


# The electronic states and vibronic absorption spectrum of berberine in aqueous solution

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## Abstract

The time-dependent density functional theory was used to calculate the vibronic absorption spectrum of berberine (BER) in an aqueous solution. The best agreement with the experimental spectrum gives the O3LYP functional. Functionals with long-range correction showed poor agreement with experiment. The molecular orbitals of BER involved in the electronic transition during light absorption in the visible spectral region have been obtained. The dipole moments and atomic charges of the ground and excited states of the BER molecule have been calculated. Maps of BER electron density and electrostatic potential have been drawn. A significant photoinduced electron transfer from the outer di-oxygen five-membered heterocycle to the center of the BER chromophore has been found. According to our calculations, vibronic coupling and Boltzmann distribution play a significant role in the absorption spectrum of BER.

## KEYWORDS

aqueous solution, berberine, electronic states, TD-DFT calculations, vibronic absorption spectrum

## 1 | INTRODUCTION

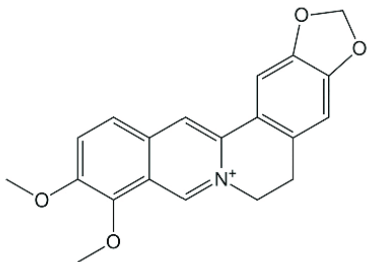
The berberine (BER) (9,10-dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinolo[3,2-a]isoquinoline-7-ium, Figure 1) is the main representative of the protoberberine family, a natural fluorescent yellow alkaloid.

BER is found in many plants, mainly as the hydrochloride or sulfate. In particular, BER is isolated from the *Coptidis rhizoma* plant, which has been used for centuries in traditional Chinese medicine to treat inflammatory diseases. BER is also found in the roots, flowers, shoots, and bark of several important medicinal plants, such as *Berberis vulgaris*, *Hydrastis canadensis*, *Coptis chinensis*, *Arcangelisia flava*, *Berberis aquifolium* [1].

BER exhibits a variety of medical and biological activities [2]. In particular, it has antimicrobial [3,4], antiparasitic [5,6], anti-inflammatory [7,8], cytotoxic [5] and antitumor [9,10] effects. BER exhibits regulatory functions, for example, it normalizes glucose metabolism [11], lowers cholesterol level [12], and modulates autophagy activity [13]. It is used to treat cardiovascular, metabolic [14] and neurodegenerative [15] diseases, as well as tuberculosis [16]. BER can efficiently bind to nucleic acids [17–30] and is used for photodynamic therapy of tumors (cleavage of <sup>1</sup>O<sub>2</sub> singlet oxygen from the BER molecule under the action of UV laser radiation) [31–33]. Fullerene molecules can be used to enhance the action and delivery of BER to cancer cells [34,35].

BER forms stable complexes with proteins [36–40], cyclodextrins [41–43] and other large molecules [44–47], as well as silver ions [48]. Since the fluorescence of BER is significantly dependent on its environment, it can be used as a fluorescent probe of these systems. Numerous derivatives of BER are also used for this purpose [49–56].

The unique biomedical properties and widespread use of BER have led to its numerous physicochemical studies using NMR [57–59], vibrational [60–62], Raman [63], and optical [64–70] spectroscopy, radiolysis [71] and also quantum chemical calculations [57,60,62,72]. Knowledge and understanding of the optical properties of BER are of particular importance for its use as a fluorescent probe and due to the widespread use



**FIGURE 1** The berberine molecule

of optical spectroscopy to study its complexes. At the same time, considering its applications, it is especially important to experimentally and theoretically analyze the *absorption* of BER in an aqueous solution, since the *fluorescence* of BER in water is very weak [63].

