ORGANIC LETTERS

2009
Vol. 11, No. 7
1471−1474

Residual Dipolar Couplings of Freely Rotating Groups in Small Molecules. Stereochemical Assignment and Side-Chain Conformation of 8-Phenylmenthol

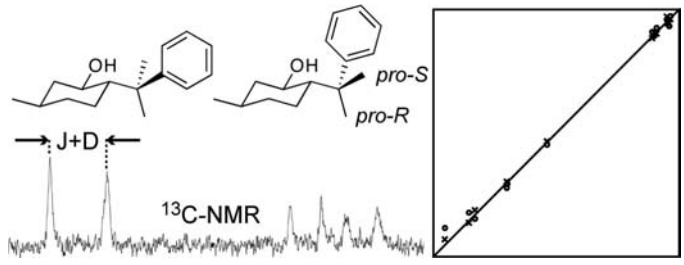
Víctor M. Sánchez-Pedregal, Raquel Santamaría-Fernández, and Armando Navarro-Vázquez*

Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

armando.navarro@usc.es

Received December 23, 2008

ABSTRACT



A procedure for the direct use of $^1D_{CH}$ residual dipolar couplings (RDCs) from freely rotating groups in the structural analysis of small molecules was implemented. $^1D_{CH}$ RDCs were used to determine both the preferred conformation and the stereochemical assignment of the diastereotopic geminal methyls of 8-phenylmenthol. Furthermore, a method was also set up to fit RDC data to a set of conformations in solution on the assumption that they all have the same alignment tensor.

The use of residual dipolar couplings (RDCs) has emerged as an attractive technique for stereochemical studies of small organic molecules.[1,2] New alignment media suitable for organic solvents[3] and methodological improvements[4] have greatly extended the applicability of this useful structural tool.

RDC-based structural analysis relies on the computation of the alignment tensor $\hat{A}$ that is a traceless symmetric 3×3 matrix that encodes the rotational probability distribution of the aligned molecule. The RDC D between two nuclei is given by[5]

$$D = \frac{\kappa}{R^3}\vec{\mathbf{r}}^T\hat{A}\vec{\mathbf{r}} \qquad (1)$$

where κ comprehends the gyromagnetic ratios and other physical constants; $\mathbf{r}$ is a unit vector in the direction connecting both nuclei; and R is the internuclear distance.

(1) (a) Thiele, C. M. *Concepts Magn. Reson. Part A* **2007**, *30A*, 65. (b) Thiele, C. M. *Eur. J. Org. Chem.* **2008**, 5673.

(2) (a) Martin-Pastor, M.; Bush, C. A. *Carbohydr. Res.* **2000**, *323*, 147. (b) Freedberg, D. I. *J. Am. Chem. Soc.* **2002**, *124*, 2358.

(3) (a) Aroulanda, C.; Boucard, V.; Guibé, F.; Courtieu, J.; Merlet, D. *Chem. Eur. J.* **2003**, *9*, 4536. (b) Thiele, C. M. *J. Org. Chem.* **2004**, *69*, 7403. (c) Haberz, P.; Farjon, J.; Griesinger, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 427. (d) Luy, B.; Kobzar, K.; Kessler, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1092. (e) Luy, B.; Kobzar, K.; Knor, S.; Furrer, J.; Heckmann, D.; Kessler, H. *J. Am. Chem. Soc.* **2005**, *127*, 6459. (f) Kummerlöwe, G.; Auernheimer, J.; Lendlein, A.; Luy, B. *J. Am. Chem. Soc.* **2007**, *129*, 6080. (g) Kummerlöwe, G.; Knör, S.; Frank, A. O.; Paululat, T.; Kessler, H.; Luy, B. *Chem. Commun.* **2008**, 5722.

(4) Thiele, C. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2787.

(5) Kramer, F.; Deshmuk, M. V.; Kessler, H.; Glaser, S. J. *Concepts Magn. Reson. Part A* **2004**, *21A*, 10.

10.1021/ol8029565 CCC: $40.75
Published on Web 03/02/2009

The five independent components of tensor $\hat{A}$ are usually determined by setting up a system of linear equations that relate the expected RDC of a given molecular geometry with the experimental ones. If more than five experimental RDC values are available, the system is overdetermined and must be solved in a least-squares sense, usually by using singular value decomposition (SVD).[6] In matrix form, the equation system can be expressed as

$$\begin{pmatrix} D_1^r \\ D_2^r \\ \dots \\ D_n^r \end{pmatrix} = \mathbf{M} \begin{pmatrix} A_{xy} \\ A_{xz} \\ A_{yy} \\ A_{yz} \\ A_{zz} \end{pmatrix} \tag{2}$$

where D^r are RDCs scaled by κ/R^3, and $\mathbf{M}$ is a $(N,5)$ matrix that represents the molecular geometry, whose terms are products of direction cosines.

