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Quantum Chemical Calculations of $^{1}J_{CC}$ Coupling Constants for the Stereochemical Determination of Organic Compounds

Giuseppe Bifulco,*,† Raffaele Riccio,† Gary E. Martin,‡ Alexei V. Buevich,§ and R. Thomas Williamson*,‖

Dipartimento di Farmacia, Università di Salerno, Via Ponte Don Melillo, 84084 Fisciano (SA), Italy, Merck Research Laboratories Discovery and Preclinical Sciences, Process and Analytical Chemistry – Structure Elucidation Group Summit, New Jersey 07901, Kenilworth, New Jersey 07033, and Rahway, New Jersey 07065, United States

bifulco@unisa.it; robert.williamson2@merck.com

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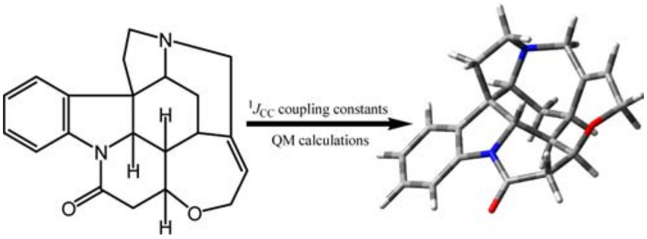
ABSTRACT



Quantum chemical calculations of one-bond carbon–carbon coupling constants are demonstrated as potential probes for the configurational assignment of organic molecules. The stereochemical analysis of strychnine and its possible stereoisomers is presented as proof of concept.

The use of NMR parameters combined with quantum mechanical calculations has recently emerged as a promising tool for the investigation of the relative configuration of organic molecules.[1] In particular, the comparison of experimental NMR chemical shifts with the calculated results for all possible stereoisomers of an unknown molecule has proven to be a facile and reliable protocol for stereochemical determination.[1] This approach has been demonstrated and reported in the literature on a wide array of structurally complex and/or flexible molecules.[2]

Besides these computer-assisted methods, the complementary *J*-based configuration analysis method (JBCA) has also proved to be a powerful tool for the determination of relative configuration.[3] The so-called JBCA method, relying on a combination of $^{3}J_{HH}$, $^{3}J_{CH}$, $^{2}J_{CH}$ coupling constants, and dipolar coupling information has been widely used for the configurational assignment of complex natural products.[1] At the core of this method lies the Karplus-like relationship between the scalar coupling constants and the dihedral angles of the atoms involved in the coupling.[4]

In an analogous and complementary fashion, quantum mechanical calculations of both homo- and heteronuclear coupling constants have been used in conjunction with

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† Università di Salerno
‡ Merck & Co. Inc., Summit, NJ
§ Merck & Co. Inc., Kenilworth, NJ
‖ Merck & Co, Inc., Rahway, NJ

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experimental NMR data and applied extensively for the determination of the configuration of organic compounds.[5] Recently, as a result of the sensitivity advances in state-of-art cryogenic NMR probes,[6] and thanks to a growing number of efficient pulse sequences such as *J*-modulated ADEQUATE,[7] we have demonstrated the feasibility of collecting a significant set of $^1J_{CC}$ and $^nJ_{CC}$ data even for relatively mass-limited samples.[8,9] It has also been shown that through the use of an appropriate DFT level of theory, excellent reproduction of the $^1J_{CC}$ and measurable $^3J_{CC}$ coupling constants may be achieved through calculation.[9] In particular, for strychnine a mean absolute error (MAE) of 0.84 Hz and a correlation coefficient of 0.9986 was observed in a comparison of experimental and calculated $^1J_{CC}$ and $^3J_{CC}$ NMR data.[9]

