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Application of the Multi-standard Methodology for Calculating ^{1}H NMR Chemical Shifts

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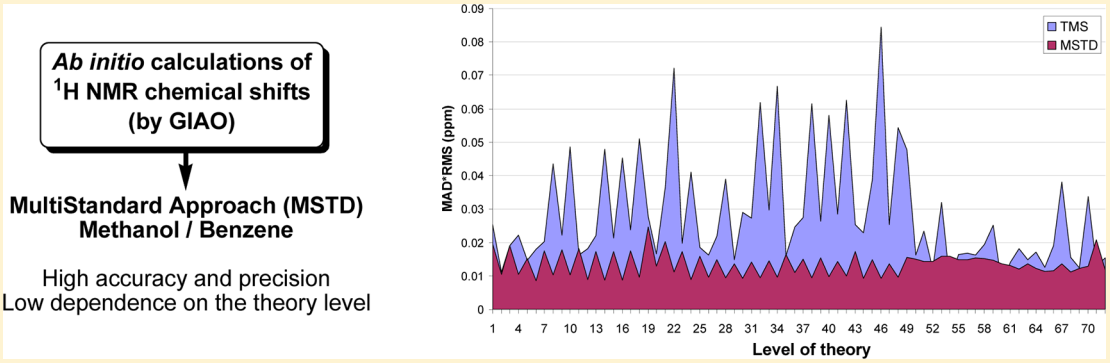

ABSTRACT: Gauge including atomic orbitals (GIAO) ^{1}H NMR chemical shift calculations have been performed for 66 organic compounds at 72 different levels of theory using the multi-standard approach (MSTD) previously developed for ^{13}C NMR. This straightforward computational technique involves the combination of methanol and benzene as standards. The studied methodology has been shown to predict ^{1}H NMR chemical shifts efficiently at different levels of theory.

INTRODUCTION

Among other problems in chemistry, structure elucidation relies heavily on modern nuclear magnetic resonance (NMR) techniques. In the past decades, many efforts have been dedicated to the development of computational methods aimed at aiding chemists to accomplish this challenging task successfully. This approach is particularly useful when uncertainties arise from the analysis of experimental spectroscopic data. Examples of structural and stereochemical misassignments in the literature abound.[1] As a result, the calculation of NMR chemical shifts with theoretical tools has gained much attention, and the development and application of different electronic structure methods have been the focus of many recent studies.[2−4] Comparison of the computed chemical shifts for the possible structures with the experimental values provides a very rapid and simple way to identify the correct isomer.[5] This useful technique is becoming common practice in organic chemistry laboratories to support structural analysis and interpret experimental results. Within the methods available, the statistical methods CP3 and DP4 developed by Smith and Goodman are of particular interest for the stereochemical assignment of diastereoisomeric compounds.[6,7]

^{1}H and ^{13}C NMR chemical shifts can be predicted reasonably well with quantum chemical calculations using empirical scaling corrections to remove systematic errors.[2−4,8] The main drawback of such procedures is that experimental data is required to obtain scaling factors. Nonetheless, computing accurate NMR chemical shifts without the need of performing empirical scaling corrections still remains a major goal. In this context, we have recently introduced a multi-standard approach (MSTD) for the calculation of ^{13}C NMR chemical shifts of common organic molecules.[9] Instead of employing the most common standard tetramethysilane (TMS), the MSTD method uses methanol and benzene as reference standards for sp^{3} and sp^{2}−sp hybridized carbon atoms, respectively. In practice, this protocol only requires identification of the different types of nuclei in the molecule and calculation of the chemical shifts using the corresponding reference compound. We found that such simple modification allowed us to obtain much better accuracy and lower dependence on the theory level employed. While developing the MSTD approach for ^{13}C nuclei, preliminary calculations suggested that the studied methodology seemed to perform well for computing ^{1}H NMR chemical shifts too. Giving the vital importance of such predictions for the organic chemistry community, in this paper we wish to present the results of a systematic study in which the performance of the MSTD methodology for calculating ^{1}H NMR chemical shifts at different levels of theory has been compared with that obtained when using TMS as standard.

