The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2020**, part ii, 113-122

Prediction of ^{15}N NMR chemical shifts for nitrogenated aromatic compounds

Marcelo T. de Oliveira,[a,*] Júlia M. A. Alves,[a] Sara F. de A. Morais,[b] and Ataualpa A. C. Braga[b,*]

[a] *São Carlos Institute of Chemistry, Av. Trabalhador São-carlense 400, São Paulo University, São Carlos – SP, Brazil 13560-970*

[b] *Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo (USP), São Paulo, SP, Brazil*

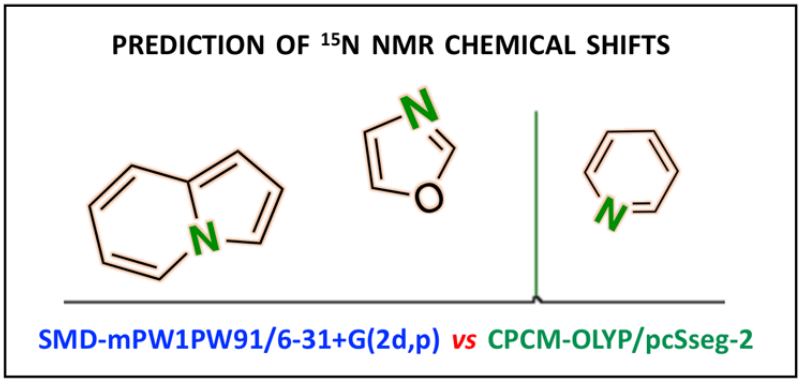
Email: mtavareso@usp.br ; ataualpa@iq.usp.br

Dedicated to Professor José Manuel Riveros on the occasion of his 80th birthday

Received 12-19-2019 **Accepted** 04-02-2020 **Published on line** 04-20-2020

Abstract

Building on recent developments, we compare performance of two distinct protocols, namely SMD-mPW1PW91/6-311+G(2d,p) and CPCM-OLYP/pcSseg-2, for the computation of ^{15}N chemical shifts of nitrogenated aromatic compounds. The latter shows best overall performance (MAD 5.3 ppm) albeit results in chloroform favors the former.



Keywords: Nuclear magnetic resonance, chemical shifts, structure elucidation, density-functional theory, polarizable continuum model, C–N

Introduction

Nuclear magnetic resonance is an essential spectroscopy method in organic chemistry with applications ranging from structure elucidation of complex natural products to routine characterizations in the organic synthesis lab. Quantum chemistry calculations of NMR spectral parameters such as chemical shifts or coupling constants have been widely used as an ancillary tool to correlate experimental data to the correct structure or deriving additional information *e.g.* conformation, which is not readily available otherwise.[1–3]

A number of chemical elements have been subjected to NMR computational studies in direct applications or method development.[4–9] In both cases, density functional theory (DFT) has been the method of choice for its cost-benefit compromise producing convincing results to molecules of interest in organic chemistry. However, there is an overwhelming number of density functionals currently available to choose from, which could be applied to a given problem.[10] Assessing the performance of density functionals available including newly developed represents a continuous effort towards increasingly accurate results.

Nitrogen is present in a multitude of bioactive natural products (e.g. alkaloids), nucleotides and various heterocycles of considerable importance to the pharmaceutical industry. After ^{1}H and ^{13}C atoms, nitrogen as ^{15}N, which is the important nucleus, is probably next in relevance to NMR applications in organic chemistry.[11] Differently from ^{1}H and ^{13}C, however, the lone pair present in the case of nitrogen is highly sensitive to its orientation in the surrounding environment and influenced by inter- and intramolecular interactions, which markedly impact resulting chemical shifts in the spectra. Moreover, chemical shifts for ^{15}N spans over the wide range of over 900 ppm. Of interest to organic chemists, it spreads over a 400–500-ppm window, which is twice larger than ^{13}C.[12]

Over the last decade or so, there have been important developments on quantum chemistry predictions of ^{15}N chemical shifts.[11,13–17] However, efficient and accurate protocols on pair to those available for ^{1}H and ^{13}C are still missing. In the present work, we focus on the class of nitrogenated aromatic compounds, which provides a suitably rigid set of compounds and chemical shifts distributed over a significant range. The present study builds on protocols from recent literature introducing adjustments, which should encourage broader application while also providing reasonably accurate results for the class. We also take note of distinct effects implicit solvation models may have on chemical shift predictions according to the polarity of solvents.

