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Theoretical investigation on the ^{1}H and ^{13}C chemical shifts of TRODAT-1 compound with density functional theory and Hartree-Fock computational methods

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Abstract: The present research work investigates the ^{1}H and ^{13}C magnetic chemical shifts of the TRODAT-1 compound by the density functional theory (DFT) and ab-initio computational methods. The molecular structure was optimized at B3LYP and HF computational methods with 6-31G(d), 6-31+G(d), 6-31++G(d),6-31G(d,p), 6-31+G(d,p) and 6-31++G(d,p) basis sets.No imaginary frequencies were shown for considered moleculein vibrational computations. So, it proves the accuracy of our calculations.Good linear relationships are obtained between theory and experiment, which allows correcting the calculated values for systematic errors. The final accuracy of the B3LYP/6-31G(d,p) method amounts to 0.023 ppm for ^{1}H and 0.181 ppm for ^{13}C.

Keywords: DFT study, Ab-initio investigation, NMR study, TRODAT-1, Radiopharmaceutical.

Introduction

Parkinson's disease (PD) is a long-term degenerative disorder of thecentral nervous system that mainly affects themotor system. The symptoms generally come on slowly over time. Early in the disease, the most obvious areshaking,rigidity,slowness of movement, and difficulty with walking.Thinking and behavioral problems may also occur.Dementia becomes common in the advanced stages of the disease. Depression and anxiety are also common occurring in more than a third of people with PD. Other symptoms include sensory, sleep, and emotional problems. The main motor symptoms are collectively called "parkinsonism", or a "parkinsoniansyndrome" [1]. PD is really the second most common neurodegenerative disorder after Alzheimer’s disease.

The recent development of tracers for positron emission tomography (PET) and single photon emission computed tomography (SPECT), in conjunction with dedicated imaging devices, provides valuable tools for in vivo diagnosis and treatment of PD and related neurodegenerative diseases [2]. Studying the central nervous system by receptor specific imaging agents is potentially useful for evaluation of brain function in normal and disease states. Dopamine is one of the neurotransmitters that control normal brain function, including movement, emotion, and other higher level cognitive functions. The most important mechanism for regulating dopamine concentration is the pumping of the dopamine back to the presynaptic neurons through the dopamine transporters (DAT). A significant reduction in the density of these transporters has been reported in patients with Parkinson’s and Alzheimer’s diseases. Thus, measurement of the decrease in the dopamine

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transporters may be a useful indicator of dopamine neuronal loss [3-5]. Tc-99m-TRODAT-1, which binds to the dopamine transporter (DAT) located on the presynaptic nerve endings in striatum, has been reported by Doctor Hank F. Kung as a SPECT imaging compound for diagnosing and monitoring the treatment of Parkinson's disease patients [6].TRODAT-1 kit, all-in-one kit formulation for the preparation of Tc^{99m}-TRODAT-1, is the second radiopharmaceutical being commercialized as imaging dopamine transporter in the world [7].

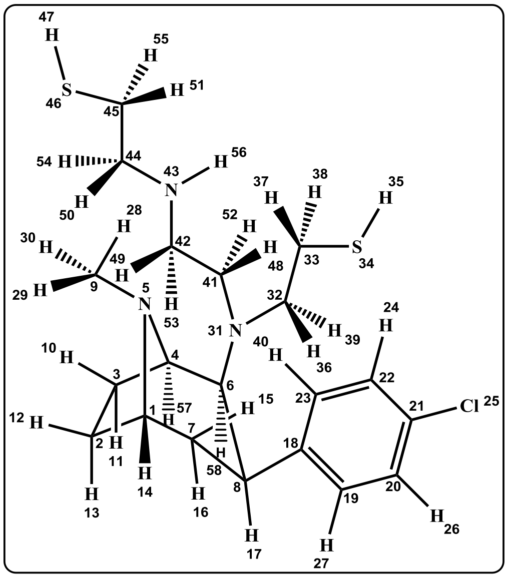
Computational chemistry is a branch of chemistry that uses computer simulation to assist in solving chemical problems. It uses methods of theoretical chemistry, incorporated into efficient computer programs, to calculate the structures and properties of molecules and solids [8].Prediction of the ^{1}H and ^{13}C NMR shifts of organic compounds greatly aids the validation of structure elucidation in synthesized products. The accuracy of the quantum chemical values for CHNO compounds even allows one to identify experimental anomalies with great confidence [9]. The synthesis of TRODAT-1 molecule and preparation of kit forTc^{99m}-TRODAT-1 radiopharmaceutical is done in Pars Isotope Company of the Islamic Republic of Iran.TRODAT-1 compound hasn't been investigated in terms of computational studies, up to now. Here, we study the ^{1}H and ^{13}C NMR chemical shifts of TRODAT-1 molecule by density functional theory (DFT) and ab-initio computational methods.