COMPUTATIONAL METHODS

All calculations were performed with the Gaussian 03 package.[10] All molecules under study were optimized at the B3LYP/6-31G(d) level

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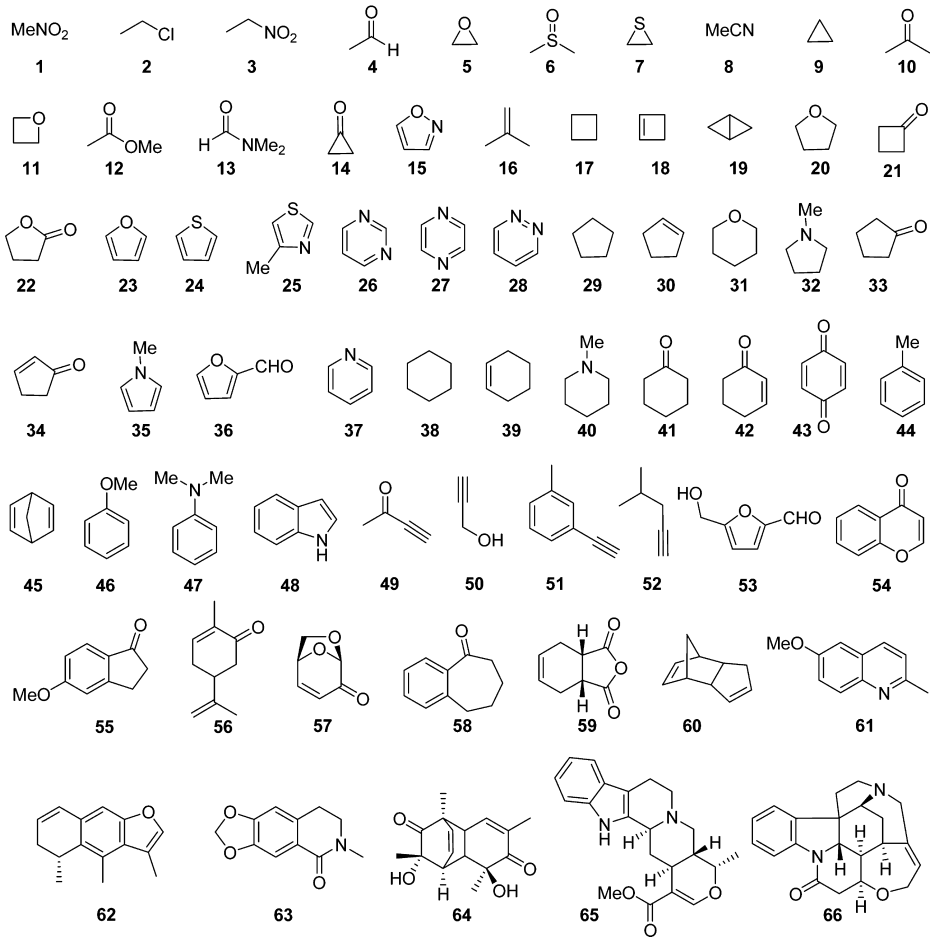

Figure 1. Test set.

of theory, which is known to afford good geometries at low computational cost. The shielding constants were computed using three different hybrid GGA functionals: B3LYP,[11] one of the most popular DFT functionals, mPW1PW91,[12] which was found to provide best results among the functionals tested within the MSTD approach for ^{13}C NMR,[9] and WP04, similar to B3LYP but parametrized to reproduce NMR chemical shifts in chloroform.[13] To evaluate the effect of the basis set, both Pople and Dunning-type double- and triple-ζ basis sets were investigated: 6-31G(d), 6-31G(d,p), 6-31+G(d), 6-31+G(d,p), 6-31++G(d,p), 6-311G(d), 6-311+G(d,p), 6-311++G-(d,p), 6-311+G(2d,p), cc-PVDZ, aug-cc-PVDZ, and cc-PVTZ. The magnetic shielding constants were computed using the gauge including atomic orbitals (GIAO) method,[14] since it is the method of choice among the different approaches that have been developed to solve the gauge origin problem.[15−17] Single point NMR calculations were carried out both in the gas phase and in solution, using the polarizable continuum model PCM with chloroform as the solvent, and the simple united atom topological model (UA0) set of solvation radii to build up the PCM cavity as implemented in Gaussian 03.[18] All possible combinations of the studied factors give a total number of 72 different calculations for each compound. Once the shielding constants were computed, the chemical shifts were calculated according to the following equation:

$$\delta^{x}_{\mathrm{calc}} = \sigma_{\mathrm{ref}} - \sigma_{x} + \delta_{\mathrm{ref}}$$

where σ_{ref} and σ_x are the NMR isotropic magnetic shielding values for the reference compound and for any X hydrogen 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. Apart from TMS (δ = 0.00 ppm), in this study we have used methanol (δ = 3.49 ppm) for sp^3−H and benzene (δ = 7.36 ppm) for sp^2−H and sp−H as references standards (MSTD methodology),[19] where sp^x−H represents a hydrogen atom attached to an sp^x-hybridized carbon atom.

