

**Calculation of Oligosaccharide  $^{13}\text{C}$  Chemical Shifts. A  
Comparative Study of Hartree-Fock and Density Functional  
Theory *Ab Initio* Methods**

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## Abstract

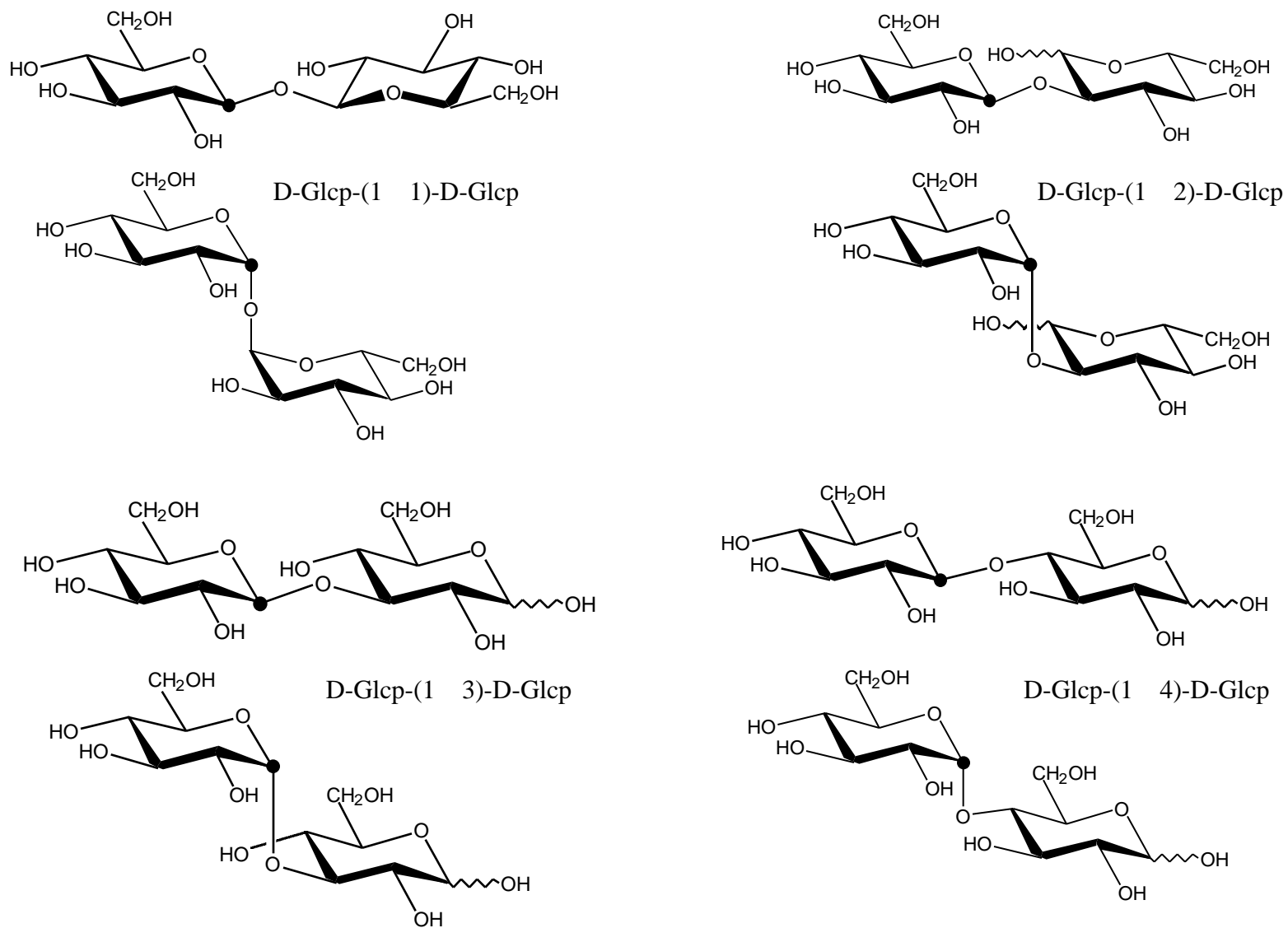
Density functional theory (DFT) employing thirty-six combinations of exchange and correlation functionals at the 3-21G theory level was used to calculate the magnetic properties for the  $^{13}\text{C}$  nuclei of eight model disaccharides using the Gauge Including Atomic Orbital (GIAO) method.  $^{13}\text{C}$  chemical shifts were computed from this data relative to TMS and compared to corresponding shifts obtained using the Hartree-Fock (HF) GIAO method at the 6-311G\*\* and 3-21G levels of theory. According to the results of this study, the DFT method that gives the best  $^{13}\text{C}$  chemical shift correlation to both of the HF methods is the combination of the exchange component of Perdew and Wang's 1991 functional and the local (non-gradient corrected) functional of Perdew (1981), PW91PL. The  $^{13}\text{C}$  chemical shifts for one of the disaccharides, trehalose, obtained using PW91PL/3-21G, is compared to the corresponding experimental shifts as well as those obtained with HF/6-311G\*\*. Using the

PW91PL/3-21G DFT method, a chemical shift surface for the  $\alpha$ -D-Glcp-(1 $\rightarrow$ 4)-D-Glcp disaccharide was constructed and compared to the respective surface created using HF/6-311G\*\*.

