Original Article[1]

^{1}H and ^{13}C NMR conformational properties calculated by Spartan 18, and 400/125.77 MHz experimental data of methyl β-orcinolcarboxylate and atranorin, a comparative study

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Keys: *NMR spectra, Spartan 18 software, Atranorin, Methyl β-orcinolcarboxylate, Chemical shifts, Lichens;* **Claves:** *Espectros de RMN, Software Spartan 18, Atranorina, Metil β-orcinolcarboxilato, Desplazamienros químicos, Líquenes.*

ABSTRACT

^{1}H and ^{13}C NMR properties calculated by Spartan 18 and 400/125.77 MHz experimental data of methyl β-orcinolcarboxylate and atranorin, a comparative study The structural parameters of methyl β-orcinolcarboxylate and atranorin were determined by B3LYP with the base set 6-31G*. The results of the optimized molecular structure are presented and compared with the available X-ray data of the molecules. A comparative analysis of the experimental ^{1}H and ^{13}C NMR spectra and calculated values is exposed and discussed. The theorectical quantum calculations resulted a good predictive structural determination approach for small organic molecules.

RESUMEN

Propiedades conformacionales de RMN de ^{1}H y ^{13}C calculadas con Spartan 18 y datos experimentales de 400/125,77 MHz de β-orcinolcarboxilato de metilo y atranorina, un estudio comparativo . Los parámetros estructurales del metil β-orcinolcarboxilato y la atranorina se determinaron mediante B3LYP con el conjunto base 6-31G*. Se presentan los resultados de la estructura molecular optimizada y se comparan con los datos de rayos X disponibles de las moléculas. Se expone y discute un análisis comparativo de los espectros de RMN ^{1}H y ^{13}C experimentales y los valores calculados. Los cálculos cuánticos teóricos dieron como resultado un buen enfoque de determinación estructural predictiva para moléculas orgánicas pequeñas.

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INTRODUCTION

Methyl β-orcinolcarboxylate (**1**) and atranorin (**2**) (Fig. 1) are important natural products isolated from Bolivian Lichens. Atranorin has been characterized in *Stereocaulon strictum*[1] *Stereocaulon ramulosum*[2], *Stereocaulon tomentosum*[3], *Physcia sorediosa*[4]; methyl β-orcinolcarboxylate is present in *Stereocaulon ramulosum*[2]. These compounds are reknown for manifesting a wide variety of biological activities, including antioxidant, antibacterial, anticancer, and antiangiogenic[5 6 7 8 9 10 11 12 13 14] among others. The growing interest in these compounds and their potential use in medical applications is evidenced by the increasing number of publications. Hence, correct structural determination and knowledge about the three-dimensional (3D) atomic structure are essential. NMR experimental data are employed in comparison with electronic and conformational properties of methyl β-orcinolcarboxylate and atranorin resulting from theoretical calculations. In the present comparative study of methyl β-orcinolcarboxylate and atranorin, precise quantum mechanical calculations were carried out, both in vacuo, with the aim of analyzing the conformational equilibria and finding the most stable corresponding equilibrium of the structures. This work is framed in a project that started with the computer-assisted study of ^{1}H and ^{13}C NMR spectra of 4-hydroxy-3-(3'-methyl-2'-butenyl)acetophenone isolated from *Senecio graveolens* and its microwave-assisted synthetic derivate, 4'-hydroxy-3'-(3-methyl-2-butenyl)chalcone[15].

EXPERIMENTAL

NMR system and operating conditions

Spectra were run at 400 MHz and 125.77 MHz for ^{1}H and ^{13}C NMR, respectively, using $CDCl_3$ as solvent. NMR assignments were done based on ^{1}H, ^{13}C 1D NMR and ^{1}H-^{13}C HSQC and HMBC 2D NMR experiments.

Compound (**1**), White crystals; m.p. 140 ºC; ^{1}H NMR ($CDCl_3$), (400 MHz); δ 3.9 (3H, *s*, H-10), 2.4 (3H, *s* , H-8), 2.1 (3H, *s*, H-9), 6.2 (1H, *s*, H-5). ^{13}C NMR ($CDCl_3$), (125.77 MHz); δ 172.6, 162.6, 159.5, 139.8, 110.6, 108.9, 104.9, 51.5, 23.8, 7.5.