Results and discussion

The current density induced in the molecular electron density by an external magnetic field is invariant under gauge transformations. In quantum chemical calculations of magnetic properties, however, the issue of gauge invariance is usually limited to the discussion of gauge-origin independence, such as the transformation properties with respect to a special class of gauge transformations. Most of the so far reported calculations of magnetically induced current densities do not satisfy gauge-origin independence due to the use of finite basis sets in the same manner as corresponding calculations of nuclear magnetic shielding constants. The use of gauge-including atomic orbitals (GIAO) also known as London orbitals, represents one, and in our opinion the most elegant possibility to resolve the gauge-origin problem in nuclear magnetic shielding calculations. By employing explicitly magnetic-field-dependent basis functions the gauge-origin dependence of calculated nuclear magnetic shielding constants as well as other magnetic properties can be eliminated. The idea to use field-dependent basis functions to remove the gauge-origin dependence can be traced back to the work of London. It was first used in nuclear magnetic shielding calculations by Hameka and later by Ditchfield and others. However, the actual breakthrough of the GIAO approach is due to the work of Wolinski et al., who demonstrated that modern analytic derivative theory can be efficiently used for the calculation of nuclear magnetic shieldings within the GIAO framework. The GIAO approach has since then been implemented in most of the popular quantum chemical program systems and also extended to computational levels beyond the DFT and Hartree–Focklevels [10-14].

Ab initio calculations have become valuable tools to help in interpreting NMR spectra as well as in deducing from these spectra information on the electronic structure of molecules and polymers. In particular, density functional theory (DFT) schemes offer a good compromise between computational cost and reliability and therefore present the potential to assist in assigning experimental spectra. Indeed, the errors on the chemical shifts are often systematic in nature and they can be corrected using linear scaling procedures. In the case of ^{1}H and ^{13}C chemical shifts, Rablen et al. determined the linear scaling parameters for a collection of exchange-correlation (XC) functional combined with different atomic basis sets and found that the root-mean-square error on the so-predicted chemical shifts in comparison with solution experimental values can be as small as 0.15 ppm. So, DFT has been broadly employed for simulating NMR spectra [15-18].

The molecular structure of the TRODAT-1 (Scheme **1**) was optimized at the B3LYP and HF methods with 6-31G(d), 6-31+G(d), 6-31++G(d),6-31G(d,p), 6-31+G(d,p) and 6-31++G(d,p) levels of theory. The NMR chemical shifts were calculated as the differences of isotropic shielding constants with respect to the TMS reference. To reduce the systematic method-related errors, the same method was employed for both the TRODAT-1 compound and TMS, for the geometry optimization as well as for the evaluation of the shielding tensor. These tensor elements and chemical shifts were evaluated adopting the coupled perturbed Kohn-Sham procedure together with the GIAO approach to ensure origin-independence. Such procedure was employed using the HF approach and DFT with the B3LYP exchange-correlation (XC) functional. The choice of this XC functional is dictated by its usually good performance while it is interesting to study the impact of different percentages of HF exchange (20% for B3LYP).



Scheme 1: The structure of TRODAT-1 compound.

The above list of rather extended atomic basis sets was used. The theoretical values of ^{1}H and ^{13}C chemical shifts of the TRODAT-1 compound obtained using different levels of theory described in the previous section are listed in Tables **1** and **2**. The theoretical chemical shifts data is compared to the experimental values. The Figures **1-4** show the comparison between the theoretical and experimental ^{1}H and ^{13}C chemical shifts of the molecular structure at studied levels of theory. The differences between calculations and experiment are partly not systematic; the linear regressions are characterized by rather large correlation coefficients. In fact, two approaches were adopted in these linear fits. First, all C atoms were considered in the fit; second, the fitness of the H atoms is less than the C atoms. Representing the relationship between the experimental and theoretical results further indicates that theories are misleading in estimating the chemical shift values for the most deshielded H37 and H56 atoms. On the other hand, at the B3LYP level, the intercept is positive while the slope is much smaller than unity, illustrating the impact of the lack of electron correlation. The corrected mean absolute error (CMAE) for the theoretical and experimental chemical shifts data is calculated by following formula [19]:

$$\mathrm{CMAE} = \frac{\sum_{n=1}^{n}\left(\delta_{\mathrm{Theor}} - \delta_{\mathrm{Exp}}\right)}{n}$$

The calculated CMAE data for the compound at studied computational methods is collected in Tables **3** and **4**. Using the linear regression parameters, the B3LYP/6-31G(d,p) approach leads to the CMAE of 0.023 and 0.181 ppm for H and C atoms, respectively. It can be concluded from the data that this method has meaningful chemical shifts for the H and C nucleus of the TRODAT-1 molecule among all studied levels of theory.