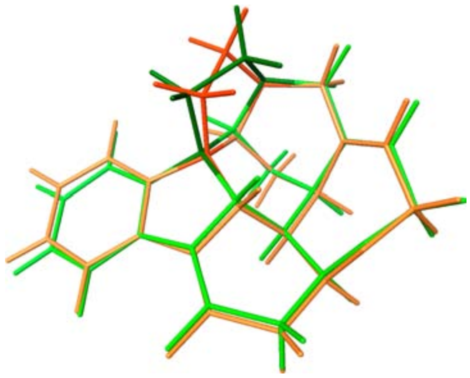

Figure 1. Lowest energy conformation (green, **1a**) and higher energy conformation (orange, **1b**) for the natural diastereomer of strychnine. The regions showing significant differences in the conformations, pertaining to C-7, C-17, C-18 and N-19, that are displayed in dark green for **1a** and dark orange for **1b**. Local differences in the geometries of **1a** and **1b** demonstrate that $^1J_{CC}$ couplings are affected by small changes in geometry.

Such high accuracy in the calculated reproduction of the experimental data, also observed by others and adopted for the analysis of the E/Z isomerism of a series of aminosulfonylamidine[10] and iminodihydrofurans,[11] prompted us to calculate the $^1J_{CC}$ coupling constants for the next higher energy conformer of strychnine, (Figure 1). Since conformer **1b** is 4.01 kcal/mol less stable than **1a**, **1b** would contribute very little (~0.11% of **1b** at 25 °C) to the conformational equilibrium. For this reason, we considered **1a** and **1b** as distinct cases without thermally averaging the pair. Comparison of the calculated and experimental data for the two different conformations of strychnine are reported in Table 1. It is noteworthy that higher energy conformer **1b** has an MAE of 1.47 Hz, significantly higher with respect to the value of 0.75 Hz observed for the natural conformer of strychnine **1a**, and despite a RMSD of only 0.524 Å between the two conformations. Most interestingly, conformer **1b** displays the largest deviations from the experimental $^1J_{CC}$ coupling constant data relative to bonds C7−C17 (5.9 Hz) and C7−C16 (3.8 Hz). In fact, these bonds make up the only differentiating connectivities between conformations **1a** and **1b**. More specifically, these bonds are involved in the ring pucker of the five-membered pyrrolidine ring in **1b** (see Figure 1).

On the basis of the above observations, which suggest the unexpected but significant variations of the $^1J_{CC}$ coupling constants dependent upon only slight conformational changes, we envisioned the possibility of conducting a stereochemical analysis based solely on the use of $^1J_{CC}$ coupling constants. These parameters are relatively easily measured in an overnight NMR experiment using a MicroCryoprobe with a few milligrams of material and should provide a practical probe for the relative configurational assignment of organic molecules.

Table 1. Calculated and Experimental $^1J_{CC}$ coupling constants for **1a** and **1b**[a]

$^1J_{CC}$	exptl, (Hz)	**1a**	**1b**
C1−C2	58.1	59.1	59.2
C2−C3	58.9	59.9	59.8
C3−C4	59.9	59.0	59.1
C4−C5	64.9	66.9	66.8
C1−C6	65.7	65.9	66.0
C7−C8	33.9	34.1	35.2
C10−C11	50.1	49.6	49.7
C11−C12	37.6	36.5	36.8
C12−C13	36.8	35.3	34.5
C8−C13	32.4	32.4	32.6
C13−C14	32.4	32.3	32.6
C14−C15	32.6	32.3	32.3
C7−C16	33.7	33.4	29.9
C15−C16	33.3	32.9	33.8
C17−C18	34.0	32.6	29.9
C20−C21	41.6	40.2	39.1
C14−C21	37.6	37.2	37.3
C21−C22	71.8	73.9	74.4
C22−C23	45.6	45.2	45.3
C7−C17	32.1	31.6	38.0
C5−C6	60.7	61.4	61.7
C6−C7	43.3	43.3	42.4
MAE, (Hz)		0.75	1.47

[a] See Figure 2 for numbering scheme.