Compound (**2**), White crystals; m.p. 140 ºC; ^{1}H NMR ($CDCl_3$), (400 MHz); δ 6.44 (1H, *s*, H-5), 6.56 (1H, *s*, H-5'), 2.71 (3H, *s*, H-8), 10.39 (1H, *s*, H-9), 2.11 (3H, *s*, H-8'), 2.59 (3H, *s*, H-9'), 4.05 (3H, *s*, CH_3O-7'), 12.53 (1H, *s*, OH), 12.59 (1H, *s*, OH). ^{13}C NMR ($CDCl_3$), (125.77 MHz); δ 103.8, 169.3, 108.8, 167.7, 113.1, 152.6, 169.9, 25.7, 194.0, 117.0, 163.1, 110.5, 152.2, 116.2, 140.1, 172.4, 24.2, 9.6, 52.5.

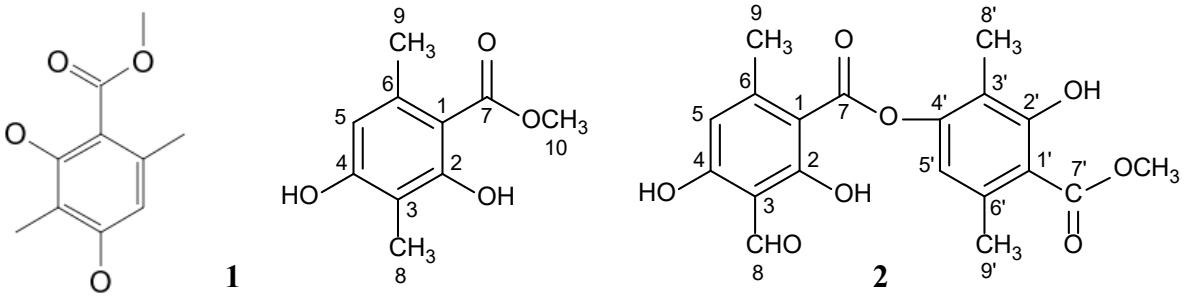

Fig. 1. Methyl β-orcinolcarboxylate (**1**); atranorin (**2**)

Computational details

The geometry of structures was optimized with the DFT methodology using ^{13}C NMR chemical shifts of the compounds. In (**1**) each geometrically optimized conformer was calculated using the parameter B3LYP/631G* basis sets. The calculations for (**2**) were carried out in the same way as for (**1**). Molecular mechanics calculations were performed using the Spartan 18 modeling software. Solvent effects were not taken into account in any calculation. From X-ray crystallography data[16 17] the existence of compounds (**1**) and (**2**) in their solid state was known. In the present work we investigated all possible conformers of methyl β-orcellinate and atranorin in order to establish a reliable starting point to further theoretically explore the complexing ability of these compounds.

RESULTS AND DISCUSSION

From X-ray crystallography data[16 17] a randomized conformational search of the methyl β-orcinolcarboxylate and atranorin was performed. The 8 more significant conformations of methyl β-orcinolcarboxylate and its ^{13}C NMR chemical shifts were saved (Fig. 2). Figures 3 and 4 show that the two most significant conformers of methyl β-orcinolcarboxylate, have the intramolecular hydrogen bond between the 2-O**H** and 7-C=**O**. They also show the two conformer differences in the 4-OH positions. Conformer I (Fig. 2) exhibits the dihedral angle of 179.24 and in conformer II the angle is 0.26 (Fig. 3). Table 1 shows the calculated (δ_{calc}) and experimental (δ_{exp}) ^{13}C-NMR, ^{1}H-NMR chemical shifts. Data comparison showed agreement between experimental and calculated NMR chemical shifts to an acceptable degree for conformer II. The comparison with image derived from X-ray analysis[16] (Fig.5) ratifies the spectral and calculated data ($C_{10}H_{12}O_4$, M_r = 196.2, Monoclinic, $P2_1/c$, a = 7.043 (2) Å, b = 18.142 (7) Å, c = 7.238 (2) Å, β = 96.44 (2)°, V = 918.9 (4) Å^3, Z = 4) [16]. The results presented in table 1 and 2 demonstrate an excellent predictive ability of this method for ^{1}H and ^{13}C NMR.

