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ORIGINAL ARTICLE

DFT investigations of the ground and excited state geometries of the benzothiazine and benzisothiazol based anticancer drugs

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KEYWORDS

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PBE0

Abstract Density-functional theory (DFT) is a prevailing method for predicting the geometry of organic compounds. The ground state geometries have been calculated at the B3LYP/6-31G** and PBE0/6-31G** levels of theories. The excited state geometries have been computed at time dependent DFT (TD-DFT) by using TD-B3LYP/6-31G** and TD-PBE0/6-31G** levels of theories. It has been revealed that the PBE0 functional is better than B3LYP to predict the S–O and S–C bond lengths. Both of the functionals could not reproduce the S–N bond lengths. The B3LYP is good to imitate the C–N and C–O bond lengths. The C–C and C–Cl bond lengths have been impersonated by both the functionals. Moreover, it has also been revealed that the S–N bond length elongated while the C–N bond length shortened from ground to excited state.

1. Introduction

Malignant tumor, i.e., cancer is a dreadful menace to human beings (Ye et al., 1999). The progress of potential and effective anticancer drugs has become one of the most intensely persuaded goals of contemporary medicinal chemistry. The role of schiff bases as intermediate products in biologically important reactions is well known (Rozwadowski et al., 2005). Benzothiazines find a number of applications in pharmaceutical chemistry (Gupta et al., 1985, 1993, 2002; Lombardino and Wiseman, 1972). The benzisothiazol derivatives are also excellent antimycobacterial and antitumor compounds.

There is no systematic structural study on 2H-1,2-benzothiazine-3-carboxylic acid, 4-hydroxy-2-(2-oxopropyl)-methyl ester, 1,1-dioxide (drug 1) which has been derived from benzothiazine of Chiaini et al. (1971) and Lorenzo et al. (1994), 2-[2-(3-chlorophenyl)-2-oxoethyl]-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (drug 2) (Khalid et al., 2010a,b) and (3-chlorophenyl)(4-hydroxy-1,1-dioxido-2H-1,2-benzothiazine-3-yl)methanone (drug 3) (Khalid et al., 2010a,b, p. o885), see Fig. 1.

The PBE1PBE (also called PBE0) functional has been recognized to provide reliable predictions and interpretations of the molecular geometries for sulfur compounds in good agreement with experimental data for organic molecules bearing

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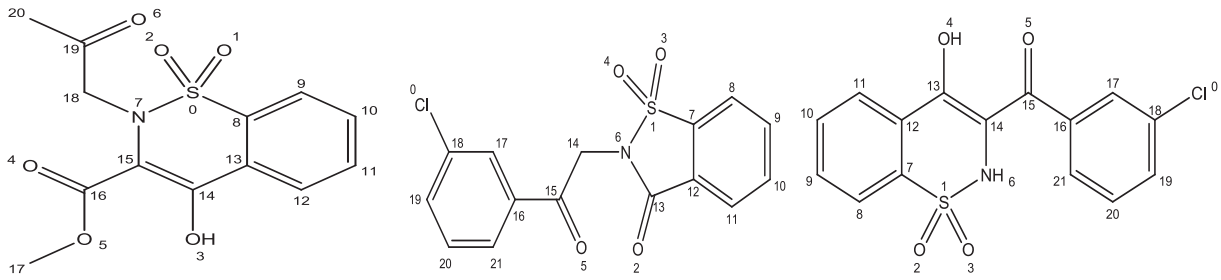

Figure 1 Investigated drugs in the present study.

sulfur atoms (Perpète et al., 2006; Tang and Zhang, 2011; Jacquemin and Perpète, 2006). In the present study we have shed light on the ground and excited state geometries of the selected compounds. We pointed out which functional B3LYP or PBE0 is good to predict the C–S, O–S, N–S, C–N and C–O bond lengths as well as the bond angles that originated from the C, N, O and S elements.

