

Quantum Mechanical Calculation of ^{13}C NMR Chemical Shift of a Lienear and Cyclo α , β Unsaturated Ketones

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Abstract: The results of *ab initio* calculations of ^{13}C NMR chemical shifts of 11 molecules of α , β -unsaturated ketones were reported. All the structures were optimized with the Gaussian 03 program at AM₁ semi-empirical method. After the optimization, ^{13}C chemical shifts were calculated with GIAO method, using corresponding TMS shielding calculated at the same theoretical levels as the reference. Calculations have been performed with using four different basis sets: [6-31+(d,2pd), 6-31++(d,2pd), 6-31+(d,3pd), 6-31+(2d, 3pd)] and as well as using four different basis sets: [6-31+(d,pd),6-31+(2d,p),6-31+(2d,pd),6-31+(2d,3pd)] for cyclo and lienear α , β unsaturated ketones respectively at HF and DFT level of theory. The results, especially with HF/6-31+(2d,3pd) are in excellent agreement with experimental values. All the computations were done using an IBM x225 Xeon computer that has 2048 MB ram.

Key words: ^{13}C NMR . GIAO . cyclo α , β unsaturated ketones . lienear α , β unsaturated ketones . DFT . HF-SCF

INTRODUCTION

α , β -unsaturated ketones have attracted increasing attention due to their numerous pharmacological properties such as anticancer activity, cytotoxicity, anti-inflammatory, analgesic and antipyretic behavior [1]. Some of them are potential antibacterial, antifungal and anti-ulcer agents [2]. They are also very useful intermediates in organic synthesis, especially for heterocycles [3]. These findings have attracted the attention of chemists, biochemists and pharmacologists to this particular group of compounds. The stereoselective synthesis of α , β -unsaturated ketones is generally accomplished by various methods such as condensation, oxidation, elimination, acylation and insertion of carbon monoxide among others [4].

NMR spectroscopy has proved to be an exceptional tool to elucidate structure and molecular conformation. But there is some doubt regarding the chemical shifts in the spectra of α , β -unsaturated ketones. This approach provided a basis for the assignment of unsaturated ketones chemical shifts and allowed prediction of the connectivity. *Ab initio* and DFT calculation of NMR shielding at very accurate levels of approximation are available in literature [5-8]. The widely used methods to calculate chemical shifts are as follows: GIAO (gauge independent or invariant or including atomic orbital). The GIAO approach [5-8] is known to give satisfactory chemical shifts for different nuclei [6-8] with larger molecules, yet this quantum chemical

calculations often have to be limited to isolated molecules in some preferred structures, while experimental NMR spectra are commonly statically averages affected by dynamic process such as conformational equilibrium as well as intra and/or intermolecular interactions.

The present work demonstrates the application of NMR chemical shift calculations to identify the effects of different connectivities of various unsaturated ketones on chemical shilding. All the structures were fully optimized with the Gaussian 03 program at AM1 semi-empirical method. After the optimization, ^{13}C chemical shifts were calculated for α , β -unsaturated ketones (with respect to TMS as the reference) with GIAO method. All the computations were done using an IBM x 225 Xeon computers that has 2048 MB ram.

On the basis of our previous work [9, 10], chemical shifts calculated at the HF level of theory for the Si species are closer to the experimental values than those determined at the B3LYP or B3PW91 levels with the same basis set and the same units. In this work this subject as well as tested again for ^{13}C at α , β -unsaturated ketones. In the present paper DFT, HF, *Ab initio* methods were used to analyze the experimental ^{13}C data of the methylene carbons of α , β -unsaturated ketones.

Theory: The NMR chemical shift δ , is a parameter, allows for distinguishing magnetically in equivalent nuclei in a molecule. Today NMR spectroscopy is a

powerful tool in chemistry because of the NMR chemical shifts. In liquid, or gas, the molecules are freely tumbling so one does observe an average chemical shift (isotropic chemical shift).

