

# Correlation Between Experimental and DFT/GIAO Computed $^{13}\text{C}$ NMR Chemical Shifts of Organic Compounds. Effects of Asymmetry

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**Abstract:** The experimental  $^{13}\text{C}$  chemical shifts of five different series of organic compounds are compared with predicted  $^{13}\text{C}$  NMR chemical shifts obtained via empirically scaled GIAO shieldings. Our results indicate that the inclusion of a scaling factor allow to obtain an excellent correlation between  $\delta_{\text{calc}}$  and  $\delta_{\text{exp}}$ . Although the inclusion of asymmetry improves this correlation, such enhancement was not observed for all the 54 tested compounds. We found  $\sigma_{\text{RMS}}$ , a parameter related with the structural feature of the whole molecule, which could indicate the benefits of including asymmetry in these calculations.

**Keywords:** DFT/GIAO calculations,  $^{13}\text{C}$  chemical shifts, Chemical shifts anisotropy asymmetry.

## INTRODUCTION

Natural products are often highly complex chemical and the structural elucidation of the bioactive constituent depends almost exclusively on the application of modern instrumental methods, particularly NMR and MS. These powerful techniques, coupled in some cases with selective chemical manipulations, are usually adequate to solve the structures of most secondary metabolites of molecular weight up about 2000. However, many times appropriate theoretical calculations are necessary to better elucidate complex structures of natural products.

The prediction of NMR chemical shifts from quantum mechanical methods has undergone major advancements within the last decade, including solutions to the gauge dependence of the chemical shift [1, 2], improvements in the basis set and the extension of higher levels of theory including density functional techniques [3, 4]. DFT calculations are now attainable and accurate enough to be useful exploring the relationship between chemical shift and molecular structure [5-13].

There are commercial softwares based on parametrized empirical or semiempirical methods that have reached an excellent accuracy predicting chemical shifts. However, this kind of software can not distinguish between some type of optical isomer like for example epimers, nor give a picture about the structure – chemical shift relationship. Recently we reported a comparative study between our approach and the ACD and MestreNova predictors [14]. Our results indicated that the method used here displayed a better performance with respect to both commercial methods. In that paper we reported

that the calculated  $^{13}\text{C}$  NMR chemical shifts of ferenes agree very well with the available experimental values. It should be noted, however, that the GIAO shieldings for the basis sets examined in that paper required empirical scaling to give good numerical agreement with experimental chemical shifts. For such reason we introduced a combination of shielding parameters instead a unique one for first time in this type of calculations. Thus, we introduced a parameter which is related to the asymmetry. Interestingly, the inclusion of such parameter in the calculations gives a better correlation with the experimental data. However, this approach has worked very well on the recently reported ferenes [14] and therefore, the appropriateness of this protocol should be tested for other structural types.

In the present work we extended our study applying such parameter to a four different series of organic compounds which were selected in function of their structural and electronic characteristics. Thus, cyclohexane and derivatives (series 1, Fig. 1), mononuclear aromatic compounds (series 2), bicyclic alyphatic compounds (series 3) and fused aromatic compounds (series 5) were evaluated in this study. The previously reported ferenes (series 4) were also included in this study for comparison; therefore part of information included in this article has been previously published in reference 14.

## COMPUTATIONAL DETAILS

A set of 54 molecules providing 817 different  $^{13}\text{C}$  chemical shifts was employed as a testing set in the present work (Table 1); all the experimental data were obtained from a NMR public data base [15] and from references [16-18]. In all these cases the solvent used was  $\text{CDCl}_3$ . Both geometry optimization and GIAO calculations were performed with Gaussian 03 [19].