Results and Discussion

The dataset comprises of 23 aromatic compounds containing 1–4 nitrogen atoms in the same molecule, and amounting to a total of 40 individual chemical shifts distributed over *ca.* 265 (-222 to 42) ppm recorded in 3 of the most common solvents in use in NMR spectroscopy (acetone, chloroform and dimethyl sulfoxide). The selected aromatic compounds represent a variety of chemical environments for nitrogen atoms (Figure 1).

The selection forms a subset of a previous study on the prediction of ^{15}N chemical shifts in which geometries were optimized at the MP2/aug-cc-pVTZ level of theory.[13] Herein we make use of these structures to compare two distinct protocols chosen from recent studies. In both cases, the gauge-independent atomic orbital approach (GIAO)[18] was used to compute ^{15}N isotropic shielding constants. Methods differs in density functional, basis set and solvation method applied.

For the first method, Gao and co-workers[14] developed scaling factors correlating experimental ^{15}N chemical shifts and computed isotropic shielding constants in chloroform and dimethyl sulfoxide. Out of a handful methods investigated using GIAO and the solvation model based on density (SMD),[19] best results were

obtained with the hybrid density functional mPW1PW91[20,21] in conjugation with the triple-ζ basis set 6-311+G(2d,p), which is referred to as Method 1 for short.