In quantum mechanics, the quantity is directly related to the NMR chemical shift. The shielding is defined as the mixed second derivative of the energy with respect to magnetic moment of the nucleus and the strength of the applied magnetic field. It is solved through the second-order perturbation theory with the Zeeman Hamiltonian [11] treated as a perturbing term. The first order contribution is called diamagnetic while the second order (which requires knowledge of excited electronic states) is termed paramagnetic [12]. With the availability of powerful workstations, it is now customary for NMR laboratories to have the capability of calculating the NMR chemical shifts. The methods currently employed are the *ab-initio* (from first principles) Hartree-Fock [13] or density functional [14-16] calculations. One first solves the electronic Schrodinger equation in the absence of any magnetic field. The density matrix is then allowed to change with the application of a magnetic moment and a static external magnetic field. The zero order and first order density matrices are then used to give the diamagnetic and paramagnetic terms, respectively. The quality of these calculations depends on the level of theory employed, the basis set used and the quality of the structure of the molecule. Gaussian basis sets are normally employed as the basis functions to fit the electronic orbital in a molecule [17].

The *ab-initio* packages also require that the molecular geometry be specified. Even with the fastest computer, *ab-initio* calculations on large systems such as proteins are still prohibitive. Thus, one needs to employ a strategy which takes advantage of the fact that the shielding property is a highly localized quantity. One can separate the total shielding into three parts: the short-range electronic (an atom present in this region, treated quantum mechanically), long-range electrostatic (atoms present in this region are treated classically or completely ignored for nuclei that are not sensitive to such factors). With this strategy, only a small fragment (10-50 atoms) needs to be treated completely with electrons and Gaussian basis function.

EXPERIMENTAL SECTION

Lienear α,β and cyclo α,β unsaturated ketones and the numbering of the atoms that have been investigated are illustrated in Fig. 1.

The calculated ^{13}C NMR chemical shift of the above compounds are given in Table 14. After the optimization, ^{13}C -chemical shifts were calculated with

GIAO method, using corresponding TMS shielding calculated at the same theoretical levels as the reference. Four different basis sets: [6-31+G(d,2pd), 6-31++G(d,2pd), 6-31+G(d,3pd), 6-31+G(2d,3pd)] and as well as four different basis sets: [6-31+G(d,pd), 6-31+G(2d,p), 6-31+G(2d,pd), 6-31+G(2d,3pd)] are used for linear and cyclo α,β -unsaturated ketones with the both RHF and B3LYP methods respectively. In all basis sets, a geometry optimization was first performed for the molecules and TMS. To compare the *ab initio* methods, the NMR parameters were calculated by using the individual geometric parameters, despite these geometries being close to each other same as the reference [11].

In order to compare the predicted values with experimental results, we also need to compute the absolute shielding value for the TMS, using exactly the same model chemistry (level of theory, basis set and method of geometry optimization). To obtain the predicted shift for the methylene carbon atoms in species, we subtract its absolute value from that of the reference molecule. The ^{13}C values in the Tables are relative to the TMS normal standard i.e., $\delta = (\delta_i - \delta_{\text{TMS}})$, in order to compare directly with the experimental values. In this study, the calculated values are compared with the estimated Hartree-Fock and DFT methods for the 11 compounds of Fig. 1.

To see how well our calculation did, we make plots of the experimental chemical shifts versus the calculated chemical shifts (calculated on the horizontal axis). We get straight-line with the worthy correlations (Fig. 2 and 3).

RESULTS AND DISCUSSION

The theoretical and experimental results, along with the error for each compound, are presented in Table 1-4 of the experimental chemical shifts versus the calculated chemical shifts are shown in Fig. 2 and 3. For empirically scaling theoretical data linear regressions, $d_{\text{calc}} = m d_{\text{exp}} + b$ was made and details are summarized in Table 5 and 6, these data show how well our calculation did. All the plots show that the correlations between the experimental and calculated shifts are good. It could be concluded the calculated and experimental peaks come in the correct order. That is, the methylene carbons from α,β -unsaturated ketones come in the same order for theory and experiment. Therefore it could be concluded the HF results agreement with the experimental values are good but the DFT values are not agrees.

