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Ab initio and density functional study on singlet and triplet states of artemisinin

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Abstract

Calculations on the singlet (S_0) and triplet (T_1) states of artimisinin were carried out to study its singlet–triplet excitations using several levels of theory. Geometries of the singlet and the triplet states were at first optimized at Hartree–Fock (HF) level using 3-21g basis. An additional calculation was performed for the triplet state using the ground-state geometry. The adiabatic transition (ΔE_{ad}) of -4.62 kcal/mol was obtained from the energy difference of S_0 and T_1 at their optimized geometries. The vertical transition (ΔE_V) of 90.96 kcal/mol was computed from the energy difference of S_0 and T_1 at the singlet optimized geometry. The result suggests that artimisinin would readily become diradical under normal condition which is in contrast to the experiments. Thus, B3LYP density functional theory calculations using 6-31g* basis were performed to confirm the HF results. In contrast to the HF calculations, the ΔE_{ad} and ΔE_V of 37.42 and 96.53 kcal/mol were obtained, respectively. Geometry optimizations at B3LYP level using 6-31g* basis were also performed on both singlet and triplet. Using B3LYP's geometries, the Møller–Plesset second order perturbation theory (MP2) were applied to the two states and in respective order ΔE_{ad} and ΔE_V of 50.81 and 117.48 kcal/mol were reported. In summary, HF theory is not sufficient to estimate the adiabatic transition of this endoperoxide compound, and correlated calculations would be required.

Keywords: Artemisinin; Ab initio calculation; Density functional calculation; Singlet–triplet splitting

Artemisinin, a compound isolated from chinese herb [1], has a unique structure with an endoperoxide linkage. This compound and its derivatives were used as antimalarial drugs. One of the proposed mechanism for its antimalarial activity [2–4] suggested that ferrous ions (Fe^{2+}) contained in the malaria parasites reduce the endoperoxide linkage of artemisinin to form an oxy-radical and in a further step to produce an intermediate radical center at C_4 (see Fig. 1).

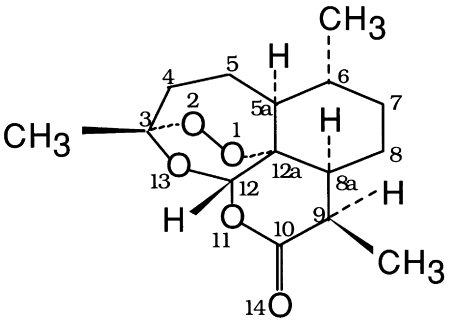

Fig. 1. Stereochemistry and atomic numbering scheme of artemisinin.

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Evidence for the importance of the C_4 position can be seen from the fact that derivatives with β-substituents at C_4 are at least 12–200 times more active than the corresponding C_4 α-substituted derivatives [5].

Without the present of ferrous ions, the oxy-radical intermediate of artemisinin has radical centers at the position O_1 and O_2. The electronic state of this oxy-radical intermediate can either be described by an open-shell singlet or triplet wavefunction. The triplet state would normally be energetically favorable and, therefore, is a good choice for representing the electronic state of the oxy-radical intermediate. Thus, the energetic profile of the electronic transition between the inactive form, the singlet ground state (closed-shell singlet), and the oxy-radical intermediate of artemisinin can be understood from electronic structures of the corresponding singlet and triplet states of artemisinin. It is possible that this singlet–triplet energy gap can be used for predicting bioactivity of artemisinin derivatives. According to the size of the molecule, the Hartree–Fock (HF) method seems to be an appropriate choice for the study. However, singlet–triplet splittings from the HF theory are usually too small by about 20 kcal/mol, which corresponds to the electron correlation energy of the broken electron pair involved in the dioxo-bond [6,7], e.g. high-level correlated methods were necessary to reproduce accurately the energy difference between $^3\Sigma_g^-$ and $^1\Delta_g$ electronic states of O_2 [8]. These methods are computationally very demanding and their use is, therefore, prohibited for investigations on molecules of the size of artemisnin. An interesting alternative offers density functional theory (DFT) which has been shown to reproduce energy differences between singlet and triplet states of systems involving first transition row elements within an accuracy comparable to Møller–Plesset second order perturbation theory (MP2) [9]. It is also the aim of this work to investigate the reliability of DFT in the context of singlet–triplet splittings of artemisinin.

