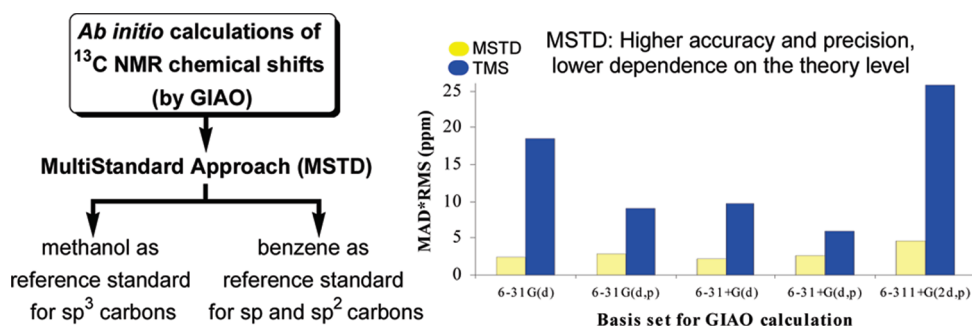# A Multi-standard Approach for GIAO ^{13}C NMR Calculations

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The influence of the reference standard employed in the calculation of ^{13}C NMR chemical shifts was investigated over a large variety of known organic compounds, using different quantum chemistry methods and basis sets. After detailed analysis of the collected data, we found that methanol and benzene are excellent reference standards for computing NMR shifts of sp^3- and sp−sp^2-hybridized carbon atoms, respectively. This multi-standard approach (MSTD) performs better than TMS in terms of accuracy and precision and also displays much lower dependence on the level of theory employed. The use of mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level is recommended for accurate ^{13}C NMR chemical shift prediction at low computational cost.

Introduction

NMR spectroscopy is one of the most valuable tools for structure elucidation. However, even with the aid of 2D and 3D NMR experiments, it is not uncommon for a structural assignment to be incomplete or incorrect.[1] Therefore, much effort has been devoted to the development of quantum chemical calculations to predict NMR chemical shifts.[2,3] Good matching between the calculated chemical shifts for one of the potential structures with the experimental values constitutes an excellent tool to support structural analysis of organic compounds. This technique was first proposed by Bifulco[4,5] and has been successfully employed in numerous reports.[6]

Most quantum chemical methods allow good predictions of ^{1}H and ^{13}C NMR chemical shifts; however, empirical scaling corrections are generally needed to remove systematic errors in the shift calculation process.[4,5,7−10] Although the results are significantly improved after scaling, an inherent limitation of the method is that experimental data are needed. For that reason, the real challenge is to compute accurate NMR chemical shifts using only quantum chemical calculations.

Different methods for calculating magnetic shielding tensors have been developed, but the GIAO method (gauge including atomic orbitals)[11] is most commonly used as it has been shown to provide better results with the same basis set size.[12] Another issue that has been recently assessed is the influence of using different theory levels in reproducing experimental ^{13}C NMR chemical shifts.[12−19] Although second-order Møller−Plesset theory (MP2) has been shown to yield excellent results,[12] this method is very time-consuming, even with modest-sized molecules. On the other hand, density functional theory (DFT) has emerged as an alternative method which provides acceptable levels of accuracy at low computational cost. For instance, Bifulco and co-workers recommended the mPW1PW91/6-31G(d,p) level for GIAO

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NMR calculations of low polarity natural products,[14] while Bagno and co-workers showed that a considerable degree of accuracy in the prediction of NMR spectra of complex molecules can be attained at the B3LYP or PBE1PBE/cc-pVTZ levels of theory.[16]

On the other hand, it seems that the effect of the reference standard used for computing ^{13}C NMR chemical shifts has not been fully evaluated since, in most cases, the calculated chemical shifts are referenced to TMS.[6] There are several obvious reasons why TMS constitutes an excellent standard for experimental NMR spectroscopy: it is chemically unreactive, easily removed from the sample after the measurement, and gives a sharp NMR signal that does not interfere with the resonances normally observed for organic compounds. Nevertheless, the standard is "virtual" in NMR calculations, so basically any molecule can be used as reference standard with the only condition that its experimental chemical shift must be known (preferentially, in different solvents). Therefore, the predicted chemical shift for a given nucleus (δ_{calc}^x) can be calculated according to

$$\delta_{calc}^x = \sigma_{ref} - \sigma_x + \delta_{ref} \qquad (1)$$

where σ_{ref} and σ_x are the NMR isotropic magnetic shielding values for the reference compound and the corresponding nucleus, respectively, computed at the same level of theory, and δ_{ref} is the experimental chemical shift of the reference compound (in the case of TMS, $\delta_{ref} = 0$).