RESULTS AND DISCUSSION

To carry out this study, we have worked with a test set of 66 small-to-medium size compounds shown in Figure 1, which were chosen to provide a wide array of chemical functionalities and molecular complexity and also because their ^{1}H NMR spectra in deuterated chloroform are well-known.[9,17]

Structures **1**−**49** were taken from Rablen's test set,[17] while compounds **50**, **51**, and **53**−**66** were selected from our previous study for ^{13}C NMR.[9] The NMR data for alkyne **52** was taken from the Spectral Data Base for Organic Compounds (SDBS).[20] Most molecules in the test set can be assumed to be represented by a single conformation in solution.[21] It is important to point out that the chemical shifts corresponding to OH and NH groups such as those present in structures **48**, **50**, **53**, and **64** were not taken into consideration in our study.

Table 1 shows the results obtained after carrying out the ^{1}H NMR calculations over the 66 studied compounds at the 72 different levels of theory (4752 calculations). To analyze the results of the calculations and compare the performances of the two methods under study (MSTD vs TMS), we used the mean absolute difference (MAD, defined as $\Sigma_n|\delta_{\mathrm{calc}}{}^{x} - \delta_{\mathrm{exp}}{}^{x}|/n$) and the RMS deviation as measurements of accuracy and precision, respectively. To have an additional idea of the dispersion of the data, we also computed the %$\Delta\delta$ > 0.4 ppm, which is defined as

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Table 1. Statistical Parameters Obtained after Computing the ^{1}H NMR Chemical Shifts of the 66 Compounds Shown in Figure 1 Using MSTD and TMS As Reference Standards