2. Computational details

It is well reported that the density-functional theory (DFT) is a useful method for the investigation of the geometries of molecules (Scott and Radom, 1996; Irfan et al., 2009; Jacob and Fiscker, 2002; Andersen et al., 1999; Song et al., 2005). The ground state geometry optimizations were performed with Becke–Lee–Yang–Parr's three-parameter hybrid functional (B3LYP) (Becke, 1993) and PBE0 (Perdew et al., 1996, 1997; Adamo and Barone, 1999) with 6-31G** basic set (Hehre et al., 1986). All calculations were performed with the Gaussian 09W program suit (Frisch, 2009). The excited state geometries have been computed by time dependent DFT (TD-DFT) (Bauernschmitt and Ahlrichs, 1996; Casida et al., 1998; Stratmann et al., 1998; Scalmani et al., 2006; Furche and Ahlrichs, 2002) by using TD-B3LYP/6-31G** and TD-PBE0/6-31G** levels of theories.

3. Results and discussion

3.1. Geometries

The bond lengths and bond angles of drug 1 have been presented in Table 1 along with the experimental data of ground state geometry. B3LYP and PBE0 overestimate the S_0–O_1 0.035, 0.019 Å, S_0–N_7 0.056, 0.038 Å, S_0–C_8 0.027 and 0.012 Å, respectively, compared to experimental data (Chiaini et al., 1971; Lorenzo et al., 1994). B3LYP and PBE0 underestimate the C_{17}–O_5 0.012, 0.023 Å, C_{14}–O_3 0.012 and 0.022 Å, respectively. B3LYP and PBE0 underestimate the C_{15}–N_7, 0.010, 0.018 Å, C_{18}–N_7 0.012 and 0.023 Å, respectively. The excited state bond lengths are analogous at both the levels of B3LYP and PBE0. Generally, C_{16}–O_4, C_{16}–O_5, and S_0–N_7 excited state bond lengths are elongated to 0.014, 0.017, and 0.091 Å, respectively, while C_{19}–O_6, C_{15}–N_7, and C_{18}–N_7 shortened to 0.012, 0.025, 0.046 Å, respectively, at B3LYP/6-31G** level of theory. The S_0–O_1, C_{16}–O_4, C_{16}–O_5, and S_0–N_7 excited state bond lengths are elongated to 0.016, 0.018, 0.026, and 0.109 Å, respectively, while C_{19}–O_6, C_{15}–N_7, and C_{18}–N_7 shortened to 0.008, 0.017, 0.033 Å, respectively, at PBE0/6-31G** level of theory.

Table 1 Bond lengths (Å) and bond angles (degree) of drug 1 at B3LYP/6-31G** and PBE0/6-31G** levels of theories.

	B3LYP[a]	PBE0[b]	Exp	B3LYP[c]	PBE0[d]
Bond lengths					
S_0–O_1	1.469	1.453	1.434	1.469	1.469
C_{16}–O_4	1.239	1.235	1.230	1.253	1.253
C_{17}–O_5	1.440	1.429	1.452	1.436	1.436
C_{14}–O_3	1.333	1.323	1.345	1.326	1.326
C_{19}–O_6	1.214	1.210	1.212	1.202	1.202
C_{16}–O_5	1.343	1.334	1.325	1.360	1.360
S_0–N_7	1.690	1.672	1.634	1.781	1.781
S_0–C_8	1.784	1.769	1.757	1.763	1.763
C_{15}–N_7	1.424	1.416	1.434	1.399	1.399
C_{18}–N_7	1.461	1.450	1.473	1.416	1.417
Bond angles					
O_1–S_0–O_2	120.62	120.83	119.25	120.20	120.20
N_7–S_0–C_8	100.56	100.71	102.07	98.83	98.83
S_0–N_7–C_{15}	115.50	115.33	114.91	117.33	117.33
C_{15}–N_7–C_{18}	120.89	120.69	119.38	123.56	123.56
S_0–C_8–C_9	120.06	120.22	121.43	118.01	118.02
S_0–C_8–C_{13}	117.91	117.81	116.52	119.45	119.44
N_7–C_{15}–C_{14}	121.46	121.64	120.99	115.52	115.52
N_7–C_{18}–C_{19}	115.35	114.98	114.36	113.55	113.55
O_3–C_{14}–C_{15}	122.50	122.54	123.04	118.07	118.07
O_3–C_{14}–C_{13}	114.78	115.12	113.34	118.11	118.10
O_6–C_{19}–C_{18}	121.96	121.75	121.98	121.96	121.75
O_6–C_{19}–C_{20}	122.57	122.75	122.74	122.57	122.75
C_{17}–O_5–C_{16}	115.62	115.20	115.78	115.62	115.20
O_4–C_{16}–O_5	121.79	121.87	123.75	121.78	121.87
O_5–C_{16}–C_{15}	114.78	114.79	113.78	114.78	114.79