The suitability of the use of TMS in the extraction of calculated NMR shifts from calculated absolute shieldings was first tackled by Siegel.[20] More recently, Schuler and co-workers found TMS to be inappropriate as computational reference for DFT calculations of the chemical shifts of ring carbons in some specific aromatic-like systems.[21] Therefore, sp²-hybridized carbons were referenced to benzene in a few publications.[22]

In principle, one should not expect a linear correlation between calculated and experimental chemical shifts for all carbons in an organic backbone, although the phenomenon may not be general.[16] Bifulco and co-workers found that, when computing chemical shifts referred to TMS, the straight lines fitting the points in the range of 10−70 ppm of the experimental chemical shift axis had a lower linear slope and a higher intercept than those fitting the data included in the range of 90−220 ppm.[4] According to them, this behavior can be attributed to electron correlation effects which produce two different linear trends in these two regions of the ^{13}C NMR spectrum. Belostotskii proposed that this effect can be explained taking into account that solvation effect is different for different types of carbons in an organic molecule (aliphatic, aromatic, functionalized).[6h] Therefore, best matching between calculated and experimental chemical shifts may be expected when comparing similar carbons (*e.g.*, TMS-aliphatic carbons or benzene-aromatic carbons).

It is surprising then that this simple but important part of the NMR chemical shift calculation has not been thoroughly investigated. Therefore, we considered that it would be of theoretical and practical importance to answer a simple (but not trivial) question: Can a reference standard that performs better than TMS at any level of theory be found for GIAO ^{13}C NMR calculations? To solve this challenging task, we computed the ^{13}C NMR chemical shifts of a big collection of known organic molecules using a variety of potential reference standard compounds at different levels of theory.

Results and Discussion

1. Finding the Optimal Reference Standard. Ideally, the selected standard should provide the following features: it must be a simple, easy-to-model molecule, whose NMR chemical shifts are well-known in different solvents. Taking these considerations in mind, 11 small molecules were selected as potential GIAO ^{13}C NMR standards: tetramethylsilane, dichloromethane, chloroform, tetrahydrofuran, acetonitrile, nitromethane, *tert*-butanol, methanol, acetic acid, acetone, and benzene (Table 1). These compounds have

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TABLE 1. Experimental ^{13}C NMR Chemical Shifts of the Proposed Standards in CDCl$_3$

reference standard	nucleus	^{13}C chemical shift (ppm)
tetramethylsilane	Si(CH$_3$)$_4$	0.00
dichloromethane	CH$_2$Cl$_2$	53.52
chloroform	CHCl$_3$	77.36
tetrahydrofuran	CH$_2$O	67.97
tetrahydrofuran	CH$_2$	25.62
acetonitrile	CH$_3$CN	1.89
acetonitrile	CH$_3$$C$N	116.43
nitromethane	CH$_3$NO$_2$	62.50
tert-butanol	(CH$_3$)$_3$COH	31.25
tert-butanol	(CH$_3$)$_3$$C$OH	69.15
methanol	CH$_3$OH	50.41
acetic acid	CH$_3$CO$_2$H	20.81
acetic acid	CH$_3$$CO_2$H	175.89
acetone	(CH$_3$)$_2$CO	30.92
acetone	(CH$_3$)$_2$$C$O	207.07
benzene	C_6H$_6$	128.37

different functionalities and chemical shifts, thus a wide NMR spectral window can be covered.[23] Note that some standards have two different carbon atoms, and in those cases, both nuclei were considered in this study.

The 50 low polarity small-to-medium size compounds shown in Figure 1 were chosen to provide a wide array of chemical functionalities and molecular complexity and also because their ^{13}C NMR spectra in deuterated chloroform are well-known.[24] Most molecules included in the test set have a clearly preferred conformation, so that a single conformer can be assumed to represent the dynamic structure in solution. However, in the case of more flexible systems, we considered only the most stable conformation in order to minimize the total number of NMR calculations.[25] Accordingly, each global minimum and the selected reference standards were optimized at the B3LYP[26]/6-31G(d)[27] level to provide a good starting point to perform NMR calculations. The isotropic magnetic shielding values were computed employing three widely used methods (HF, B3LYP, and mPW1PW91[28]), and two basis sets: the simple 6-31G(d) and the more complex and time-consuming 6-311+G(2d,p). For further analysis, we divided the data in three main

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(25) It is well-known that magnetic shielding values frequently show a strong conformational dependence. If a molecule has more than one significantly populated conformer, then a prediction of chemical shifts requires a separate calculation for each conformer, followed by the calculation of the Boltzmann-weighted average. The assumption that neglecting the contributions of other low-energy conformers do not affect the results might be questionable. However, we found that for the chosen compounds the chemical shifts calculated using the global minima and all significant conformers showed no significant variations. This issue is discussed in more detail in the Supporting Information.

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(29) Throughout this study, we will use this term. In order to avoid misinterpretation, we aim to clarify that the type of hybridization refers only to the carbons of compounds shown in Figure 1 and not to the carbons of the reference standards.

groups depending on the type of hybridization of the carbon atoms (sp^3, sp^2, and sp).[29] Several statistical parameters are available to judge the quality of a calculation, but none of them, if taken alone, is fully satisfactory. As we were initially focused on the quality of chemical shift prediction using different standards, we used the mean absolute difference (MAD, defined as $\Sigma_n|\delta^x_{calc} - \delta^x_{exp}|/n$) and the RMS error as measurements of accuracy and precision of the calculations, respectively. The results are presented in Table 2.