				MAD (ppm)		RMS (ppm)		%$\Delta\delta$ > 0.4 ppm	
entry	functional	basis set	SCRF	MSTD	TMS	MSTD	TMS	MSTD	TMS
1	B3LYP	6-31G(d)	no	0.16	0.18	0.124	0.142	5	8
2	B3LYP	6-31G(d)	yes	0.12	0.12	0.090	0.092	0	1
3	B3LYP	6-31G(d,p)	no	0.15	0.15	0.125	0.125	4	4
4	B3LYP	6-31G(d,p)	yes	0.11	0.17	0.094	0.133	1	6
5	B3LYP	6-31+G(d)	no	0.14	0.13	0.109	0.109	3	4
6	B3LYP	6-31+G(d)	yes	0.10	0.15	0.083	0.120	1	3
7	B3LYP	6-31+G(d,p)	no	0.15	0.16	0.117	0.128	6	6
8	B3LYP	6-31+G(d,p)	yes	0.11	0.23	0.092	0.188	1	23
9	B3LYP	6-31++G(d,p)	no	0.15	0.17	0.117	0.134	4	7
10	B3LYP	6-31++G(d,p)	yes	0.11	0.25	0.091	0.197	1	26
11	B3LYP	6-311G(d)	no	0.15	0.14	0.123	0.116	5	5
12	B3LYP	6-311G(d)	yes	0.11	0.16	0.085	0.117	1	4
13	B3LYP	6-311+G(d,p)	no	0.14	0.16	0.123	0.136	4	7
14	B3LYP	6-311+G(d,p)	yes	0.10	0.25	0.088	0.192	2	28
15	B3LYP	6-311++G(d,p)	no	0.14	0.16	0.124	0.134	4	6
16	B3LYP	6-311++G(d,p)	yes	0.10	0.24	0.088	0.189	2	25
17	B3LYP	6-311+G(2d,p)	no	0.15	0.17	0.121	0.141	4	8
18	B3LYP	6-311+G(2d,p)	yes	0.10	0.25	0.092	0.201	2	28
19	B3LYP	cc-PVDZ	no	0.18	0.19	0.137	0.146	8	9
20	B3LYP	cc-PVDZ	yes	0.13	0.15	0.102	0.110	1	2
21	B3LYP	aug-cc-PVDZ	no	0.16	0.22	0.125	0.166	6	15
22	B3LYP	aug-cc-PVDZ	yes	0.12	0.33	0.094	0.217	3	38
23	B3LYP	cc-PVTZ	no	0.14	0.15	0.120	0.130	4	5
24	B3LYP	cc-PVTZ	yes	0.10	0.22	0.089	0.183	2	21
25	mPW1PW91	6-31G(d)	no	0.14	0.15	0.114	0.121	5	5
26	mPW1PW91	6-31G(d)	yes	0.11	0.15	0.088	0.112	1	3
27	mPW1PW91	6-31G(d,p)	no	0.13	0.17	0.116	0.129	2	6
28	mPW1PW91	6-31G(d,p)	yes	0.11	0.22	0.089	0.181	1	22
29	mPW1PW91	6-31+G(d)	no	0.13	0.14	0.106	0.108	2	3
30	mPW1PW91	6-31+G(d)	yes	0.11	0.19	0.086	0.152	1	12
31	mPW1PW91	6-31+G(d,p)	no	0.13	0.19	0.112	0.147	3	11
32	mPW1PW91	6-31+G(d,p)	yes	0.11	0.27	0.088	0.228	1	34
33	mPW1PW91	6-31++G(d,p)	no	0.13	0.19	0.113	0.157	4	13
34	mPW1PW91	6-31++G(d,p)	yes	0.11	0.28	0.088	0.237	0	35
35	mPW1PW91	6-311G(d)	no	0.14	0.14	0.120	0.113	4	4
36	mPW1PW91	6-311G(d)	yes	0.12	0.18	0.094	0.140	2	10
37	mPW1PW91	6-311+G(d,p)	no	0.12	0.18	0.122	0.150	3	10
38	mPW1PW91	6-311+G(d,p)	yes	0.10	0.27	0.092	0.226	2	34
39	mPW1PW91	6-311++G(d,p)	no	0.13	0.18	0.122	0.147	3	11
40	mPW1PW91	6-311++G(d,p)	yes	0.11	0.26	0.092	0.222	2	33
41	mPW1PW91	6-311+G(2d,p)	no	0.12	0.19	0.118	0.152	2	11
42	mPW1PW91	6-311+G(2d,p)	yes	0.11	0.27	0.094	0.230	2	32
43	mPW1PW91	cc-PVDZ	no	0.14	0.19	0.121	0.134	4	7
44	mPW1PW91	cc-PVDZ	yes	0.10	0.19	0.090	0.123	1	6
45	mPW1PW91	aug-cc-PVDZ	no	0.13	0.22	0.117	0.178	3	18
46	mPW1PW91	aug-cc-PVDZ	yes	0.10	0.33	0.091	0.253	2	42
47	mPW1PW91	cc-PVTZ	no	0.11	0.18	0.119	0.142	2	10
48	mPW1PW91	cc-PVTZ	yes	0.10	0.25	0.093	0.216	2	30
49	WP04	6-31G(d)	no	0.15	0.27	0.106	0.176	2	23
50	WP04	6-31G(d)	yes	0.15	0.15	0.103	0.108	3	3
51	WP04	6-31G(d,p)	no	0.14	0.18	0.105	0.133	2	6
52	WP04	6-31G(d,p)	yes	0.15	0.13	0.097	0.096	2	2
53	WP04	6-31+G(d)	no	0.15	0.21	0.105	0.149	2	13
54	WP04	6-31+G(d)	yes	0.16	0.10	0.099	0.086	2	0
55	WP04	6-31+G(d,p)	no	0.14	0.14	0.106	0.115	2	5
56	WP04	6-31+G(d,p)	yes	0.15	0.14	0.098	0.118	2	2
57	WP04	6-31++G(d,p)	no	0.14	0.14	0.107	0.116	2	4
58	WP04	6-31++G(d,p)	yes	0.15	0.15	0.098	0.127	2	4

