ORGANIC LETTERS

2004
Vol. 6, No. 6
1025−1028

Quantum Mechanical Calculations of NMR *J* Coupling Values in the Determination of Relative Configuration in Organic Compounds

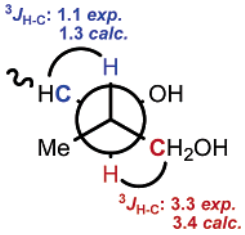
Giuseppe Bifulco, Carla Bassarello, Raffaele Riccio, and Luigi Gomez-Paloma*

Dipartimento di Scienze Farmaceutiche, Università di Salerno, 84084 Fisciano (SA), Italy

gomez@unisa.it

Received January 14, 2004

ABSTRACT



An approach relying on quantum mechanical calculations of proton–proton and proton–carbon *J* coupling values is proposed as a tool for assigning the relative configuration on chiral organic compounds. The method is suitable for carbon frameworks containing several adjacent stereogenic centers and may allow significant advances in the extensive use of spin–spin couplings in structural elucidation.

In addition to the methodologies based on stereoselective synthesis and on the use of NMR chemical shift databases,[1] lately the techniques relying on experimental heteronuclear NMR *J* values in configurational assignments of organic compounds have shown their great potential, and accordingly, they have been used to tackle a number of stereochemical problems.[2] Particularly relevant in the configurational assignment of complex natural products is the case of one or more pairs of adjacent stereocenters. However, the extensive use of J_{CH} couplings in the analysis of the relative configuration has been hampered due to (a) the difficulties arising from the need to make reliable judgments on the size (*large* or *small*) of a given heteronuclear *J* coupling value in the absence of a desirable wealth of literature data and of efficient empirical rules,[3] unlike the case of $^1H-^1H$ *J* values, and (b) the impossibility to deal with cases in which the dominant conformation of the C_2 fragment under investigation is represented by an anti arrangement between protons. Indeed, in this particular instance, the sole pattern, however extensive, of homo- and heteronuclear *J*-couplings does not allow us to distinguish between the two possible relative configurations (*erythro* and *threo*).

We envisaged that a remarkable advancement in this particular field may be attained if reliable values of the *J* couplings, experimentally measurable on the molecule of interest, could be thoroughly computed. We anticipated that this, in fact, would address the two main above-cited drawbacks associated with the use of such NMR parameters, therefore allowing the full exploitation of the great potential

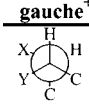
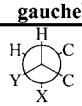
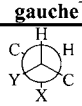
(1) Kokayashi, Y.; Tan, C.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2001**, *123*, 2076−2078.

(2) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura., H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866−876. (b) Bassarello, C.; Bifulco, G.; Zampella, A.; D'Auria, M. V.; Riccio, R.; Gomez-Paloma, L. *Eur. J. Org. Chem.* **2001**, *1*, 39−44. (c) Bassarello, C.; Bifulco, G.; Evidente, A.; Riccio, R.; Gomez-Paloma, L. *Tetrahedron Lett.* **2001**, *42*, 8611−8613. (d) Cimino, P.; Bifulco, G.; Evidente, A.; Abouzeid, M.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2002**, *4*, 2779−2782.

(3) Hansen, P. E. *Prog. NMR Spectrosc.* **1981**, *14*, 175−295. (b) Munzarova, M. L.; Sklenar, V. *J. Am. Chem. Soc.* **2003**, *125*, 3649−3658. (c) Morvai, M.; Nagy, T.; Kocsis, A.; Szabo, L. F.; Podanyi, B. *Magn. Reson. Chem.* **2000**, *38*, 343−359.

10.1021/ol049913e CCC: $27.50
Published on Web 02/19/2004

Table 1. Main Staggered Rotamers for Each Relative Stereochemical Arrangement

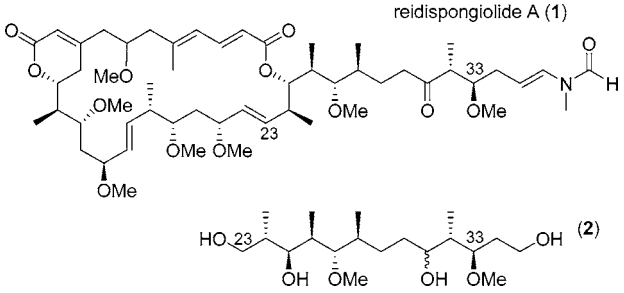
erythro			threo		
gauche$^+$	anti	gauche$^-$	gauche$^+$	anti	gauche$^-$
					

of *J* values in the context of configurational analysis. With this aim, we realized that a strategy for configurational analysis of flexible organic compounds could be based on the use of QM calculations at DFT (density functional theory)[4] level to accurately predict *J* coupling values and to subsequently compare them against their corresponding experimental counterparts. Indeed, QM methods have lately proved to be invaluable tools for computing faithfully a number of atomic and molecular properties, including relevant NMR parameters, such as chemical shifts and coupling constants.[5]