For the series of molecules studied here, the RMS and mean absolute errors for the data of ^{13}C chemical shifts of Table 1 and 2 have been calculated. Statistical

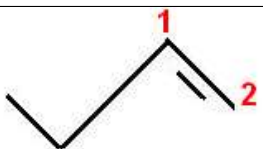

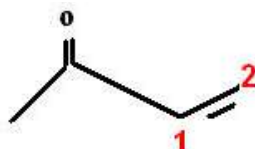
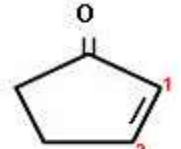

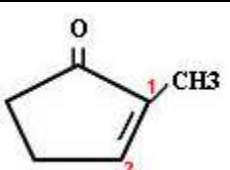
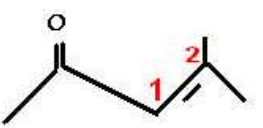
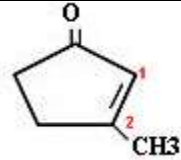
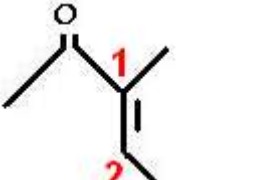
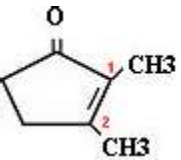
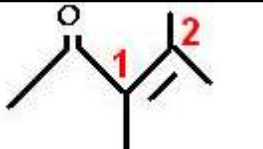
Number	Presentation	Number	Presentation
1		7	
2		8	
3		9	
4		10	
5		11	
6			

Fig. 1: Lienear and cyclo α,β -unsaturated ketones that have been investigated

measures, namely the RMS error and mean absolute error, with respect to experiment, for the ^{13}C chemical shifts of the molecules calculated with the four different basis sets: [6-31+G(d,2pd), 6-31++G(d,2pd), 6-31+G(d,3pd), 6-31+G(2d, 3pd)] and as well as four different basis sets; [6-31+G(d,pd), 6-31+G(2d,p), 6-31+G(2d,pd), 6-31+G(2d,3pd)] for cyclo α,β unsaturated ketones and linear α,β unsaturated ketones respectively were shown in Table 3 and 4 respectively for the both HF and DFT levels. As can be seen ^{13}C chemical shifts obtained using the larger 6-31+(2d,3pd) basis set have smaller RMS and mean absolute error with respect to the other basis sets at the same level HF and or DFT. The experimental and theoretical results, along with the error for each compound, are presented in Table 14. ^{13}C chemical shifts obtained using the

large 6-31+(2d,3pd) basis set have minimum Mean absolute error and therefore this basis set could be used to predict the ^{13}C chemical shifts of α,β Unsaturated ketones studied here.

On the basis of previous work [9], chemical shifts calculated at the HF level of theory for the Si species are closer to the experimental values than those determined at the B3LYP level with the same basis set and the same units. In this work this was tested again for ^{13}C at the α,β -unsaturated ketones. The R-square results and the errors on Table 14 indicate that the B3LYP hybrid functional predicted chemical shifts are less accurate than the HF level of theory. So it suffices to say that the HF/6-31+(2d,3pd) level works well for all our investigation. Therefore, in general, if we are aiming for the minimum error within a reasonable