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Table 1. continued

				MAD (ppm)		RMS (ppm)		%Δδ > 0.4 ppm	
entry	functional	basis set	SCRF	MSTD	TMS	MSTD	TMS	MSTD	TMS
59	WP04	6-311G(d)	no	0.14	0.17	0.104	0.144	2	8
60	WP04	6-311G(d)	yes	0.14	0.10	0.096	0.075	2	0
61	WP04	6-311+G(d,p)	no	0.13	0.13	0.101	0.111	2	2
62	WP04	6-311+G(d,p)	yes	0.13	0.15	0.092	0.118	2	4
63	WP04	6-311++G(d,p)	no	0.13	0.13	0.102	0.115	2	4
64	WP04	6-311++G(d,p)	yes	0.13	0.15	0.092	0.117	2	3
65	WP04	6-311+G(2d,p)	no	0.11	0.12	0.099	0.102	2	2
66	WP04	6-311+G(2d,p)	yes	0.12	0.16	0.094	0.120	2	3
67	WP04	cc-PVDZ	no	0.13	0.25	0.103	0.154	2	16
68	WP04	cc-PVDZ	yes	0.13	0.15	0.088	0.106	1	2
69	WP04	aug-cc-PVDZ	no	0.12	0.12	0.101	0.104	2	2
70	WP04	aug-cc-PVDZ	yes	0.14	0.22	0.093	0.155	1	15
71	WP04	cc-PVTZ	no	0.17	0.12	0.119	0.104	6	2
72	WP04	cc-PVTZ	yes	0.13	0.14	0.092	0.109	2	2

the percentage of hydrogens in the test set for which $|\delta_{calc}{}^{x} - \delta_{exp}{}^{x}| > 0.4$ ppm.

Inspection of the results presented in Table 1 reveals a number of interesting observations.

MSTD Performance. MSTD afforded lower MAD and RMS errors than TMS in 83 and 90% of the cases, respectively. It is also important to remark that when TMS afforded better results than MSTD, the improvement was, in general, negligible. On the other hand, in ca. 50% of the cases in which MSTD worked better than TMS, a very good improvement over TMS was observed. For MSTD, MADs ranged from 0.10 to 0.18, while the corresponding values for TMS were between 0.10 and 0.33. Furthermore, RMSs varied in the ranges 0.083−0.137 and 0.075−0.253 for MSTD and TMS, respectively. The %Δδ > 0.4 ppm were clearly lower for MSTD for the vast majority of the levels of theory. It is interesting to note that these values are below 10% for MSTD, while for TMS values higher than 30% are observed in many cases, which indicates the poorer overall performance of TMS. From these results, it can be concluded that the use of the simple MSTD approach affords better, or at least, similar results than those obtained using TMS, regardless the level of theory used in the NMR calculation procedure, as can be clearly seen in Figures 2−4 (vide infra). The better overall performance of MSTD might be explained in terms of error cancellation in isotropic magnetic shielding constants when using multiple standards that resemble different types of hydrogens within a molecule. The largest deviations were observed for chemical shifts of hydrogens attached to sp-hybridized carbons (compounds **49**−**52**). This can be attributed to the acidic nature of this type of protons, which present intermolecular interactions that are difficult to model and also give variable experimental chemical shifts.[4] Contrary to what was observed for hydrogens attached to sp^3 and sp^2-hybridized carbons, in such cases MSTD did not show any improvement over TMS. However, it is important to bear in mind that terminal alkynes constitute rare motifs in natural products.

Dependence on the Level of Theory. The quality of the calculated chemical shifts are much less dependent on the level of theory using the MSTD approach, as can be observed in Figure 2, where the levels of theory represented in the *x* axis correspond to the entry number in Table 1. In clear opposition, when using TMS a small change in the level of theory can turn a good result into a very bad one. This means that the MSTD

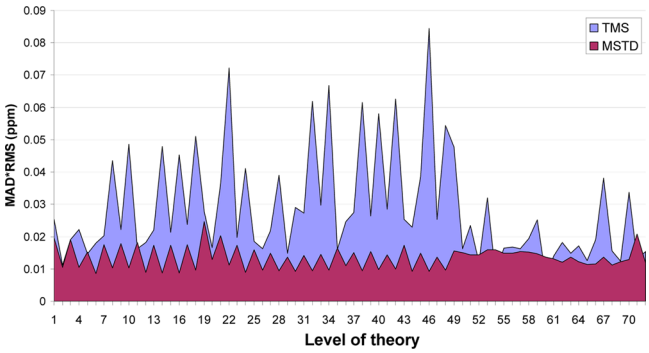

Figure 2. Effect of the level of theory used in the calculation of GIAO ^{1}H NMR chemical shifts.

approach provides high quality prediction of ^{1}H NMR chemical shifts regardless the level of theory employed (similar observations were made for ^{13}C NMR calculations).[9] Further observations can be drawn from the data collected in Table 1:

(a) *Functional effect*: Among the studied functionals, in general B3LYP and mPW1PW91 afforded best results for the MSTD approach, being mPW1PW91 the suggested method of choice (the same happened for ^{13}C NMR). When using TMS as reference standard, WP04 afforded optimal results. However, in general the quality of the results obtained with the more common functionals such as B3LYP or mPW1PW91 using the MSTD approach was better (and in some cases much better) than that obtained with WP04 using TMS as reference. This is a nontrivial observation, since the last functional was specifically designed to reproduce NMR chemical shifts in chloroform using TMS as standard.