## **Introduction**

NMR is one of the most useful spectroscopic techniques available to chemists. The use of computationally derived NMR parameters where data of this sort is unavailable is of growing interest, as demonstrated by results obtained by us and others during the study of the conformational behavior of different biomolecules.<sup>1-3</sup> DFT has emerged as an efficient method for these calculations done on mid-sized to larger molecules such as oligosaccharides.<sup>4</sup> A large number of exchange and correlation functionals have been developed, each having varying degrees of accuracy depending on the type of physical property being calculated. Much of the accuracy in chemical shift calculations stems from the selection of larger basis sets, with

this accuracy leveling off as the basis sets become increasingly diffuse.<sup>5</sup> An accurate yet demanding method for calculating  $^{13}\text{C}$  chemical shifts in sugars is HF theory using large basis sets, such as the triple-zeta 6-311G\*\* basis.<sup>6</sup> However, the use of large basis sets is very time consuming even on today's computers. By comparing the  $^{13}\text{C}$  chemical shifts derived using different combinations of pure exchange and correlation functionals, a DFT method may be discovered which is computationally inexpensive, yet yields results similar in quality to methods that use large basis sets. To the best of our knowledge, there have not been any comprehensive studies comparing DFT methods to reveal which one is actually the best for a particular class of compounds. In this poster, we present a comparison of thirty-six DFT/3-21G methods against the HF/3-21G and HF/6-311G\*\* methods in the estimation of  $^{13}\text{C}$  chemical shifts for eight D-Glcp-D-Glcp model disaccharides.



**Figure 1.** Disaccharides used in DFT and HF GIAO <sup>13</sup>C chemical shift calculations.

## Computational Methods

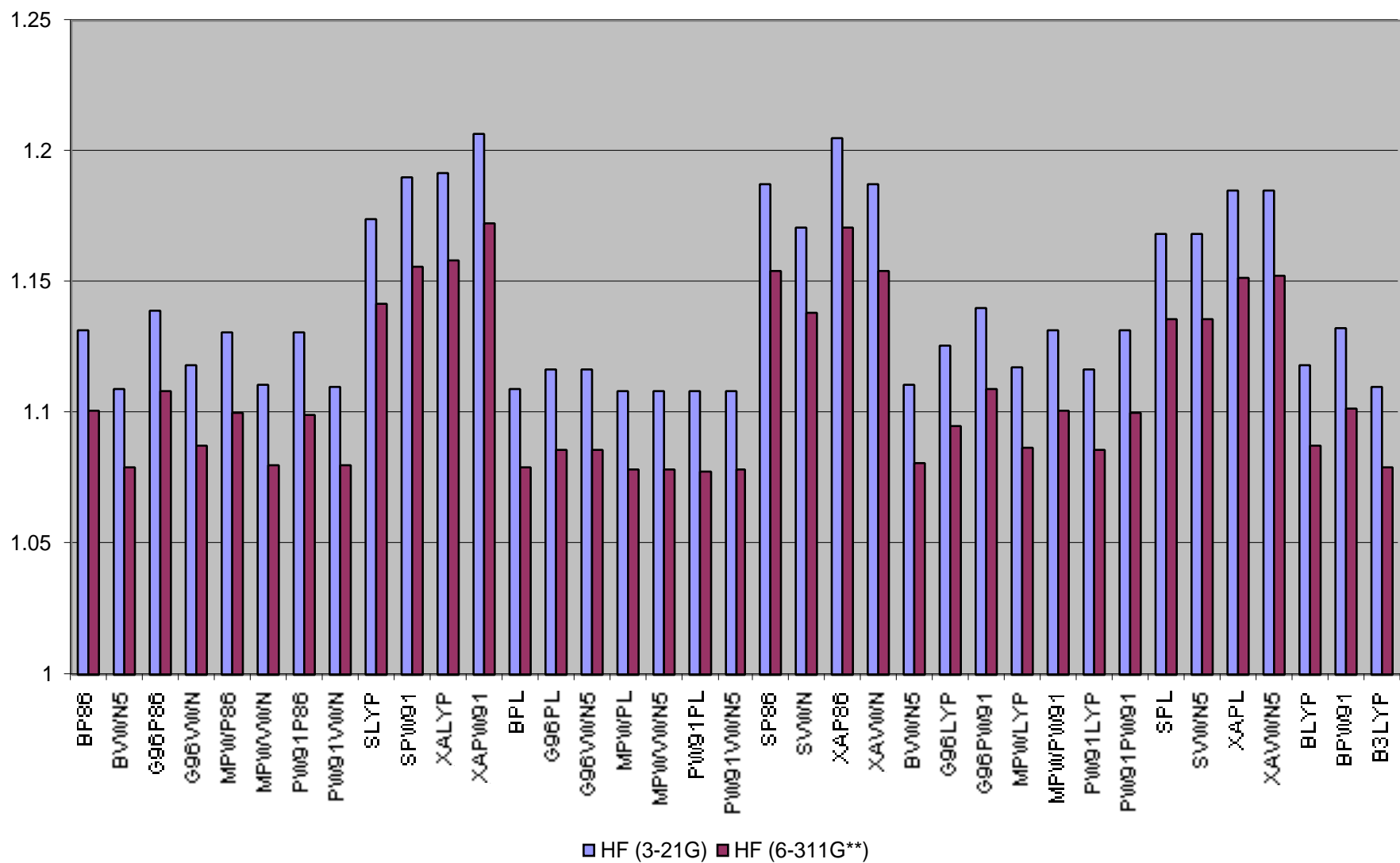
Eight isomers of a D-Glcp-D-Glcp model disaccharide, which included 1 → 1, 1 → 2, 1 → 3, and 1 → 4 glycosidic linkages in both  $\alpha$  and  $\beta$  configurations (**Figure 1**), were built using Sybyl 6.5 (Tripos Inc.) and optimized using the AM1 semiempirical with Spartan 5.0.1 (Wavefunction, Inc.) on a Silicon Graphics O2 R10000 workstation. The eight minimized disaccharides were used as input structures for the calculation of  $^{13}\text{C}$  chemical shifts relative to TMS using the GIAO method as implemented on Gaussian 98.<sup>7</sup> HF/3-21G, HF/6-311G\*\*, and thirty-six DFT/3-21G methods composed of combinations of different exchange and correlation functionals were employed. Calculations of the magnetic properties were performed on a 17-node Beowulf supercomputer cluster (450 MHz Pentium III).