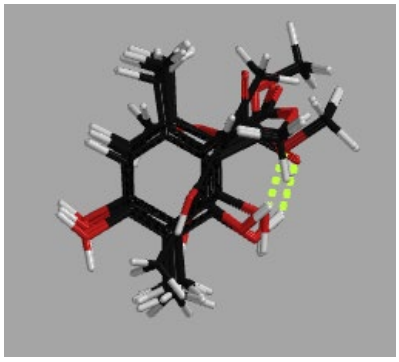

Fig. 2. Eigth Conformers

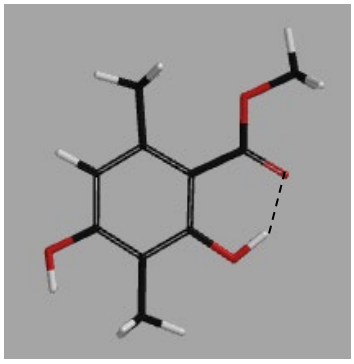

Fig. 3. Conformer I

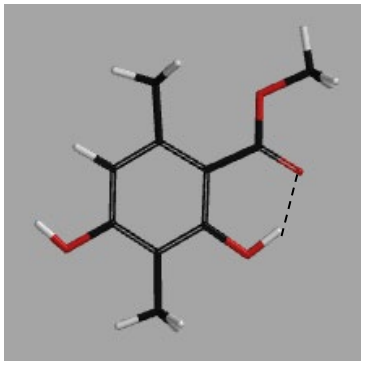

Fig. 4. Conformer II

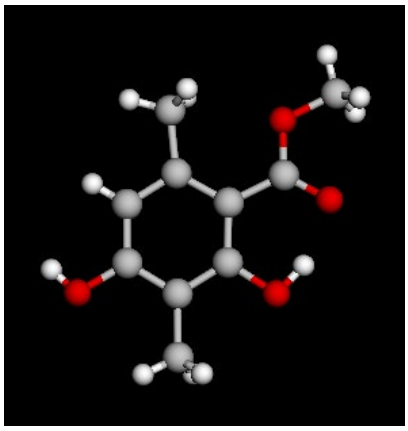

Fig. 5. X-ray crystallography[15]

Table 1. Experimental and calculated ^{13}C-NMR chemical shifts, $CDCl_3$,δ from TMS, conformers I and II, compound **1**

			Conformer I	Conformer II
Atom		Exp. δ (ppm) ^{13}C	Calc. δ (ppm) ^{13}C	Calc. δ (ppm) ^{13}C
1	**C**	104,9	104,2	104,5
2	**C**	162,6	163,4	165,2
3	**C**	108,9	105,8	110,7
4	**C**	159,5	158,3	156,0
5	**C**H	110,6	110,2	109,2
6	**C**	139,8	142,0	140,2
7	**C**=O	172,6	173,6	173,3
8	**C**H_3	23,8	25,5	25,3
9	**C**H_3	7,5	6,6	10,0
OCH3	**C**H_3	51,1	51,9	51,9

Atranorin (**2**) being a more complex molecule than compound **1**, 128 conformers (at least) can be determined out of calculations using our current-use method. Thus, the fully optimized structure of atranorin was obtained at the *B3LYP/6-31G** level. Two conformers were picked out and saved, ^{13}C-NMR and ^{1}H-NMR chemical shifts were scaled.

Table 2. The experimental and calculated ^{1}H-NMR chemical shifts,$CDCl_3$,δ from TMS, conformers I and II, compound **1**

			Conformer I	Conformer II
Atom		Exp. δ (ppm) ^{1}H	Calc. δ (ppm) ^{1}H	Calc. δ (ppm) ^{1}H
1	C			
2	C			
3	C			
4	C			
5	C**H**	6,2	6,0	5,4
6	C			
7	C=O			
8	C**H$_3$**	2,4	2,3	2,3
9	C**H$_3$**	2,1	1,9	2,0
OCH3	C**H$_3$**	3,9	3,8	3,8

Tables 3 and 4 show the calculated (δ_{calc}) and experimental (δ_{exp}) ^{13}C-NMR and ^{1}H-NMR chemical shifts of compound 2, respectively. The data comparison demonstrated a great agreement between experimental and calculated NMR chemical shifts for conformers A (Fig. 6) and B (Fig. 7). On the other hand, the comparison of X-ray crystallography structure of Fig. 8,[17] ($C_{19}H_{18}O_8$, M_r = 374.33 Monoclinic, $P2_1/n$, a = 10.929 (3) Å, b = 10.976 (3) Å, c = 14.843 (3) Å, β = 109.745 (12)°, V = 1675.7 (7) Å^3, Z =4)[17] with both conformers shows a good matching with conformer B . These results (Tables 3 and 4) demonstrate an excellent predictive ability of the method for ^{1}H and ^{13}C NMR data.