With an increase in the solvent polarity, the visible absorption maximum  $\lambda_{\max}$  of BER shifts to the short-wavelength spectral region (hypsochromic shift, negative solvatochromism), and the Stokes shift decreases. In particular, in the visible region in alcohols  $\lambda_{\max} = 431$  nm, and water  $\lambda_{\max} = 422$  nm [64]. The hypsochromic shift indicates a greater stabilization of the ground state by a more polar solvent in comparison with the excited state. Consequently, the magnitude of the dipole moment of the molecule in the ground state should be greater than in the excited state [73]. The visible peak corresponds to the  $n \rightarrow \pi^*$  electronic transition [64,67], while the UV peaks are due to the  $\pi \rightarrow \pi^*$  transitions [67]. The addition of HCl to alcoholic and aqueous solutions of BER does not affect the absorption spectrum, just like the addition of KOH to an aqueous solution of BER. However, the addition of KOH to alcohol solutions leads to a decrease in the values of their extinction coefficients in the visible region and, ultimately, to the disappearance of the absorption peak with  $\lambda_{\max} = 431$  nm (decolorization of solutions) [64]. In this case, the UV peaks are shifted to longer wavelengths. The authors of Gasperec and Weber [64] explain this effect by cleavage of the conjugated N1=C6 double bond upon hydroxylation of the C8 atom in a strongly alkaline medium. The literature contains sufficient experimental data on the spectral properties of BER in various solvents. However, their theoretical interpretation is practically absent—only one work [74] calculated molecular orbitals (B3LYP/6-31G(d) theory level), as well as light absorption by the isoquinoline BER fragment and the BER complex with a 20-mer DNA (semiempirical ZINDO method). According to Hirakawa [74], the excitation of the isoquinoline moiety of the BER molecule corresponds to the lowest excited state of BER ( $S_1$ ); lowest unoccupied molecular orbital (LUMO) is localized to the BER isoquinoline part. In this case, highest occupied molecular orbital (HOMO) is localized on the dimethoxybenzene part of the BER; therefore,  $S_1$  can be quenched by intramolecular charge transfer (ICT) from the isoquinoline part to the dimethoxybenzene part. In complex with DNA, due to the attraction between the negative charges of DNA phosphates and the positive charge of BER, ICT slows down and BER fluorescence is enhanced.

The disadvantage of theoretical studies of BER spectra is the neglect of vibronic coupling. At the same time, specialized works have shown that considering the vibronic coupling is very important for the correct reproduction of the electronic spectra of organic dyes [75–78]. The vibronic spectra are calculated in the Franck-Condon (FC) approximation [79,80] with an implicit specification of the solvent (polarizable continuum model—PCM). The disadvantage of the latter is the averaged (nonspecific) accounting of H-bonds and thermal motion. At the same time, explicit specification of the solvent and (or) simulation of thermal motion using molecular mechanics does not allow applying the FC principle to calculate the vibronic coupling. Therefore, the combined method (QM/MM) is sometimes used [81–83]. However, the constant improvement of the theory and parameterization of the PCM has made it more correct to describe the properties of a solvent (even highly polar as water) and the use of QM/MM is no longer necessary [84].

In this work, using the TD-DFT method, we performed a theoretical calculation of the absorption spectrum of an aqueous solution of BER in the visible region, considering the vibronic coupling and the Boltzmann distribution [84], and compared it with experimental spectrum.

## 2 | METHODS

The initial spatial structure of the BER molecule was taken from the <http://www.chemspider.com> database (ChemSpider ID 2263). The addition of hydrogen atoms and their preliminary optimization were performed using the HyperChem8.0 program. All basic calculations were performed using the Gaussian16 software package [85]. The calculation results were visualized using the GaussView package [86].

The aquatic environment was considered implicitly using the PCM adapted for TD-DFT [87,88]. Its feature is the combined use of equilibrium and non-equilibrium solvation. When a photon is absorbed by a molecule of a solute in the  $S_0$  ground state (GS) according to the FC principle, a redistribution of the electron density occurs in it at constant positions of the nuclei, that is, a molecule of a solute passes into excited nonequilibrium (FC) state [89]. In this case, a similar process (polarization with immobile nuclei) occurs in the nearest solvation shell

(nonequilibrium solvation). Then the "solute-solvent" system relaxes to an equilibrium excited state (EX) by displacement of nuclei and the corresponding redistribution of electron density (equilibrium solvation). From the EX state during fluorescence, the molecule can emit a photon.

In an exciting nonequilibrium state, not only the electronic energy of the molecule changes, but also the vibrational energy, that is, the molecule undergoes an electronic-vibrational (vibronic) transition. The probability of transition between vibrational states is proportional to the overlap integral between them.

It should be considered that the vibrational energies of various molecules of a solute in a sample at a nonzero temperature differ from each other, obeying the Boltzmann distribution. Therefore, when a sample is irradiated with light, many energy transitions occur from various vibrational levels of the ground state to various vibrational levels of the excited state [90].