For the construction of the  $^{13}\text{C}$  chemical shift surface of  $\beta$ -D-Glcp-(1 → 4)-D-Glcp (trehalose), the method previously reported by our laboratory was employed.<sup>8</sup> Briefly, a grid with  $18 \times 18 \times 20^\circ$

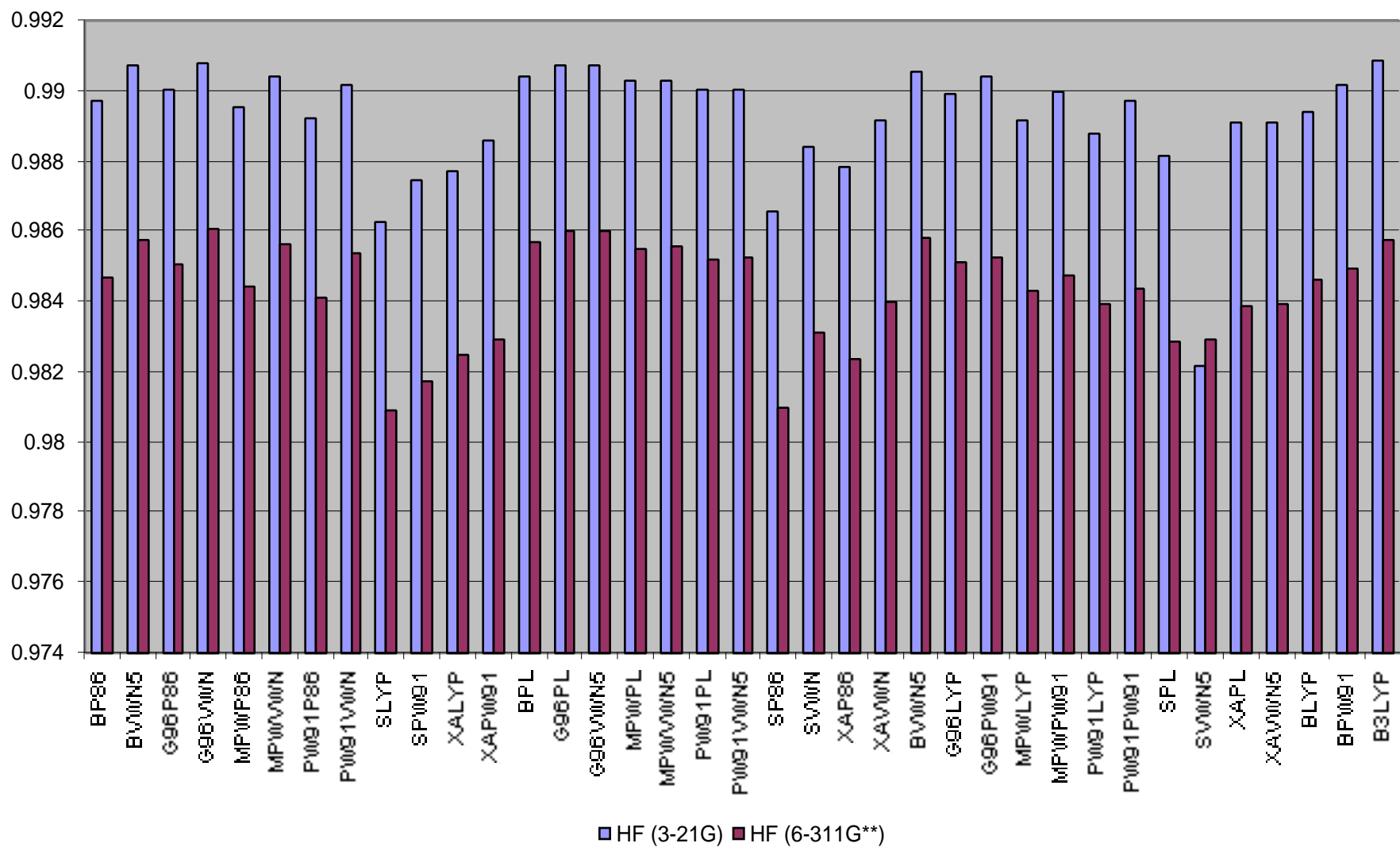
intervals in the 0 – 340° range for the glycosidic bond  $\phi$  and dihedral angles was constructed, to give a total of 324 input structures for the disaccharide. For each structure in the grid, the  $\phi$  and  $\psi$  dihedrals were held constant and the rest of the molecule fully optimized (AM1 semiempirical, Spartan 5.0.1). The resulting structures were employed in  $^{13}\text{C}$  chemical shift estimations. These results were then fitted to a trigonometric series expansion, to give an equation of the form  $^{13}\text{C}(\delta) = f(\phi, \psi)$  which was used to obtain the two dimensional surface plots.