Computational methods

All computations have been carried out using the Gaussian 03 software package [20]. The computations employ a variety of levels of theory for comparative purposes. Wave-function based methods considered include Hartree–Fock (HF) and density functional theory (DFT), including the B3LYP functional. Choice of optimal methodology to use was made by performing computations on a training compound, using these wave-function methods in combination with a variety of basis sets, including 6-31G(d), 6-31+G(d), 6-31++G(d),6-31G(d,p), 6-31+G(d,p) and 6-31++G(d,p).

Conclusions

In the present study, the ^{1}H and ^{13}C magnetic chemical shifts of the TRODAT-1 compound were investigated by density functional theory (DFT) and ab-initio methods. The molecular structure was optimized at B3LYP and HF computational methods with 6-31G(d), 6-31+G(d), 6-31++G(d),6-31G(d,p), 6-31+G(d,p) and 6-31++G(d,p) basis sets. All computations were done without any structural restrictions at standard conditions (293.15 K and 1 atmosphere). In vibrational computations, no imaginary frequencies were shown for considered molecule. So, it proves the accuracy of our calculations. The NMR computations were done at mentioned levels of theory. The comparison between the theoretical and experimental chemical shifts for H and C atoms of the TRODAT-1 molecule shows that all studied computational methods are good, but the CMAE computations indicate that the B3LYP/6-31G(d,p) method has meaningful chemical shifts for the H and C nucleus of the TRODAT-1 molecule among all studied computational methods.

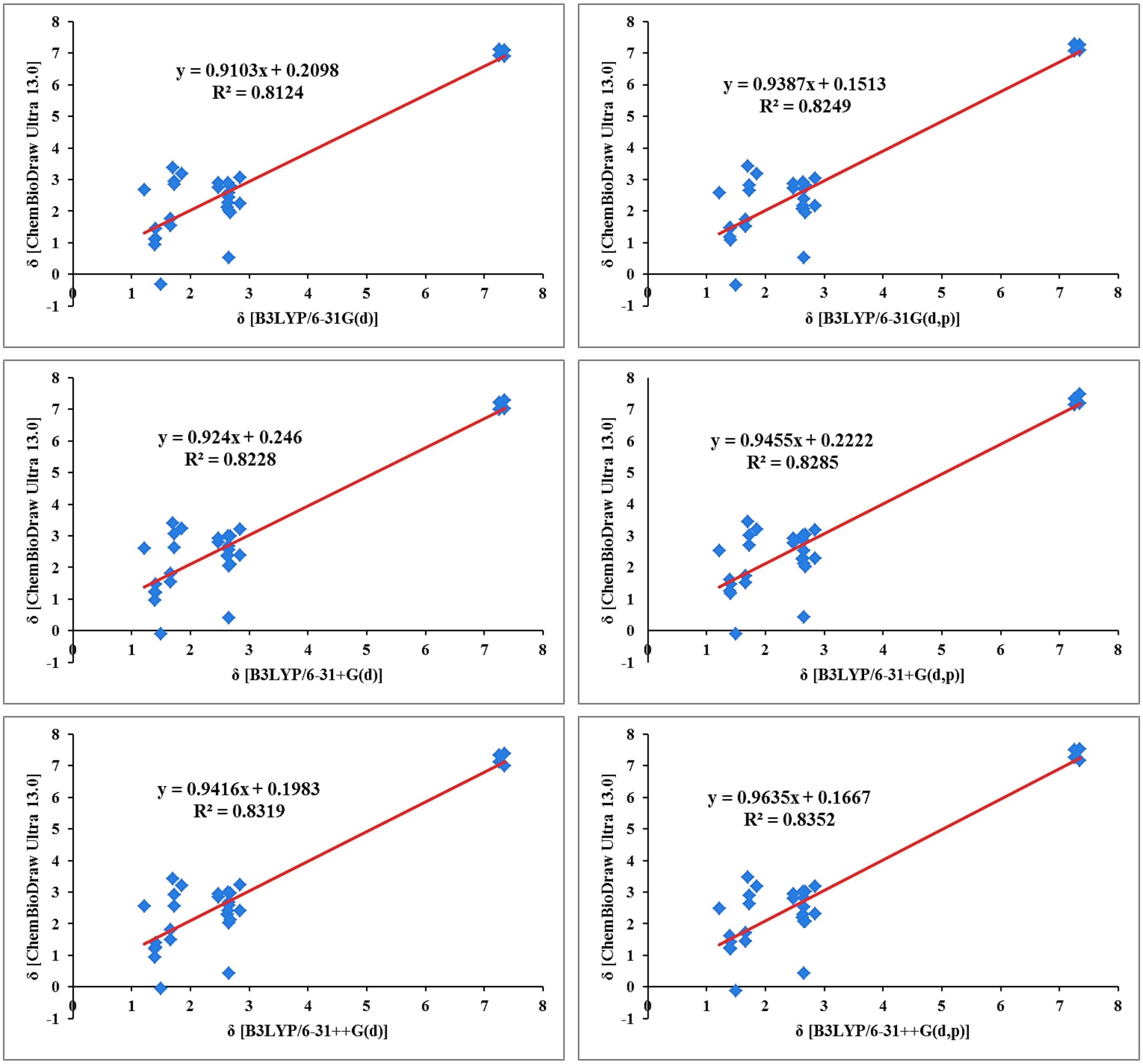


Figure 1: The relationship between theoretical (DFT computations) and experimental ^{1}H chemical shifts of the TRODAT-1 structure.

