ABSTRACT

**Background:** Numbers of methods have been developed for the calculation of molecular magnetic properties. It is generally accepted that accurate prediction of these properties within the finite basis approximation, requires gauge-invariant procedures.

**Methods:** In this work, we calculate the $^{13}$C nuclear magnetic resonance chemical shielding tensors of five cyclic ketones using three procedures: gauge including atomic orbitals (GIAO), the individual gauges for atoms in molecules (IGIAM) and continuous set of gauge transformations (CSGT) at both the Hartree-Fock (HF) and density functional theory (DFT) levels of theory using the 6-311G (d, p) basis set. **Results:** The statistical analysis shows that B3LYP combined with the GIAO NMR method are the best for the calculation of $^{13}$C chemical shifts of carbonyl carbon in the considered cyclic ketones. **Conclusion:** The agreement between computed and experimental chemical shifts fully validates our approach.

**Keywords:** $^{13}$C NMR chemical shifts, carbonyl carbon group, DFT, HF, cyclic ketones, GIAO, CSGT, IGIAM.

1. INTRODUCTION

NMR spectroscopy has proved to be a powerful experimental method for the characterization of electronic and structural properties of molecules [1,2,3]. A great attention has been devoted to the measurement of $^{13}$C chemical shift of organic and bioorganic molecules [4,5,6]. A number of methods have been developed for the calculation of nuclear shieldings. It is generally accepted that accurate prediction of these properties within the finite basis approximation, requires gauge-invariant procedures [7,8]. This paper will focus on predicting NMR shielding tensors using three of these procedures, namely GIAO (gauge including atomic orbitals) [9,10,11], CSGT (continuous set of gauge transformations) [12-11] and IGIAM (individual gauges for atoms in molecules) [12] at both the Hartree-Fock and DFT levels of theory, which achieve “gauge-invariance” in different ways.

The importance of the carbonyl functional group, particularly the cyclic functionality, is demonstrated by the fact that this functional group is present in some antibiotics [13,14,15,16]. In the present work, theoretical and experimental NMR spectra of five cyclic ketones (Figure.1) have been studied both to collect a complete set of experimental NMR data and to test the performance of different NMR methods.

![Figure 1](image_url): The figure presents the molecular structures of the cyclic ketones.
2. MATERIALS AND METHODS

2.1 Quantum-chemical calculations:

Calculations were performed with the use of the Gaussian 09 set of programs [17]. All structures were fully optimized with the density functional theory (DFT) using Becke’s three parameter hybrid method [18] and correlation functional of Lee–Yang–Parr (B3LYP) [19, 20] in conjunction with the 6-311G (d, p) basis set. In all cases, the analytical vibrational frequencies were computed to confirm that the optimized structures correspond to real minima on the potential energy surface.

$^{13}$C nuclear shieldings of the considered cyclic ketones have been calculated over the fully optimized geometries within the gauge-including atomic orbital (GIAO), the individual gauges for atoms in molecules (IGIAM) and continuous set of gauge transformations (CSGT) methods. Absolute isotropic magnetic shieldings were transformed into chemical shifts by referencing to the shieldings of a standard compound (TMS) computed at the same level [21,22].

After computing the values of the $^{13}$C chemical shifts using all the cited methods, a statistical analysis was carried out to determine which method produced the best results. Statistical analysis included the mean absolute error (MAE/ppm, Eq.1); the mean squared error (MSE/ppm$^2$, Eq. 2); and the root mean squared error (RMSE/ppm, Eq.3). The error calculations were performed using Microsoft Excel 2013.

\[ MAE = \frac{1}{n} \sum_{i=1}^{n} |\delta_{i}^{\text{cal}} - \delta_{i}^{\text{exp}}| \]  \hspace{1cm} (1)
\[ MSE = \frac{1}{n} \sum_{i=1}^{n} (\delta_{i}^{\text{cal}} - \delta_{i}^{\text{exp}})^2 \]  \hspace{1cm} (2)
\[ RMSE = \sqrt{MSE} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (\delta_{i}^{\text{cal}} - \delta_{i}^{\text{exp}})^2} \]  \hspace{1cm} (3)

2.2 Experimental section

NMR spectra were recorded on a Bruker 300 spectrometer at 300 K. $^{13}$C NMR spectra were measured at 75 MHz. Chemical shifts were referenced to external TMS. Samples were contained in 5 mm tubes. For locking purposes, a 2 mm capillary coaxial tube containing (CD$_3$)$_2$CO was used. The general reproducibility of chemical shifts data was estimated to be better than 0.01 ppm. All compounds used in this work were commercially available and were dried and purified before use by distillation. Their purities were checked from their $^1$H and $^{13}$C spectra. Samples were prepared by weight and volumetrically.

3. RESULTS AND DISCUSSION

Theoretical and experimental $^{13}$C chemical shifts of the carbonyl carbon group, for all compounds studied are collected in Table 1.