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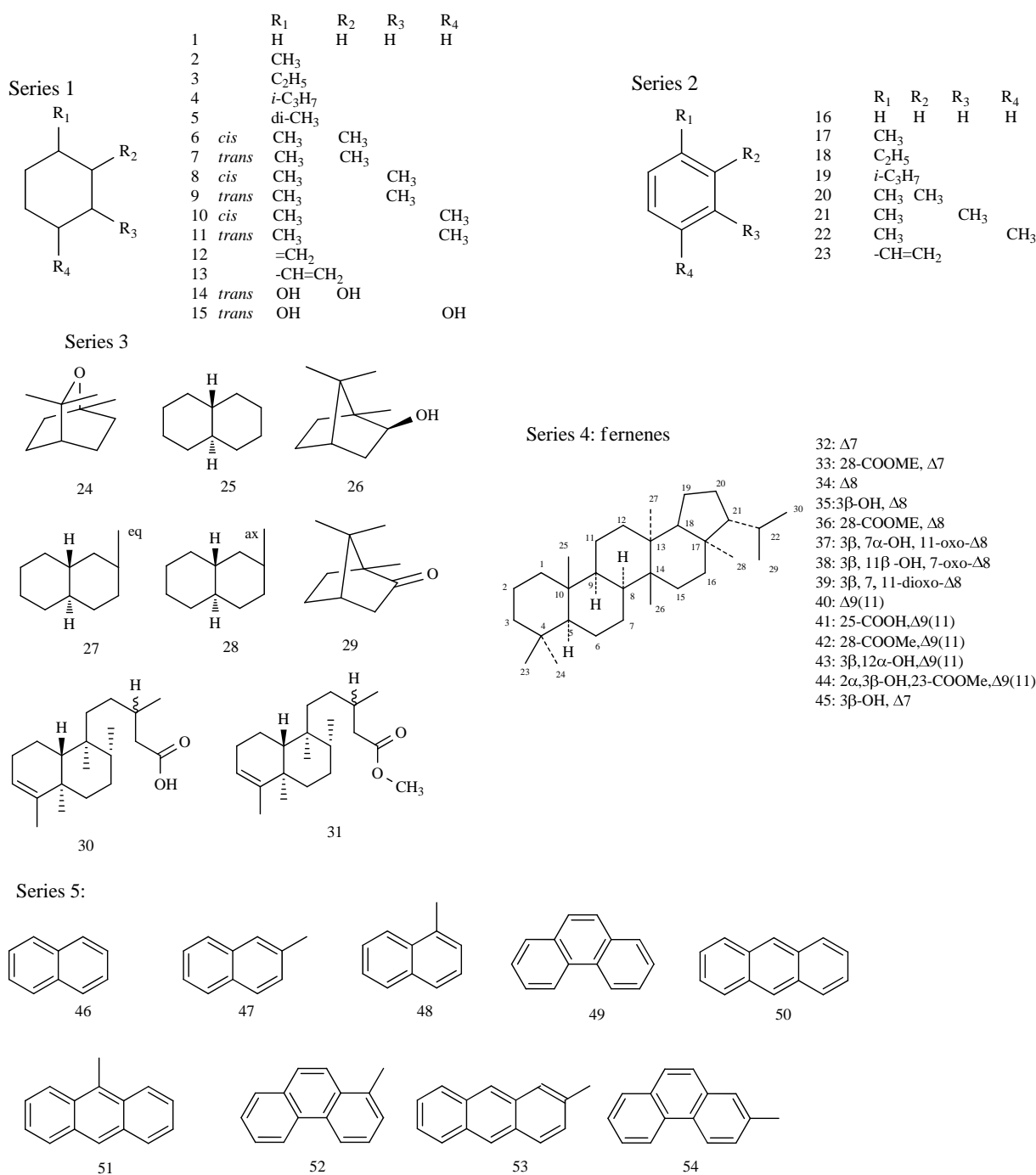


Fig. (1). Structural features of the 54 compounds reported here.

### Scaling of GIAO Absolute Shielding

A fertile proposal of Forsyth and Sebag [6] has been to use empirically scaled absolute isotropic shielding, including a term in order to take into account the reference magnitudes.

$$\delta_{calc} = m \cdot \sigma_{iso} + i \quad (1)$$

The equation proposed by Forsyth and Sebag is the most general form for these relationships. The proposal from

Aliev, Courtier-Murias and Zhou [20] can be reduced to a similar form considering that the scaling factor 0.95 is equal to  $-m$ . Our hypothesis is that it is also reasonable to consider the other parameters derived from the shielding tensor to take into account the anisotropy which can not be eliminated by orientational averaging. With this purpose, recently we proposed to include the chemical shifts anisotropy asymmetry,  $\eta$ :

**Table 1.** Statistical Parameters Obtained for the Correlations of  $\delta_{exp}$  vs  $\delta_{calc}$  using Equations 1 and 2 for the 54 Compounds Reported Here