Our approach consists of the calculation of homo- and heteronuclear coupling constant values for each of the six main staggered rotamers (three for each relative stereochemical arrangement) in which any given two-carbon (chiral) fragment can be ideally represented (see Table 1). For molecules containing more than a single pair of stereocenters, a preliminary consideration has to be made. In principle, if one wanted to examine all the possible combinations of staggered rotamers around every C_2 fragment, the number of staggered arrangements that should be investigated is $N_r = 6^n$, where n is the number of pairs of stereocenters with undetermined relative configuration. From a computational viewpoint, this would limit the applicability of such analysis to compounds with no more than two to three stereogenic centers (i.e., $n = 1$ or 2; $N_r = 6$ or 36). However, test calculations of ours have shown that such an intensive computational task is seldom necessary, since magnitudes of coupling constants are affected mainly by the local atomic environment and effects extending further than two atoms away from the nuclei involved in the coupling are usually not relevant. The observation that accurate values of *J* couplings can be predicted ab initio on a series of appropriate reduced systems, independent from one another, has led us to formulate and to validate (see below) a strategy based on the dissection of the full molecular system into a series of simplified fragments which, in most cases, are nothing else than suitable versions of each pair of stereocenters in which our molecule can be ideally divided.[6] This approach has a profound impact on the complexity of the system that can be examined. Indeed, full independence in the analysis of each pair of adjacent stereocenters, requires only $6*n$ staggered arrangements on which *J* couplings have to be computed. The so-obtained data sets of *J* coupling values can then be analyzed against the experimental values, allowing us to draw conclusions on the relative configuration of the examined C_2 molecular fragment. Then, the same approach is repeated for all the other C_2 fragments of our system. *Indeed, in all the cases that we examined (five independent C_2-fragments and the full molecule* **2***), it can be seen that for only one of the six arrangements are the J values in agreement with the experimental ones* (Figure S1, Supporting Information).

In practice, once the simplified C_2 fragments of the molecule under investigation have been selected, all six staggered rotamers of a given C_2 fragment are first subjected to a high-level geometry optimization, and then *J* coupling values are computed for all optimized rotamers. In particular, full geometry optimization was performed using the mPW1PW91[7] functional and the 6-31G(d) basis set (Gaussian03W software package[8]); on the obtained geometries, the calculation of the *J* couplings was run using the same functional and the 6-31G-(d,p) basis set. Spin−spin coupling calculations were performed taking into account the contributions of the following interactions: Fermi contact (FC), paramagnetic spin−orbit (PSO), diamagnetic spin−orbit (DSO), and spin−dipole (SD). Individual values of such contributions are reported in the Supporting Information (Table S4). As expected, the FC contribution is the most important term, though we feel that the accuracy and precision needed for a thorough application of the present approach also require the other contributions. The latter consideration is especially true when the range of observed values is tight, as for J_{CH} values, also considering the recent results regarding the importance of contributions other than FC for such couplings.[9]

reidispongiolide A (**1**)



To test the robustness, the accuracy and the precision attainable by the present method, we decided to work with a fairly complicated system (**2**), namely the side chain of the marine macrolide reidispongiolide A (**1**) (Figure 1),[10] since such system (from a methodological viewpoint) can be representative of a vast number of open-chain chiral molecules, including many natural products. The selected molecule (**2**) features seven stereogenic centers, among which the first five are in a row (C24−C28) and are separated from the last couple (C32−C33).[11] By neglecting the case of C31, whose configuration has never been determined because it is irrelevant for the study of the parent natural product, five

(4) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864−B871. (b) Kohn, W.; Sham, L. J. *Phys. Rev.* **1965**, *140*, A1133−A1138.