Exp = experimental data at ground state (Chiaini et al., 1971; Lorenzo et al., 1994).
[ab] Ground state.
[cd] Excited state.

All the angles O–S–O, N–S–C, N–C–C, O–C–C, O–C–O, and S–C–C deviate by $<2°$ compared to experimental data computed at B3LYP/6-31G** and PBE0/6-31G** levels of theories which disclosed that both of the levels are good to reproduce the bond angles. The excited state bond angles of C_{15}–N_7–C_{18} and O_3–C_{14}–C_{13} are 2.67° and 3.33° larger, respectively, compared to ground state. The excited state bond angles of S_0–C_8–C_9, N_7–C_{15}–C_{14}, and O_3–C_{14}–C_{15} are 2.05°, 5.94°, and 4.43° smaller, respectively, compared to ground state at

Table 2 Bond lengths (Å) and bond angles (degree) of drug 2 at B3LYP/6-31G** and PBE0/6-31G** levels of theories.

	B3LYP[a]	PBE0[b]	Exp	B3LYP[c]	PBE0[d]
Bond lengths					
S_1–O_3	1.462	1.453	1.428	1.461	1.460
C_{15}–O_5	1.215	1.211	1.206	1.288	1.288
C_{13}–O_2	1.216	1.211	1.207	1.219	1.217
N_6–C_{13}	1.394	1.388	1.387	1.395	1.395
S_1–N_6	1.728	1.708	1.671	1.742	1.743
S_1–C_7	1.786	1.772	1.755	1.787	1.787
N_6–C_{14}	1.446	1.436	1.456	1.445	1.445
C_{18}–Cl_0	1.757	1.738	1.740	1.764	1.764
Bond angles					
O_4–S_1–O_3	118.99	119.01	117.00	119.84	119.84
N_6–S_1–C_7	91.20	91.42	92.64	90.90	90.90
S_1–N_6–C_{13}	115.19	115.47	115.43	114.89	114.89
C_{14}–N_6–C_{13}	121.96	121.59	122.70	121.89	121.88
S_1–C_7–C_8	126.88	126.95	127.13	126.61	126.60
S_1–C_7–C_{12}	110.51	110.50	109.90	110.80	110.80
N_6–C_{14}–C_{15}	112.16	111.74	111.71	114.02	114.01
N_6–C_{13}–C_{12}	109.05	108.83	108.81	109.29	109.29
O_3–S_1–C_7	112.66	112.77	112.54	111.88	111.87
O_4–S_1–N_7	110.09	109.85	108.98	108.19	108.18
O_2–C_{13}–C_{12}	126.92	127.13	127.45	127.32	127.32
O_2–C_{13}–N_6	124.02	124.02	123.68	123.38	123.38
O_5–C_{15}–C_{16}	121.67	121.69	121.92	124.86	124.86
O_5–C_{15}–C_{14}	120.28	120.30	120.69	110.86	110.87
Cl_0–C_{18}–C_{17}	119.26	119.34	119.19	118.67	118.66
Cl_0–C_{18}–C_{19}	119.45	119.52	118.06	118.63	118.63

Exp = experimental data at ground state (Khalid et al., 2010a,b).
[ab] Ground state.
[cd] Excited state.