Once the alignment tensor is determined, quality of fit of back-calculated values to experimental RDCs can be used as a merit function to select the correct structure among a set of trial geometries and/or stereochemical assignments. This approach has already been reported for the stereochemical assignment of small molecules.[7] Provided that good quality trial structures are chosen, it is assumed that the "correct" structure is the one that best fits the experimental RDCs.

Unfortunately, a potential problem with small molecules is the lack of enough independent vectors to span the three-dimensional space appropriately since in most cases only $^1D_{CH}$ RDCs are available, thus making the fitting problem underdetermined. This scarcity of vectors is often due to the parallel orientation of several of the C−H bonds in cyclic moieties such as the cyclohexyl ring. It is, therefore, crucial to use all accessible experimental data. In this regard, it is desirable to have an easy-to-use methodology for the treatment of RDCs resulting from the most common freely rotating groups, namely, methyl and phenyl groups.

Fast methyl group rotation, either considering a free rotor or a 3-fold jumping model, renders an averaged RDC equal to

$$\langle D \rangle = \frac{3\cos^2\phi - 1}{2} D_{\parallel} \tag{3}$$

where ϕ is the angle between the C−H vector and the rotation axis, and $D_{\parallel}$ is the coupling of a virtual C−H vector pointing in the direction of the rotation axis. For an ideal tetrahedral angle,[8] this results in a $-1/3$ scaling factor. This relationship has been exploited by Griesinger et al. in their study of (+)-menthol.[9]

C−H vectors in ortho and meta positions of phenyl groups give a single averaged value. If a 2-fold jumping model is assumed, the averaged D contains information about the components of the alignment tensor on the ring plane. For the typical angle of 60° in phenyl rings, this results in the following equation

$$\langle D \rangle = \frac{1}{4} D_{\parallel} + \frac{3}{4} D_{\perp} \tag{4}$$

where $D_{\parallel}$ represents the coupling of a virtual C−H vector pointing along the rotation axis, and $D_{\perp}$ represents the coupling of a vector orthogonal to the axis and lying in the plane of the ring.

In this paper, we incorporate freely rotating methyl and phenyl groups to structure determination by using simple 2-fold and 3-fold jump models. The necessary computer code was implemented in a modified version of the program MSpin.[10] After reading molecular geometry and experimental RDCs, the program automatically detects methyl and phenyl[11] free rotors and generates the corresponding entries in eq 2. As the alignment tensor does not change when these rotors jump from one site to another, we can simply average matrix elements in the model matrix $\mathbf{M}$ (eq 2). Finally, the alignment tensor is determined by SVD, and back-calculated RDCs and fitting quality factors Q[12] are obtained for each trial structure (see Supporting Information for a detailed procedure).

We applied this algorithm to the RDC analysis of compound **1** to simultaneously determine the stereochemical assignment of the two diastereotopic geminal methyls and the conformation of **1** in solution, taking advantage of the additional experimental RDC values derived from the fast-rotating methyl and phenyl groups.

Compound **1** was aligned with PELG[3b] using $CDCl_3$ as solvent. $^1D_{CH}$ RDCs were extracted from the difference in C−H splittings of two samples: one oriented with PELG (splitting $= {}^1D_{CH} + {}^1J_{CH}$) and another one isotropic (splitting $= {}^1J_{CH}$). We measured C−H splittings from 1D-^{13}C and 2D-HC-HSQC NMR proton-coupled spectra. We obtained 8 $^1D_{CH}$ restraints from nonaveraged C−H bonds (among which only four stem from nonparallel CH vectors, namely C1−H1, C4−H4eq, C6−H6eq, and C4′−H4′) and five D from averaged freely rotating groups (four of them being non-colinear), resulting in a total of eight independent restraints.

(6) Losonczi, J. A.; Andrec, M.; Fischer, M. W. F.; Prestegard, J. H. *J. Magn. Reson.* **1999**, *138*, 334.