Equation	$r^2$	RMS	MAE	RMS <sub>2</sub> /RMS <sub>1</sub> %	MAE <sub>2</sub> /MAE <sub>1</sub> %
1	0.99830	3.6331	1.4142	92.790	94.525
2	0.99842	3.3712	1.3367		

$$\delta_{calc} = M \cdot (\sigma_{iso} + \eta) + I \quad (2)$$

The NMR chemical shift tensor is given by the second derivative of the electronic energy,  $E$ , with respect to the external magnetic field  $B$  and the nuclear magnetic moment  $m_N$ . The tensor can be described by distinct parameters. One is referred to as the chemical shift anisotropy asymmetry,  $\eta$ :

$$\eta = \frac{\delta_{22} - \delta_{11}}{\delta_{33} - \delta_{iso}}$$

Although in solution it is reasonable to consider that the orientations of the molecules are randomly oriented and therefore the interactions between the electrons and the external magnetic field are averaging, recently we reported that, at least for ferenes molecules, the inclusion of asymmetry ( $\eta$ ) in the correlation between the chemical shift and the principal values of the shielding tensor enhanced the GIAO/DFT calculations [14].

The scaling factor "M" and the interception "I" in equation 2 can be obtained from a linear regression between the experimental chemical shifts of a significant number of C atoms, and their respective calculated values of isotropic shielding and asymmetry. Basis set employed and conformational analysis in our previous work indicated that B3LYP/6-31G(d) GIAO calculations using B3LYP/6-31G(d) geometries gives one of the best cost-benefit ratio. Thus, in that work we employed the commonly used hybrid functional B3LYP [2, 21, 22]. On the basis of our previously results we adopted the 6-31G(d) basis set. DFT calculations were carried out using Gaussian 03 [19]. Experimental NMR spectra in solution are commonly statistical averages affected by dynamic process such as conformational equilibrium as well as intra and/or intermolecular interactions. In the present study the influences of conformational changes have been also taken into account in those compounds possessing a significant molecular flexibility. The conformational analysis was carried out as previously reported [14], weighting the contribution of the different conformers by using the Boltzmann distribution:

$$N_j = \frac{\exp\left(-E_j/RT\right)}{\sum_i \exp\left(-E_i/RT\right)}$$

## RESULTS AND DISCUSSION

In the present study we calculated the  $\delta_{calc}$  for a set of 54 molecules (817 C atoms) including the previously reported ferenes molecules (Fig. 1). For these calculations we used the previously explicit equations 1 and 2.

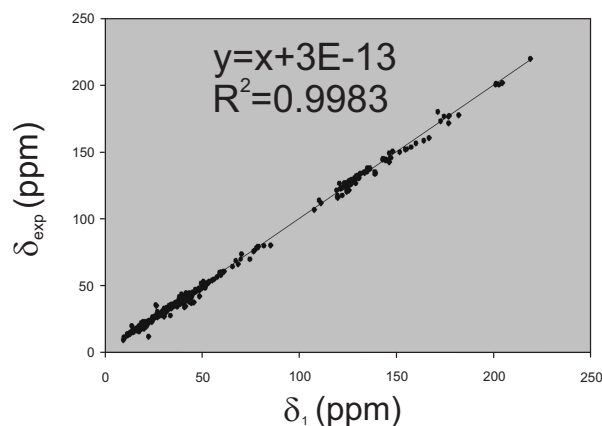
Isotropy ( $\sigma_{iso}$ ), asymmetry ( $\eta$ ) and the corresponding chemical shifts ( $\delta_{calc}$ ) were calculated for the compounds in

Fig. (1) via the GIAO method at the B3LYP/6-31G(d) level with the same level of theory geometries and by using equations 1 and 2. The results of the linear regression analysis comparing experimental  $^{13}\text{C}$  shifts  $\delta_{exp}$ , to GIAO calculated chemical shifts ( $\delta_{calc}$ ) for all series, are also summarized in Table 1.

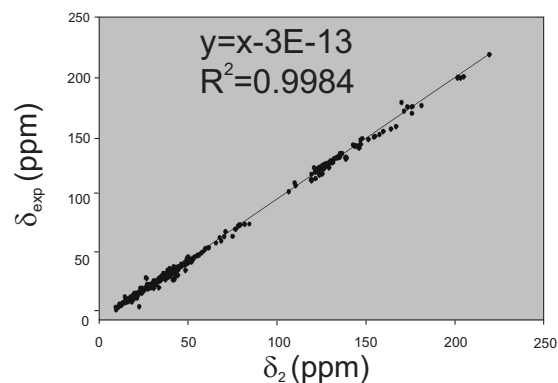
Figs. (2) and (3) show graphically the correlations obtained from equations 1 and 2, respectively.