For this purpose, we proceeded to analyze the entire array of 32 possible relative stereoisomers for strychnine. A preliminary molecular modeling investigation of all

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possible stereoisomers established that only thirteen stereoisomers, including natural strychnine, may arrange in three-dimensional structures that do not involve significant distortion of the expected geometries of all sp^3 carbon atoms in the molecule (Figure 2). The 12 structurally viable stereoisomers were subjected to an extensive conformational search at the empirical level (see Supporting Information), and the lowest energy conformers for each stereoisomer were subsequently geometry- and energy-optimized at the B3LYP/6-31G(d) level of theory.[12]

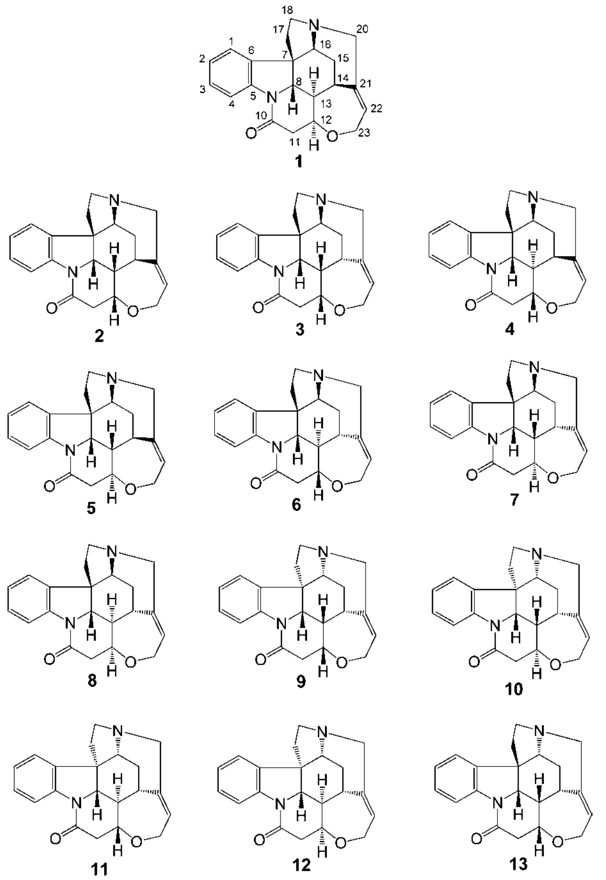

Figure 2. Twelve diastereoisomers of strychnine used for DFT calculations.

High accuracy was previously shown using the B3LYP functional and the 6-311+G(d,p) basis set in reproducing the $^1J_{CC}$ coupling constants.[9] In particular, the Fermi contacts (FC) were calculated by adding tighter polarization functions for the s and d orbitals to the original 6-311+G(d,p) basis set.[13] This level of theory was also used in the present study to calculate the theoretical $^1J_{CC}$ coupling constants for all thirteen stereoisomers of strychnine. As expected, the analysis of these data indicate the lowest MAE value (0.75 Hz) for calculated $^1J_{CC}$ coupling constants of natural strychnine **1a** (Figure 3). Larger and more significant errors are observed for all other stereoisomers. Only two of these stereoisomers, namely **4** and **9** have values close to strychnine (1.08 and 1.30 Hz, respectively), but they also display maximum errors consistently larger than the natural stereoisomer. In particular, a maximum error of 4.1 Hz is observed for stereoisomer **4** (C21–C22) and 4.4 Hz is observed for **9** (C21–C22), vs the maximum error of 2.1 Hz displayed by strychnine (see Supporting Information). Interestingly, among all possible relative diastereoisomers of natural strychnine, **4** and **9** are different from strychnine by one stereogenic center only. It is noteworthy that in the case of strychnine, presumably due to the polycyclic nature of the molecule, the biosynthesis of strychnine may have converged toward the most thermodynamically stable stereoisomer (see Supporting Information).

