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Correlations among experimental and theoretical NMR data to determine the absolute stereochemistry of darcyribeirine, a pentacyclic indole alkaloid isolated from *Rauvolfia grandiflora*

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ABSTRACT

Darcyribeirine (**1**) is a pentacyclic indole alkaloid isolated from *Rauvolfia grandiflora*. Stereochemistry of **1** was previously proposed based on 1D (coupling constant data) and 2D (NOESY correlations) NMR techniques, having been established a configuration 3*R*, 15*S*, and 20*R* (isomer **1a**). Stereoisomers of **1** (i.e., **1a**–**1h**) can be grouped into four sets of enantiomers. Carbon chemical shifts and hydrogen coupling constants were calculated using BLYP/6-31G* theory level for the eight isomers of **1**. Calculated NMR data of **1a**–**1h** were correlated with the corresponding experimental data of **1**. The best correlations between theoretical and experimental carbon chemical shift data were obtained for the set of enantiomers **1e**/**1f** to structures in the gaseous phase and considering solvent effects (using PCM and explicit models). Similar results were obtained when the same procedure was performed to correlations between theoretical and experimental coupling constant data. Finally, optical rotation calculations indicate **1e** as its absolute stereochemistry. Orbital population analysis indicates that the hydrogen bonding between N–H of **1e** and DMSO is due to contributions of its frontier unoccupied molecular orbitals, mainly LUMO+1, LUMO+2, and LUMO+3.

1. Introduction

Nuclear Magnetic Resonance (NMR) is a spectroscopic method which has widely used for structural determination of many organic compounds, mainly from the early 1970s [1,2]. Initially, hydrogen coupling constant though two and three bonds ($^2J_{H,H}$ and $^3J_{H,H}$, respectively) and hydrogen and carbon chemical shifts (δ_H and δ_C, respectively) gave useful and important information about chemical structure of a significant amount of organic compounds [3,4]. However, only the use of one-dimentional (1D) NMR experiments was not enough sufficient to structural elucidation of many other organic compounds.

Structural information was considerably better when two-dimensional (2D) NMR techniques were applied to investigate the stereochemistry of organic compounds, mainly ^1H–^{13}C-HSQC, ^1H–^{13}C-HMBC, ^1H–^1H–COSY, and ^1H–^1H-NOESY techniques. As a result, the literature describes an exponentially increasing number of new organic compounds which had their structures fully elucidated from the use of 2D NMR techniques [5–7]. Moreover, 2D NMR techniques have been largely used to revision of hydrogen and carbon chemical shift data previously described in the literature for organic compounds of different chemical classes. Thus, a correct attribution of NMR signals can also be usually established for hydrogen and carbon atoms of natural products [8–12].

However, this powerful experimental tool does not allow determine the stereochemistry of certain natural products, especially for those ones which do not adequately crystallize to X-ray diffraction analysis and 2D NMR techniques do not provide sufficient information to their structural analysis. In addition, enlargement or even disappearance of the resonance signals has been observed on the NMR spectra mainly for hydrogen and carbon atoms bonded to nitrogen atoms, due to its quadrupole moment [13].

An alternative procedure to structural elucidation of natural

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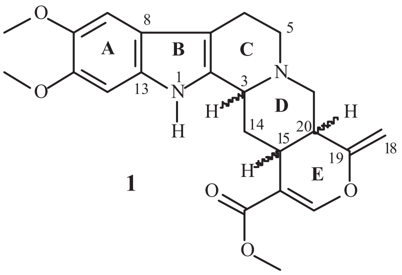

1

1a: H-3β; H-15α; H-20α ($\beta\alpha\alpha$ configuration)
1b: H-3α; H-15β; H-20β ($\alpha\beta\beta$ configuration)
1c: H-3β; H-15β; H-20α ($\beta\beta\alpha$ configuration)
1d: H-3α; H-15α; H-20β ($\alpha\alpha\beta$ configuration)
1e: H-3β; H-15β; H-20β ($\beta\beta\beta$ configuration)
1f: H-3α; H-15α; H-20α ($\alpha\alpha\alpha$ configuration)
1g: H-3β; H-15α; H-20β ($\beta\alpha\beta$ configuration)
1h: H-3α; H-15β; H-20α ($\alpha\beta\alpha$ configuration)

Fig. 1. Chemical structure of the different isomers of darcyribeirine (**1**): sets of enantiomers **1a**/**1b**, **1c**/**1d**, **1e**/**1f**, and **1g**/**1h** (β and α configurations are position in front of and behind the plane of the molecule, respectively).

Table 1
BLYP/6-31G* electronic-nuclear energies (*E*) calculated for **1a**–**1h**, considering structures in the gaseous phase and without intermolecular interactions, including energy variations in relation to **1e**/**1f** (ΔE) and dipole moment values.