(5) Barone, G.; Gomez-Paloma, L.; Duca, D.; Silvestri, A.; Riccio, R.; Bifulco, G. *Chem. Eur. J.* **2002**, *64*, 3233−3239. (b) Barone, G.; Duca, D.; Silvestri, A.; Gomez-Paloma, L.; Riccio, R.; Bifulco, G. *Chem. Eur. J.* **2002**, *64*, 3240−3245. (c) Bassarello, C.; Cimino, P.; Gomez-Paloma, L.; Riccio, R.; Bifulco, G. *Tetrahedron* **2003**, *59*, 9555−9562.

(6) Our current choice is that any substituent around our C_2 fragment may be represented by a shortened version containing two heavy atoms in the main chain and one heavy atom for every branched chain (Figure S1, Supporting Information).

relative spatial relationships have to be established for the stereochemical characterization of **2**, therefore requiring five individual C_2 fragments to be analyzed (Figure S1, Supporting Information). Table 2 reports the experimental data sets of *J* values of **2**, along with all the calculated coupling constants for the various conformational and configurational arrangements of each of the five C_2 fragments originating from **2** (Figure S1, Supporting Information). A good to excellent agreement between calculated and experimental data can be observed for the most populated rotamers with correct configuration while much poorer data correlations are found for the "wrong" alignments. Thus, the test shows that full stereochemical knowledge of **2** could have been deduced from the data analysis of calculated vs experimental *J* couplings of the five simplified systems chosen to represent **2**. However, we propose that once the conformational arrangement and the relative configuration of all the examined molecular fragments have been obtained, the full system may be built, using the information gathered by the reduced systems, and subjected to the same computational protocol involving geometry optimization and computation of *J* values. This last step has the goal to rule out any possible mistake arising from having worked on simplified fragments. However, we wish to point out that, at least in the case of **2**, the *J* values calculated on the whole molecule with correct configurational and conformational features did not differ significantly from those obtained on the reduced systems (Tables S1−S3, Supporting Information). As a matter of fact, the mean absolute error ($\Sigma|J_{calc}-J_{exp}|/n$; n = total number of couplings) calculated for the five fragments is 0.7 vs 0.6 Hz in the case of the computation of the whole molecule **2**.

Concerning the data analysis, it is noteworthy that if individual *J* values are reproduced with somewhat variable precision, a very informative parameter is given by the sum of absolute errors $\Sigma|J_{calc}-J_{exp}|$(total absolute error, TAE). Thus, one has simply to choose, for a given C_2 fragment, the three-dimensional arrangement giving the lowest TAE. However, this does not mean at all that individual *J* values are not useful themselves. On the contrary, upon close inspection very interesting patterns emerge. For instance, the accuracy with which experimental values are theoretically reproduced is sufficiently high to permit the distinction of the two different anti arrangements, a differentiation that would be impossible if one had to rely only on a semiquantitative classification (*small*, *medium*, and *large*) of the heteronuclear *J* values. For such cases, before the development of the present strategy, one had only to resort to dipolar effects (for example ROESY contacts) which, sometimes, make up the deficiency of the *J*'s and support a final word in the assignment. Particularly instructing from this viewpoint are, for instance, the calculated values of $^3J_{H25-Me24}$ and $^3J_{H25-C23}$, nicely exchanging their values upon inversion of the relative configuration around the C24−C25 stereocenters. A similar trend is also observed in the C27−C28 segment, also characterized by a dominant anti arrangement, this time for the values relative to $^3J_{H27-Me28}$ and $^3J_{H27-C29}$. A compara-

Table 2. Calculated Data Sets of *J* Values for the Various Conformational and Configurational Arrangements of **2** in Comparison with the Experimental Values