After detailed analysis of the data shown in Table 2, we realized that TMS is a very good standard only in the case of sp^3 carbons at B3LYP or mPW1PW91/6-31G(d) levels. However, we were unable to locate a single reference standard that performed in optimal fashion for all types of carbons at any level of theory. In most cases, the results depend upon the carbon hybridization and the method employed for computing the isotropic magnetic values. Moreover, the quality of NMR prediction for a particular standard can vary dramatically just by changing the level of theory (for instance, note the case of computing the chemical shifts of sp^2 carbons relative to dichloromethane using HF, B3LYP, and mPW1PW91 methods). Consequently, we thought that it would be useful for general purposes to detect reference standards that performed reasonably well regardless of the level of theory employed. With this consideration in mind, we found that methanol and benzene were excellent references for calculating NMR chemical shifts of sp^3- and sp–sp^2-hybridized carbon atoms, respectively. Therefore, a multi-reference standard approach (MSTD) was proposed to achieve accurate predictions of ^{13}C NMR parameters at any level of theory. This method basically implies the use of methanol as reference standard for all sp^3 carbons in a given molecule, while benzene must be used for the rest of the carbons atoms (sp and sp^2). After application of this methodology to the ^{13}C NMR chemical shift prediction of all compounds shown in Figure 1, we were glad to note that in all cases MSTD performed much better than TMS. As shown in Table 3, an important improvement in both accuracy and precision was achieved, especially when GIAO calculations were carried out using DFT methods, while there was no evident dependence on the quality of the results by changing from the low computational cost 6-31G(d) to the more time-consuming 6-311+G(2d,p) basis sets.

2. Influence of the Theory Level. Given the clear improvement of the MSTD method over TMS as reference standard, an excursion directed toward finding the level of theory that allowed optimal results at lower computational cost seemed to be appropriate. To achieve our goal, we decided to fully investigate the factors which could have a significant effect on the quality of the NMR prediction. Therefore, the chosen factors included the following: (a) functional for geometry optimization (B3LYP and mPW1PW91), (b) basis set for geometry optimization (3-21G, 6-31G(d), 6-31G(d,p), and 6-31+G(d)), and (c) basis set for mPW1PW91 GIAO NMR calculation (6-31G(d), 6-31G(d,p), 6-31+G(d), 6-31+G(d, p), and 6-311+G(2d,p)).[30] Eight representative organic molecules were selected for the study, with differences in size, structural complexity, oxidation state, and number of

(30) Since the functional mPW1PW91 gave slightly lower MAD and RMS errors than B3LYP, the first was selected for the GIAO NMR calculations.
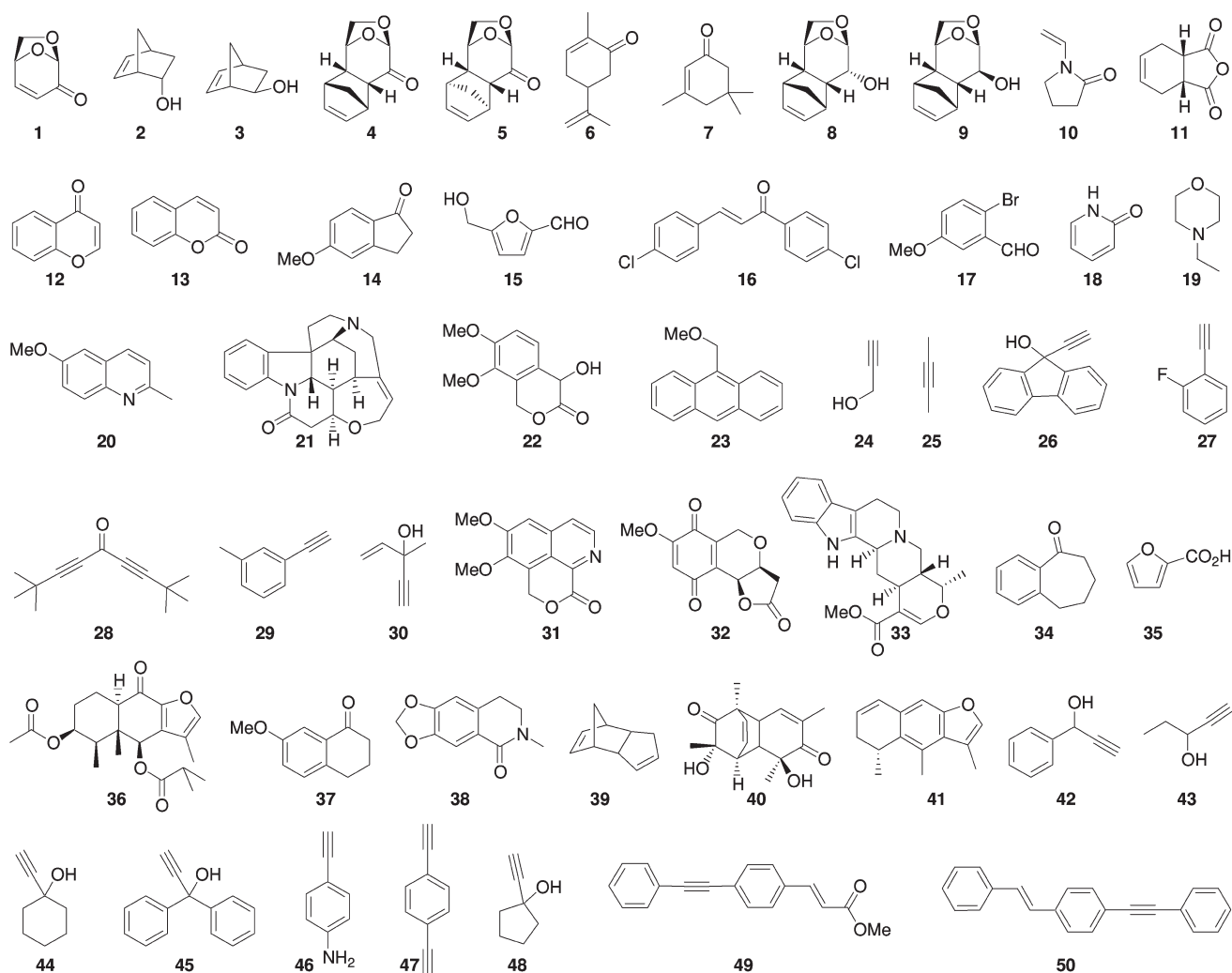
FIGURE 1. Chemical structures of the compounds used in this study.