It is known that the results of TD-DFT calculations of the excited electronic states of organic molecules are largely determined by the functional used [76,91–99]. In the case of significant ICT, it is recommended to use functionals with long-range correction [100–105], such as CAM-B3LYP [106], LC- $\omega$ PBE [107], and  $\omega$ B97X-D [108]. Therefore, in this work, we used a set of different hybrid functionals, including, besides, B3LYP [109], BMK [110], M06 [111], O3LYP [112], and X3LYP [113].

### 3 | RESULTS AND DISCUSSION

We analyzed the intense transition of  $n \rightarrow \pi^*$  type, which causes absorption of BER in the visible region (Table 1). The different functionals give transitions between different MOs for the longest-wave absorption band.

It should be noted that there are significant discrepancies between the values of  $\lambda_{\text{vert}}$  and  $\lambda_{\text{vibron}}$  in Table 1. This indicates the importance of considering the vibronic coupling and the Boltzmann distribution when calculating electronic spectra (see Section 2). Although a direct comparison of experimental  $\lambda_{\text{max}}$  and calculated  $\lambda_{\text{vert}}$  values is widespread in computational work, it is not entirely correct; it is more correct to compare  $\lambda_{\text{max}}$  and  $\lambda_{\text{vibron}}$  [77]. It can be seen from Table 1 that the  $\lambda_{\text{vibron}} = 421$  nm calculated using the O3LYP functional is in excellent agreement with the experimental  $\lambda_{\text{max}} = 422$  nm [64]. At the same time, the functionals with long-range correction (CAM-B3LYP, LC- $\omega$ PBE, and  $\omega$ B97X-D) gave  $\lambda_{\text{vibron}}$  values that are significantly lower than the experimental  $\lambda_{\text{max}}$  value. The use in this work of the 6-31G(d,p) compact basis set (including only polarization functions, without diffuse ones) gave good agreement with the experiment. It was noted in Barboza et al. [114] that diffuse functions are necessary for calculating transitions with energies above 5 eV (below 243 nm). Therefore, further analysis of the electronic states of the BER molecule was carried out at the level of the O3LYP/6-31G(d,p) theory. According to the calculations, the long-wavelength absorption maximum of the BER molecule corresponds to the  $S_0 \rightarrow S_2$  transition, while the transitions nearest to it are characterized by small values of the oscillator

**TABLE 1** The calculated values of the energies of the vertical transitions  $\lambda_{\text{vert}}$  and the maxima of the vibronic absorption spectra  $\lambda_{\text{vibron}}$  (with a half-width at half-height [HWHM] of  $600 \text{ cm}^{-1}$ ) with the 6-31G(d,p) basis set

Functional	Transition	Involved transitions	<i>a</i> (%)	$\lambda_{\text{vert}}$ (nm)	$\lambda_{\text{vibron}}$ (nm)
B3LYP	$S_0 \rightarrow S_3$	(HOMO-1) $\rightarrow$ LUMO	10	359	383
		HOMO $\rightarrow$ (LUMO+1)	87		
BMK	$S_0 \rightarrow S_1$	(HOMO-1) $\rightarrow$ LUMO	7	376	402
		HOMO $\rightarrow$ LUMO	89		
CAM-B3LYP	$S_0 \rightarrow S_1$	(HOMO-1) $\rightarrow$ LUMO	18	359	387
		HOMO $\rightarrow$ LUMO	80		
LC- $\omega$ PBE	$S_0 \rightarrow S_1$	(HOMO-1) $\rightarrow$ LUMO	31	326	- <sup>a</sup>
		HOMO $\rightarrow$ LUMO	58		
		HOMO $\rightarrow$ (LUMO+1)	3		
M06	$S_0 \rightarrow S_2$	(HOMO-1) $\rightarrow$ LUMO	54	354	372
		HOMO $\rightarrow$ LUMO	41		
O3LYP	$S_0 \rightarrow S_2$	(HOMO-1) $\rightarrow$ LUMO	64	384	421
		HOMO $\rightarrow$ (LUMO+1)	33		
$\omega$ B97X-D	$S_0 \rightarrow S_1$	(HOMO-1) $\rightarrow$ LUMO	24	354	378
		HOMO $\rightarrow$ LUMO	68		
X3LYP	$S_0 \rightarrow S_3$	(HOMO-1) $\rightarrow$ LUMO	22	354	374
		HOMO $\rightarrow$ (LUMO+1)	75		

Note: *a* is transition contribution.