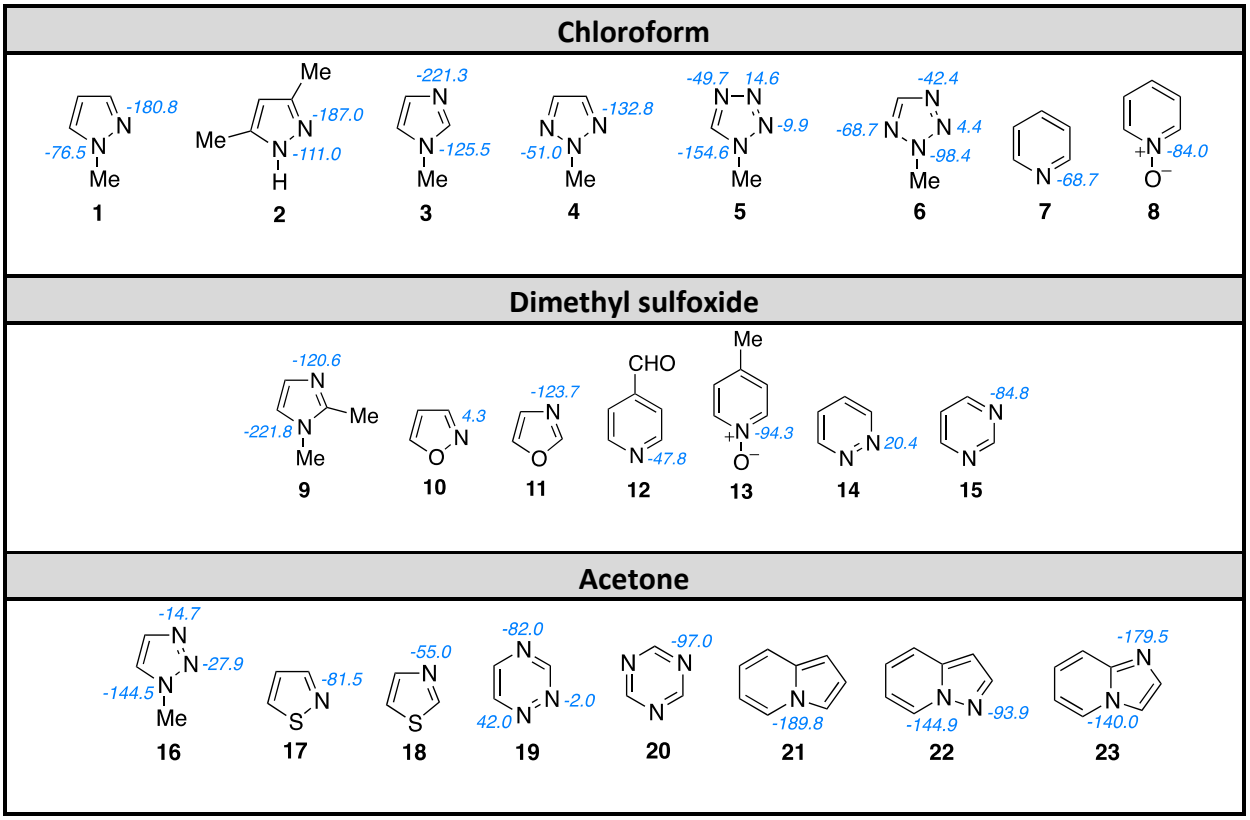


Figure 1. Experimental ^{15}N chemical shifts for aromatic nitrogenated compounds.

For the second method in this exercise, we aimed to apply the DFT protocol used by Semenov and co-workers.[13] Their contribution evaluated coupled cluster singles and doubles (CCSD), Møller-Plesset perturbation theory (MP2) and DFT protocols to compute isotropic shifts. In all cases, the conductor-like polarizable model (CPCM) was applied to account for solvent corrections.[22,23] A composite method approximation (CMA)[24] with Jensen's triple (pcSseg-2) and quintuple-ζ (aug-pcSseg-4) basis sets was used.[25] In view of the performance obtained, we applied the generalized gradient approximation (GGA) functional OLYP, which is a combination of the Handy and Cohen's hybrid functional (OPTX)[26] and Lee, Yang and Parr's correlation functional (LYP).[27] In all fairness of comparison, however, we have opted to use the triple-ζ basis set pcSseg-2 as such allowing prompt access through different quantum chemistry codes.

Calculated isotropic shielding constants were converted to chemical shifts following two approaches. We used a reference compound, nitromethane, which is the experimental standard for ^{15}N according to IUPAC guidelines,[28] and a linear regression correlating experimental chemical shifts and calculated isotropic shielding constants producing scaled values. The latter allows error cancelation in cases including when various reference compounds are present in the dataset compiled or multiple solvents are used.

Both methods investigated for the series of compounds display high values of R^2, 0.9872 and 0.9907, respectively, which indicates a tight correlation and very little random error (Figure 2), and in agreement with the general recommendation (1.00±0.05).[3] Therefore, equations derived from the linearization could be applied to predict isotropic shielding values for similar compounds and computed at the same level of theory

to produce results with reduced systematic errors. Such fitted empirical scaling factors are available from various sources.[29]

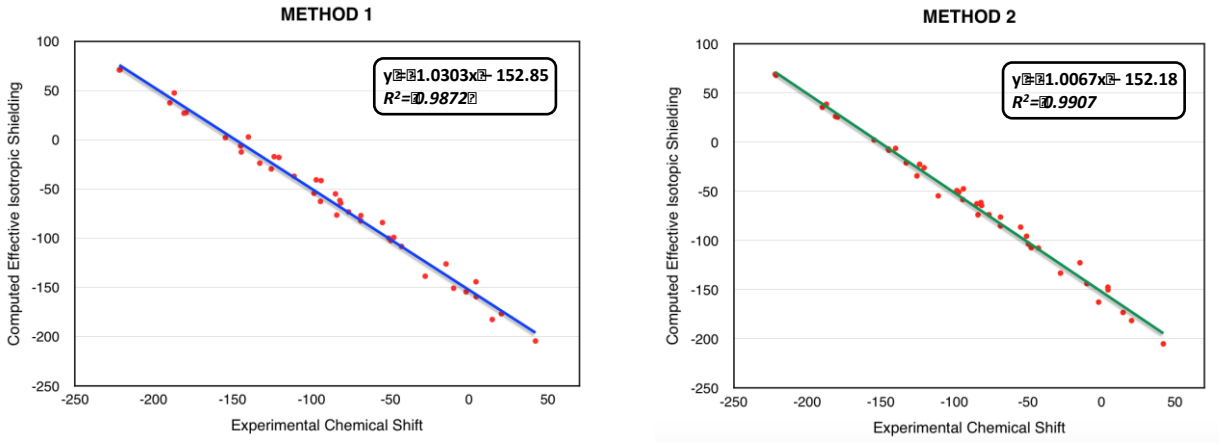


Figure 2. Linear correlation between experimental chemical shifts and calculated isotropic shielding constants. Left: Method 1, SMD-mPW1PW91/6-311+G(2d,p); Right: Method2, CPCM-OLYP/pcSseg-2.