The two aromatic rings form a dihedral angle of 60.38°, differing from the previously reported *Pbca* polymorph, *viz*. 84°.[5] In this work we calculated at the *B3LYP/6-31G** two conformers A and B with the two aromatic rings forming a dihedral angle of 86.95°, different from the reported by X-ray crystallography. Nevertheless there is good agreement with the experimental values of NMR ^{1}H and ^{13}C.

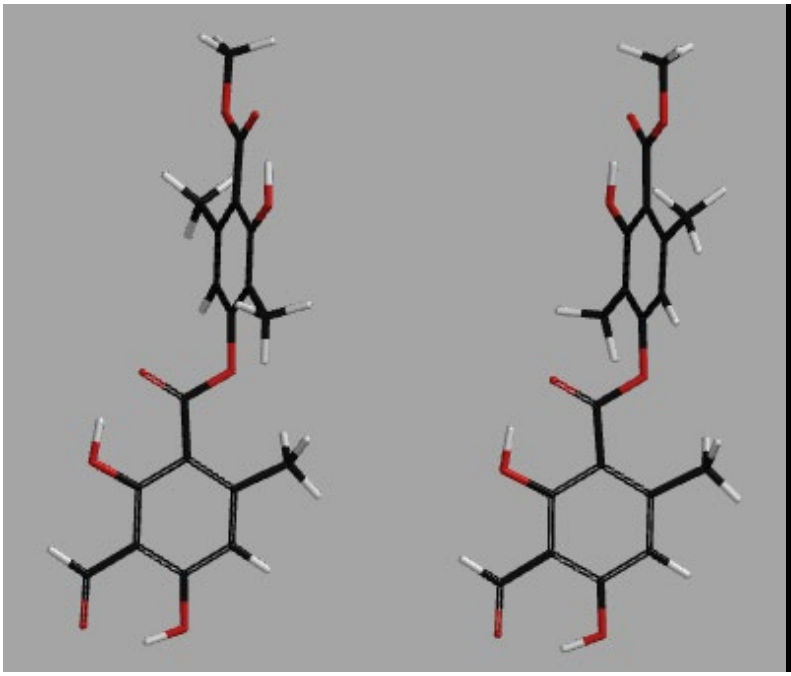

Fig. 6. Conformer A

Fig. 7. Conformer B

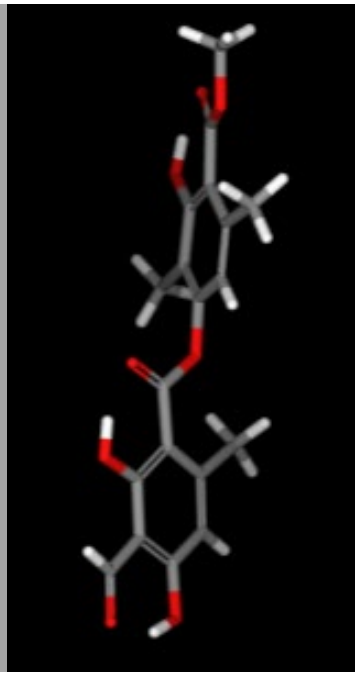

Fig. 8. X-ray image[17]

Data statistical approach

Plotting the experimental ^{13}C NMR (δ_{exp}) in $CHCl_3$ vs. the δ_{calc} for all species, a linear regression is obtained. This relationship is used to predict the chemical shifts (δ_{calc}).