All quantum chemical calculations were carried out using the Gaussian 92/DFT suite of programs [10]. For the density functional we selected the B3LYP hybrid parameterization [11]. Open-shell MP2 calculations were based on both the spin-restricted HF (ROHF) and the UHF method. Throughout all unrestricted calculations on the triplet state, spin contamination was found to be very low with a deviation of $< S^2 >$ of at most 0.03 from the theoretical value of 2.

Table 1
Vertical and adiabatic singlet–triplet splittings of artemisinin using the HF, B3LYP and MP2 methods

Method	Basis set	Vertical transition (kcal/mol)	Adiabatic transition (kcal/mol)
HF/3-21G optimized geometries			
RHF/UHF	3-21G	90.96	– 4.62
RHF/ROHF	3-21G	—	– 0.76
RHF/UHF	6-31G*	91.53	– 5.88
B3LYP	6-31G*	96.53	37.42
B3LYP/6-31G* optimized geometries			
B3LYP	6-31G*	96.31	31.24
RMP2/UMP2	6-31G*	117.63	50.73
RMP2/ROMP2	6-31G*	117.48	50.81

In a first step, we performed geometry optimization at the HF level on the lowest singlet and triplet electronic states of artemisinin, employing the 3-21G basis set. Surprisingly, it was found that at this level of theory the triplet state is lower in energy by 4.6 kcal/mol as compared with the singlet state (see Table 1).

The optimized geometries (compare with Fig. 2) show that the O_1–O_2 bond of the endoperoxide bridge is indeed opened in going from the singlet to the triplet state showing a large separation of both oxygen atoms of about 2.62 Å. Spin densities of the triplet state confirm the existence of two radical electrons at these oxygen atoms. Whereas the C–O bonds of the endoperoxide bridge are shortened considerably by about 0.1 Å, especially the C_3–C_4 bond becomes stretched by more than 0.05 Å with a bond length of 1.60 Å upon excitation into the triplet state. Bond length elongations are visible for the C_{12}–C_{12a} bond as well as for the C_3–C_4. Bond length shortenings of about 0.01 Å can be observed for C_{12}–O_{13} and C_{12}–O_{11} distances. The distances in the cyclohexane ring remain unchanged upon excitation. Changes of the bond angles in triplet state can be observed around O_2 of the dioxo bond. Interestingly, the position of O_1 is kept constant (O_1–C_{12a}–C_{12}). Broad changes of the torsional angles show the rearrangement of the whole molecular skeleton owing to the opening of the strained O–O bond.

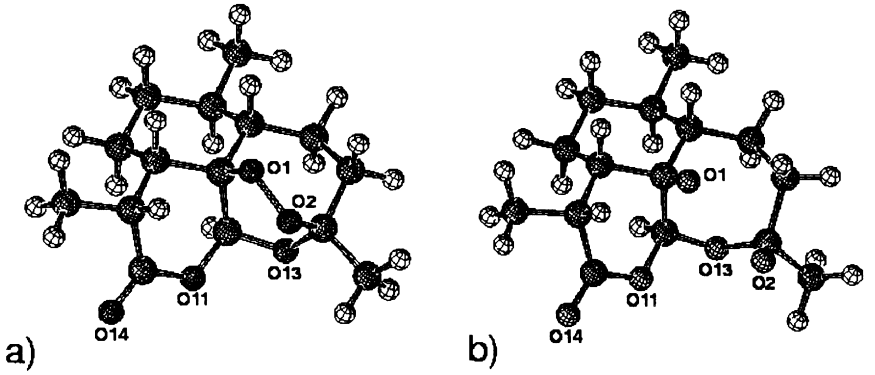

Fig. 2. B3LYP/6-31G* optimized geometries of artemisinin in its: (a) singlet; and (b) triplet state.