Application of Method 1, SMD-mPW1PW91/6-311+G(d,p), leads to a mean absolute deviation (MAD) of 17.5 ppm (Figure 3a) and maximum deviation on ^{15}N chemical shift of 31.4 ppm (Table S2). Application of the scaling factor obtained, 'y= -1.0303x – 152.85', produces substantial reduction in both values. Mean absolute deviation (MAD) drops to 7.3 ppm and maximum deviation decreases to 20.8 ppm (Figure 3b, Table S3). We proceeded to Method 2, CPCM-OLYP/pcSseg-2, to evaluate the same parameters. Unscaled MAD value was lower at 13.8 ppm while maximum error remained essentially unchanged (31.3 ppm). These values improve considerably when the developed fitted scaling equation (y=-1.0067x – 152.18) is applied. For the same method, scaled MAD went down by *ca.* 30% to 5.3 ppm (Figure 3a) and maximum deviation was 14.0 ppm (Table S4).

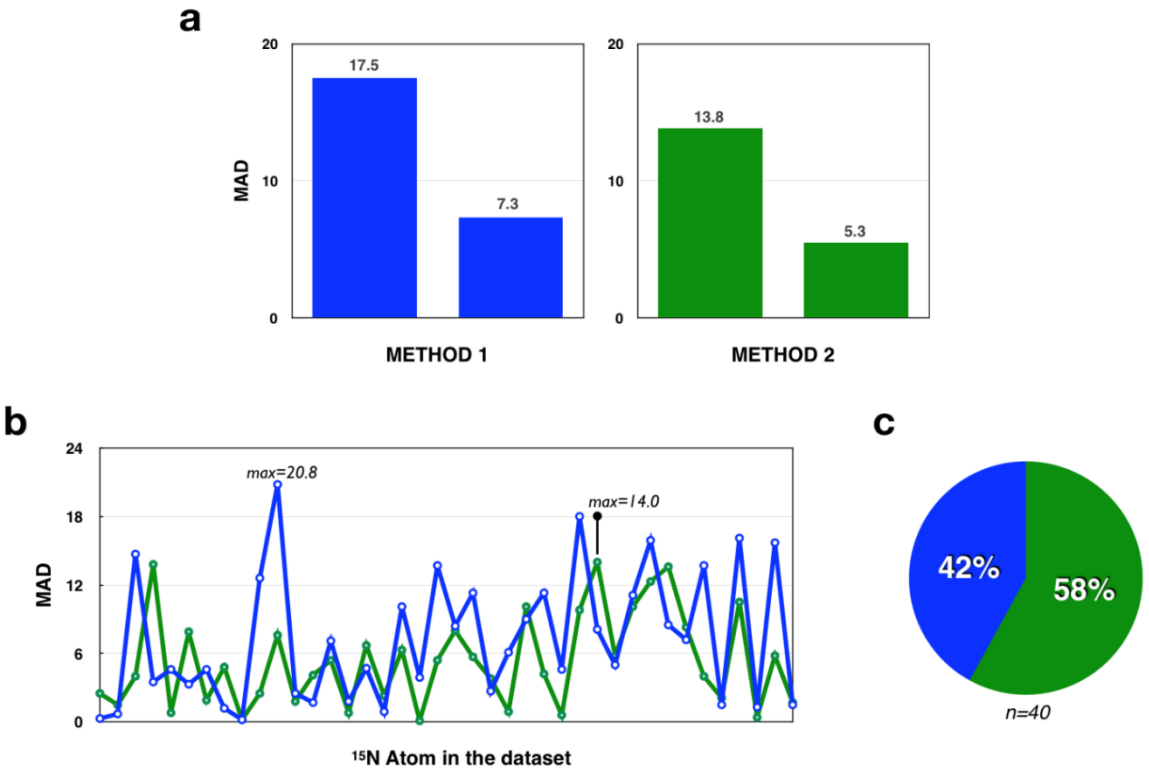


Figure 3. Performance comparison of methods 1 and 2. (a) MAD values. Unscaled (left) and scaled after normalization (right); (b) MAD for all ^{15}N atoms in the dataset showing maximum for each method; (c) analysis of frequency each method yields best prediction. Method 1 (blue), Method 2 (green).