## Results and Discussion

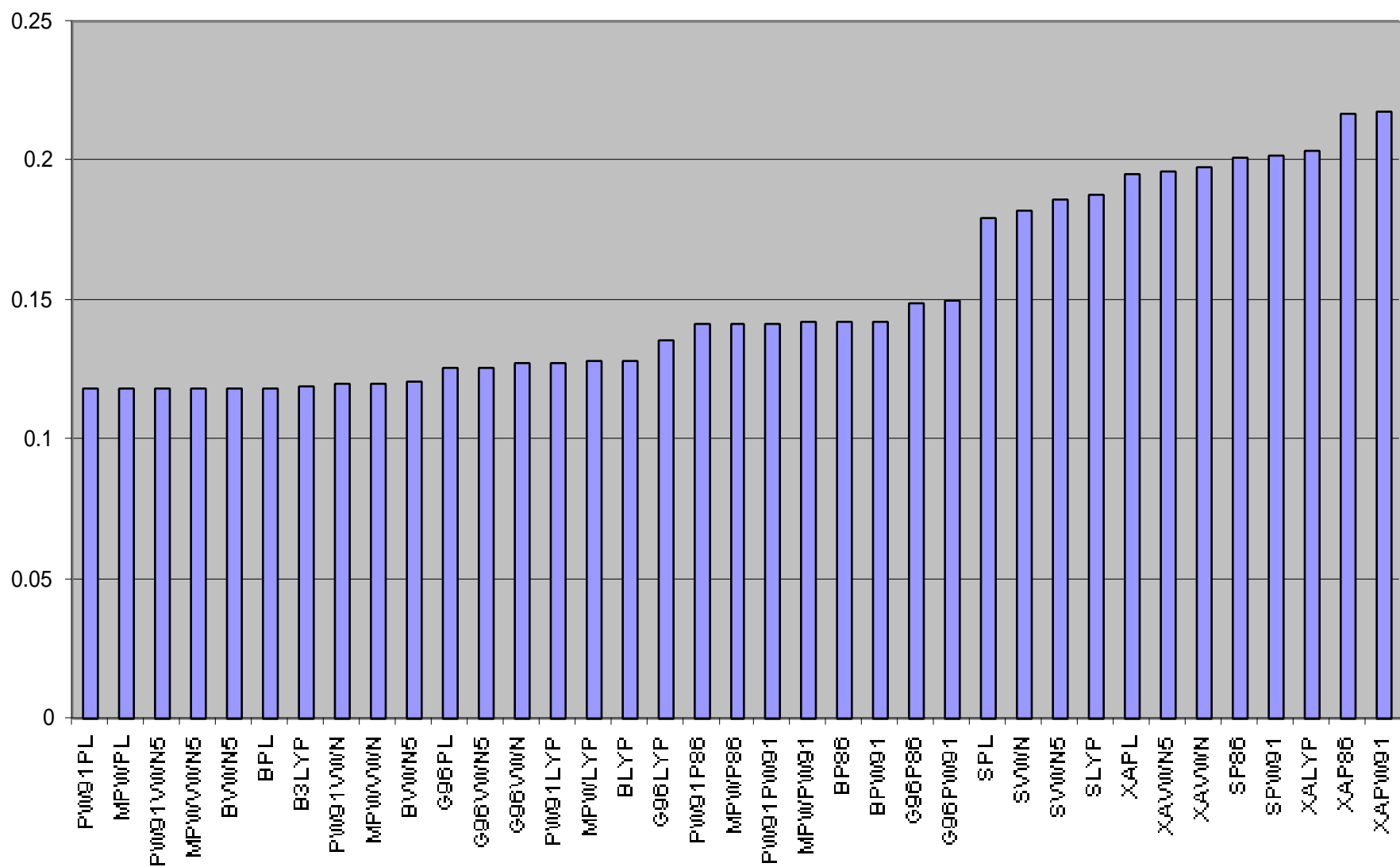
The  $^{13}\text{C}$  chemical shifts for the DFT/3-21G methods were each plotted against the  $^{13}\text{C}$  chemical shifts obtained using HF/3-21G and HF/6-311G\*\*. The slopes and correlation coefficients corresponding to the DFT methods in these plots are presented in **Figures 2** and **3**, respectively. The difference between the slope and correlation coefficient from each graph was recorded and arranged in ascending order. The DFT/3-21G method with the best correlation has its slope and its correlation coefficient nearest to one. No slope value in the data obtained is less than one, and by definition no correlation coefficient can be greater than one. Therefore, the DFT/3-21G method with the smallest difference between slope and correlation coefficient has the best correlation to the HF/3-21G and HF/6-311G\*\* methods. The DFT/3-21G method with the best correlation to HF/3-21G and HF/6-311G\*\* in calculation of  $^{13}\text{C}$  chemical shifts for these disaccharides was found to be the PW91PL