insaturations (compounds **1**, **4**, **20**, **21**, **32**, **33**, **39**, and **41**, Figure 1). A full general factorial design was employed, in which each factor is treated as categorical and is varied over the selected number of levels.[31] In this case, 40 experiments were needed for each compound.[32]

Interestingly, in only 11 cases (3.4%) of all 320 NMR calculations, a slightly lower MAD was observed when using TMS instead of MSTD approach. In other words, just using methanol and benzene as reference standards for all sp^3 and sp^2 carbon atoms, respectively, a great deal of improvement in accuracy and precision can be obtained when computing ^{13}C NMR chemical shifts.

We next analyzed in detail the collected data to draw conclusions about the significance of each of the studied factors. Figure 2 shows the average effect of the DFT functional employed during geometry optimization with the quality of the NMR prediction. We found that using B3LYP or mPW1PW91 methods affects the final results only in a moderate fashion. In particular, mPW1PW91 is slightly preferred in the MSTD approach, while when using TMS as

reference standard, B3LYP and mPW1PW91 are better for computing the chemical shifts of sp^2 and sp^3 carbons, respectively.

On the other hand, the basis set chosen for geometry optimization seemed to be a rather important issue for consideration. As shown in Figure 3, the basis set 3-21G displayed higher MAD and RMS errors than the other basis sets under consideration, especially for sp^2-hybridized carbon atoms. Nevertheless, even though no significant variations were noted when optimizing geometries at higher levels of theory, the 6-31G(d) and 6-31+G(d) basis sets gave better results than 6-31G(d,p), and any of them should be used when computational resources do not constitute a serious inconvenience.

Finally, a strong dependence between MAD and RMS parameters with the basis set used for GIAO NMR calculations was found when using TMS as reference standard (Figure 4). In the case of sp^3 carbons, the accuracy and precision decrease with the increase of the basis set size. On the other hand, for sp^2-type carbon atoms, a considerable improvement was observed at the 6-31+G(d,p) level. This interesting behavior may be responsible for Bifulco's observation that 6-31G(d,p) is the basis set of choice for GIAO ^{13}C NMR calculations[14] because most organic molecules possess

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(32) For detailed discussion on this issue, see the Supporting Information.

TABLE 2.   MAD and RMS (in parentheses) Parameters Obtained after Computing the ^{13}C NMR Chemical Shifts of the 50 Compounds Shown in Figure 1 Using Different Reference Standards