Comparison of scaled values for both methods shows that scaled MAD for Method 2 has best overall predictions of ^{15}N chemical shifts for the class of aromatic nitrogenated compounds outperforming Method 1 (MAD_{scaled} 7.3 ppm) by about 27%. Moreover, Method 2 shows best prediction values for 58% of the dataset (Figure 3c). Although there are peaks showing deviations above 10 ppm (Figure 3B), the obtained MAD_{scaled} for Method 2 (5.3 ppm) represents an error of only 2% for the covered range (*ca.* 265 ppm) in the dataset, which is a promising result pointing towards the desired target error ≤1% for accurate chemical shift prediction.

Methods 1 and 2 differ in diverse aspects and we are currently looking into the impact of basis sets, density functionals and solvation methods on the ^{15}N chemical shift predictions. Further results should be published in the due course. Herein, we also analyzed the performance of both methods for the solvents under consideration. In doing so, we obtained correlations for each solvent for methods 1 and 2. For acetone and dimethyl sulfoxide, methods reproduced the general trend with CPCM-OLYP/psSeg-2 (Method 2) presenting lower deviations (Figure 4a). Interestingly, the tendency was reversed in chloroform with SMD-mPW1PW91/6-311+G(2d,p) being by far superior (MAD_{scaled} = 6.0 ppm). Inspection of individual deviations after considering scaling factors taking into account each solvent separately reveals a striking difference for method 2 in chloroform (Figure 4b, area in salmon red).