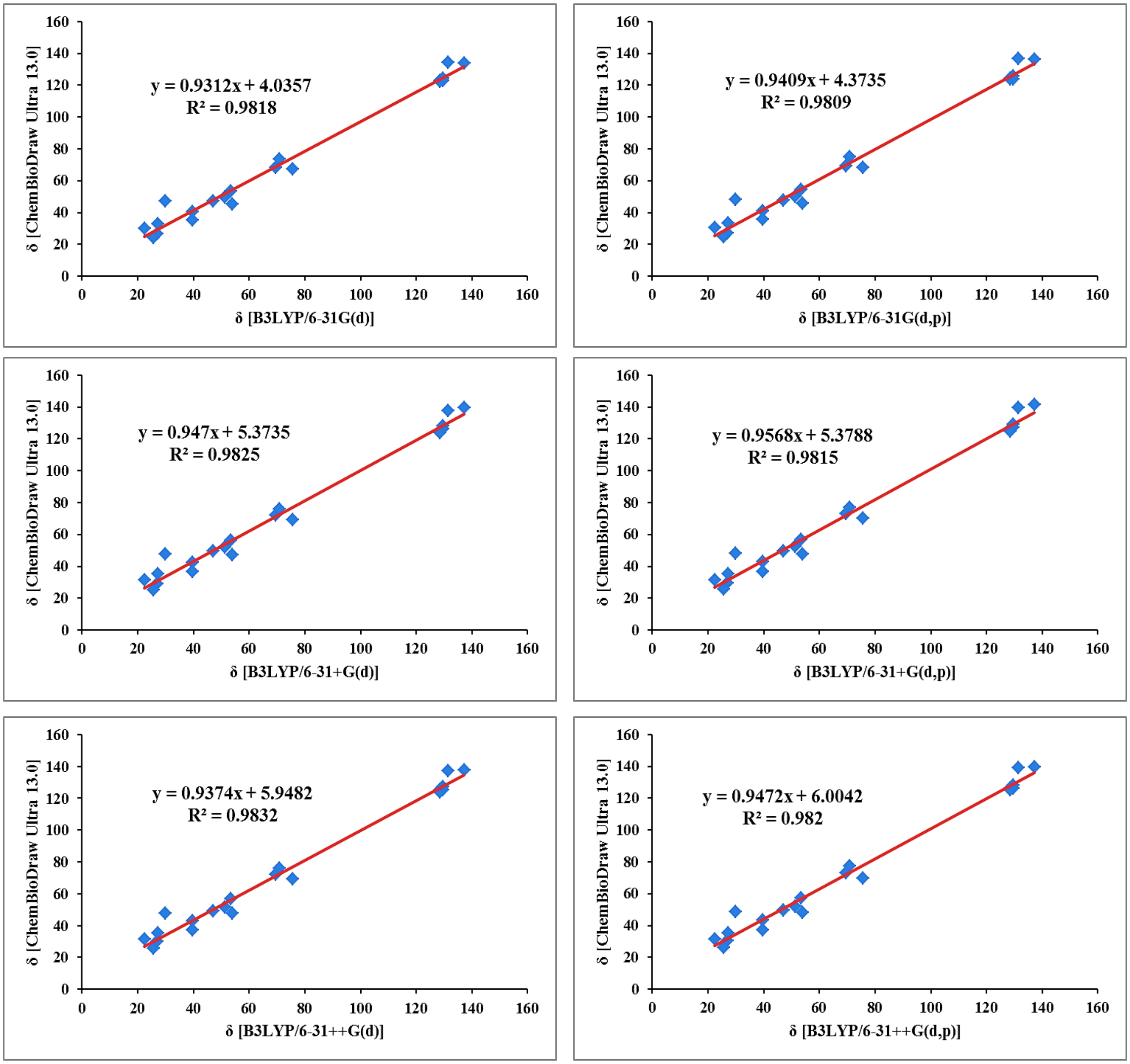


Figure 2: The relationship between theoretical (DFT computations) and experimental ^{13}C chemical shifts of the TRODAT-1 structure.

