

## $^{13}\text{C}$ chemical shift predictions for bakuchiol—a recently discovered agent against organ damage

Tính toán độ dịch chuyển hóa học  $^{13}\text{C}$  của bakuchiol—tác nhân mới điều trị tổn thương các cơ quan

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### Abstract

The calculations of  $^{13}\text{C}$  NMR chemical shifts for bakuchiol, a promising anti-aging agent, were performed using 11 functionals (B3LYP, B3PW91, BPV86, CAM-B3LYP, HCTH, HSEH1PBE, mPW1PW91, PBEPBE, TPSSTPSS, and  $\omega\text{B97XD}$ ) and 10 common basis sets (3-21G, 6-31G(d,p), 6-31G(d,3p), 6-31G(3d,p) 6-31G++(d,p), DGDZVP, DGDZVP2, LANL2DZ, LANL2MB) to compare with experimental data. While functionals did not strongly impact the computed  $^{13}\text{C}$  chemical shifts, basis sets showed a significant influence on the results. For those functionals, B3LYP, B3PW91, CAM-B3LYP, HSEH1PBE, mPW1PW91, and  $\omega\text{B97XD}$  were found to have strong correlations ( $r^2 \geq 0.9987$ ) and low errors (CMAEs  $\leq 1.96$  ppm and CMAEs  $\leq 2.49$  ppm); among the tested basis sets 3-21G, DGDZVP provided the best results ( $r^2 \geq 0.9980$ , CMAEs  $\leq 2.37$  ppm and CMAEs  $\leq 2.67$  ppm). These results would allow meaningful predictions of  $^{13}\text{C}$  chemical shifts for bakuchiol.

**Keywords:**  $^{13}\text{C}$  chemical shifts; NMR; DFT functionals; basis sets; bakuchiol.

### Tóm tắt

Phổ  $^{13}\text{C}$  của bakuchiol, tác nhân chống lão hóa, được tính toán bằng 11 hàm mật độ (B3LYP, B3PW91, BPV86, CAM-B3LYP, HCTH, HSEH1PBE, mPW1PW91, PBEPBE, TPSSTPSS, và  $\omega\text{B97XD}$ ) và 10 mức lý thuyết (3-21G, 6-31G(d,p), 6-31G(d,3p), 6-31G(3d,p) 6-31G++(d,p), DGDZVP, DGDZVP2, LANL2DZ, LANL2MB) nhằm so sánh với dữ liệu thực nghiệm. Trong khi các hàm mật độ thể hiện ảnh hưởng nhỏ lên độ dịch chuyển hóa học  $^{13}\text{C}$ , các kết quả tính toán bằng mức lý thuyết cho thấy sự phân hóa rộng hơn về độ chính xác. B3LYP, B3PW91, CAM-B3LYP, HSEH1PBE, mPW1PW91, và  $\omega\text{B97XD}$  có độ tương quan cao ( $r^2 \geq 0.9987$ ) và lỗi thấp (CMAEs  $\leq 1.97$  ppm và CMAEs  $\leq 2.49$  ppm); trong các mức lý thuyết, 3-21G, DGDZVP cho các kết quả với độ chính xác cao ( $r^2 \geq 0.9980$ , CMAEs  $\leq 2.37$  ppm and CMAEs  $\leq 2.67$  ppm).