Abbreviations: HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital.

<sup>a</sup>The calculation of  $\lambda_{\text{vibron}}$  (excited state optimization) requires the third derivative of the LC- $\omega$ PBE functional, which is not supported by Gaussian. The calculation of  $\lambda_{\text{vert}}$  requires a second derivative.

strength  $f$  (Table 2). We believe that  $S_1 \rightarrow S_0$  transition with small oscillator strength  $f \approx 0.02$  corresponds to extremely weak fluorescence of BER in the aqueous solution with a maximum around 545 nm when excited at 350 nm [17].

As seen from Table 2, the transitions  $S_0 \rightarrow S_6$ ,  $S_0 \rightarrow S_9$  and  $S_0 \rightarrow S_{10}$  correspond to absorption maxima in the UV region of the spectrum (and are not considered in this work). According to our calculations, the BER molecule contains 465 MOs, of which 88 are occupied and 377 are unoccupied. So MO #88 is the HOMO and MO #89 is the LUMO. MOs involved in the  $S_0 \rightarrow S_2$  electronic transitions, which causes the absorption maximum in the visible region of the spectrum, are shown in Figure 2.

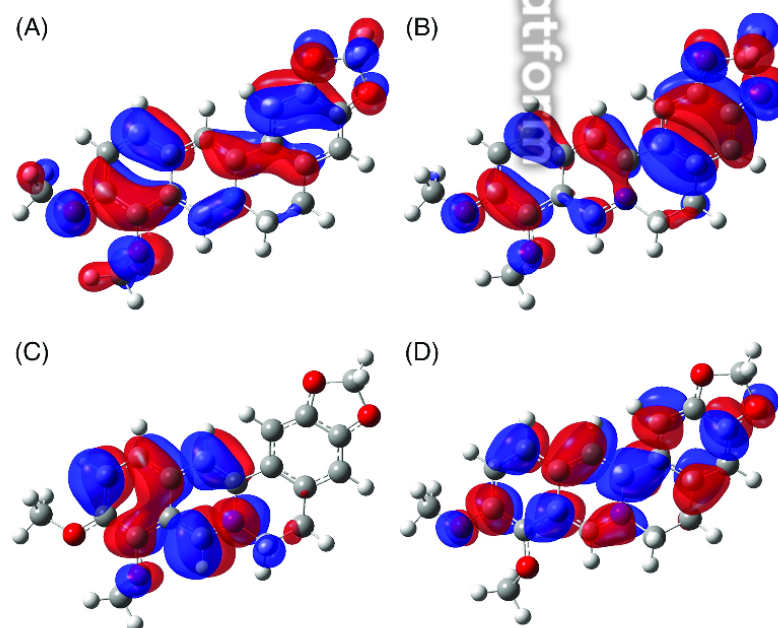
As seen in Figure 2, the LUMO is localized on the dimethoxybenzene part of the BER, which agrees with the results of Hirakawa [74] (see Section 1). At the same time, according to our calculations, HOMO is distributed throughout the molecule. Figure 3 shows the calculated vibronic absorption spectra (HWHM =  $600 \text{ cm}^{-1}$ ).

It can be seen that the calculated vibronic spectrum is close in shape to the experimental one [17,64,67,69]. Since at the simulated temperature  $T = 298 \text{ K}$ , the vibrational degrees of freedom are still "frozen," all vibronic transitions occur from the ground vibrational state  $\nu_0$ . As follows from Table 3, the most intense vibronic transitions (except  $0 \rightarrow 0$ ) are  $0 \rightarrow 4$  and  $0 \rightarrow 104$ .