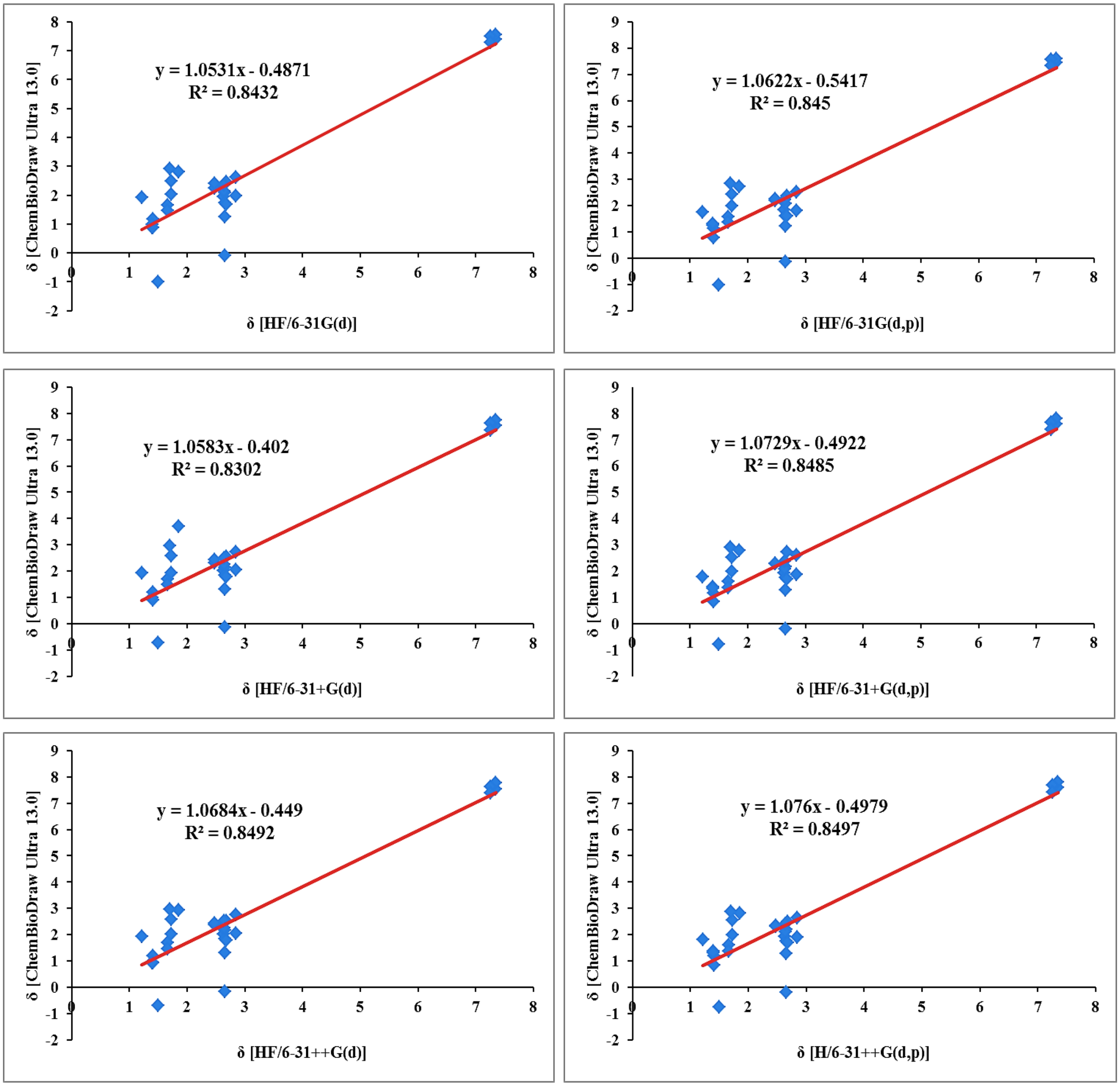


Figure 3: The relationship between theoretical (Hartree-Fock computations) and experimental ^{1}H chemical shifts of the TRODAT-1 structure.