(7) (a) Thiele, C. M.; Berger, S. *Org. Lett.* **2003**, *5*, 705. (b) Aroulanda, C.; Lesot, P.; Merlet, D.; Cortieu, *J. Phys. Chem. A* **2003**, *107*, 10911. (c) Yan, J.; Delaglio, F.; Kaerner, A.; Kline, A. D.; Mo, H.; Shapiro, M. J.; Smitka, T. A.; Stephenson, G. A.; Zartler, E. R. *J. Am. Chem. Soc.* **2004**, *126*, 5008. (d) Freudenberger, J. C.; Spiteller, P.; Bauer, R.; Kessler, H.; Luy, B. *J. Am. Chem. Soc.* **2004**, *126*, 14690. (e) Freudenberger, J. C.; Knör, S.; Kobzar, K.; Heckmann, D.; Paululat, T.; Kessler, H.; Luy, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 423. (f) Thiele, C. M.; Marx, A.; Berger, R.; Fischer, J.; Biel, M.; Giannis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4455. (g) Gil, R. R.; Gayathri, C.; Tsarevsky, N. V.; Matyjaszewski, K. J. *Org. Chem.* **2008**, *73*, 840.

(8) (a) Ottiger, M.; Bax, A. *J. Am. Chem. Soc.* **1999**, *121*, 4690. (b) Suryaprakash, N. *Concepts Magn. Reson.* **1998**, *10*, 167.

(9) Verdier, L.; Sakhaii, P.; Zweckstetter, M.; Griesinger, C. *J. Magn. Reson.* **2003**, *163*, 353.

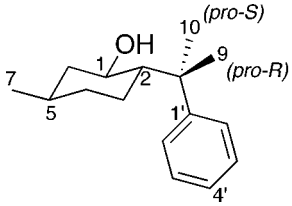
(10) Program MSpin. http://www.mestrelab.com, accessed January 2009.

(11) We used the ring perception algorithm from: Hanser, Th.; Jauffret, Ph.; Kaufmann, G. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 1146.

(12) Cornilescu, G.; Bax, A. *J. Am. Chem. Soc.* **2000**, *122*, 10143.

All trial geometries of phenylmenthol were optimized at the B3LYP[13] and MP2 (with core orbitals excluded from correlation computation) levels and the 6-311+G** basis set. The nature of the stationary points and thermochemical magnitudes were determined by analytical computation of vibrational frequencies at the DFT level. To include solvation effects, single-point computations were performed on optimized structures using the IPCM[14] solvation model with relative dielectric constant $\varepsilon = 4.90$ and isodensity value of 0.0004. Carbon and proton chemical shifts were computed using the GIAO[15] method combined with the OPBE[16,17] functional and the 6-311+G** basis set, including solvation effects at the IEF-PCM[18] level using chloroform parameters and the radii = pauling option. All computations were performed with Gaussian03.[19]

Inversion of the cyclohexane chair conformation is blocked in **1** due to the simultaneous equatorial disposition of all substituents. However, three possible conformations arise from rotation around the C2−C8 bond. We named the possible rotamers after the nature of the H2−C2−C8−C1′ dihedral angle. The anti conformation (*Anti*) and two *gauche* conformations (G+ and G−) with positive and negative dihedral angles, respectively (Figure 2). We also included



	Assignments	
	δ_C(C-10)	δ_C(C-9)
I:	24.3	28.6
II:	28.6	24.3

Figure 1. Structure of 8-phenylmenthol showing the atom numbering and the two possible stereochemical assignments of the *gem*-dimethyl. δ_C in ppm.

an alternative form (G−_HB), in which the hydroxyl proton is turned toward the phenyl side, thus allowing for an attractive phenyl/OH interaction.[20] This contact resembles the $\pi-\pi$ interaction that has been claimed to be responsible for the high stereoselectivity when **1** is used as a chiral auxiliary.[21] According to B3LYP energies, G−_HB and G+ are the most favored conformers in solution. Note that the

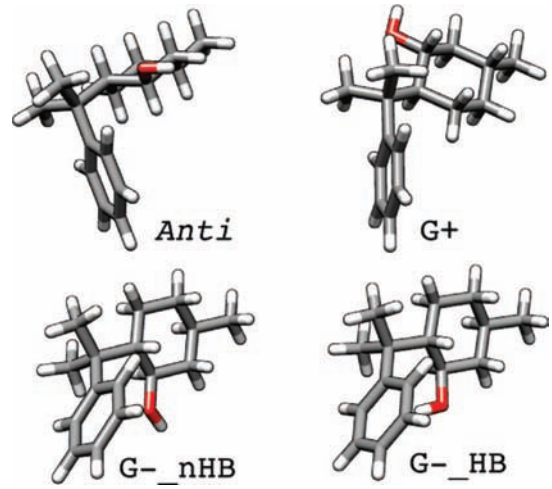


Figure 2. Calculated conformers of **1**. The two G− rotamers are named as follows. G−_HB: with hydrogen bond between the OH and the Ph. G−_nHB: non-hydrogen bonded.