**Từ khóa:** Phổ  $^{13}\text{C}$ ; NMR; hàm DFT; mức lý thuyết; bakuchiol.

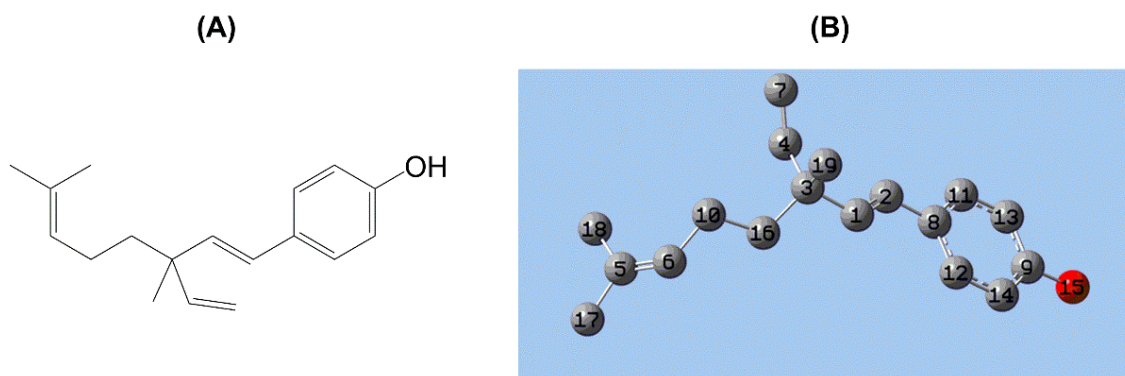
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## 1. Introduction

Bakuchiol (Figure 1), a prenylated phenolic monoterpene isolated from the fruit of *Psoralea corylifolia*, has recently shown a variety of pharmacological effects such as antioxidant, anti-bacterial, anti-inflammatory, anti-aging, and estrogen-like effects[1][2]. It also has protective effects in the heart, liver skin, and other organs. In addition, bakuchiol inhibits the

proliferation of various cancer cells, including stomach, breast, and skin cancer cells and liverfibrosis via promoting myofibroblast apoptosis. It relieves the hepatotoxic of multiple toxicants by suppressing oxidative stress and inflammatory changes[3]. Understanding the structure of bakuchiol would provide insights into its pharmacological effects.



**Figure 1.** (A) Bakuchiol and (B) its optimized structure at the IEFPCM(CHCl<sub>3</sub>)/B3LYP-631G(d,p) level of theory with numbered carbons (H atoms were omitted for clarity).

The combination of experimental and computational NMR techniques has been a strong tool for providing the structural information of biologically active natural products, which can support the difficult assignments and the confirmation of their structures and provide valuable insights into the electronic environments of active NMR nucleus [4][5][6]. The gauge-including atomic orbitals (GIAO)/density functional theory (DFT) method are generally accepted as a standard method in computing shielding constants due to its reliability and applicability [7][8][9]. The accuracy of calculated chemical shifts typically depends on an appropriate combination of exchange-correlation functionals and basis sets [10]. Aimed to find suitable methods with high accuracy, this present study evaluated 11 DFT functionals and 11 common basis sets in the calculations of <sup>13</sup>C chemical shifts for bakuchiol.

## 2. Computational methods

All calculations were performed using the Gaussian09 [11]. Geometry optimizations of bakuchiol were performed at the IEFPCM(CHCl<sub>3</sub>)/B3LYP/6-31G(d,p) level[12][13]. Subsequent frequency calculations ensured that a potential energy surface (PES) local minimum was attained during the energy minimization. Cartesian coordinates of the resulting structures are given in the Supporting Information.

The following 11 functionals coupled with 6-31G(d,p) [14] and 10 basis set coupled with B3LYP [15] were evaluated:

- Functionals: B3LYP (Becke's 3-parameter hybrid functional[16] using B exchange[17] and LYP correlation),[15] B3PW91 (Perdew and Wang's 1991 gradient-corrected correlation functional),[18][19] BPV86 (Perdew's 1986 functional),[16][20][21] CAM-B3LYP (Handy

and co-workers' long-range corrected version of B3LYP using the Coulomb-attenuating method),[22] HCTH (Hamprecht-Cohen-Tozer-Handy GGA functional),[23][24][25] HSEH1PBE (The exchange part of the screened Coulomb potential of Heyd, Scuseria, and Ernzerhof),[26][27] LSDA (Local spin-density approximation),[28] mPW1PW91 (mPW exchange and PW91 correlation),[29][30] PBEPBE (The functional of Perdew, Burke, and Ernzerhof),[31] TPSS (The exchange component of the Tao-Perdew-Staroverov-Scuseria),[32][33] and  $\omega$ B97XD (Head-Gordon and coworkers' dispersion corrected long-range corrected hybrid functional)[34][35].