(b) *Solvent effect*: The MSTD approach worked slightly better in solution than in the gas phase for B3LYP and mPW1PW91, while for WP04 the differences were variable. The data depicted in Figure 3 give a clear picture of this observation.

(c) *Basis set effect*: The MSTD approach showed no significant dependence on the basis set: all basis sets included in our study performed well (Figure 4). However, slightly better results were generally obtained using triple-ζ basis sets such as cc-PVTZ (entries 24 and 48) or 6-311+G(d,p) (entries 14 and 38), specially in

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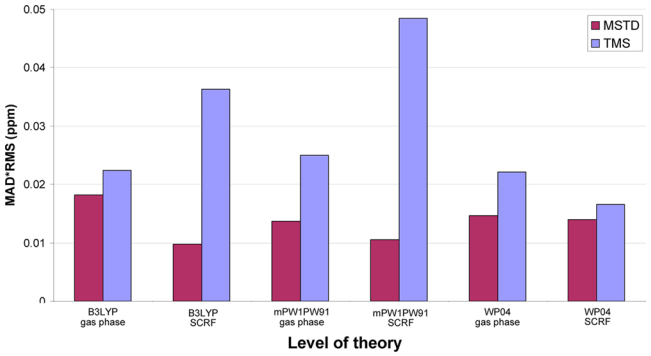

Figure 3. Effect of the functional used in the calculation of GIAO ^{1}H NMR chemical shifts, both in the gas phase and in solution.

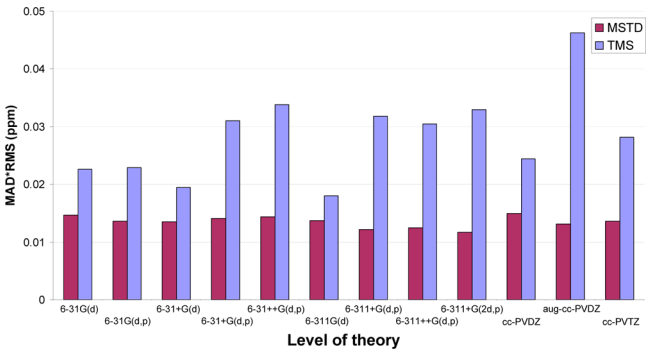

Figure 4. Effect of the basis set used in the calculation of GIAO ^{1}H NMR chemical shifts.

solution. Therefore, if the computational cost is not a problem, we recommend such triple-ζ basis sets. Otherwise, use a less demanding double-ζ basis sets such as 6-31+G(d), which gave good results as well (entries 6 and 30).

In summary, the results of our calculations indicate that the combination of methanol and benzene as standards for hydrogens attached to sp^3 and sp^2–sp carbons, respectively (MSTD approach), gives more confident ^{1}H NMR chemical shifts than those computed with TMS as a single standard, as was previously demonstrated for ^{13}C NMR.[9] Moreover, the method is less dependent on the level of theory used to perform the calculations. The final recommendation for computing ^{1}H NMR chemical shifts with the MSTD methodology is to use either the B3LYP or the mPW1PW91 functionals in solution. Since all basis sets considered in our study gave good results, any of them can be used. Our present study shows that both ^{1}H and ^{13}C nuclei can be treated effectively with MSTD, which facilitates the application of the methodology to problems in organic chemistry.

To demonstrate the performance of the MSTD approach for predicting ^{1}H NMR chemical shifts, we present further data for selected compounds. Table 2 gathers the experimental chemical shifts for compounds **54**, **57**, and **66**, together with the calculated values using the methods that performed best and worst for MSTD and also for TMS. In addition, MADs, RMSs and maxima $\Delta\delta$s for each molecule are given.