Table 3 Bond lengths (Å) and bond angles (degree) of drug 3 at B3LYP/6-31G** and PBE0/6-31G** levels of theories.

	B3LYP[a]	PBE0[b]	Exp	B3LYP[c]	PBE0[d]
Bond lengths					
S_1–O_2	1.462	1.454	1.424	1.459	1.460
C_{15}–O_5	1.257	1.252	1.250	1.273	1.275
C_{13}–O_4	1.322	1.312	1.327	1.334	1.336
Cl_0–C_{18}	1.759	1.739	1.739	1.766	1.766
S_1–N_6	1.681	1.664	1.604	1.759	1.759
S_1–C_7	1.788	1.780	1.747	1.781	1.782
C_{14}–N_6	1.431	1.436	1.422	1.341	1. 342
Bond angles					
O_2–S_1–O_3	121.52	121.65	118.25	120.85	120.86
N_6–S_1–C_7	100.59	100.66	101.04	98.61	98.61
S_1–N_6–C_{14}	117.62	117.25	119.33	125.03	125.05
S_1–C_7–C_{12}	118.42	118.35	117.44	120.61	120.61
O_2-S_1-N_6	106.79	106.90	108.38	105.11	105.11
O_3–S_1–C_7	108.72	108.63	106.32	110.36	110.36
N_6–C_{14}–C_{15}	120.49	120.87	120.78	119.02	119.00
N_6–C_{14}–C_{13}	120.23	120.35	118.69	121.34	121.36
O_5–C_{15}–C_{16}	117.99	118.12	117.93	129.91	129.91
O_5–C_{15}–C_{14}	119.32	119.37	119.18	107.60	107.61
O_4–C_{13}–C_{14}	121.79	121.80	122.35	116.26	116.26
O_4–C_{13}–C_{12}	115.34	115.76	115.07	119.86	119.86
Cl_0–C_{18}–C_{19}	119.34	119.42	119.31	118.27	118.27
Cl_0–C_{18}–C_{17}	119.40	119.49	119.03	119.11	119.12

Exp = experimental data at ground state (Khalid et al., 2010a,b, p. o885).
[ab] Ground state.
[cd] Excited state.

B3LYP/6-31G** level of theory. The excited state bond angles of C_{15}–N_7–C_{18} and O_3–C_{14}–C_{13} are 2.87° and 2.99° larger, respectively, compared to ground state. The excited state bond angles of S_0–C_8–C_9, N_7–C_{15}–C_{14}, and O_3–C_{14}–C_{15} are 2.20°, 6.12°, and 4.47° smaller, respectively, compared to ground state at PBE0/6-31G** level of theory.

The experimental and computed bond lengths and bond angles of drug 2 have been tabulated in Table 2. B3LYP (PBE0) overestimate the S_1–O_3, S_1–N_6, S_1–C_7 and C_{18}–Cl_0 as 0.034 Å (0.025 Å), 0.057 Å (0.034 Å), 0.031 Å (0.017 Å) and 0.017 Å, respectively, compared to experimental geometries (Khalid et al., 2010a,b). B3LYP and PBE0 underestimate the N_6–C_{14}, as 0.010 and 0.020 Å, respectively. The excited state bond lengths are analogous at both the levels. Generally, C_{15}–O_5, and S_1–N_6 of excited state bond lengths are elongated to 0.073 and 0.014 Å, respectively, at B3LYP/6-31G** level of theory. The C_{15}–O_5, S_1–N_6, S_1–N_6, and C_{18}–Cl_0 of excited state bond lengths are elongated to 0.077, 0.035, 0.015, and 0.026 Å, respectively, at PBE0/6-31G** level of theory.