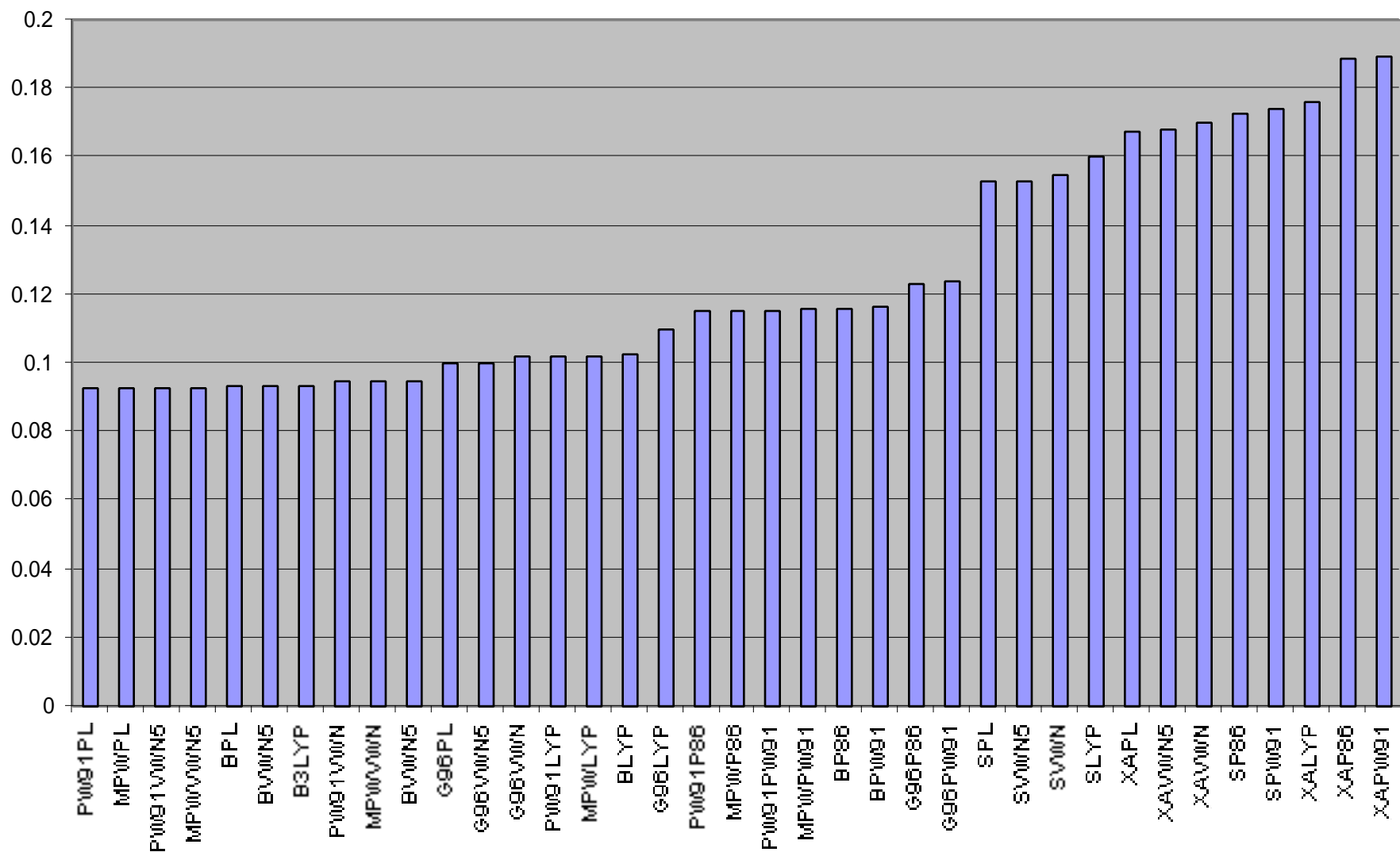
**Figure 2.** Slopes From Linear Correlations of DFT/3-21G Methods vs HF/3-21G and HF/6-311G\*\* in the GIAO Calculation of  $^{13}\text{C}$  Chemical Shifts in D-Glcp-D-Glcp Model Disaccharides