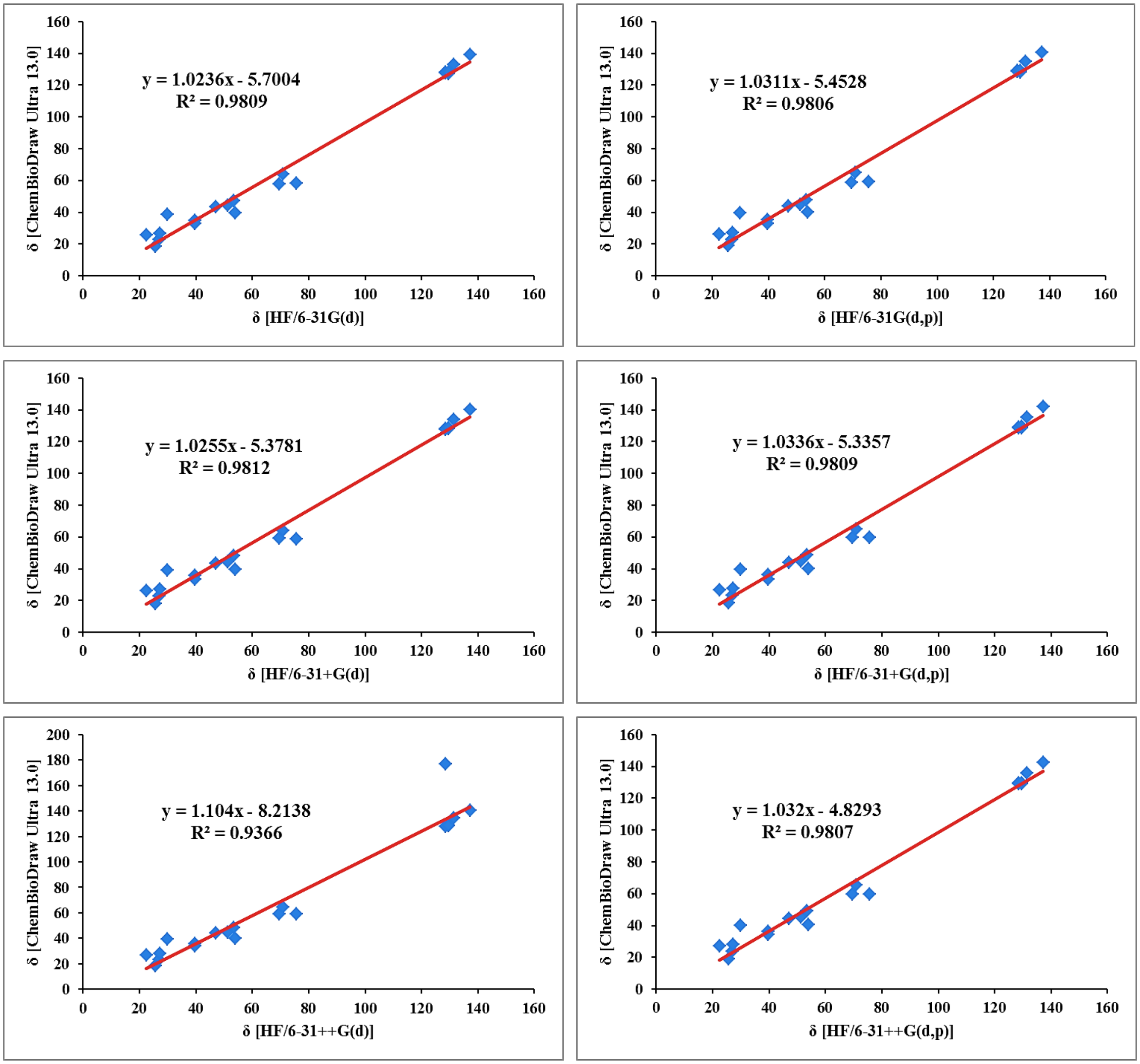


Figure 4: The relationship between theoretical (Hartree-Fock computations) and experimental ^{13}C chemical shifts of the TRODAT-1 structure.

Table 1: The theoretical (DFT computations) and experimental ^{1}H and ^{13}C chemical shifts data of the TRODAT-1 structure.