We have observed that all the angles, i.e., O–S–O, N–S–C, N–C–C, O–C–C, O–C–O, S–C–C and Cl–C–C are in good agreement with experimental data. The excited state bond angle of O_5–C_{15}–C_{16} is almost 3.19° larger while O_5–C_{15}–C_{14} is 9.42° smaller than the ground state at both the levels of theories.

In Table 3, we have tabulated the experimental and computed bond lengths and bond angles of drug 3. B3LYP overestimate the S_1–O_2, C_{18}–Cl_0, S_1–N_6, and S_1–C_7 as 0.038, 0.020, 0.077 and 0.041 Å, respectively, compared to experimental bond lengths (Khalid et al., 2010a,b, p. o885). PBE0 overestimate the S_1–O_2, S_1–N_6, and S_1–C_7 as 0.030, 0.060, and 0.033 Å, respectively, compared to experimental data. PBE0 underestimate the C_{13}–O_4, as 0.015 Å. Usually, C_{15}–O_5, and S_1–N_6 of excited state bond lengths are elongated to 0.016 and 0.078 Å, respectively, while C_{14}–N_6 shortened to 0.09 Å compared to ground state at B3LYP/6-31G** level of theory. C_{15}–O_5, C_{13}–O, C_{18}–Cl_0 and S_1–N_6 of excited state bond lengths are elongated to 0.023, 0.020, 0.027 and 0.095 Å, respectively, while C_{14}–N_6 shortened to 0.094 Å compared to ground state at PBE0/6-31G** level of theory.

We noticed that B3LYP and PBE0 overestimate bond angles, i.e., O_1–S_1–O_2 and O_3–S_1–C_7 as 3.27° and 2.40°, respectively. The excited state bond angles of S_1–N_6–C_{14}, S_1–C_7–C_{12}, O_5–C_{15}–C_{16}, and O_4–C_{13}–C_{12}, are almost 7.41°, 2.19°, 11.92°, and 4.52° larger while O_5–C_{15}–C_{14} and O_4–C_{13}–C_{14} are 11.72° and 5.53° smaller, respectively, than the ground state at the B3LYP/6-31G** and PBE0/6-31G** levels of theories.

We have observed that B3LYP is not good to predict the S–O, S–N and S–C bond lengths while PBE0 is reliable to envisage the S–O and S–C bond lengths up to some extent. It was also revealed that B3LYP is good to reproduce the C–N and C–O bond lengths. Both the functionals are good to predict C–C and C–Cl bond lengths. B3LYP would be a better choice if investigated compounds have C–N, C–O, C–C or C–Cl. But selection of PBE0 to expect the S–O and S–C might be good but not for all the cases. Both of the functionals are not reliable to imitate S–N experimental data. Moreover, it has also been

revealed that S–N bond length elongated while C–N bond length shortened from ground to excited state. In the excited state, a major change in O–C–C bond angles toward superior or inferior has been observed compared to the ground state especially with the carbonyl angles.

4. Conclusions

In the framework of our present theoretical investigation, we can draw the following conclusions:

(a) B3LYP is not good to predict the S–O, S–N and S–C bond lengths while PBE0 is reliable to envisage the S–O and S–C bond lengths.
(b) The S–N bond length elongated while the C–N bond length shortened from ground to excited state.
(c) In the excited state, a major change in O–C–C bond angles toward superior or inferior has been observed compared to the ground state especially with the carbonyl angles.
(d) B3LYP is good to reproduce the C–N and C–O bond lengths.
(e) Both the functionals are good to predict C–C and C–Cl bond lengths.
(f) B3LYP would be a better choice if investigated compounds have C–N, C–O, C–C or C–Cl but selection of PBE0 is expected to predict S–O and S–C in a reasonable manner but not for all the cases.
(g) Both of the functionals are not reliable to imitate S–N experimental data.

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