<table>
<thead>
<tr>
<th>Cyclic ketones</th>
<th>GIAO DFT</th>
<th>GIAO HF</th>
<th>CSGT DFT</th>
<th>CSGT HF</th>
<th>IGIAM DFT</th>
<th>IGIAM HF</th>
<th>Exp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobutanone</td>
<td>208.076</td>
<td>213.325</td>
<td>206.358</td>
<td>212.056</td>
<td>206.364</td>
<td>212.067</td>
<td>209.829</td>
</tr>
<tr>
<td>Cyclopentanone</td>
<td>218.680</td>
<td>223.361</td>
<td>216.262</td>
<td>221.714</td>
<td>211.156</td>
<td>223.361</td>
<td>217.939</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>209.419</td>
<td>215.110</td>
<td>206.857</td>
<td>212.972</td>
<td>206.862</td>
<td>224.382</td>
<td>211.887</td>
</tr>
<tr>
<td>Cycloheptanone</td>
<td>213.673</td>
<td>219.857</td>
<td>211.151</td>
<td>217.740</td>
<td>211.156</td>
<td>217.750</td>
<td>215.285</td>
</tr>
<tr>
<td>Cyclooctanone</td>
<td>218.294</td>
<td>223.595</td>
<td>216.508</td>
<td>224.382</td>
<td>216.513</td>
<td>222.168</td>
<td>218.300</td>
</tr>
</tbody>
</table>

GIAO: gauge-including atomic orbital; CSGT: continuous set of gauge transformations; IGIAM: individual gauges for atoms in molecules.
A comparison of the calculated NMR chemical shifts with the experimental values revealed that $^{13}$C chemical shifts calculated at the Hartree-Fock 6-311G (d, p) level of theory are not much better, than those predicted at the density functional methods in the same level. The coefficients of linear correlations of the theoretical to the experimental data, which can be treated as a certain measure of goodness of theoretical values, are of the order of 0.99, 0.98 and 0.90 for GIAO, CSGT, and IGIAM methods, respectively. Among the three approaches for calculating chemical shifts, gauge including atomic orbital method has shown to provide results that are more accurate than those achieved by CSGT and IGIAM approaches at the same basis set size. The agreement between the experimental and calculated values is excellent as shown in Figure 2. The standard deviations remain close to zero.

Figure 2: A plot of the relative experimental $^{13}$C chemical shifts of the carbonyl carbon of cyclic ketones versus the theoretical (B3LYP/6-311G (d, p)).

To quantify the performance of each functional, the statistical analysis using mean the absolute error (MAE), the mean squared error (MSE) and the root mean squared error (RMSE) was employed (Table 2).

<table>
<thead>
<tr>
<th>Functional</th>
<th>GIAO</th>
<th>CSGT</th>
<th>IGIAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAE</td>
<td>1,316</td>
<td>4,402</td>
<td>3,221</td>
</tr>
<tr>
<td>MSE</td>
<td>2,462</td>
<td>20,190</td>
<td>12,092</td>
</tr>
<tr>
<td>RMSE</td>
<td>1,569</td>
<td>4,493</td>
<td>3,477</td>
</tr>
</tbody>
</table>

Table 2: Statistical parameters defined in eq. 1-3. MAE = mean absolute error; MSE = mean squared error; RMSE = the root mean squared error of carbonyl carbon in the considered cyclic ketones.

GIAO: gauge-including atomic orbital; CSGT: continuous set of gauge transformations; IGIAM: individual gauges for atoms in molecules.

The first three parameters (MAE, MSE and RMSE) are measures of the fitting error. These are used to estimate directly which functional gives a more accurate prediction, as smaller values indicate smaller error.

For $^{13}$C NMR chemical shifts, the best results were obtained using DFT combined with GIAO, while IGIAM NMR method at the Hartree-Fock 6-311G (d, p) level of theory have the worst performance (figure.3).
4. CONCLUSION

The examination of our results leads to the following conclusions: using the DFT/6-311G (d, p) based computational methodology employed in the present study it was possible to predict the $^{13}$C NMR chemical shifts of carbonyl carbon in the considered cyclic ketones. The correlations between experimental and calculated chemical shifts were subjected to statistical analysis to identify the best-performing NMR methods. The GIAO method combined with the functional B3LYP, showed the lowest values of RMSE and MAE, i.e., better agreement of calculated values with the experimental $^{13}$C NMR chemical shift. The information contained in this work can be used for the assignment of experimental NMR spectra and will motivate further studies involving the theoretical calculation of $^{13}$C NMR organic compound.

5. REFERENCES


![Figure 3: Results from the statistical treatment. MAE= mean absolute error, MSE= mean squared error and RMSE= root mean squared error of the theoretical calculations of $^{13}$C NMR chemical shifts of carbonyl carbon in the considered cyclic ketones.](image-jpg)


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