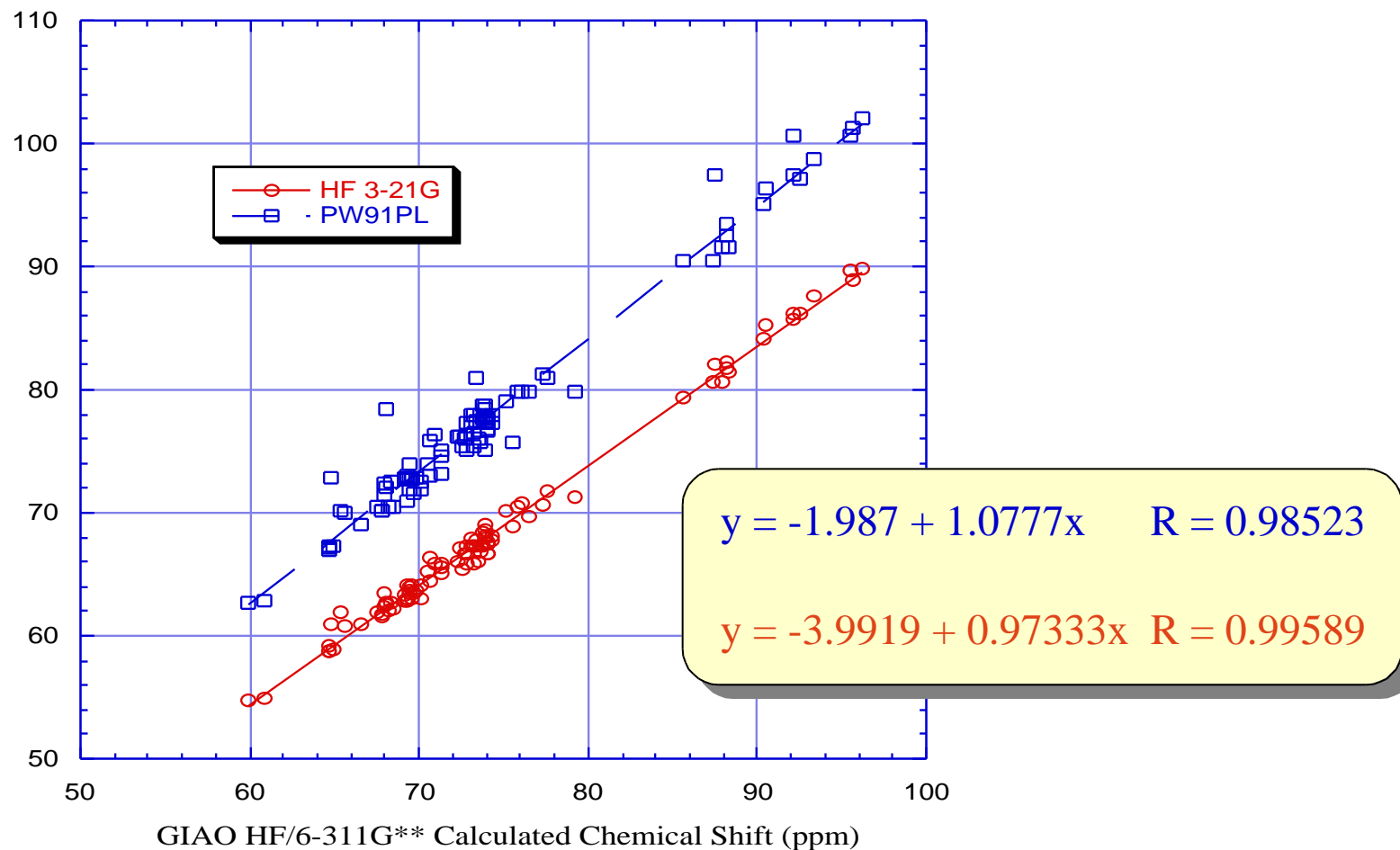
**Figure 3.** Correlation Coefficients From Linear Correlations of DFT/3-21G vs HF/3-21G and HF/6-311G\*\* Methods in the GIAO Calculation of  $^{13}\text{C}$  Chemical Shifts in D-Glcp-D-Glcp Model Disaccharides



**Figure 4.** Differences Between Slopes and Correlation Coefficients From Linear Correlations of DFT/3-21G Methods vs HF/3-21G in the GIAO Calculation of  $^{13}\text{C}$  Chemical Shifts in D-Glcp-D-Glcp Model Disaccharides



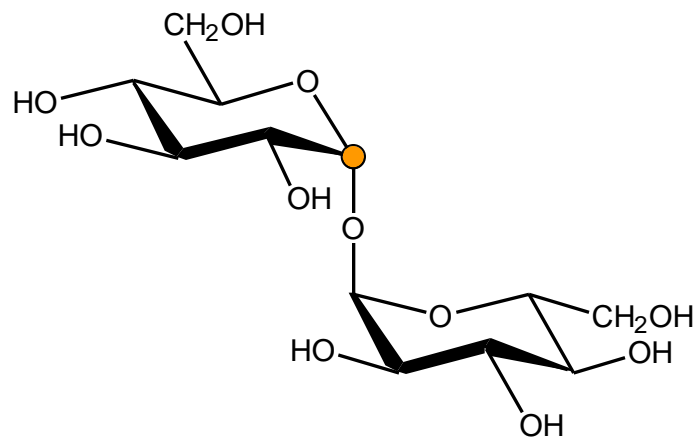
**Figure 5.** Differences Between Slopes and Correlation Coefficients From Linear Correlations of DFT/3-21G Methods vs HF/6-311G\*\* in the GIAO Calculation of  $^{13}\text{C}$  Chemical Shifts in D-Glcp-D-Glcp Model Disaccharides