- Basis sets: Pople's 3-21G, 6-31G(d,p), 6-31G(3d,p), 6-31G(d,3p), 6-31++G(d,p), and 6-311G;[36][37][14] DGDZVP, DGDZVP2 ;[38] LANL2MB and LANL2DZ (Los Alamos ECP).[39][40]

Unless specified otherwise, single-point NMR GIAO calculations were carried out in gas phase[41]. The GIAO NMR results were observed and extracted using GaussView06. Each optimized structure was used for computing the corresponding isotropic shielding constants ( $\sigma_{cal}$ ). The chemical shifts ( $\delta_{cal}$ ) given in the Supporting Information were obtained using Equation 1. For both  $^{13}\text{C}$  NMR calculations, an average of values of equivalent atoms was assumed. For example, a single proton/carbon signal is observed for the two symmetrically aromatic CH groups of bakuchiol. To reduce the systematic error of the calculations, the linear regression analysis of the calculated chemical shifts versus the experimental ones ( $\delta_{exp}$ ) (Equation 2) were performed and the scaled chemical shifts ( $\delta_{scal}$ ) were computed according to Equation 3. As reference had a negligible impact on the linear regression analysis, the fix values of 197 ppm was chosen as TMS shielding constants for

$^{13}\text{C}$ . Computed results were evaluated using mean absolute value ( $|\Delta\delta|$ /ppm, Equation 4); corrected mean absolute error (CMAE/ppm, Equation 5); corrected root mean squared error (CRMSE/ppm, Equation 6); and the Pearson correlation coefficient ( $r^2$ ). The smaller values of CMAE and CRMSE indicate smaller errors and the larger value of  $r^2$  means a stronger correlation between theoretical and experimental data. Error calculations and linear correlations were performed using Microsoft Excel 2013.

$$\delta_{cal} = \sigma_{TMS} - \sigma_{cal} \quad (1)$$

$$\delta_{cal} = a\delta_{exp} + b \quad (2)$$

$$\delta_{scal} = \frac{\delta_{cal} - b}{a} \quad (3)$$

$$|\Delta\delta| = |\delta_{scal} - \delta_{exp}| \quad (4)$$

$$\text{CMAE} = \sum_1^n |\delta_{scal} - \delta_{exp}| / n \quad (5)$$

$$\text{CRMSE} = \sqrt{\sum_1^n (\delta_{scal} - \delta_{exp})^2 / n} \quad (6)$$