stability of G−_HB is due to the favorable phenyl/OH interaction. Otherwise, the G+ form would be energetically preferred over the G− form. MP2 computations yield a larger gap (2.0 kcal/mol) between G−_HB and G+.

Table 1 shows the results of the fit of each of the four conformers derived from the B3LYP computations to the experimental RDC. For each conformer, we tried both

Table 1. Relative Free Energies (kcal/mol) and RDC Quality Factors *Q* of Rotamers of **1**

conformer	$\Delta G_{298.15K}$[a]	Q(I)[b]	Q(II)[b]
Anti	2.1 [1.7]	0.159	0.148
G+	0.0 [2.0]	0.110	0.127
G−_nHB	2.0 [1.5]	0.145	0.065
G−_HB	0.2 [0.0]	0.136	0.053

[a] B3LYP (IPCM)/6-311+G**//B3LYP/6-311+G**. [MP2/6-311+G**-(IPCM)//MP2/6-311+G**]. [b] Q(I) and Q(II): RDC quality factors Q computed for each conformer with the stereochemical assignments shown in Figure 1.

possible stereochemical assignments (I and II, Figure 1) of the diastereotopic *gem*-dimethyl. The conformer G− with stereoassignment II is the one that fits best to the experimental data (Q = 0.053 and 0.065 for the HB and nHB forms, respectively).

Runsink et al.[20] reported, however, that **1** exists as a mixture of conformers in solution, as shown by low-temperature NMR experiments where large displacements of the ^{13}C resonances of methyls 9 and 10 are observed (Figure 3). As the Me9 and Me10 groups swap their positions in G+ and G− conformers, they cannot be assigned in terms of ^{13}C chemical shifts. However, as these authors noted, the H3eq proton should be strongly shielded in the G+ conformer due to the anisotropic effect of the phenyl group. We

(13) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
(14) Foresman, J. B.; Keith, T. A.; Wiberg, K. B.; Snoonian, J.; Frisch, M. J. *J. Phys. Chem.* **1996**, *100*, 16098.
(15) Wolinski, K.; Hinton, J. F.; Pulay, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251.
(16) (a) Cohen, A. J.; Handy, N. C. *Chem. Phys. Lett.* **2000**, *316*, 160. (b) Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865.
(17) Zhang, Y.; Wu, A.; Xu, X.; Yan, Y. *Chem. Phys. Lett.* **2006**, *421*, 383.
(18) (a) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253. (b) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43.
(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B. *Gaussian03*, Revision E.01; Gaussian, Inc.: Wallingford, CT, 2004.
(20) Runsink, J.; Koch, H.; Nehrings, A.; Scharf, H.-D.; Nowack, E.; Hahn, T. *J. Chem. Soc., Perkin Trans. 2* **1988**, 49.
(21) Whitesell, J. K.; Younathan, J. N.; Hurst, J. R.; Fox, M. A. *J. Org. Chem.* **1985**, *50*, 5499.

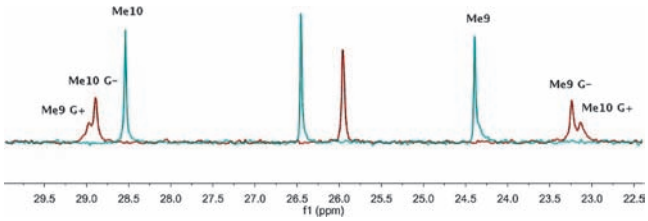


Figure 3. ^{13}C spectrum (125 MHz) of **1** in $CDCl_3$ at 233 K (red) and 298 K (green). The resonances of the diaestereotopic geminal methyls are resolved at low temperature.

quantified this shielding by DFT GIAO/OPBE that predicts a remarkable shielding of about 1.3 ppm of this proton as compared to the rest of the equatorial protons (see Supporting Information). Given that such shielding is not observed experimentally in the ^1H spectrum, it can be safely concluded that the conformational equilibrium is dominated by the G− form, which is consistent with our RDC analysis (vide infra).