The data collected in Table 2 support the general conclusions discussed above. For each compound, the best performances using MSTD and TMS are similar, although the former gives slightly better results. However, the worst TMS performances are much worse than the MSTD counterpart. In fact, the method that performs worst for the MSTD approach gives results close to those obtained with the method that performs best for TMS. This observation reinforces the idea that while the ^{1}H NMR chemical shifts obtained with TMS are highly dependent on the level of theory used in the calculations,

Table 2. Experimental and Calculated ^{1}H NMR Chemical Shifts for Compounds 54, 57, and 66 Using MSTD and TMS as Reference Standards[a–c]

compound	atom	δ_{exp}	best MSTD	best TMS	worst MSTD	worst TMS
54	H3	8.21	8.23	8.21	8.37	8.86
	H4	7.43	7.48	7.53	7.60	8.02
	H5	7.68	7.75	7.77	7.71	8.23
	H6	7.47	7.54	7.54	7.57	8.03
	H1	7.88	7.83	7.85	8.05	8.43
	H2	6.34	6.35	6.23	6.44	6.78
	MAD		**0.05**	**0.07**	**0.12**	**0.56**
	RMS		**0.024**	**0.044**	**0.056**	**0.070**
	max $\Delta\delta$		**0.07**	**0.11**	**0.17**	**0.65**
57	H1	5.36	5.33	5.28	5.54	5.49
	H3	6.12	6.03	6.10	6.23	6.51
	H4	7.27	7.42	7.37	7.53	8.02
	H5	5.00	4.94	4.83	5.14	5.19
	H6a	3.77	3.73	3.60	3.85	3.84
	H6b	3.90	3.93	3.92	4.16	4.10
	MAD		**0.07**	**0.09**	**0.17**	**0.29**
	RMS		**0.047**	**0.067**	**0.076**	**0.250**
	max $\Delta\delta$		**0.15**	**0.17**	**0.26**	**0.75**
66	H1	7.16	7.11	7.27	7.12	7.03
	H2	7.10	7.01	7.22	7.00	6.92
	H3	7.25	7.17	7.42	7.15	7.06
	H4	8.09	8.04	8.13	7.97	7.85
	H8	3.85	3.94	3.82	3.62	3.68
	H12	4.28	4.35	4.37	4.09	4.00
	H13	1.27	1.18	1.17	0.85	0.97
	H14	3.15	3.20	3.10	2.99	2.91
	H16	3.93	4.04	4.01	3.74	3.63
	H22	5.90	5.80	5.98	5.81	5.66
	H11a	3.11	3.04	2.95	2.75	2.69
	H11b	2.67	2.63	2.70	2.48	2.46
	H15a	2.35	2.28	2.33	2.16	1.97
	H15b	1.45	1.35	1.41	1.24	1.18
	H17a	1.88	1.92	1.99	1.74	1.71
	H17b	1.89	1.87	1.84	1.73	1.70
	H18a	3.19	3.09	3.11	2.97	2.84
	H18b	2.87	2.93	2.86	2.80	2.70
	H20a	3.70	3.71	3.78	3.66	3.41
	H20b	2.72	2.64	2.67	2.39	2.39
	H23a	4.07	4.21	4.17	3.99	3.89
	H23b	4.14	4.13	4.14	3.97	3.78
	MAD		**0.07**	**0.07**	**0.17**	**0.25**
	RMS		**0.033**	**0.046**	**0.100**	**0.081**
	max $\Delta\delta$		**0.14**	**0.17**	**0.42**	**0.42**

[a] $\Delta\delta = |\delta_{calc}{}^x - \delta_{exp}{}^x|$ [b] For numbering, see the Supporting Information. [c] For **54**, best MSTD: WP04/6-311+G(2d,p); best TMS: WP04/6-311G(d); worst MSTD: WP04/aug-cc-PVDZ; worst TMS: mPW1PW91/aug-cc-PVDZ. For **57**, best MSTD: mPW1PW91/6-31G(d); best TMS: WP04/6-311G(d); worst MSTD: WP04/6-31++G(d,p); worst TMS: B3LYP/aug-cc-PVDZ. For **66**, best MSTD: mPW1PW91/cc-PVTZ; best TMS: B3LYP/6-311G(d); worst MSTD: B3LYP/cc-PVDZ; worst TMS: WP04/cc-PVDZ.

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the MSTD approach guarantees good results even at the worst scenarios.