standard	HF		B3LYP		mPW1PW91	
	6-31G(d)	6-311+G(2d,p)	6-31G(d)	6-311+G(2d,p)	6-31G(d)	6-311+G(2d,p)
sp³-hybridized carbon atoms						
TMS	4.8 (7.2)	3.1 (4.8)	1.8 (3.3)	4.6 (5.3)	1.4 (1.4)	3.2 (3.2)
CH_2Cl_2	5.4 (8.3)	10.3 (6.5)	10.6 (5.6)	16.4 (6.1)	10.1 (3.1)	15.6 (4.4)
$CHCl_3$	8.0 (9.7)	14.6 (6.5)	22.8 (5.9)	31.4 (6.1)	20.9 (3.1)	28.8 (4.4)
THF (CH_2O)	3.1 (6.7)	2.5 (4.1)	2.3 (3.8)	1.9 (2.5)	1.8 (2.0)	1.6 (1.9)
THF (CH_2)	4.5 (6.6)	3.9 (5.7)	2.6 (4.7)	1.9 (3.0)	2.4 (2.8)	1.8 (2.7)
CH_3CN	6.1 (9.1)	2.9 (4.3)	1.8 (3.3)	5.6 (5.9)	1.5 (1.6)	3.5 (3.5)
$\overline{C}H_3CN$	3.7 (5.3)	13.1 (5.6)	14.4 (5.9)	2.5 (2.7)	10.2 (3.1)	1.7 (2.5)
CH_3NO_2	3.4 (5.0)	3.2 (4.9)	3.4 (4.3)	3.3 (3.8)	2.1 (2.3)	2.4 (2.5)
$(CH_3)_3COH$	3.2 (4.7)	2.2 (3.0)	2.1 (3.6)	4.0 (4.8)	1.7 (1.9)	3.4 (3.3)
$(\overline{C}H_3)_3COH$	5.1 (8.8)	3.5 (5.2)	3.0 (4.2)	1.9 (2.8)	3.0 (2.8)	1.6 (1.9)
$CH_3O\overline{H}$	2.9 (4.2)	2.2 (2.8)	1.8 (3.3)	2.2 (2.5)	1.4 (1.3)	1.7 (2.0)
CH_3CO_2H	4.4 (6.5)	2.9 (4.4)	3.3 (4.3)	5.5 (5.8)	2.0 (2.2)	4.0 (3.8)
$\overline{C}H_3CO_2H$	2.9 (6.2)	7.3 (6.5)	17.5 (5.9)	3.1 (3.5)	14.8 (3.1)	2.6 (2.7)
$(CH_3)_2CO$	2.9 (4.1)	2.2 (2.8)	3.6 (4.5)	4.5 (5.3)	2.3 (2.4)	3.2 (3.1)
$(\overline{C}H_3)_2\underline{C}O$	3.2 (6.8)	6.6 (6.5)	15.2 (5.9)	1.9 (2.7)	12.5 (3.1)	1.6 (2.1)
C_6H_6	4.0 (5.9)	9.4 (6.5)	8.2 (4.7)	1.9 (3.0)	6.1 (3.1)	2.0 (3.1)
sp²-hybridized carbon atoms						
TMS	2.5 (6.4)	7.6 (13.1)	6.5 (7.5)	6.6 (11.1)	5.1 (6.7)	5.8 (9.5)
CH_2Cl_2	2.7 (6.6)	2.8 (7.6)	17.6 (10.9)	14.4 (11.3)	15.3 (10.1)	13.0 (10.1)
$CHCl_3$	4.4 (7.6)	5.0 (10.8)	29.8 (11.6)	29.3 (12.5)	25.5 (10.9)	26.0 (11.1)
THF (CH_2O)	6.9 (11.0)	12.3 (15.4)	5.6 (7.2)	3.0 (8.4)	4.2 (6.5)	3.4 (8.1)
THF (CH_2)	2.5 (6.3)	6.7 (12.4)	9.4 (9.2)	2.5 (7.6)	7.7 (7.8)	2.4 (7.2)
CH_3CN	3.0 (6.9)	7.9 (13.3)	6.5 (7.5)	7.7 (11.6)	6.3 (7.2)	6.1 (9.8)
$\overline{C}H_3CN$	2.6 (6.8)	3.8 (9.4)	7.5 (10.9)	4.1 (9.4)	5.2 (9.1)	2.5 (7.3)
$CH_3\overline{N}O_2$	2.8 (7.1)	7.5 (13.1)	4.3 (7.0)	5.2 (10.2)	3.9 (6.5)	4.8 (9.0)
$(CH_3)_3COH$	2.9 (7.3)	9.0 (13.9)	5.9 (7.3)	6.0 (10.8)	4.4 (6.5)	6.0 (9.7)
$(\overline{C}H_3)_3\underline{C}OH$	9.2 (11.9)	13.5 (15.7)	4.8 (7.0)	2.6 (7.8)	3.1 (6.5)	3.3 (8.0)
$CH_3O\overline{H}$	3.2 (7.9)	9.3 (14.1)	6.5 (7.5)	3.6 (9.0)	5.4 (6.8)	3.7 (8.4)
CH_3CO_2H	2.5 (6.3)	7.8 (13.3)	4.5 (7.0)	7.6 (11.6)	4.0 (6.5)	6.6 (10.0)
$\overline{C}H_3\underline{C}O_2H$	6.5 (10.9)	3.8 (9.2)	10.6 (11.6)	5.0 (10.1)	9.7 (10.8)	5.1 (9.2)
$(CH_3)_2CO$	3.2 (8.8)	9.2 (14.1)	4.1 (7.0)	6.5 (11.1)	3.7 (6.5)	5.7 (9.5)
$(\overline{C}H_3)_2\underline{C}O$	7.0 (11.1)	4.4 (9.8)	8.2 (11.1)	2.7 (7.9)	7.4 (10.2)	2.9 (7.6)
C_6H_6	2.5 (6.5)	2.9 (7.7)	2.4 (7.1)	2.5 (7.6)	2.3 (6.6)	2.3 (6.8)
sp-hybridized carbon atoms						
TMS	6.9 (23.6)	5.3 (17.1)	7.1 (11.6)	4.3 (8.2)	5.0 (11.6)	5.2 (8.3)
CH_2Cl_2	7.1 (28.3)	5.6 (21.7)	18.3 (14.8)	16.7 (9.3)	14.9 (18.1)	13.5 (9.6)
$CHCl_3$	8.7 (42.0)	8.9 (29.8)	30.5 (14.8)	31.7 (9.3)	25.6 (18.1)	26.7 (9.6)
THF (CH_2O)	6.2 (15.9)	8.5 (27.3)	6.2 (10.4)	2.0 (5.1)	4.3 (10.2)	2.8 (7.1)
THF (CH_2)	6.8 (20.8)	5.0 (14.1)	10.0 (14.8)	2.4 (4.4)	7.3 (14.9)	1.9 (6.5)
CH_3CN	7.5 (33.3)	5.4 (18.2)	7.1 (11.5)	5.3 (8.7)	6.0 (13.3)	5.6 (8.4)
$\overline{C}H_3CN$	6.6 (15.6)	7.4 (29.2)	6.8 (14.8)	2.2 (6.3)	5.5 (16.8)	2.0 (6.8)
$CH_3\overline{N}O_2$	6.5 (14.2)	5.2 (16.8)	5.0 (9.3)	2.9 (7.8)	4.0 (9.6)	4.2 (7.9)
$(CH_3)_3COH$	6.5 (13.3)	6.1 (20.5)	6.5 (10.7)	3.7 (8.0)	4.4 (10.4)	5.5 (8.4)
$(\overline{C}H_3)_3COH$	6.6 (28.5)	9.6 (28.8)	5.5 (9.8)	2.3 (4.5)	3.6 (8.0)	2.7 (7.1)
$CH_3O\overline{H}$	6.4 (11.5)	6.2 (20.8)	7.1 (11.5)	2.0 (5.9)	5.2 (12.1)	3.2 (7.3)
CH_3CO_2H	6.8 (20.4)	5.4 (18.1)	5.2 (9.4)	5.2 (8.6)	4.1 (9.8)	6.1 (8.7)
$\overline{C}H_3\underline{C}O_2H$	6.2 (14.4)	5.0 (10.8)	9.9 (14.8)	2.7 (7.5)	10.1 (18.1)	4.6 (8.0)
$(CH_3)_2CO$	6.4 (11.3)	6.2 (20.7)	4.8 (9.1)	4.2 (8.1)	3.9 (9.2)	5.2 (8.2)
$(\overline{C}H_3)_2\underline{C}O$	6.2 (16.4)	5.0 (9.7)	7.5 (14.8)	2.3 (4.5)	7.8 (18.1)	2.2 (7.2)
C_6H_6	6.7 (17.7)	5.3 (18.0)	3.1 (4.9)	2.4 (4.4)	3.8 (5.1)	1.9 (6.0)