Nucleus	Chemical Shift (ppm)						
	Theoretical chemical shifts ($\delta = \delta_{TMS} - \delta'$)						δ (Chemical shifts from ChemBioDraw Ultra 13.0)
	B3LYP/6-31G(d)	B3LYP/6-31G(d,p)	B3LYP/6-31+G(d)	B3LYP/6-31+G(d,p)	B3LYP/6-31++G(d)	B3LYP/6-31++G(d,p)	
H-10	1.761	1.723	1.811	1.737	1.796	1.712	1.66
H-11	1.129	1.087	1.194	1.169	1.249	1.208	1.41
H-12	1.540	1.507	1.538	1.512	1.485	1.432	1.66
H-13	1.445	1.456	1.460	1.464	1.399	1.424	1.41
H-14	3.186	3.183	3.232	3.206	3.215	3.177	1.85
H-15	2.928	2.660	2.621	2.705	2.552	2.621	1.73
H-16	2.841	2.811	3.060	3.011	2.927	2.890	1.73
H-17	2.123	2.065	2.349	2.268	2.290	2.202	2.63
H-24	6.908	7.097	7.024	7.201	7.003	7.169	7.35
H-26	7.091	7.266	7.274	7.485	7.375	7.539	7.35
H-27	7.123	7.297	7.214	7.342	7.333	7.503	7.26
H-35	1.116	1.456	1.227	1.622	1.208	1.617	1.40
H-36	2.567	2.701	2.672	2.838	2.678	2.821	2.66
H-37	0.519	0.524	0.408	0.424	0.428	0.421	2.66
H-38	2.031	2.072	2.049	2.115	2.026	2.078	2.66
H-39	2.425	2.388	2.561	2.539	2.567	2.527	2.66
H-40	6.915	7.062	6.996	7.137	7.115	7.255	7.26
H-47	0.938	1.169	0.967	1.253	0.941	1.235	1.40
H-48	2.738	2.723	2.805	2.777	2.834	2.799	2.48
H-49	2.274	2.175	2.392	2.288	2.403	2.294	2.65
H-50	2.246	2.174	2.393	2.298	2.400	2.304	2.85
H-51	2.791	2.818	2.981	3.026	2.972	3.016	2.68
H-52	2.885	2.857	2.923	2.925	2.933	2.935	2.48
H-53	2.898	2.905	2.999	3.001	2.998	3.019	2.65
H-54	3.056	3.043	3.212	3.176	3.220	3.192	2.85
H-55	1.957	1.941	2.087	2.030	2.130	2.066	2.68
H-56	-0.308	-0.347	-0.096	-0.111	-0.051	-0.120	1.50
H-57	3.375	3.425	3.391	3.458	3.424	3.481	1.70
H-58	2.668	2.577	2.604	2.531	2.564	2.487	1.22
C-1	68.103	69.299	72.034	72.923	72.080	72.980	69.60
C-2	26.615	27.014	29.170	29.460	30.026	30.274	27.00
C-3	30.200	30.647	31.513	31.536	31.380	31.496	22.40
C-4	67.097	68.209	69.309	69.973	69.178	69.625	75.70
C-6	73.499	74.948	75.800	76.830	76.072	77.235	70.80
C-7	47.021	48.212	47.471	48.369	47.552	48.481	29.80
C-8	40.388	41.084	42.618	43.041	43.009	43.481	39.60
C-9	35.344	35.661	36.634	36.546	37.013	37.063	39.80
C-18	134.068	136.179	139.812	141.662	137.728	139.753	137.20
C-19	122.716	124.020	126.115	126.974	125.295	126.265	129.50
C-20	122.797	124.071	124.955	126.009	125.163	126.181	128.60
C-21	134.537	136.674	137.726	139.604	137.005	138.943	131.50
C-22	122.344	123.620	123.901	124.825	124.052	125.027	128.60
C-23	124.464	125.767	127.978	128.963	127.048	128.069	129.50
C-32	45.170	45.867	47.263	47.760	47.545	48.080	54.10
C-33	24.341	24.933	25.365	25.665	25.628	26.019	25.60
C-41	49.395	50.106	51.945	52.403	51.585	52.151	51.40
C-42	47.030	47.768	49.424	49.700	49.362	49.773	47.00
C-44	53.374	54.316	56.475	56.954	56.659	57.179	53.40
C-45	32.921	33.533	35.126	35.385	35.159	35.466	27.20

Table 2: The theoretical (Hartree-Fock computations) and experimental ^{1}H and ^{13}C chemical shifts data of the TRODAT-1 structure.