We were intrigued if GIAO calculation employing equation 2 enhanced the correlation for all the series reported here in a similar way. Thus, at this stage of our study we considered very important to looking for a kind of descriptor or parameter, which could be used to discriminate which equation is more appropriate for each series under study. In an attempt to obtain such descriptor we defined the parameter  $\sigma_{RMS}$ , using the following equation:

$$\sigma_{RMS} = \sqrt{[\overline{\sigma_{11}}]^2 + [\overline{\sigma_{22}}]^2 + [\overline{\sigma_{33}}]^2}$$



**Fig. (2).** Plot of  $\delta_{exp}$  vs  $\delta_{calc}$  calculated using equation 1 for all the compounds shown in Fig. (1).



**Fig. (3).** Plot of  $\delta_{exp}$  vs  $\delta_{calc}$  calculated using equation 2 for all the compounds shown in Fig. (1).

Where

$$\bar{\sigma}_{ii} = \frac{\sum \sigma_{ii}}{n}$$

and where “n” is the number of atoms for each molecule. In other words  $\bar{\sigma}_{ii}$  is the arithmetic average for the principal

values  $\sigma_{11}$ ,  $\sigma_{22}$  and  $\sigma_{33}$  weighted by using the Boltzmann distribution.

Using  $\sigma_{RMS}$  as descriptor we observe that all the molecules evaluated here might be clustered in three groups: compounds type A in which the  $\sigma_{RMS}$  adopts values ranging between 180 and 210; compounds type B with  $\sigma_{RMS}$  from 230 to 270 and compounds type C displaying  $\sigma_{RMS}$  values

**Table 2. The 54 Compounds (Series 1-5) Grouped in Function of their  $\sigma_{RMS}$  Values**

Molecule	Series	$\sigma_{RMS}$	Type	Molecule	Series	$\sigma_{RMS}$	Type
16	2	190.51	A	12	1	232.77	B
17	2	190.59		13	1	237.62	
18	2	193.71		14	1	251.83	
19	2	198.14		15	1	249.44	
20	2	193.62		24	3	262.39	
21	2	193.85		26	3	262.11	
22	2	193.95	180 – 210	27	3	269.29	
23	2	184.31		29	3	240.91	
46	5	183.84		30	3	249.31	230 – 270
47	5	184.34		31	3	248.85	
48	5	185.92		32	4	260.94	
49	5	184.18		33	4	251.82	
50	5	181.53		34	4	261.80	
51	5	185.00		35	4	259.76	
52	5	186.37		36	4	252.59	
53	5	181.95		37	4	245.74	
54	5	184.30		38	4	245.54	
				39	4	238.55	
1	1	281.30	C	40	4	261.25	
2	1	276.64		41	4	253.19	
3	1	278.04		42	4	252.06	
4	1	276.34		43	4	256.26	
5	1	276.01	270 - 300	44	4	247.40	
6	1	280.78		45	4	258.89	
7	1	274.93					
8	1	273.86					
9	1	278.41					
10	1	278.75					
11	1	274.05					
25	3	270.73					
28	3	272.23					

ranging from 270 to 300. This distribution might be well appreciated in Fig. (4) and Table 2.

In the next step of our analysis we compare the correlations obtained for each type (A, B and C) using both equations (1 and 2) (Table 3). The linear correlations between  $\delta_{calc}$  and  $\delta_{exp}$  are very strong, as indicated by high squares of correlation coefficients  $r^2$ , ranging from 0.9989 to 0.9763. The statistics listed in Table 3 are more adequate to distinguish the qualities of the correlations. Both RMS error and MAE (mean absolute error) are particularly indicative of correlation quality.