TABLE 3.   MAD and RMS Parameters Obtained after Computing the ^{13}C NMR Chemical Shifts of the 50 Compounds Shown in Figure 1 Using MSTD and TMS as Reference Standards

level of theory	average MAD		average RMS	
	MSTD	TMS	MSTD	TMS
HF/6-31G(d)	3.2	3.9	8.6	11.0
HF/6-311+G(2d,p)	3.0	5.7	7.8	14.4
B3LYP/6-31G(d)	2.3	5.0	5.7	11.3
B3LYP/6-311+G(2d,p)	2.4	5.4	5.1	9.4
mPW1PW91/6-31G(d)	2.1	3.8	4.9	8.1
mPW1PW91/6-311+G(2d,p)	2.1	4.7	4.6	8.2

sp²- and sp³-hybridized carbon atoms, and this basis set constitutes a compromise between an acceptable level of accuracy and precision for both types of carbons. In contrast, the use of the MSTD approach ensures high-quality NMR prediction regardless of the level of theory employed for GIAO calculations.

In summary, calculation of ^{13}C NMR chemical shifts of sp³- and sp²−sp-hybridized carbon atoms relative to methanol and benzene, respectively, has several advantages, such as higher accuracy and precision and much lower dependence on the level of theory employed during geometry
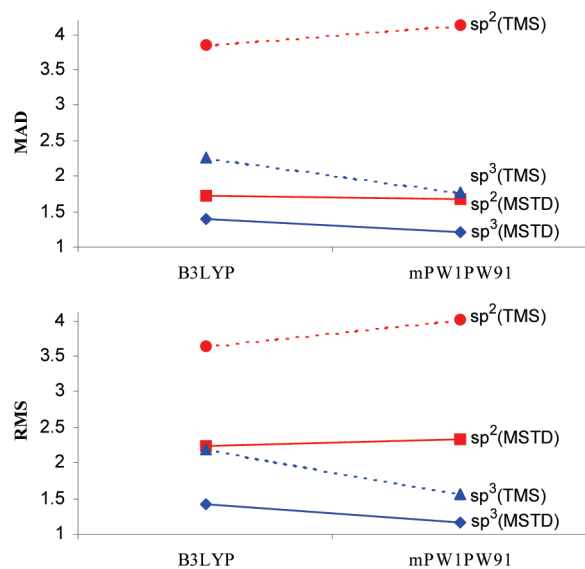
FIGURE 2. Effect of the functional used in the geometry optimization step in GIAO ^{13}C NMR chemical shift calculations.
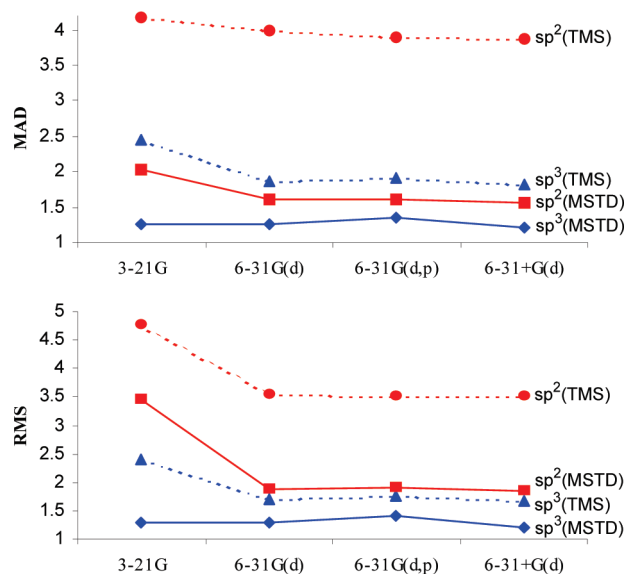