Set of enantiomers	Configuration	Energy (*E* in Hartree)	ΔE (kcal/mol)	Dipole moment (μ in Debye)
1a/**1b**	$\beta\alpha\alpha/\alpha\beta\beta$	−1377.13431310	2.98	1.884
1c/**1d**	$\beta\beta\alpha/\alpha\alpha\beta$	−1377.13753223	0.95	2.585
1e/**1f**	$\beta\beta\beta/\alpha\alpha\alpha$	−1377.13905926	0.00	2.282
1g/**1h**	$\beta\alpha\beta/\alpha\beta\alpha$	−1377.12776604	7.09	2.928

products has been computational predictions of hydrogen and carbon chemical shift data, by correlating them with corresponding experimental data [14]. Correlations between calculated and experimental data of hydrogen and carbon chemical shifts provide more accurate results to structural analysis of some organic compounds than the corresponding thermodynamic calculations [15]. Moreover, carbon chemical shift calculations have been an important tool for reinforcing the NMR signal assignments of mixtures of isomers [16–18].

The present work describes the use of carbon chemical shift and hydrogen coupling constant calculations to determine the absolute stereochemistry of darcyribeirine (**1** in Fig. 1), a pentacyclic indole alkaloid isolated from *Rauvolfia grandiflora* [19]. Alkaloids are largely found in vegetal species of different families, obtained from metabolic processes involving amino acids [20], and exhibit a large spectrum of biological activities [21–23]. Chemical structure of **1** has three stereocenters, i.e., the asymmetric carbon atoms placed on C-3, C-15, and C-20 (see Fig. 1). NOESY correlation data provided little information about the stereochemistry of **1** [19]. Even so, the proposed stereochemistry for this alkaloid (**1a** in Fig. 1) was also based on coupling constant data recorded in the ^{1}H NMR spectrum, which suggested configuration H-3β, H-15α, and H-20α ($\beta\alpha\alpha$ configuration). However, the absolute stereochemistry of **1** has not been determined.

BLYP/6-31G* theoretical calculations were employed to geometry optimization and to evaluate the carbon chemical shifts and hydrogen coupling constants of **1**. This theory level has been efficiently employed to structural determination of different organic compounds containing nitrogen [24–26]. Moreover, optical rotation data were considered to establish its absolute stereochemistry.

2. Computational details

Theoretical studies were carried out using the software package Gaussian 09 [27]. Geometries previously obtained from PM3 semi-empirical calculations [28] were used as initial models in the geometry optimizations employing BLYP calculations with the 6-31G* Pople's split valence basis set [29–33]. Theoretical calculations were performed for the eight isomers of **1** (**1a** to **1h** in Fig. 1). The optimized geometries were characterized as true minima on the potential energy surface (PES) when all harmonic frequencies were real.

The electronic-nuclear energy (*E*) of the optimized geometries was given in atomic units (a.u.; Hartree). The polarizable continuum model (PCM), as implemented in the package Gaussian 09, was taken into account to investigate solvent effect (DMSO, $\varepsilon = 46.7$) on the geometry optimizations using BLYP/6-31G* calculations [34,35]. Solvent effect was also investigated by the use of an explicit solvent model [25]. In this case, one DMSO molecule was randomly placed close to the oxygen- or nitrogen-functionalized sites of **1a**–**1h**. Geometry of the corresponding systems was previously obtained by PM3 semi-empirical calculations and used as initial model to the further geometry optimizations also using BLYP/6-31G* calculations. The energy of the isomer–solvent interactions was calculated by the combination of the formation energy of each system with those separately calculated for the correspondent isomer and solvent (DMSO).

Molecular orbital energies were calculated for optimized geometries at the same level of theory. Orbital populations (c^2) of atoms were calculated from the sum of the square of their contributions in each molecular orbital.

The optimized geometries were used to carbon chemical shift calculations at the same level of theory. Values of calculated carbon chemical shift (σ_C) were determined in relation to the corresponding calculated values for tetramethylsilane (σ_C 187.97 ppm). Calculated carbon chemical shifts were correlated with the corresponding ^{13}C NMR data (125 MHz; DMSO-d$_6$) previously described in the literature for **1** [19]. Correlations between σ_C values and experimental carbon chemical shifts (δ_C) were obtained using the software package Origin™ Standard 7.5. The δ_C and σ_C values were plotted on the *x* and *y* axes, respectively. The δ_C/σ_C correlation curves were given as linear fits with correlation coefficients (R^2) and slope of the R^2 curve (α) furnished by the program.

Table 2
Adjusted linear correlation coefficient (R^2), mean-square error (*MSE*), and slope (α) values of σ_C/δ_C correlations for **1a**–**1h** from BLYP/6-31G* calculations, considering structures in the gaseous phase and without intermolecular interactions.

Set of enantiomers	Configuration	R^2	*MSE* (ppm)	α
1a/**1b**	$\beta\alpha\alpha/\alpha\beta\beta$	0.99586	8.885	1.090
1c/**1d**	$\beta\beta\alpha/\alpha\alpha\beta$	0.99420	12.397	1.105
1e/**1f**	$\beta\beta\beta/\alpha\alpha\alpha$	0.99540	9.827	1.105
1g/**1h**	$\beta\alpha\beta/\alpha\beta\alpha$	0.99576	9.080	1.085