Nucleus	Chemical Shift (ppm)						
	Theoretical chemical shifts ($\delta = \delta_{TMS} - \delta'$)						δ (Chemical shifts from ChemBioDraw Ultra 13.0)
	HF/6-31G(d)	HF/6-31G(d,p)	HF/6-31+G(d)	HF/6-31+G(d,p)	HF/6-31++G(d)	HF/6-31++G(d,p)	
H-10	1.647	1.573	1.688	1.595	1.680	1.602	1.66
H-11	0.876	0.792	0.910	0.832	0.922	0.845	1.41
H-12	1.462	1.374	1.475	1.378	1.462	1.378	1.66
H-13	1.172	1.123	1.207	1.172	1.207	1.182	1.41
H-14	2.820	2.738	3.712	2.798	2.931	2.811	1.85
H-15	2.036	1.985	1.919	1.991	2.029	1.999	1.73
H-16	2.485	2.427	2.574	2.532	2.581	2.544	1.73
H-17	1.952	1.843	2.017	1.916	2.022	1.939	2.63
H-24	7.386	7.437	7.528	7.586	7.537	7.596	7.35
H-26	7.552	7.605	7.754	7.802	7.774	7.817	7.35
H-27	7.514	7.554	7.611	7.653	7.625	7.673	7.26
H-35	0.876	1.255	0.988	1.400	0.945	1.372	1.40
H-36	2.091	2.088	2.141	2.175	2.164	2.199	2.66
H-37	-0.088	-0.149	-0.143	-0.193	-0.156	-0.197	2.66
H-38	1.256	1.217	1.306	1.269	1.299	1.276	2.66
H-39	1.738	1.606	1.835	1.746	1.848	1.755	2.66
H-40	7.282	7.319	7.347	7.383	7.376	7.414	7.26
H-47	0.996	1.310	0.976	1.344	0.937	1.318	1.40
H-48	2.255	2.184	2.325	2.285	2.372	2.329	2.48
H-49	2.144	2.230	2.255	2.091	2.250	2.106	2.65
H-50	1.962	1.816	2.055	1.884	2.059	1.898	2.85
H-51	2.450	2.385	2.560	2.716	2.533	2.491	2.68
H-52	2.414	2.260	2.427	2.296	2.445	2.322	2.48
H-53	2.340	2.230	2.487	2.361	2.516	2.394	2.65
H-54	2.618	2.512	2.735	2.608	2.756	2.643	2.85
H-55	1.668	1.599	1.787	1.683	1.793	1.682	2.68
H-56	-1.008	-1.027	-0.732	-0.771	-0.701	-0.769	1.50
H-57	2.926	2.853	2.968	2.897	2.959	2.889	1.70
H-58	1.910	1.763	1.919	1.786	1.932	1.800	1.22
C-1	57.909	58.844	58.986	59.645	59.205	59.888	69.60
C-2	22.617	22.988	22.874	23.178	23.200	23.612	27.00
C-3	25.797	26.216	26.251	26.474	26.566	26.895	22.40
C-4	58.128	58.943	58.910	59.484	59.067	59.718	75.70
C-6	63.776	64.836	64.125	64.971	64.403	65.346	70.80
C-7	38.797	39.724	38.917	39.565	39.163	39.899	29.80
C-8	34.927	35.475	35.652	36.056	35.754	36.335	39.60
C-9	33.013	33.081	33.548	33.492	34.092	34.106	39.80
C-18	138.933	140.733	140.267	142.017	140.494	142.288	137.20
C-19	127.331	128.275	128.013	128.773	128.176	129.036	129.50
C-20	128.321	129.264	128.237	129.045	176.977	129.415	128.60
C-21	132.976	134.648	133.849	135.435	134.199	135.835	131.50
C-22	127.793	128.738	127.735	128.528	127.983	128.857	128.60
C-23	128.304	129.262	128.535	129.344	128.704	129.613	129.50
C-32	39.322	39.818	39.588	39.997	39.804	40.305	54.10
C-33	18.536	18.989	18.076	18.371	18.556	18.980	25.60
C-41	44.305	44.793	44.549	44.933	44.807	45.299	51.40
C-42	43.428	43.960	43.494	43.715	44.052	44.448	47.00
C-44	47.068	47.779	48.063	48.554	48.425	48.971	53.40
C-45	26.479	27.000	27.297	27.612	27.854	28.186	27.20

Table 3: Linear regression parameters for all H atoms characterizing the relationship between the theoretical and experimental ^{1}H chemical shifts of the TRODAT-1 structure.

Computational Method	$\delta_{Exp} = a \times \delta_{Theor} + b$			CMAE
	a	b	R^2	
B3LYP/6-31G(d)	0.9103	0.2098	0.8124	0.045
B3LYP/6-31G(d,p)	0.9387	0.1513	0.8249	0.023
B3LYP/6-31+G(d)	0.9240	0.2460	0.8228	0.030
B3LYP/6-31+G(d,p)	0.9455	0.2222	0.8285	0.067
B3LYP/6-31++G(d)	0.9416	0.1983	0.8319	0.032
B3LYP/6-31++G(d,p)	0.9635	0.1667	0.8352	0.063
HF/6-31G(d)	1.0531	-0.4871	0.8432	0.336
HF/6-31G(d,p)	1.0622	-0.5417	0.8450	0.365
HF/6-31+G(d)	1.0583	-0.4020	0.8302	0.236
HF/6-31+G(d,p)	1.0729	-0.4922	0.8485	0.285
HF/6-31++G(d)	1.0684	-0.4490	0.8492	0.255
HF/6-31++G(d,p)	1.0760	-0.4979	0.8479	0.282

Table 4: Linear regression parameters for all C atoms characterizing the relationship between the theoretical and experimental ^{13}C chemical shifts of the TRODAT-1 structure.

Computational Method	$\delta_{Exp} = a \times \delta_{Theor} + b$			CMAE
	a	b	R^2	
B3LYP/6-31G(d)	0.9312	4.0357	0.9818	0.844
B3LYP/6-31G(d,p)	0.9409	4.3735	0.9809	0.181
B3LYP/6-31+G(d)	0.9470	5.3735	0.9825	1.617
B3LYP/6-31+G(d,p)	0.9568	5.3788	0.9815	2.314
B3LYP/6-31++G(d)	0.9374	5.9482	0.9832	1.512
B3LYP/6-31++G(d,p)	0.9472	6.0042	0.9820	2.262
HF/6-31G(d)	1.0236	-5.7004	0.9809	4.027
HF/6-31G(d,p)	1.0311	-5.4528	0.9806	3.247
HF/6-31+G(d)	1.0255	-5.3781	0.9812	3.567
HF/6-31+G(d,p)	1.0336	-5.3357	0.9809	2.956
HF/6-31++G(d)	1.1040	-8.2138	0.9366	0.841
HF/6-31++G(d,p)	1.0320	-4.8293	0.9807	2.563

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