Transition	$\lambda_{\text{vert}}$ (nm)	$f$
$S_0 \rightarrow S_1$	510	0.0187
$S_0 \rightarrow S_2$	384	0.389
$S_0 \rightarrow S_3$	335	0.0070
$S_0 \rightarrow S_4$	334	0.0070
$S_0 \rightarrow S_5$	325	0.0147
$S_0 \rightarrow S_6$	319	0.1460
$S_0 \rightarrow S_7$	289	0.0412
$S_0 \rightarrow S_8$	276	0.0213
$S_0 \rightarrow S_9$	268	0.1664
$S_0 \rightarrow S_{10}$	265	0.3688

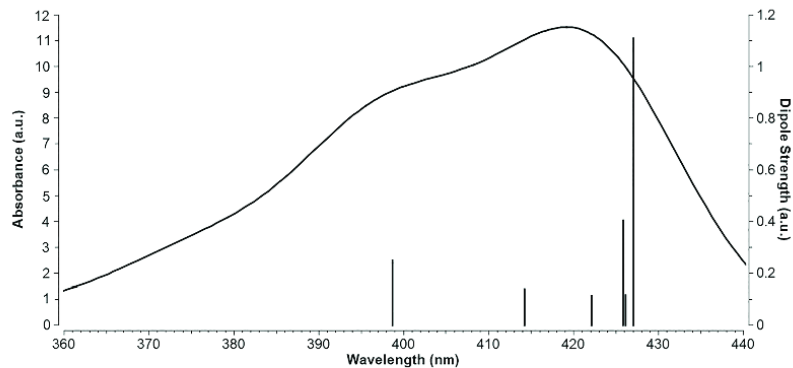
**TABLE 2** The excited states of BER molecule (O3LYP/6-31G(d,p) theory level)

Abbreviation: BER, berberine.



**FIGURE 2** The molecular orbitals between which the investigated transitions occur: (HOMO-1) (A), highest occupied molecular orbital (HOMO) (B), lowest unoccupied molecular orbital (LUMO) (C) and (LUMO+1) (D). Positive lobes are colored red and negative lobes are colored blue

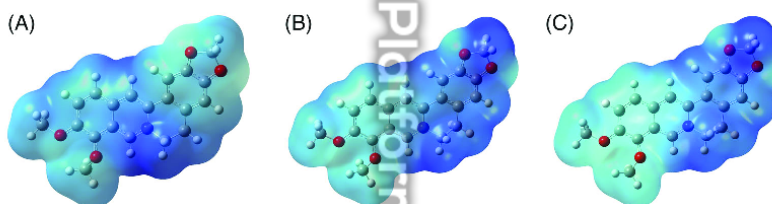
**FIGURE 3** Calculated vibronic absorption spectra ( $S_0 \rightarrow S_2$ ) of berberine (BER) aqueous solution



**TABLE 3** Vibronic absorption transitions ( $S_0 \rightarrow S_2$ ) in the BER molecule

No	Transition	$\lambda$ (nm)	$\Delta\nu$ ( $\text{cm}^{-1}$ )	$I$	$p$ (a.u.)	Definition of vibrations
1	$\nu_0 \rightarrow \nu'_0$	427	0	14 300	1.11	-
2	$\nu_0 \rightarrow \nu'_3$	426	52.6	1494	0.116	Torsional vibrations around the long axis of the chromophore
3	$\nu_0 \rightarrow \nu'_4$	426	67.0	5231	0.405	
4	$\nu_0 \rightarrow \nu'_{17}$	422	273	1474	0.113	Bending vibrations around the long axis of the chromophore
5	$\nu_0 \rightarrow \nu'_{40}$	414	726	1856	0.140	Tension-compression of all five rings
6	$\nu_0 \rightarrow \nu'_{104}$	399	1664	3426	0.248	Vibrations of hydrogens of C17 atom

Note:  $\lambda$  is wavelength,  $\Delta\nu$  is relative frequency,  $I$  is line intensity, and  $p$  is dipole strength.  
Abbreviation: BER, berberine.



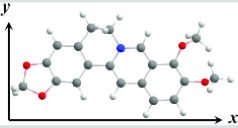
**FIGURE 4** The visualization of the electrostatic potential of berberine (BER) as a mapped surface in the ground (A), Franck-Condon (B) and equilibrium excited (C) states. A darker blue color corresponds to a larger value of the positive electrostatic potential

For a quantitative analysis of the photoinduced charge transfer in the BER molecule, we calculated the Merz–Kollman charges of heavy atoms in the ground and excited states (see Table S1 and Figures S1, S2). As can be seen from Table S1 and Figure 4, the redistribution of charges during the transition of the BER molecule from the ground state to the FC state is significant. The greatest transfer of an electron occurs from the C2 atom to the C1, and less—from C17 to O1. According to our calculations, the values of BER dipole moment  $\mu_{\text{GS}} > \mu_{\text{FC}} > \mu_{\text{EX}}$ , that is, it decreases with excitation (Table 4). This feature is consistent with the hypsochromic effect observed for BER solutions in the visible region of the spectrum (see Section 1). The transition dipole moment  $M$  is directed mainly along the chromophore (see Table 4).