Table 3. The experimental and calculated ^{13}C-NMR chemical shifts, $CDCl_3$, δ from TMS, compound A and B

			Conformer A	Conformer B
Atom		Exp. δ (ppm) ^{13}C	Calc. δ (ppm) ^{13}C	5 Calc. δ (ppm) ^{13}C
1	C	103,1	102,1	102,3
2	C	169,3	169,8	169,7
3	C	108,8	109,1	109,1
4	C	167,7	167,5	167,5
5	CH	113,1	113,0	113,1
6	C	152,6	152,0	151,9
7	C=O	169,9	171,5	172,0
9	CH_3	25,7	26,2	25,2
8	CHO	194,0	192,4	192,4
1’	C	110,5	109,0	108,9
2’	C	163,1	164,6	164,9
3’	C	117,0	120,1	119,5
4’	C	152,2	153,5	153,3
5’	CH	116,2	116,5	117,3
6’	C	140,1	140,6	140,4
7’	C=O	172,4	174,0	174,0
8’	CH_3	24,2	25,2	25,2
9’	CH_3	9,6	11,6	11,4
OCH_3	OCH_3	52,5	52,4	52,4

Table 4. The experimental and calculated ^{1}H-NMR chemical shifts,$CDCl_3$, δ from TMS, conformers A and B

			Conformer A	Conformer B
Atom		Exp. δ (ppm) ^{1}H	Calc. δ (ppm) ^{1}H	Calc. δ (ppm) ^{1}H
1	C			
2	C			
3	C			
4	C			
5	CH	6,44	5,9	5,9
6	C			
7	C=O			
9	CH_3	2,71	2,4	2,4
8	CHO	10,39	10,3	10,3
1’	C			
2’	C			
3’	C			
4’	C			
5’	CH	6,56	6,2	6,2
6’	C			
7’	C=O			
8’	CH_3	2,11	2,4	2,4
9’	CH_3	2,59	2,0	2,0
OCH_3	OCH_3	4,05	3,9	3,9

The correlation between experimental chemical shifts and calculated isotropic screening constants for ^{13}C, shows a homogeneous behavior for ^{13}C independently on the calculated species with a correlation coefficient R^2 0.9974 for methyl β-orcinolcarboxylate (Fig. 9) and 0.9966 for atranorin (Fig. 10).

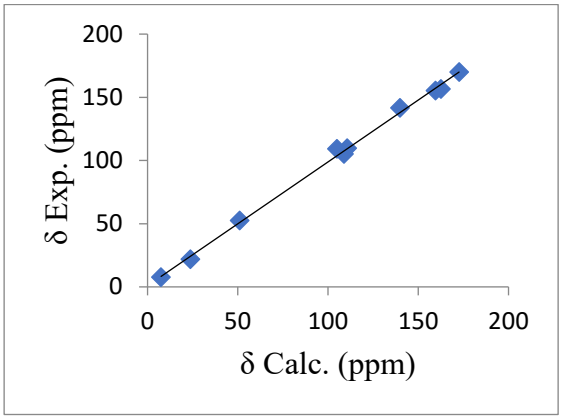

Fig. 9. Experimental chemical shifts of methyl β-orcinolcarboxylate vs. isotropic magnetic from /B3LYP/6-31G* calculations for ^{13}C

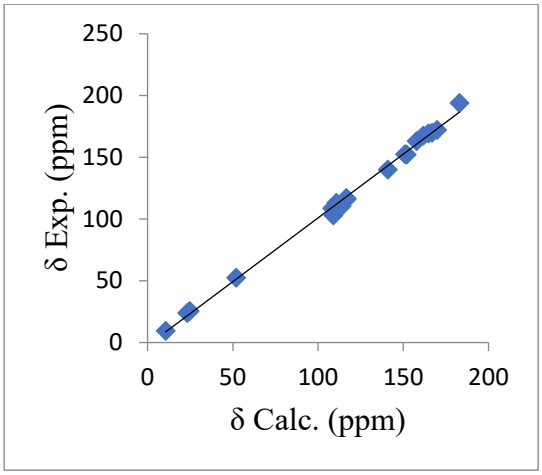

Fig. 10. Experimental chemical shifts of atranorin vs. isotropic magnetic from /B3LYP/6-31G* calculations for ^{13}C

CONCLUSION

The experimental geometric parameters of the compound are comparable to the calculated values. The molecular structure was established by the evidence of short intra-molecular contact interactions. The ^{1}H and ^{13}C NMR chemical shifts calculations showed an excellent agreement with the experimental data. Overall, the agreement between theoretical and experimental values is agreeable for every structural and spectroscopic calculation. From X-ray bibliography we established the more stable conformers of **1** and **2,** II and B, respectively.

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