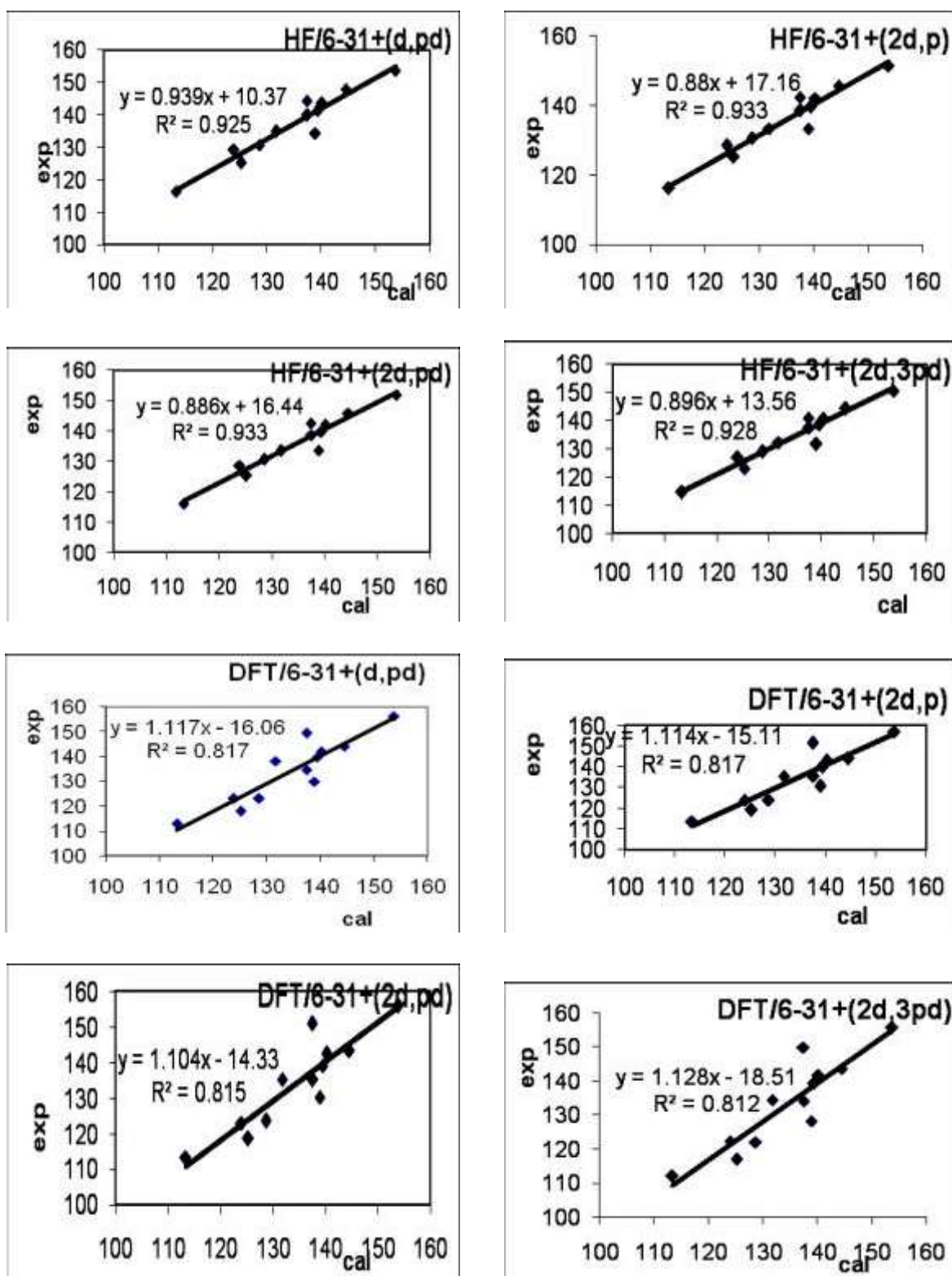


Fig. 2: Plot of experimental ^{13}C chemical shifts against calculated isotropic shielding constants (ppm), for the four basis sets and the level of theories HF and DFT which calculated from the date of Table 1 for linear α,β Unsaturated ketones

