally stable furanose rings, and compared them with the conformation determined by other methods.[6-8,10] An excellent agreement was usually obtained. We have also verified that for furanoid derivatives, which populate opposite segments of the itinerary,[13] no single region can be identified which matches calculated and experimental couplings, but a good fit was obtained by averaging the calculated J for those opposite segments.

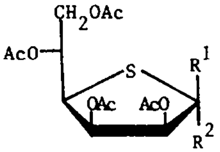
Besides a good correlation between the calculated and experimental J values, the following additional criteria of stability[5,6] of a furanose ring were considered for conformational assignments: (a) the anomeric substituent will prefer a *quasi*-axial orientation (anomeric effect), (b) the bulky side chain will tend to take up a *quasi*-equatorial disposition, and (c) ring substituents will locate in staggered orientation, to avoid eclipsing interactions. Also, for the sulfur containing five-membered rings, 1,3-diaxial interactions between substituents and lone electron pairs of sulfur ("hockey sticks" effect[18]), were considered.



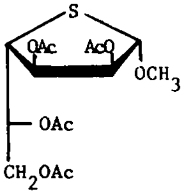
1 R^1=Ac, R^2=OAc
2 R^1=Ac, R^2=H
3 R^1=CH_3, R^2=OAc



4 R^1=Ac, R^2=OAc
5 R^1=Ac, R^2=H
6 R^1=CH_3, R^2=OAc



7 R^1=H, R^2=OAc
8 R^1=OAc, R^2=H



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Resolution of eq. (2) for compound 1 is shown in table I. Examination of the table allows identification of a single segment of the pseudorotational cycle, which matches with the observed J values[1,2] for compounds 1, 2, and 3 (for 1 $J_{1,2}$ 4.3, $J_{2,3}$ 9.7, and $J_{3,4}$ 7.7 Hz). This segment corresponds to P=144-180°, which would indicate a distortion of the ring in the region of C-2, and hence a $^2T_1 \rightleftharpoons {}^2E \rightleftharpoons {}^2T_3$ conformation for those compounds. The rms between calculated and experimental couplings (for example rms 0.7 Hz for the ^2E conformation of 2) lay below the value (1 Hz) considered limiting to indicate no serious errors in the model used.[14] Furanoses configurationally related to 1-3 adopt in solution[5] and in the crystalline state[17] a $^2T_1$ conformation. The shift in the ring distortion from C-2 in the 4-thiofuranose to C-1 in the furanose may be attributed to the weaker anomeric effect in sulfur systems when compared with oxygen systems.[19]

Table I. Calculated $^3J_{H,H}$ values (Hz) for compound 1, (ϕ_m=48.6°).

Conform.	*P*(°)	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	*Conform.*	*P*(°)	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$
$^3T_2$	0	4.5	3.3	1.5	$^2T_3$	180	4.7	9.0	9.7
^3E	18	5.9	2.9	2.3	E_3	198	6.1	8.7	10.5
$^3T_4$	36	7.4	2.0	2.7	$^4T_3$	216	7.5	7.8	10.8
E_4	54	8.1	0.9	2.3	^4E	234	8.1	6.0	10.5
$^0T_4$	72	7.5	0.6	1.5	$^4T_0$	252	7.4	3.6	9.7
^0E	90	6.1	1.5	0.7	E_0	270	5.9	1.5	7.9
$^0T_1$	108	4.7	3.6	0.9	$^1T_0$	288	4.5	0.6	5.2
E_1	126	3.7	6.0	2.5	^1E	306	3.5	0.9	2.5
$^2T_1$	144	3.4	7.8	5.2	$^1T_2$	324	3.2	2.0	0.9
^2E	162	3.7	8.7	7.9	E_2	342	3.5	2.9	0.7