### 3. Results and Discussion

#### 3.1. The evaluation of 11 DFT functionals

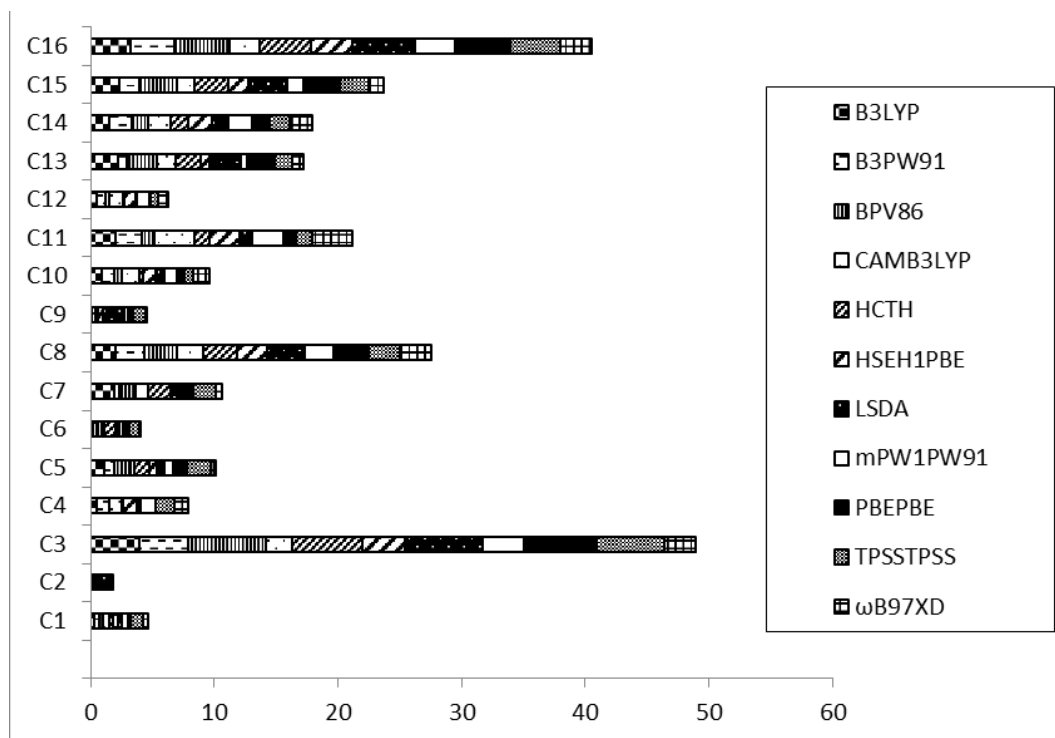
11 Functionals were evaluated, and the results were showed in Table 1 and Figure 2. The functionals were sorted alphabetically by name. Table 1 shows statistical parameters using 11 different DFT functionals coupled with 6-31G(d,p) basis set and Figure 2 illustrates absolute deviations. Overall, the correlation coefficients and error results indicate that the calculations provided a qualitatively accurate description of the  $^{13}\text{C}$  NMR chemical shifts. The CMAE and CRMSE values were in the ranges of 1.44 to 2.62 ppm and 1.72 to 3.53 ppm, respectively. The coefficients of determination ( $r^2$ ) were above 0.9976 for all tested functionals. **C3** and **C16** were consistently observed with the noticeable deviations ranged from 2.18 to 6.28 ppm and 2.39 to 4.98 ppm, respectively (Figure 2). The

two best performers with strong correlations and low errors for  $^{13}\text{C}$  calculations were CAM-B3LYP (CMAE = 1.44 ppm, CRMSE = 1.72

ppm, and  $r^2 = 0.9991$ ),  $\omega\text{B97XD}$  (CMAE = 1.48 ppm, CRMSE = 1.80 ppm, and  $r^2 = 0.9990$ ).

**Table 1.**  $^{13}\text{C}$  NMR chemical shifts of bakuchiol calculated using 11 functionals

Entry	Functional	$\delta(^{13}\text{C})$		
		$r^2$	CMAE	CRMSE
1	B3LYP	0.9987	1.79	2.33
2	B3PW91	0.9988	1.97	2.49
3	BPV86	0.9978	2.36	3.17
4	CAM-B3LYP	0.9991	1.44	1.72
5	HCTH	0.9981	2.23	2.96
6	HSEH1PBE	0.9989	1.91	2.34
7	LSDA	0.9976	2.62	3.53
8	mPW1PW91	0.9989	1.91	2.36
9	PBEPBE	0.9989	1.91	2.34
10	TPSSTPSS	0.9981	2.50	2.94
11	$\omega\text{B97XD}$	0.9990	1.48	1.80