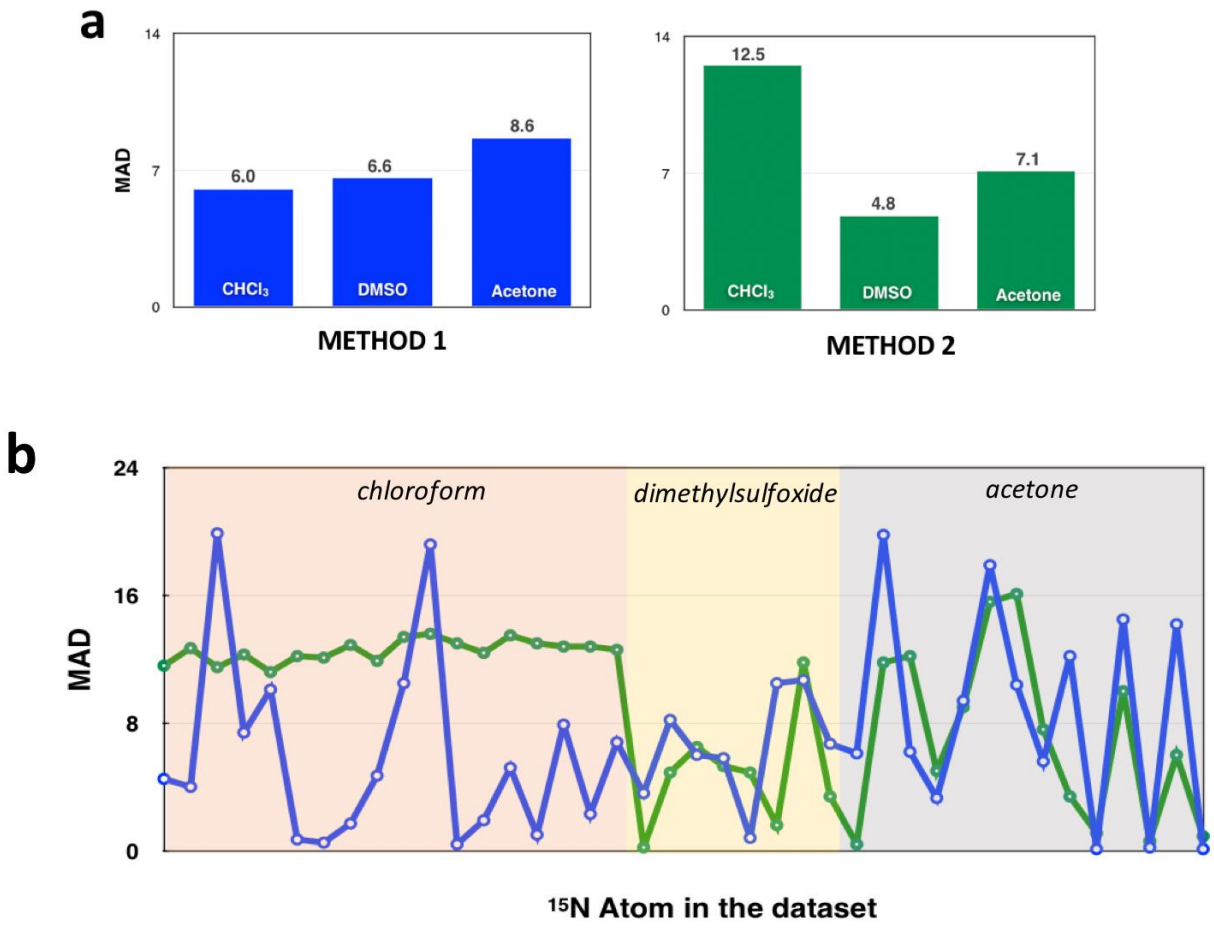


Figure 4. Method performance according to solvent. (a) MAD in various solvents; (b) MAD for all ^{15}N atoms in the dataset separated by solvent. Method 1 (blue), Method 2 (green).

That solvent may have a significant impact on ^{15}N chemical shifts is well documented, particularly when intra- or intermolecular interactions are present.[30] For this element, the solvent effect in the context of NMR studies has also been investigated computationally.[31–33] Gao and co-workers[14], who applied method 1 previously, noticed that scaling factors afforded better ^{15}N chemical shift prediction in chloroform than in dimethyl sulfoxide.[14] By using two distinct methods differing in various parameters including solvation model used (CPCM versus SMD), we note that predictions in chloroform are far better when method 1 is applied. While the influence of density functionals and basis sets used in the methods cannot be ruled out, it is likely that solvation models perform differently according to the polarity of the solvent (Figure 5).

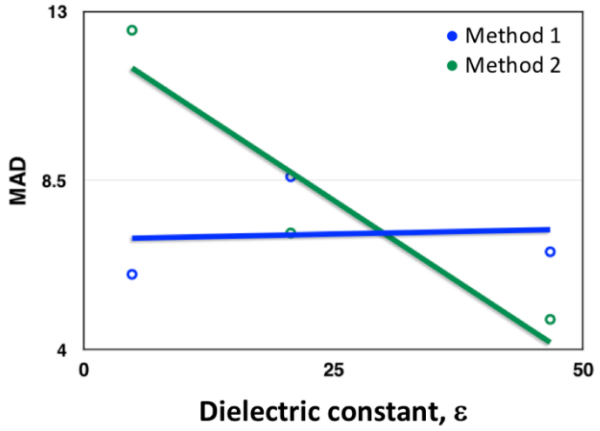


Figure 5. Mean absolute deviation (MAD) against dielectric constant of solvents analyzed.

Method 1 shows little variation along the dielectric constant values contrasting with Method 2 that shows a clear slope towards better predictions in increasingly more polar solvents. That acetone (ε= 20.7) and dimethyl sulfoxide (ε= 46.7) are much more polar than chloroform (ε= 4.8) possibly suggests better performance of the SMD model in non-polar solvents. Further investigation into this point is currently underway, which is critical to the development of improved predictive protocols for ^{15}N chemical shifts and other elements.

Conclusions

Of the methods evaluated, scaled values for method 2 (CPCM-OLYP-pcSseg-2), which was adapted from a recent contribution, showed best overall predictions (MAD 5.3 ppm). The mean deviation represents only 2% of the range of chemical shifts covered in the dataset encouraging application of empirical scaling parameters developed for this class of compounds regardless of solvent in question. When errors were computed by solvent, method 1 (SMD-mPW1PW91-6-311+G(2d,p) provides significantly better results in chloroform. That being the case, an alternative empirical scaling could be considered as provided.

Various are the challenges in developing a protocol resulting in scaling parameters that could cover all across the large distribution of ^{15}N chemical shifts. Towards that end, the present contribution may indicate that there are issues regarding the solvent and, by consequence, the solvation model that needs to be addressed in future studies.