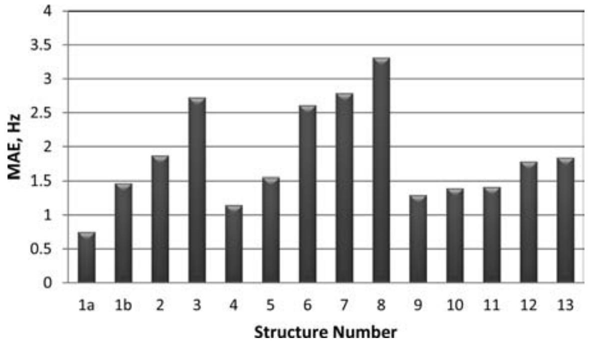

Figure 3. Mean absolute errors (MAE) obtained by comparison of all the $^1J_{CC}$ values for stereoisomers **1**–**13** with the experimental data. MAE = $\Sigma[|(J_{exp} - J_{calcd})|]/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and $^1J_{CC}$ calculated NMR coupling constants), normalized to the number of the carbon–carbon bonds considered. The lowest MAE is reflected by the natural isomer of strychnine (**1a**).

In order to illustrate the relative selection efficiency of the $^1J_{CC}$ coupling constants in identifying the correct stereoisomer, we have compared the results presented in Figure 3 with the results of the well-established method based on the QM calculation of ^{13}C chemical shifts (Figure 4).[5] This approach has been used widely and successfully for addressing a wide variety of stereochemical problems.[1] Such results (Figure 4) represent excellent concordance between the calculated and experimental ^{13}C data for all the possible stereoisomers of strychnine.

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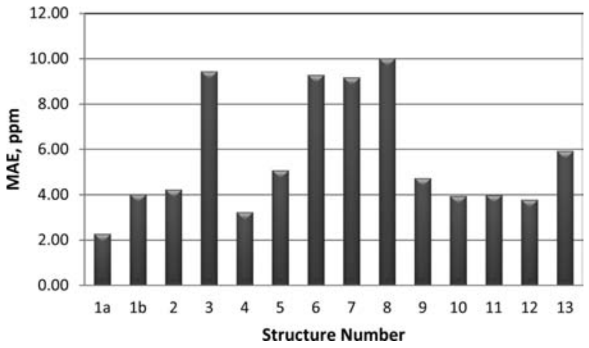

Figure 4. Mean absolute error (MAE) found for the ^{13}C NMR calculated chemical shifts of stereoisomers **1**–**13** vs the experimental values. MAE = $\Sigma[|(\delta_{\text{exp}} - \delta_{\text{calcd}})|]/n$, summation through n of the absolute error values (difference of the absolute values between corresponding experimental and calculated ^{13}C NMR chemical shifts), normalized to the number of the carbon atoms considered. The lowest MAE is reflected by the natural isomer of strychnine (**1a**).

The analysis of the two sets of results clearly show comparable selection efficiency in correctly discriminating the natural stereoisomer. Moreover, the parallel distribution of the errors observed for the stereoisomers of strychnine, compared to errors obtained using the ^{13}C chemical shift calculation protocol, indicate that $^{1}J_{\text{CC}}$ NMR coupling constants have significant utility as a new and effective stereochemical fingerprint identification descriptors for organic compounds.

All of the observations noted above suggest the use of $^{1}J_{\text{CC}}$ coupling constants as important and self-consistent parameters for the determination of the conformational and configurational features of complex organic molecules. The experimental measurement of $^{1}J_{\text{CC}}$ coupling constants is also much easier experimentally than the measurement of $^{n}J_{\text{CC}}$ coupling constants.[8] These parameters come at a higher computational cost than shielding calculations alone but they should provide a powerful adjunct to the chemical shift data for the determination of relative configuration.[5] The use of $^{1}J_{\text{CC}}$ coupling constants to define stereochemistry should prove to be a powerful tool that can be interfaced and combined with other currently available spectroscopic methods to corroborate and confirm the relative stereochemical assignment of unknown molecules.[14]

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Supporting Information Available. Computational details and tables of calculated and experimental ^{13}C NMR chemical shift data and calculated and experimental $^{1}J_{\text{CC}}$ NMR coupling constants for strychnine and a plot of MAE vs energies for **1**–**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.