**Figure 6.** Linear Correlation Plot of PW91PL/3-21G and HF/3-21G GIAO Methods vs GIAO HF/6-311G\*\* for the Calculation of  $^{13}\text{C}$  Chemical Shifts in D-Glcp-D-Glcp Model Disaccharides

combination of exchange and correlation functionals (**Figures 4 and 5**).<sup>9,10</sup> **Figure 6** compares the correlation between the <sup>13</sup>C chemical shifts obtained using PW91PL/3-21G and HF/3-21G against HF/6-311G\*\*. Interestingly, PW91PL/3-21G overestimates the chemical shift produced by HF methods in a systematic way, revealing a scalable relationship between the two methods.

We then investigated the ability of the PW91PL/3-21G DFT method to reproduce experimental data. One of the problems in the direct computation of <sup>13</sup>C chemical shifts is that no consideration for the dynamic behavior of the molecule is taken into account by *ab initio* methods. Therefore, for molecules with high conformational freedom such as disaccharides, results from single-point calculations may differ considerably from experiment. However, the disaccharide trehalose has been shown to possess a highly preferred conformer in solution similar to the one obtained by energy minimization, and good correlation between point calculations of <sup>13</sup>C chemical shifts and experimental <sup>13</sup>C chemical shifts should be expected.<sup>11</sup> **Table 1**

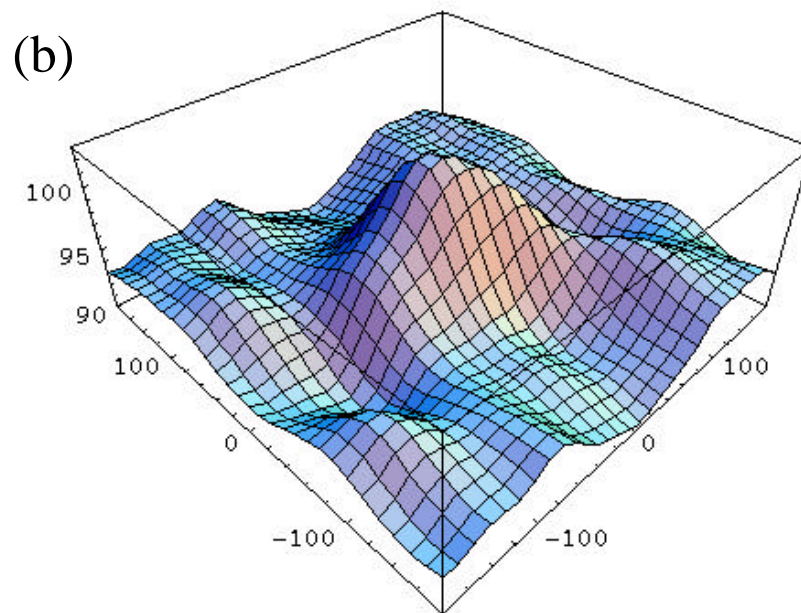
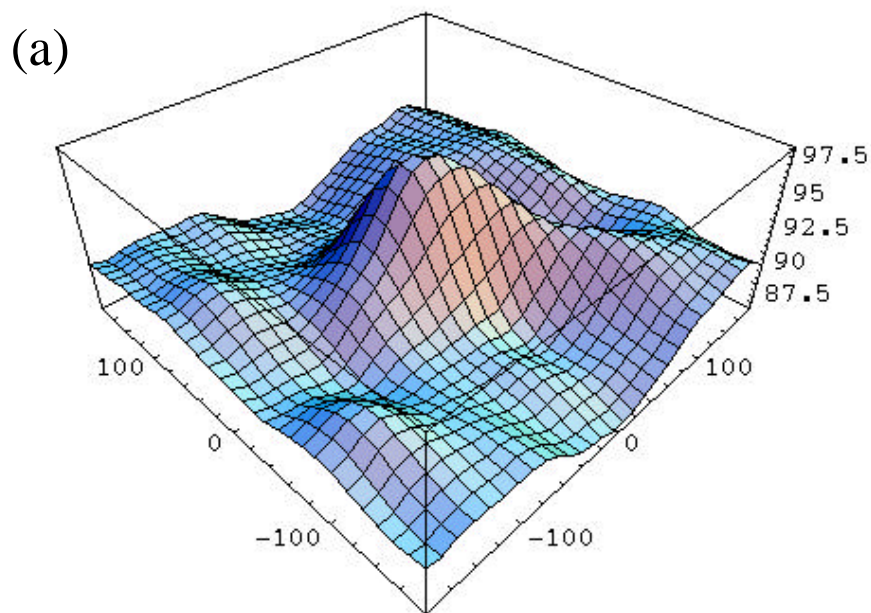
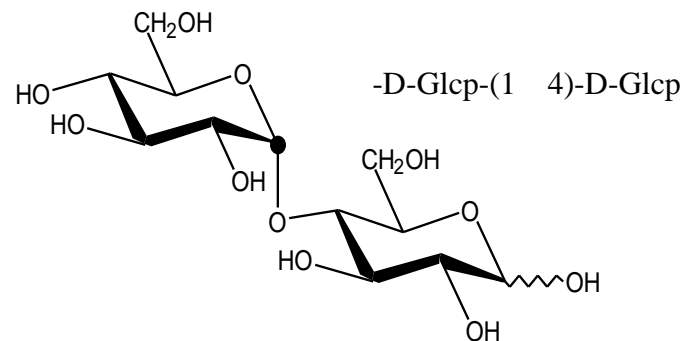
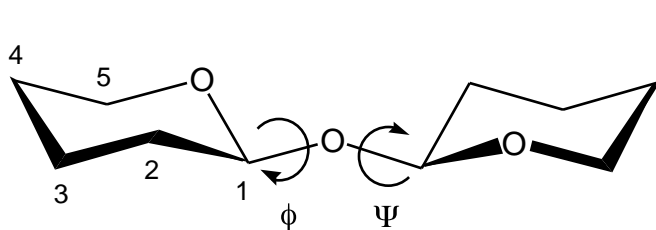