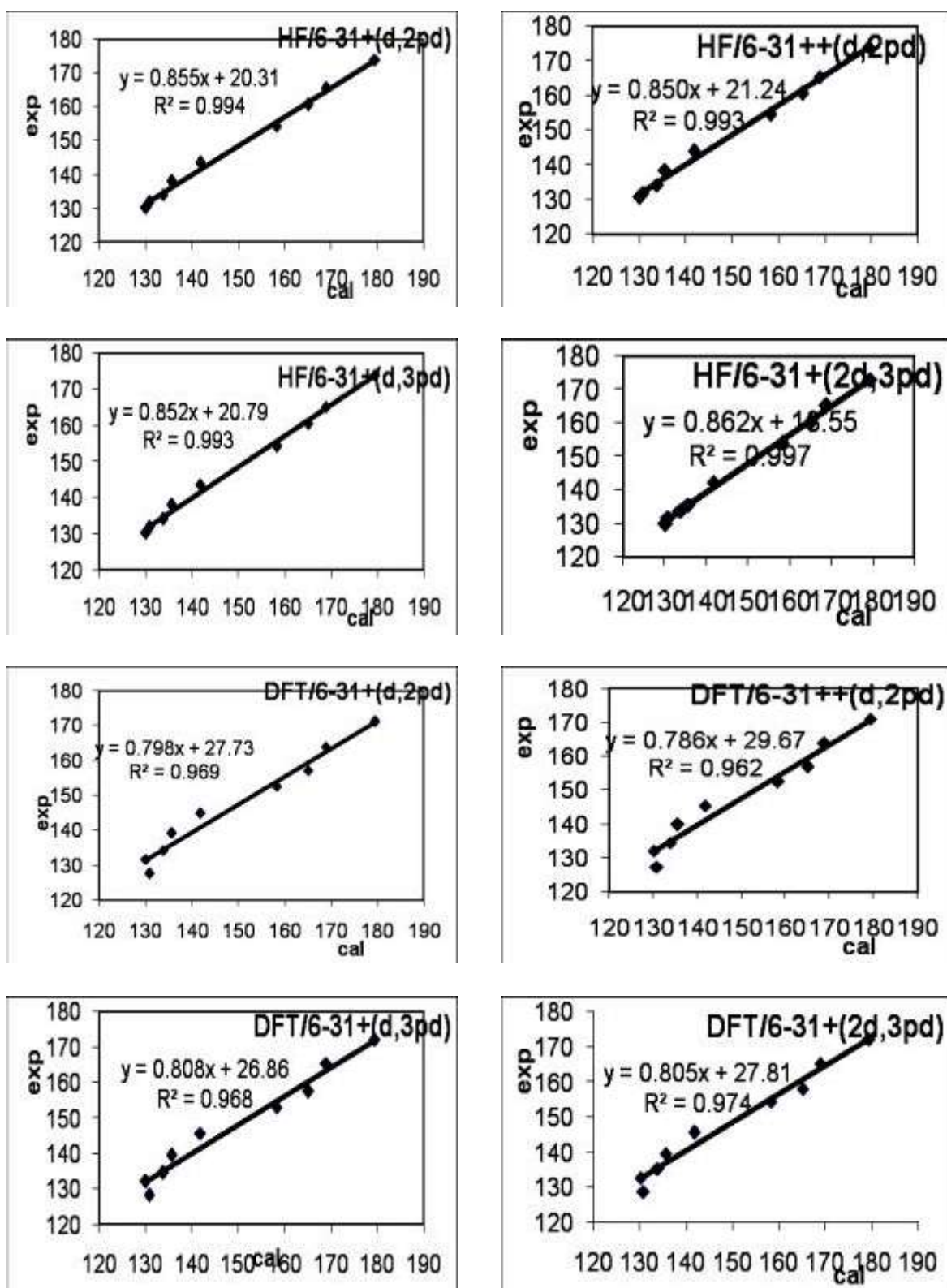


Fig. 3: Plot of experimental ^{13}C chemical shifts against calculated isotropic shielding constants (ppm), for the four basis sets and the level of theories HF and DFT which calculated from the date of Table 2 for cyclo α,β Unsaturated ketones

Table 1: Calculated (RHF and B3LYP) and experimental ^{13}C NMR chemical shifts (ppm from TMS, $d_{\text{TMS}} = 0.00$) for linear α,β -unsaturated ketones