Case Study. To give a further example on the utility of our MSTD methodology to solve a real life problem, we present a case study from colleagues in our laboratory. Kaufman and co-workers carried out the synthesis of the tricyclic chromone structure originally assigned to aspergillitine (**67**) (Figure 5).[22]

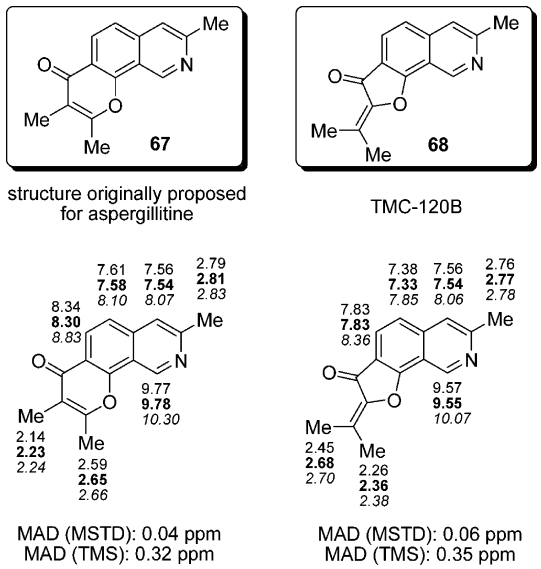

Figure 5. Experimental (top) and calculated ^{1}H NMR chemical shifts at the mPW1PW91/6-311+G(d,p) level of theory in solution for compounds **67** and **68**. MSTD in bold, TMS in italics.

However, the ^{1}H and ^{13}C NMR spectroscopic data of the synthetic compound did not match those reported for the natural product. On the other hand, a good agreement with the spectral data described in literature for the related alkaloid TMC-120B (**68**) was observed (Figure 5). To analyze whether the MSTD method could distinguish between these two structures, we have optimized both compounds and computed the ^{1}H NMR chemical shifts using MSTD and TMS at different levels of theory (Table 3). Figure 5 presents the experimental ^{1}H NMR chemical shifts in deuterated chloroform for synthetic **67** and **68**, together with calculated ^{1}H NMR chemical shifts at the mPW1PW91/6-311+G(d,p) level of theory in solution using MSTD and TMS.

Table 3. MADs Obtained after Computing the mPW1PW91/SCRF ^{1}H NMR Chemical Shifts of Compounds 67 and 68 Using MSTD and TMS as Reference Standards and Different Basis Sets

	67	67	68	68
basis set	MSTD	TMS	MSTD	TMS
6-31G(d)	0.04	0.16	0.06	0.15
6-31G(d,p)	0.04	0.24	0.06	0.24
6-311+G(d,p)	0.04	0.32	0.06	0.35
cc-PVTZ	0.05	0.30	0.06	0.32

Once again, the data collected in Figure 5 and Table 3 clearly demonstrate that MSTD performs much better than TMS, for all the studied basis sets. As noted before, TMS has a much higher dependence on the basis set than MSTD. In particular, the major differences arise from the chemical shifts calculated for the aromatic protons, which are much better predicted using benzene as standard within the MSTD approach.

CONCLUSION

We have investigated the application of the MSTD approach for computing ^{1}H NMR chemical shifts, using methanol and benzene as reference standards for hydrogens attached to sp^3 and sp^2–sp carbons, respectively. To assess the performance of the presented methodology, the results were compared with those obtained with the use of the typical TMS standard. Overall, the MSTD approach has proven to give more accurate and precise ^{1}H NMR chemical shifts. An additional advantage of the method is that the computational results do not depend much on the level of theory used in the calculations.

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates and energies of B3LYP/6-31G(d) optimized geometries and GIAO isotropic magnetic shielding values for all structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) The MSTD approach does not necessarily have to involve benzene and methanol as standards. Potentially, any reference compound could be used to study a particular system of interest. However, methanol and benzene were found to be the optimal reference standards for ^{13}C NMR chemical shift calculations. Although they might not be the optimal standards for ^{1}H NMR calculations, we wanted to assess the performance of the MSTD approach as originally developed for ^{13}C NMR.

(20) SDBSWeb: http://riodb01.ibase.aist.go.jp/sdbs/ (National Institute of Advanced Industrial Science and Technology, date of access 05/23/2012).

(21) We have shown that the calculated ^{13}C NMR chemical shifts for flexible systems using either the global minima or all significant conformers were very similar. Consequently, for performing the ^{1}H NMR calculations we decided to follow the same strategy, so only the global minimum was considered in all cases. To test this hypothesis, we analysed the performance of both methods (MTSD and TMS) for compounds **53**, **55**, and **61**, which can adopt two or more populated conformers, and observed that a very modest improvement in the MADs were obtained when using Boltzmann weighted values, particularly for MSTD. See the Supporting Information.

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