FIGURE 3. Effect of the basis set used in the geometry optimization step in GIAO ^{13}C NMR chemical shift calculations.

optimization and NMR calculations. Moreover, on the basis of the study discussed above, we propose that mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) constitutes a level of theory that provides maximal reliability at minimal computational cost when applying the MSTD approach.

3. Testing the MSTD Approach. The MSTD approach at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory was next tested over a bigger collection of known organic molecules (compounds **1**, **4**, **13**, **14**, **15**, **20**, **21**, **26**, **32**, **33**, **34**, **36**, **37**, **39**, **40**, **41**, **42**, **46**, **49**, and **50**, Figure 1). At this stage of the study, for flexible compounds, all significant conformations were considered for ^{13}C NMR chemical shift calculations. However, we observed that similar results were obtained when using the global minimum only (see Supporting Information). Table 4 shows the results obtained,
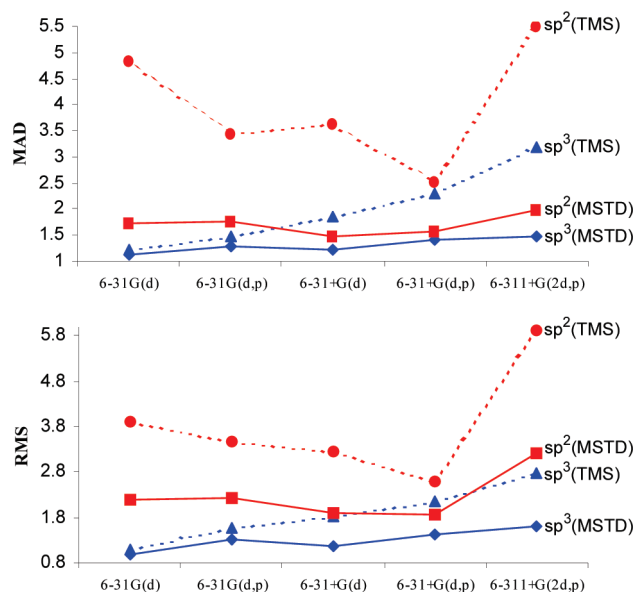

FIGURE 4. Effect of the basis set used in the NMR calculations in GIAO ^{13}C NMR chemical shift calculations.

TABLE 4. Statistical Parameters Obtained after Computing the ^{13}C NMR Chemical Shifts of Selected Compounds Using MSTD and TMS as Reference Standards at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) Level of Theory

compound (no. of carbons)	MAD		RMS		no. $\Delta\delta > 4$ ppm[a]	
	MSTD	TMS	MSTD	TMS	MSTD	TMS
1 (6)	1.4	3.0	2.4	8.7	0	2
4 (11)	1.6	2.1	1.6	4.1	0	1
13 (9)	1.6	5.7	3.0	5.9	1	8
14 (10)	2.2	5.1	3.4	13.4	1	5
15 (6)	1.6	6.2	1.9	8.5	0	5
20 (11)	1.1	4.9	1.6	4.8	0	8
21 (21)	1.3	2.8	1.4	7.4	0	6
26 (15)	1.5	4.5	0.8	5.0	0	5
32 (12)	1.7	3.9	2.1	8.9	1	5
33 (21)	1.6	3.3	1.8	6.8	0	8
34 (11)	1.3	4.0	2.5	10.3	1	6
36 (21)	1.5	3.1	1.3	8.2	0	7
37 (11)	1.7	4.6	2.3	10.6	0	6
39 (10)	1.6	1.7	1.8	2.0	0	0
40 (16)	1.9	2.1	2.6	3.0	3	2
41 (15)	1.6	3.7	1.4	4.2	0	7
42 (9)	1.3	4.8	1.8	7.5	0	4
46 (8)	3.1	6.4	3.7	14.7	2	4
49 (18)	2.3	4.0	3.6	5.4	2	8
50 (22)	1.4	4.8	3.0	3.5	2	13
Average	**1.7**	**4.0**	**2.2**	**7.1**	**5%**	**42%**

[a]The $\Delta\delta$ is defined as the absolute value of the difference between the calculated and experimental chemical shifts for each nuclei of a given compound.

together with those for TMS as reference standard at the same level of theory.