We explored the possibility of fitting the experimental RDC to the mixture of conformers to extract the relative populations as follows. Experimental RDCs are the weighted average of the contribution of each species in solution

$$\langle D \rangle = \sum_{i=1}^{N} w_i \frac{\kappa}{R_i^3} \vec{\mathbf{r}}_i{}^T \hat{A}_i \vec{\mathbf{r}}_i \qquad (5)$$

where w_i is the molar fraction of the ith species.

In the general case, the alignment tensor is different for each conformer, and a high number of unknowns are present.[22] However, the number of unknowns is reduced dramatically to $5 + (N - 1)$ if all alignment tensors are assumed to be equal.[23]This is a reasonable approximation if the shape and the alignment mechanism are similar for all conformations. Since the G−_HB and G−_nHB forms would be indistinguishable in the RDC experiments, we only have to include the most stable according to computations, the G−_HB form, totaling $N = 3$ conformers. As we obtained eight independent $^1D_{CH}$ RDCs of phenylmenthol, the problem can be in principle solved.

We performed this fitting with our set of experimental RDCs, considering an equilibirum of three conformers (*Anti*, G+, and G−_HB) and the two possible stereochemical assignments of the *gem*-dimethyl. In the single tensor approach that we propose, the alignment tensor should not change during conformer interconversion with respect to a chosen rigid moiety, the cyclohexyl ring in this case. Thus, the three structures were rotated to a common frame by superposition of their cyclohexyl rings, and then populations were computed by a grid search combined with a constrained Levenberg−Marquadt least-squares procedure.[24] Table 2

Table 2. Populations (in %) and Quality Factors Q Resulting from SVD Fitting of RDCs to a Mixture of Conformers

assignment	$p(Anti)$	p(G+)	p(G−_HB)	Q^a
I	0 (0)[b]	38 (2)	62 (2)	0.048 (0.083)
II	10 (4)	13 (3)	76 (3)	0.023 (0.035)

[a] Quality factors in parenthesis were calculated considering only RDCs from the side chain methyl and phenyl groups. [b] Standard deviations of the populations shown in parentheses.

shows the populations and Q factors of assignments I and II. Again, the best fit is obtained for stereochemical assignment II, whose quality factor is nearly one-half of that of assignment I. If we focus only on the RDCs of the side chain, the difference between Q factors is even larger. Moreover, a large population of G−_HB is predicted, in agreement with the chemical shift data. Note that the obtained populations indicate a small energy gap more in accord to B3LYP than to MP2 computations. To estimate the precision of this methodology, we used a bootstrapping procedure where 250 normalized Gaussian distributions were generated taking measured RDCs as mean values and a standard deviation of 2.5 Hz. The obtained standard deviations of the populations were not larger than 4%, thus indicating a very acceptable precision.

In conclusion, we used RDCs to simultaneously determine the stereochemical assignment and the conformational distribution of 8-phenylmenthol. We automated the averaging of RDCs from freely rotating groups in the program MSpin by using a simple equal-probability jumping model. We expect that this methodology facilitates the use of RDC among a broader community of users interested in solving structural questions of small molecules. Work is in progress to apply this methodology to other molecules in fast conformational equilibrium.

Acknowledgment. We acknowledge research grants from Xunta de Galicia (PGIDIT07 PXIB 209025PR) and the Spanish MEC (CTQ2007-65310), research fellowships "Ramón y Cajal" from the Spanish MEC (V.M.S.-P.) and "Isidro Parga Pondal" from Xunta de Galicia (A.N.V.), Centro de SuperComputación de Galicia (CESGA) for computer time allocation, and M. Martín-Pastor and R. Gesto for technical help with the NMR spectrometers at the USC.

Supporting Information Available: Computed structure energies and chemical shifts. Alignment tensor computation details, tensor graphical representation, and the full citation for ref 19. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8029565

(22) See ref 1b and references therein for considerations on the subject.

(23) (a) Schuetz, A.; Junker, J.; Leonov, A.; Lange, O. F.; Molinski, T. F.; Griesinger, C. *J. Am. Chem. Soc.* **2007**, *129*, 15114. (b) Schuetz, A.; Murakami, T.; Takada, N.; Junker, J.; Hashimoto, M.; Griesinger, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 2032. (c) Farès, C.; Hassfeld, J.; Menche, D.; Carlomagno, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 3722.

(24) The lmift library was used for the LM step. http://messen-un-deuten.de/lmfit, accessed July 2008.