Carbon atom	Experimental <sup>13</sup> C shift	GIAO PW91PL/3-21G Computed <sup>13</sup> C shift	GIAO HF/6-311G** Computed <sup>13</sup> C shift
1	89.8 - 92.0	91.0	89.2
2	69.4 - 72.0	72.4	69.0
3	70.8 - 73.5	76.7	73.8
4	68.1 - 70.6	71.3	68.3
5	70.6 - 73.0	72.7	71.0
6	59.0 - 61.5	64.9	62.2

**Table 1.** Comparison of experimental and computed (GIAO/PW91PL/3-21G and GIAO/HF/6-311G\*\*, AM1 optimized geometry) <sup>13</sup>C chemical shifts (in ppm) for the anomeric carbon (marked orange) of the disaccharide trehalose, D-Glcp-a-(1 → 1)-D-Glcp.

shows the chemical shifts for each carbon atom in trehalose from both experimental, calculated HF/6-311G\*\* and PW91PL/3-21G methods. All of the shifts obtained using PW91PL/3-21G slightly overshoot those obtained using HF/6-311G\*\* and two fall within the range of the experimentally obtained shifts. Despite that the other four shifts calculated with PW91PL/3-21G are slightly greater than the experimental shift ranges, the differences are similar in magnitude to those obtained when using HF with large basis sets.

As a final test of the suitability of the PW91PL/3-21G DFT method for the calculation of disaccharide  $^{13}\text{C}$  chemical shifts, we evaluated its capacity to reproduce the well known periodic dependence between the  $^{13}\text{C}$  chemical shift of the anomeric carbon of the glycosidic linkage and the  $\phi$  and  $\psi$  dihedral angles.<sup>12</sup> Therefore, we constructed a  $^{13}\text{C}$  chemical shift surface for the  $\alpha$ -D-Glcp-(1  $\rightarrow$  4)-D-Glcp disaccharide using PW91PL/3-21G and compared it to the corresponding surface constructed with HF/6-311G\*\* (**Figures 7a** and **7b**). As evident from the figures, both surfaces correlate well.



**Figure 7.** Comparison of the  $^{13}\text{C}$  Anomeric Carbon Chemical Shift Surfaces for the Disaccharide  $\alpha\text{-D-Glcp-(1-4)-D-Glcp}$  obtained with HF/6-311G\*\*, (a) and PW91PL/3-21G (b). See text for details.

## Conclusions

Through the comparison of different combinations of exchange and correlation functionals used in the GIAO calculation of  $^{13}\text{C}$  chemical shifts in model disaccharides, we found that the PW91PL combination gave results closest to those obtained using the computationally expensive HF/6-311G\*\* method. In comparison of the anomeric carbon  $^{13}\text{C}$  chemical shift surfaces obtained using PW91PL/3-21G and those using HF/6-311G\*\*, we have shown that both methods can predict the dependence between the  $^{13}\text{C}$  chemical shift of the anomeric carbon of the glycosidic linkage and the  $\phi$  and  $\psi$  dihedral angles with similar accuracy. Furthermore,  $^{13}\text{C}$  chemical shift values calculated using PW91PL/3-21G compare very well to experimental data for trehalose, and are similar to those obtained using HF/6-311G\*\*. On the other hand, calculation of trehalose  $^{13}\text{C}$  chemical shifts using just HF/3-21G grossly underestimates the experimental values.<sup>8</sup> This seems to indicate that results from DFT

GIAO calculations at low theory levels are a reasonable substitute to high level HF GIAO calculations for oligosaccharides. It is worth mentioning that only upon scaling to reference high level results (6-311G\*\*) can low level (3-21G) HF GIAO calculations be used for the estimation of oligosaccharide chemical shifts.<sup>8</sup> The DFT method found in this study can, on the other hand, be used in oligosaccharide chemical shift calculations without the need of scaling, thus doing away with the need of carrying out reference calculations at high theory levels for representative compounds or databases of compounds.

There is one aspect of this study that remains to be investigated; a final validation of our results can only be achieved through comparison with a larger set of experimental data. Since experimental <sup>13</sup>C chemical shifts of oligosaccharides are affected by time-averaging, this would require the development of a method that takes these effects into account. These investigations are currently under way, and will be reported in due course.

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