	calcd						exptl
	erythro			threo			
	g^+	anti	g^-	g^+	anti	g^-	
			C32−C33				
$^3J_{H32-H33}$	2.4	9.6	2.9	0.7	9.1	4.5	2.6
$^2J_{H32-C33}$	−4.7	−3.5	0.9	0.4	−3.4	−4.2	−5.4
$^3J_{H32-C34}$	4.4	1.5	1.1	2.9	1.4	5.1	4.8
$^3J_{H33-C31}$	1.9	1.7	6.1	3.7	0.8	6.1	0.5
$^3J_{H33-Me32}$	4.8	2.2	3.6	3.7	3.1	1.9	4.4
$\Sigma\lvert J_{calc}-J_{exp}\rvert$	3.1	15.6	16.7	13.5	13.5	11.5	
			C27−C28				
$^3J_{H27-H28}$	3.2	8.6	3.4	2.4	9.0	3.5	8.9
$^2J_{H28-C27}$	1.5	−3.5	−3.8	1.5	−4.0	−4.0	−3.6
$^3J_{H28-CH26}$	0.8	1.6	5.0	1.0	1.3	5.1	1.0
$^3J_{H27-CH29}$	6.1	2.7	1.2	3.1	0.6	5.1	2.2
$^3J_{H27-Me28}$	2.7	1.9	5.7	5.5	3.5	2.0	1.4
$\Sigma\lvert J_{calc}-J_{exp}\rvert$	16.2	2.0	15.0	16.8	4.5	13.4	
			C26−C27				
$^3J_{H26-H27}$	0.6	7.5	1.9	2.8	8.7	3.0	2.4
$^2J_{H26-C27}$	−5.8	−3.1	0.9	0.7	−4.2	−5.0	−1.5
$^3J_{H26-C28}$	1.8	4.9	0.4	0.2	1.3	5.6	0.5
$^3J_{H27-C25}$	5.4	0.3	5.0	2.7	5.9	4.6	6.7
$^3J_{H27-Me26}$	3.2	5.4	3.3	6.0	3.4	1.9	3.1
$\Sigma\lvert J_{calc}-J_{exp}\rvert$	8.8	19.8	4.9	9.8	10.9	12.5	
			C25−C26				
$^3J_{H25-H26}$	2.6	8.6	3.4	3.6	8.4	4.2	1.2
$^2J_{H26-C25}$	0.7	−3.4	−3.7	0.8	−3.7	−3.7	−0.5
$^3J_{H26-C24}$	0.9	0.8	4.5	0.7	0.7	4.9	0.5
$^3J_{H25-C27}$	6.6	3.0	1.5	1.3	0.4	6.5	0.9
$^3J_{H25-Me26}$	3.5	0.8	5.5	5.7	3.6	2.3	6.7
$\Sigma\lvert J_{calc}-J_{exp}\rvert$	11.9	18.6	11.2	5.3	14.2	20.6	
			C24−C25				
$^3J_{H24-H25}$	2.8	8.6	0.1	0.3	8.2	4.2	9.9
$^2J_{H24-C25}$	−4.2	−3.7	−0.9	−0.6	−3.0	−3.8	−2.4
$^3J_{H24-C26}$	5.1	1.3	2.3	3.3	1.0	5.7	1.1
$^3J_{H25-C23}$	1.0	3.4	4.1	7.5	0.8	6.2	3.3
$^3J_{H25-Me24}$	4.6	1.2	6.2	3.0	3.5	1.8	1.4
$\Sigma\lvert J_{calc}-J_{exp}\rvert$	18.4	3.1	18.1	19.4	7.0	15.0	

(7) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664−675.

(8) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R. J.; Montgomery, A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.;. Voth, A G.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.01, Gaussian, Inc., Pittsburgh, PA, 2003.

(9) Bagno, A.; Rastrelli, F.; Saielli, G. *J. Phys. Chem.* A **2003**, *107*, 9964−9973.

(10) Zampella, A.; Bassarello, C.; Bifulco, G.; Gomez-Paloma, L.; D'Auria, M. V. *Eur. J. Org. Chem* **2002**, *5*, 785−790.

(11) Zampella, A.; Sepe, V.; D'Orsi, R.; Bifulco, G.; Bassarello, C.; D'Auria, M. V. *Tetrahedron: Asymmetry* **2003**, *14*, 1787−1798.7.

tive analysis of the corresponding experimental values points in both cases, without any ambiguity, to the correct three-dimensional arrangement.

Finally, it has to be taken into account that, at least at this preliminary stage, we chose to represent each C_2 fragment as "pure" gauche and anti staggered conformers,[12] a simplification whose price is, in our opinion, a limit on the achieved precision with which experimental data are actually reproduced.

(12) *Gauche* or *anti* conformers, which are in practice subjected to geometry optimization, are actually meant as the potential energy minimum conformations found around the "pure" three-dimensional arrangements.

Acknowledgment. The University of Salerno and MIUR are gratefully acknowledged for financial support.

Supporting Information Available: Four tables (Tables S1, S2, S3, and S4) with listings of the experimental and calculated *J* values for **2** and its simplified fragments and details about the four FC, SD, PSO, and DSO contributions to the coupling constants. Chemical structures of the five simplified fragments chosen for representing the full system **2** are described in Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049913E