Number of compound	Atom	Method	Basis sets				Experimental
			6-31+G (d,pd)	6-31+G (2d,p)	6-31+G (2d,pd)	6-31+G (2d,3pd)	
1	C1	RHF/GIAO	143.4	142.0	142.2	141.1	140.2
	C1	B3LYP/GIAO	142.2	142.7	142.4	141.5	
	C2	RHF/GIAO	116.4	116.1	116.1	114.6	
	C2	B3LYP/GIAO	112.8	113.5	113.3	112.1	
2	C1	RHF/GIAO	139.8	138.6	138.6	137.6	137.5
	C1	B3LYP/GIAO	134.7	135.5	135.1	134.2	
	C2	RHF/GIAO	130.8	130.5	130.6	129.0	
	C2	B3LYP/GIAO	123.0	123.8	123.6	122.0	
3	C1	RHF/GIAO	148.0	145.7	145.8	144.2	144.5
	C1	B3LYP/GIAO	144.0	144.0	143.5	143.7	
	C2	RHF/GIAO	125.2	125.2	125.2	123.2	
	C2	B3LYP/GIAO	118.0	119.0	118.5	117.0	
4	C1	RHF/GIAO	129.2	128.5	128.6	126.9	123.9
	C1	B3LYP/GIAO	123.0	124.0	123.0	122.4	
	C2	RHF/GIAO	153.7	151.5	151.8	150.5	
	C2	B3LYP/GIAO	156.3	157.0	156.0	155.5	
5	C1	RHF/GIAO	141.3	139.5	139.6	138.6	139.4
	C1	B3LYP/GIAO	139.8	140.0	139.2	139.2	
	C2	RHF/GIAO	134.2	133.4	133.6	131.6	
	C2	B3LYP/GIAO	130.0	130.6	130.3	128.2	
6	C1	RHF/GIAO	134.9	133.3	133.5	132.2	131.7
	C1	B3LYP/GIAO	138.2	135.7	135.4	134.4	
	C2	RHF/GIAO	144.3	142.3	142.6	140.9	
	C2	B3LYP/GIAO	149.3	151.4	151.0	149.8	

Table 2: Calculated (RHF and B3LYP) and experimental ^{13}C NMR chemical shifts (ppm from TMS, $d_{\text{TMS}} = 0.00$) for cyclo α,β -unsaturated keton

Number	Atom	Method	Basis sets				Experiment
			6-31+G (d,2pd)	6-31++G (d,2pd)	6-31+G (d,3pd)	6-31+G (2d,3pd)	
7	C1	RHF/GIAO	131.9	132.0	131.9	131.6	130.8
	C1	B3LYP/GIAO	127.5	127.4	128.3	128.9	
8	C1	RHF/GIAO	134.1	134.3	134.1	133.8	133.8
	C1	B3LYP/GIAO	134.2	134.4	134.6	135.3	
	C2	RHF/GIAO	160.7	160.7	160.6	160.5	
	C2	B3LYP/GIAO	157.1	156.9	157.5	158.2	
9	C1	RHF/GIAO	143.6	143.9	143.7	142.4	141.8
	C1	B3LYP/GIAO	144.8	145.4	145.7	145.6	
	C2	RHF/GIAO	154.4	154.6	154.4	154.2	
	C2	B3LYP/GIAO	152.6	152.5	153.2	154.5	
10	C1	RHF/GIAO	130.2	30.6	130.2	129.8	130.1
	C1	B3LYP/GIAO	131.7	32.1	132.2	132.7	
	C2	RHF/GIAO	174.0	174.1	174.0	173.1	
	C2	B3LYP/GIAO	171.2	171.1	172.2	172.3	
11	C1	RHF/GIAO	138.0	138.3	138.1	135.6	135.6
	C1	B3LYP/GIAO	139.2	139.8	139.5	139.7	
	C2	RHF/GIAO	165.5	165.5	165.2	165.1	
	C2	B3LYP/GIAO	164.0	163.7	165.5	165.4	

Table 3: Statistical data for ^{13}C chemical shift calculated at the four basis sets and the level of theories HF and DFT which calculated from the date of Table 1 for linear α,β Unsaturated ketones