In a further step we included electron correlation effects using B3LYP/6-31G* single point calculations at the HF/3-21G optimized singlet and triplet geometries. In these calculations, the triplet state was found to be 37.4 kcal/mol higher in energy than the singlet state (Table 1). The unusually large difference of 42.0 kcal/mol in the singlet–triplet splittings obtained at the HF/3-21G and B3LYP/6-31G* levels cannot be attributed to the use of different basis sets as demonstrated by HF/6-31G* single point calculations which confirm the HF/3-21G results (see Table 1). Obviously, DFT lowers the energy of the singlet ground state in comparison to HF by roughly twice the correlation energy of a single electron pair. In contrast, HF and B3LYP vertical singlet–triplet excitation energies at the singlet geometry are in remarkable agreement with values of 91.5 and 96.5 kcal/mol,

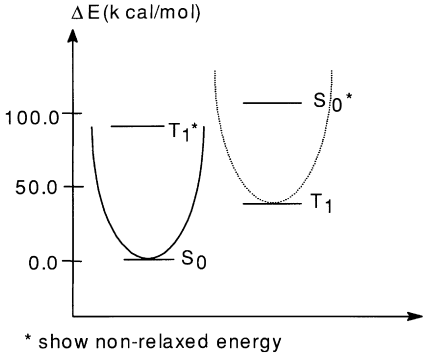

Fig. 3. Energy diagram of singlet and triplet state excitation.

respectively (see Table 1 and Fig. 3). Obviously, relaxation of ring strain plays an important role in the energetics of the opening of the endoperoxide bridge which influences significantly the singlet–triplet

Table 2
Most important structural parameters for the singlet and triplet states of artemisinin at the B3LYP/6-31G* optimized geometries (distances in Å and angles in degrees)

Bond length			Bond angle			Torsional angle		
	Singlet	Triplet		Singlet	Triplet		Singlet	Triplet
C_3–C_4	1.547	1.605	C_4–C_3–O_{13}	109.4	110.4	C_4–C_3–O_{13}–C_{12}	– 89.5	– 73.4
C_3–C_{13}	1.436	1.452	C_3–O_{13}–C_{12}	114.1	121.7	C_3–O_{13}–C_{12}–C_{12a}	27.3	41.8
C_{12}–C_{12a}	1.529	1.562	O_1–C_{12a}–C_{12}	111.3	111.6	O_2–O_1–C_{12}–C_{12a}	11.7	29.3
O_1–C_{12a}	1.477	1.360	O_2–O_1–C_{12a}	111.6	102.7	C_3–O_2–O_1–C_{12a}	47.9	31.1
O_1–O_2	1.462	2.625	O_1–O_2–C_3	108.3	88.1	O_1–O_2–C_3–C_4	46.9	57.8
O_2–C_3	1.414	1.330	O_2–C_3–C_4	111.9	105.7	O_1–C_{12a}–C_{12}–O_{11}	73.1	54.4
C_{12}–O_{13}	1.396	1.386	O_{11}–C_{12}–O_{13}	107.5	108.8	O_1–C_{12a}–C_{8a}–C_8	167.9	171.5
O_{11}–C_{12}	1.439	1.430	C_{10}–O_{11}–C_{12}	124.7	122.4	C_3–O_{13}–C_{12}–O_{11}	– 100.9	– 86.3
C_{10}–O_{11}	1.365	1.362	O_{11}–C_{10}–O_{14}	118.3	118.6	C_{12}–O_{11}–C_{10}–O_{14}	165.5	161.6
C_{10}–O_{14}	1.207	1.207	C_{5a}–C_{12a}–C_{8a}	112.9	112.1	C_{10}–C_9–C_{8a}–C_{12a}	– 51.7	– 44.6

splittings in artemisinin and makes them difficult to predict from estimates based on HF calculations.

To check the reliability of the HF/3-21G geometries, the geometries of both singlet and triplet state were reoptimized at the B3LYP/6-31G* level. The most important structure parameters obtained from these calculations are collected in Table 2.

These geometries were found to be very similar to the HF/3-21G geometries, and owing to the similarity of the HF/3-21G and B3LYP/6-31G* geometries the singlet–triplet splittings obtained at these levels should not differ much. At this stage we performed MP2/6-31G* single point calculations as a check of the accuracy of B3LYP. The singlet ground state is confirmed by the MP2 with the stabilization energy of around 50 kcal/mol, a number which is even larger in comparison to that of B3LYP. It is known that certain functionals could not describe lone pair interactions very well and some functionals require basis set of sufficient flexibility to represent interactions properly. It is probably that B3LYP quantitatively underestimates the singlet–triplet splitting. Unlike HF, B3LYP still predicts correct ground state. It is concluded that the B3LYP calculations should give the more reliable results and is in preference over the qualitatively incorrect HF method.

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