Experimental Section

All computations were carried out with Gaussian 09 (revision D.01) suite of quantum chemical programs.[34] Geometries were readily obtained from the literature available at the MP2/aug-cc-pVTZ level of theory considering solvent effects using the conductor-like polarizable model (CPCM). NMR calculations were computed using the gauge-including atomic orbital (GIAO) approach at the following levels of theory: SMD-mPW1PW91/6-311+G(2d,p) and CPCM-OLYP/pcSseg-2, named as Method 1 and Method 2, respectively. As Jensen's pcSeg-2 basis set is not available in Gaussian 09, parameters were obtained from the well-known

basis set exchange portal.[35] Calculated shielding constants were converted into ^{15}N chemical shifts using nitromethane as a standard reference following recommendation from IUPAC. In doing so, shielding constants were computed using both methods and in all solvents (acetone, chloroform and dimethyl sulfoxide). Chemical shifts were also computed using scaling factors generated by plotting experimental chemical shifts against calculated isotropic shielding values following equation 1:

$$\sigma_{exp.} = slope\ x\ \theta_{isotropic} + intercept \quad (1)$$

Scaling factors at each level of theory were then applied to compounds as in equation 2:

$$\sigma_{scaled} = \frac{\theta_{isotropic} - intercept}{slope} \quad (2)$$

Acknowledgements

This research was supported by the São Paulo Research Foundation – FAPESP (grants 2013/07600-3, 2014/25770-6 and 2015/01491-3). AACB (grant 309715/2017-2) also thanks the Brazilian National Research Council (CNPq) for financial support and fellowships. This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001. We acknowledge the Euler cluster at the Center for Mathematical Sciences Applied to the Industry (CeMEAI) funded by FAPESP (2013/07375-0). The authors also thank Gilmar Bertolote Jr for invaluable IT support.

Supplementary Material

Tables with isotropic values and chemical shifts, and correlation plots.

References

1. Hehre, W.; Klunzinger, P.; Deppmeier, B.; Driessen, A.; Uchida, N.; Hashimoto, M.; Fukushi, E.; Takata, Y. *J. Nat. Prod.* **2019**, *82*, 2299. https://doi.org/10.1021/acs.jnatprod.9b00603
2. Grimblat, N.; Sarotti, A. M. *Chem. -Eur. J.* **2016**, *22*, 12246. https://doi.org/10.1002/chem.201601150
3. Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. *Chem. Rev.* **2012**, *112*, 1839. https://doi.org/10.1021/cr200106v
4. Iron, M. A. *J. Chem. Theory Comput.* **2017**, *13*, 5798. https://doi.org/10.1021/acs.jctc.7b00772
5. Samultsev, D. O.; Semenov, V. A.; Krivdin, L. B. *Magn. Reson. Chem.* **2014**, *52*, 222. https://doi.org/10.1002/mrc.4055
6. Fedorov, S. V.; Rusakov, Y. Y.; Krivdin, L. B. *Magn. Reson. Chem.* **2014**, *52*, 699. https://doi.org/10.1002/mrc.4122