From the results in Table 3 it is clear that the correlations obtained for compounds grouped as type A (series 2 and 5) are very similar using equations 1 or 2, just a slightly enhancement may be observed by the correlations using equation 2. In contrast, for the compounds grouped as type B (series 3 and 4 and compounds of series 1 possessing no alkyl substituents) the correlations obtained using equation 2 displayed an enhancement with respect to those attained from equation 1. However, it is clear that calculations using equation 2 for the compounds type C (series 1 with alkyl substituents and trans-decaline moiety) were the least successful. In this case the inclusion of asymmetry clearly impaired the correlation between  $\delta_{exp}$  and  $\delta_{calc}$  displaying a RMS which is almost the double with respect to that obtained from equation 1.

On the basis of our results it is evident that the inclusion of asymmetry might be operative or not in these calculations. The question which arises is when is convenient to include asymmetry in the equations correlating experimental and calculated chemical shifts? From the results obtained in Table 3 it appears that inclusion of asymmetry calculating chemical shifts is advisable for compounds possessing  $\sigma_{RMS}$  values minor than 270 indicating that the  $\sigma_{RMS}$  parameter gives a good criteria in order to answer the above question.

## CONCLUSIONS

The  $^{13}\text{C}$  NMR chemical shifts of 54 different organic compounds were calculated using the DFT/GIAO method. In our strategy of using a small basis set for GIAO calculations along with non-expensive DFT calculations to achieve maximum practicality, B3LYP/6-31G(d)// B3LYP/6-31G(d) computations were used. Also the  $^{13}\text{C}$  chemical shifts were calculated empirically scaling the isotropy and including the

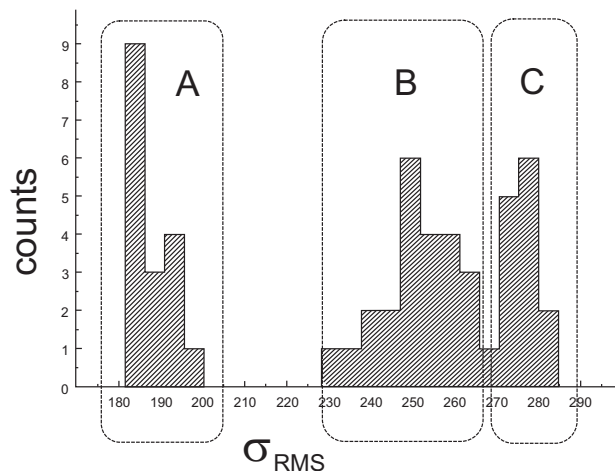


Fig. (4). Histogram showing the distribution of frequency of  $\sigma_{RMS}$  for the 54 compounds. The clusters (compounds type A, B and C) might be appreciated in this figure.

asymmetry obtained from eigenvalues of the shielding tensor as an additional parameter.

The calculated  $^{13}\text{C}$  NMR chemical shifts of the compounds reported here agree very well with the available experimental values. Isotropic  $^{13}\text{C}$  NMR shieldings from GIAO calculations account well for relative chemical shifts even with relatively modest basis sets. It should be noted that the GIAO shieldings for the basis sets examined in this paper require empirical scaling to give good numerical agreement with the experimental data. Thus, we introduce a combination of shielding parameters instead a unique in this type of calculations. The inclusion of asymmetry in the calculations gives a better correlation with the experimental data for several compounds tested here (particularly for compounds included in series 3 and 4). Considering that this inclusion is not advantageous for all the compounds, we use  $\sigma_{RMS}$  as a parameter to determine the benefits to consider the asymmetry in such computations. Our results indicate that the inclusion of asymmetry ( $\eta$ ) is advisable for compounds with  $\sigma_{RMS}$  minor than 270. However, the appropriateness of this protocol should be tested carefully for other structural types.

Table 3. Statistical Parameters Obtained for the Correlations of  $\delta_{exp}$  vs  $\delta_{calc}$  using Equations 1 and 2 for the 54 Compounds Grouped in the Three Different Types A, B and C. The Best Correlations Obtained are Shown in Bold

Type	Eqn.	$r^2$	RMS	MAE	RMS <sub>2</sub> /RMS <sub>1</sub> %	MAE <sub>2</sub> /MAE <sub>1</sub> %
A	1	0.99890	1.1313	0.7563	98.988	96.871
	2	0.99891	1.1199	0.7327		
B	1	0.99739	3.4884	1.3255	92.564	91.690
	2	0.99759	3.2290	1.2153		
C	1	0.98835	0.5081	0.5673	202.998	133.806
	2	0.97636	1.0315	0.7591		

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## CONFLICT OF INTEREST

None declared.

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