Resolution of eq. (2) for 4-thio-β-D-galactofuranose derivatives (4, 5, and 6) gave a poor correlation between calculated and observed values, unless a broad segment or different sides of the pseudorotational itinerary are populated. Nevertheless, the $^4T_3$ conformer seems to contribute considerably to the conformational equilibrium of those compounds. Interestingly, the J values[1,2] for 4, 5, and 6 (for 6, $J_{1,2}$ 2.5, $J_{2,3}$ 5.0, and $J_{3,4}$ 5.3 Hz) greatly differ from those observed for methyl 2,3,5,6-tetra-*O*-benzoyl-β-D-galactofuranoside[20] ($J_{1,2}$ <1, $J_{2,3}$ 1.1, and $J_{3,4}$ 5.4 Hz). Methyl β-D-galactofuranoside would populate the $^1T_0$ segment of the itinerary[5] which appears to be the most stable, as the O-1 is *quasi*-axial, the lateral chain *quasi*-equatorial, and it is free of 1,2- or 1,3-interactions. However, in the 4-thio-β-D-galactofuranose derivatives (4-6), the $^1T_0$ conformation would be destabilized by the weaker anomeric effect and by the repulsive "hockey sticks" effect[18] of the *quasi*-axial lone pair of the ring-sulfur atom and the *quasi*-axial acetoxy group at C-2.

Conformational analysis was also performed for peracetylated derivatives of 4-thio-α- (7) and β-D-mannofuranose[21] (8), and for methyl 4-thio-α-D-talofuranoside[22] (9). The calculated couplings for compound 7 showed a good correlation with the experimental values ($J_{1,2}$ 6.6, $J_{2,3}$ 3.4, and $J_{3,4}$ 3.9 Hz) for the $^3T_2$ segment of the itinerary (calculated J for $^3T_2$: $J_{1,2}$ 7.7, $J_{2,3}$ 3.4, and $J_{3,4}$ 4.2 Hz). In this conformation the lateral chain is *quasi*-equatorially disposed, and 1,2- and 1,3-interactions are absent. The tetraacetate of methyl α-D-mannofuranoside ($J_{1,2}$ 3.0 Hz) is partly in the opposite $^2T_3$ form,[5] likely owing to the larger anomeric effect.

The coupling data for 4-thio-β-D-mannofuranose pentaacetate (8) fit, similar to its α-anomer 7, the $^3T_2$ conformation, with the anomeric substituent in a favorable *quasi*-axial disposition. Probably for this reason, the methyl β-D-mannofuranoside was also found in the $^3T_2$ conformation.[5]

The distortion of the ring of methyl 4-thio-α-D-talofuranoside peracetate[22] (9) would occur in the C-2—C-3 region in order to avoid eclipsing 1,2-interactions between the vicinal, *cis* acetate groups. The calculated J values for the $^2T_3$ conformation ($J_{1,2}$ 2.0, $J_{2,3}$ 3.2, and $J_{3,4}$ 9.7 Hz) showed an excellent correlation with the experimental values ($J_{1,2}$ 1.7, $J_{2,3}$ 3.5, and $J_{3,4}$ 8.9 Hz). This conformation is free of eclipsing or dipolar interactions, satisfies the anomeric effect and locates the bulkier substituent, the lateral chain, *quasi*-equatorially. Similarly, methyl α-D-talofuranoside prefers a $^2T_3$ conformation.[5]

The different conformational behavior of the five-membered ring of furanoses and 4-thiofuranoses, having the same configuration, seems to be the result of the different magnitude of the anomeric effect in each system. This effect appears to dominate all other factors in determining ring conformation in furanoses,[6] but being weaker in 4-thiofuranose rings, their conformation may be also determined by other competing non-bonded interactions. In this case, as the anomeric effect is not able to block the furanoid ring in a single conformation, the assignment[23] of the anomeric configuration on the basis of J values must be done with caution. The rule that $J_{1,2} < 4.0$ Hz is diagnostic of a *trans* relationship for H-1, H-2 in a furanose,[23] is not valid for example for compound 7, and it could be also invalid for conformationally unstable oxygen containing five-membered ring.

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