**Figure 2.** Absolute deviations of  $^{13}\text{C}$  chemical shift calculations using 11 functionals.

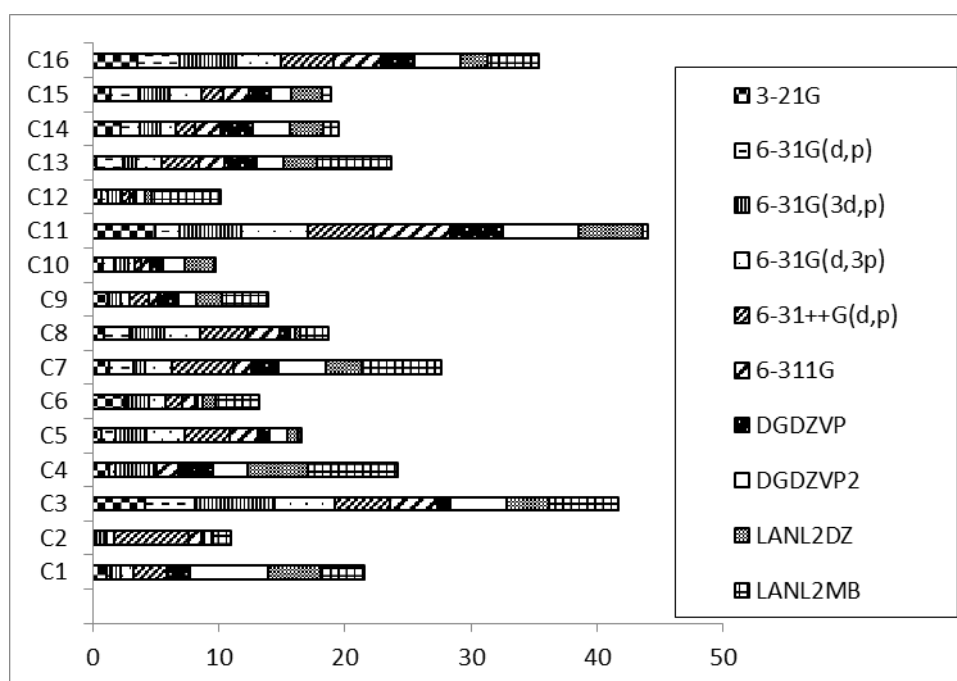
### 3.2. The evaluation of 11 basis sets

11 Basic sets were employed for computing  $^{13}\text{C}$  chemical shifts of bakuchiol. In general, the calculated results were observed with low associated errors and strong linear correlations ( $r^2 \geq 0.9958$ ). CMAE and CRMSE values were

ranged from 1.79 to 4.97 ppm and 2.22 to 5.13 ppm, respectively (Table 3). The largest deviations were found for **C3**, **C11**, and **C16** with CMAE and CRMSE values in the ranges of 1.05 to 6.25 ppm, 0.46 to 6.11 ppm, and 2.13 to 4.47 ppm, respectively (Figure 1).

**Table 2.** The calculated  $^{13}\text{C}$  NMR chemical shifts of **Bakuchiol** in  $\text{CHCl}_3$  using 10 basic sets. All chemical shifts, CMAEs, and CRMSEs are in ppm.

Entry	Basis set	$\delta(^{13}\text{C})$		
		$r^2$	CMAE	CRMSE
1	3-21G	0.9981	2.37	2.67
2	6-31G(d,p)	0.9987	1.79	2.33
3	6-31G(3d,p)	0.9971	2.62	3.21
4	6-31G(d,3p)	0.9975	2.33	2.67
5	6-31++G(d,p)	0.9958	3.35	3.43
6	6-311G	0.9976	1.93	2.71
7	DGDZVP	0.9985	2.19	2.22
8	DGDZVP2	0.9962	4.97	5.13
10	LANL2DZ	0.9970	3.13	3.28
11	LANL2MB	0.9970	3.80	3.81



**Figure 3.** Absolute deviations of  $^{13}\text{C}$  chemical shift calculations using 10 basis sets.

#### 4. Conclusion

We have performed the evaluation of 11 DFT functionals and 11 basis sets using GIAO method on the calculation of  $^{13}\text{C}$  chemical shifts for bakuchiol. Our results showed the two best performing functionals were CAM-B3LYP (CMAEs  $\leq 1.44$  ppm) and  $\omega\text{B97XD}$  (CRMSEs  $\leq 1.80$  ppm), and the best basis set was 6-31G(d,p) (CMAEs  $\leq 1.79$  ppm). In these cases,

excellent correlations between theoretical and experimental data ( $r^2 > 0.9987$ ) were observed. Given such high degree of accuracy achieved in calculating  $^{13}\text{C}$  chemical shifts of bakuchiol, this work can be useful for supporting the assignments of the experimental NMR spectra of bakuchiol and similar retinoid compounds. Further studies on the chemical shift calculations of these compounds are under-investigation.

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