Statistical measures	Basis sets			
	6-31+(d,pd)	6-31+(2d,p)	6-31+(2d,pd)	6-31+(2d,3pd)
Mean absolute error _(HF)	3.0	2.3	2.3	2.0
Mean absolute error _(DFT)	4.1	3.9	3.9	4.2
RMS _(HF)	3.6	2.9	2.9	2.8
RMS _(DFT)	5.5	5.5	5.4	5.8

Table 4: Statistical data for ^{13}C chemical shift calculated at the four basis sets and the level of theories HF and DFT which calculated from the date of Table 2 for cyclo α,β Unsaturated ketones

Statistical measures	Basis Sets			
	6-31+(d,2pd)	6-31++(d,2pd)	6-31+(d,3pd)	6-31+(2d,3pd)
Mean absolute error _(HF)	2.3	2.5	2.4	2.0
Mean absolute error _(DFT)	4.3	4.6	4.1	3.9
RMS _(HF)	3.0	3.0	3.0	3.1
RMS _(DFT)	5.0	5.2	4.6	4.3

Table 5: Linear regression between experimental chemical shifts and calculated isotropic shielding constants (ppm), $d_{\text{calc}} = m d_{\text{exp}} + b$, (R = correlation coefficient). For the four basis sets and the level of theories HF and DFT (in bracket) which calculated from the date of Table 1 for linear α,β Unsaturated ketones

Parameter	6-31+(d,pd)	6-31+(2d,p)	6-31+(2d,pd)	6-31+(2d,3pd)
b	10.37 (16.06)	17.16 (-15/12)	16.45 (-14.34)	13.56 (-18.51)
m	0.940 (1.118)	0.880 (1.114)	0.886 (1.105)	0.897 (1.129)
R ²	0.9255 (0.8179)	0.9331(0.8175)	0.9331(0.8156)	0.9283(0.8124)

Table 6: Linear regression between experimental chemical shifts and calculated isotropic shielding constants (ppm), $d_{\text{calc}} = m d_{\text{exp}} + b$, (R = correlation coefficient). For the four basis sets and level of theories HF and DFT (in bracket) which calculated from the date of Table 2 for cyclo α,β Unsaturated ketones

Parameter	6-31+(d,2pd)	6-31++(d,2pd)	6-31+(d,3pd)	6-31+(2d,3pd)
b	20.313 (27.73)	21.244 (29.68)	20.799 (26.87)	18.556 (27.82)
m	0.856 (0.7983)	0.850 (0.786)	0.852 (0.809)	0.863 (0.805)
R ²	0.994 (0.969)	0.9938 (0.963)	0.9937 (0.968)	0.9975 (0.974)

CPU-time, the Hartree–Fock 6-31+G(2d,3pd) approach might be used to calculate the shifts of the methylene carbons of α,β -unsaturated ketones in these molecules. Use of a larger basis set would be more accurate, but would be prohibitively expensive. All of the ^{13}C isotropic chemical shifts obtained by the HF/6-31+G(2d,3pd) approach are sufficiently accurate to aid in experimental peak assignments, at least in this range of molecules.

As the same as previous work [9], the data obtained from the HF level of theory with the 6-31+G(2d,3pd) basis set are closer to the experimental values than those determined at the B3LYP. For the sake of conciseness, the choice of method is not

discussed further here; it suffices to say that the 6-31+G(2d,3pd) level was chosen for all further investigations.

CONCLUSION

The work demonstrates the application of NMR chemical shift calculations to identify the effects of different connectivities of various groups in α,β -unsaturated ketones. This approach might be provided a basis for the assignment and allowed prediction of the connectivity. In this way, ^{13}C NMR can provide structural information regarding the environment of methylene carbons in α,β -unsaturated ketones through

the use of both calculated and experimental chemical shift data. Considering the time required for the calculations, the available systems and the optimal molecular specifications, we have found that calculations at the HF level of theory with the 6-31+(2d,3pd) basis set yield accurate ^{13}C chemical shifts for the α , β -unsaturated ketones.

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