7. Kupka, T.; Stachów, M.; Kaminsky, J.; Sauer, S. P. A. *Magn. Reson. Chem.* **2013**, *51*, 482. https://doi.org/10.1002/mrc.3974
8. Semenov, V. A.; Samultsev, D. O.; Krivdin, L. B. *Magn. Reson. Chem.* **2014**, *52*, 686. https://doi.org/10.1002/mrc.4119
9. Fedorov, S. V.; Rusakov, Y. Y.; Krivdin, L. B. *Russ. Chem. Bull.* **2015**, *64*, 551. https://doi.org/10.1007/s11172-015-0899-1
10. Goerigk, L.; Hansen, A.; Bauer, C.; Ehrlich, S.; Najibi, A.; Grimme, S. *Phys. Chem. Chem. Phys.* **2017**, *19*, 32184. https://doi.org/10.1039/C7CP04913G
11. Krivdin, L. B. *Prog. NMR Spectrosc.* **2017**, *102-103*, 98. https://doi.org/10.1016/j.pnmrs.2017.08.001
12. Levy, G. C.; Licther, R. L. Nitrogen-15 Nuclear magnetic resonance Spectropy. John Wiley and Sons Inc., 1979.
13. Semenov, V. A.; Samultsev, D. O.; Krivdin, L. B. *J. Chem. Phys. A* **2019**, *123*, 8417. https://doi.org/10.1021/acs.jpca.9b06780
14. Gao, P.; Wang, X.; Yu, H. *Adv. Theory Comp.* **2019**, *2*, 1800148. https://doi.org/10.1002/adts.201800148
15. Semenov, V. A.; Samultsev, D. O.; Krivdin, L. B. *Magn. Reson. Chem.* **2019**, *57*, 346. https://doi.org/10.1002/mrc.4851
16. Xin, D.; Sader, C. A.; Fischer, U; Wagner, K.; Jones, P. –J.; Xin, M.; Fandrick, K. R.; Gonnella, N. C., *Org. Biomol. Chem.* **2017**, *15*, 928. https://doi.org/10.1039/C6OB02450E
17. Laxer, A.; Major, D. T.; Gottlieb, H. E.; Fischer, B. *J. Org. Chem.* **2001**, *66*, 5463. https://doi.org/10.1021/jo010344n
18. Ditchfield, R. *Mol. Phys.*, **1974**, *27*, 789. https://doi.org/10.1080/00268977400100711
19. Marenich, A.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378. https://doi.org/10.1021/jp810292n
20. Renzerhof, M.; Scuseria, G. E. *J. Chem. Phys.* **1999**, *110*, 5029. https://doi.org/10.1063/1.478401
21. Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664. https://doi.org/10.1063/1.475428
22. Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995. https://doi.org/10.1021/jp9716997
23. Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669. https://doi.org/10.1002/jcc.10189
24. Reid, D. M.; Collins, M. A. *J. Chem. Theory Comput.* **2015**, *11*, 5177. https://doi.org/10.1021/acs.jctc.5b00546
25. Jensen. F. *J. Chem. Theory Comput.* **2015**, *11*, 132. https://doi.org/10.1021/ct5009526
26. Handy, N. C.; Cohen, A. J. *Mol. Phys.* **2001**, *99*, 403. https://doi.org/10.1080/00268970010018431
27. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785. https://doi.org/10.1103/PhysRevB.37.785

28. Harris, R. K.; Becker, E. D.; Cabral de Menezes, S. M.; Granger, P.; Hoffman, R. E.; Zilm, K. W. *Pure Appl. Chem.* **2008**, *80*, 59. http://dx.doi.org/10.1351/pac200880010059
29. CHESHIRE CCAT, the Chemical Shift Repository for Computed NMR scaling factors, with Coupling Constants Added Too, http://cheshirenmr.info/index.htm (accessed: December, 2019).
30. Andersson, H.; Carlsson, A.-C. C.; Nekoueishahraki, B.; Brath, U.; Erdélyi, M. In *Annual Reports on NMR Spectroscopy*, Elsevier: Amsterdam, 2015; Vol. 86, pp 73–210. https://doi.org/10.1016/bs.arnmr.2015.04.002
31. Phillips, A.; Marchenko, A.; Ducati, L. C.; Autschbach, J. *J. Chem. Theory. Comput.* **2019**, *15*, 509. https://doi.org/10.1021/acs.jctc.8b00807
32. Batista, P. R.; Karas, L. J.; Viesser, R. V.; de Oliveira, C. C.; Gonçalves, M. B.; Tormena, C. F.; Rittner, R.; Ducati, L. C.; de Oliveira, P. R. *J. Chem. Phys. A* **2019**, *40*, 8583. https://doi.org/10.1021/acs.jpca.9b05619
33. Rusakov, Y. Y.; Rusakova, I. L.; Semenov, V. A.; Samultsev, D. O.; Federov, S. V.; Krivdin, L. B. *J. Chem. Phys. A* **2018**, *122*, 6746. https://doi.org/10.1021/acs.jpca.8b05161
34. Frisch, M. J.; Trucks, G. W.; Schlegel, H.B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford, CT, 2013, Revision D.01.
35. Pritchard, B. P.; Altarawy, D.; Didier, B.; Gibson, T. D.; Windus, T. L. *J. Chem. Inf. Model.* **2019**, *59*, 4814. https://doi.org/10.1021/acs.jcim.9b00725