These results clearly indicate that high accuracy and precision can be obtained at low computational cost when using the MSTD approach at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level. For instance, the MAD and RMS parameters were in the range of 1.1−3.1 and 0.8−3.7 ppm, respectively. Moreover, only 5% of the 263 data points displayed $\Delta\delta > 4$ ppm, which may account for the

effectiveness of this method in reproducing experimental ^{13}C NMR chemical shifts. In contrast, TMS was shown to be a much less effective reference standard when computing ^{13}C NMR spectra at the same level of theory. In all cases, the MAD and RMS parameters were higher than the ones observed when using the MSTD approach (up to 4.5 and 6.3 times, respectively). The poorer fit between calculated and experimental NMR chemical shifts was also evidenced by the fact that almost 50% of the calculated chemical shifts displayed $\Delta\delta > 4$ ppm. Finally, it is important to point out that the MSTD method does not change the calculated absolute shielding values. Therefore, if the shielding values computed for a pair of carbons are not in the correct order, this will be reflected in the calculated chemical shifts regardless of the reference standard employed.[32]

4. Effect of Empirical Scaling. Throughout this study, we addressed the question of finding reference standards that performed better than TMS at any level of theory, thus unscaled chemical shifts were employed for comparison. However, when experimental data are available, the computed chemical shifts (δ_{calc}) can be empirically scaled using the slope and intercept obtained after linear regression from a plot of calculated against experimental data (δ_{exp}). To test the robustness of the MSTD approach, we next investigated the effect of empirical scaling in the chemical shift calculation procedure. Therefore, the chemical shifts computed at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level of theory (Table 4) were empirically scaled (see Supporting Information).[32] The results showed that, among scaled values, the fit was slightly better for TMS-derived chemical shifts (1.1 ppm of averaged MAD) than for those obtained using MSTD (1.4 ppm). However, the most significant observation was that the accuracies of the MSTD$_{unscaled}$ and TMS$_{scaled}$ methods were very similar (1.7 vs 1.1 ppm of averaged MAD, respectively). This constitutes a great advantage, especially when experimental data are incompletely assigned or unavailable.

Conclusion

In this study, we demonstrated that high accuracy and precision in GIAO ^{13}C NMR calculations can be attained when referring sp^3 and sp$-$sp^2 carbon atoms to methanol and benzene, respectively. After extensive investigation, we found that this multi-standard approach (MSTD) has a low dependence on the level of theory employed during the geometry optimization and the GIAO NMR calculation steps. The mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) level is recommended for highly satisfactory ^{13}C NMR chemical shift prediction at low computational cost. Finally, preliminary results suggest that this MSTD methodology can be efficiently employed in ^1H NMR prediction and will be published in due course.

Computational Methods

All calculations were performed using Gaussian03.[33] Conformational searches of all structures were performed to locate accurate geometries for further GIAO calculations. Initially, a large number of geometries were generated using the conformational search module of Hyperchem[34] with the MM+ force field.[35] Selected structures were then optimized at the RHF/AM1 and RHF/3-21G levels of theory. Finally, the more stable RHF/3-21G minimum energy conformers were reoptimized with the B3LYP/6-31G(d) method. For each compound, the lowest energy conformer found at the B3LYP/6-31G(d) level was used as input for NMR calculations. The theoretical ^{13}C NMR chemical shift values (δ_{calc}^x) were obtained according to the following equation

$$\delta_{calc}^x = \sigma_{ref} - \sigma_x + \delta_{ref}$$

where σ_{ref} and σ_x are the NMR isotropic magnetic shielding values for the reference compound and for any X carbon atom of a given molecule, respectively, both computed at the same level of theory, and δ_{ref} is the chemical shift of the reference compound in deuterated chloroform (Table 1).

For section 2 of this work, the selected structures were reoptimized with the DFT functionals B3LYP and/or mPW1PW91 using the 3-21G, 6-31G(d), 6-31G(d,p), and/or 6-31+G(d) basis sets, starting from the B3LYP/6-31G(d) optimized geometries.

For section 3 of this work, the NMR shielding constants for all significant conformers were calculated at the mPW1PW91/6-31G(d)//mPW1PW91/6-31G(d) and then subjected to Boltzmann averaging according to

$$\sigma_x = \left[\sum \sigma_x^i \exp(-G_i/RT)\right] / \left[\sum \exp(-G_i/RT)\right]$$

where σ_x is the Boltzmann-averaged calculated shielding constant for carbon x, σ_x^i is the shielding constant for carbon x in conformer i, R is the molar gas constant (8.3145 J K^{-1} mol^{-1}), T is the temperature (298 K), and G_i is the Gibbs free energy in solution of conformer i (relative to the global minimum), computed at the mPW1PW91/6-31G(d) level of theory with the polarizable continuum model (PCM),[36] using chloroform as solvent.

Supporting Information Available: Cartesian coordinates, energies, and GIAO isotropic magnetic shielding values for all structures discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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