In the ground state of the BER molecule, the positive charge is concentrated in the center of the molecule, near the nitrogen atom (see Figure 1). Upon absorption of a photon, the BER molecule first passes into a nonequilibrium excited (FC) state. This transition, according to our calculations, is accompanied by a significant shift of the electron density from the outer di-oxygen five-membered heterocycle to the center of the molecule (Figure 5). In this case, the value of the dipole moment BER decreases (see Table 4). During the relaxation of the BER molecule from the FC state to the equilibrium excited state, the redistribution of the electron density is insignificant (see Figures 4 and S2).

For a more complete understanding of the changes in the BER molecule upon photoexcitation, we calculated the bond lengths between heavy atoms in the calculated structures (Figure 6).

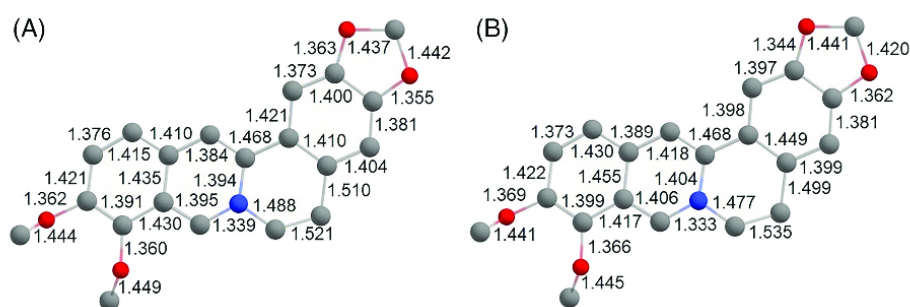
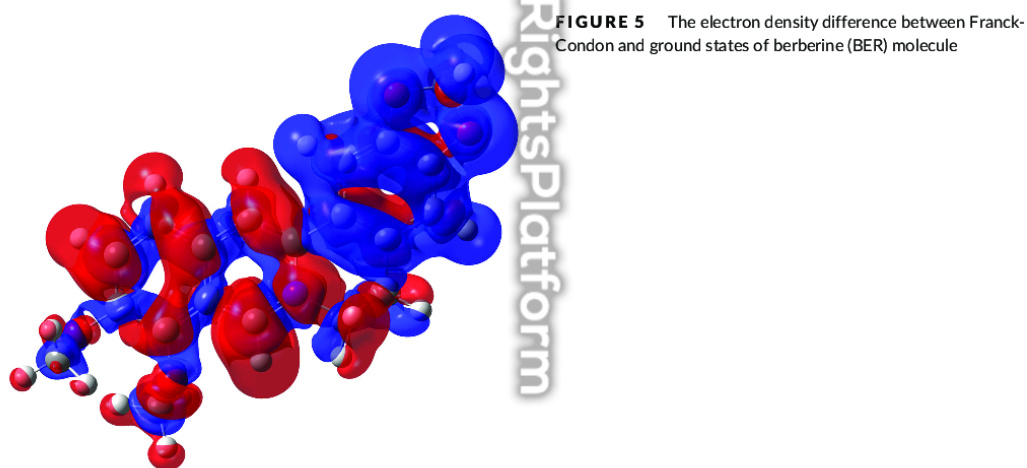
As seen in Figure 6, changes in bond lengths are quite significant (considering their high rigidity).

**TABLE 4** Calculated dipole moments and transition dipole moment of BER molecule


The coordinate axes are directed along the principal axes of inertia of the molecule

Dipole moment (D)	Ground state	Franck-Condon state	Equilibrium excited state
$\mu_x$	1.65	1.84	0.776
$\mu_y$	3.03	2.83	2.77
$\mu_z$	0.441	0.113	0.579
$\mu$	3.48	3.38	2.93
Ground to Franck-Condon state transition electric dipole moments			
$M_x$ (D)	-8.13		
$M_y$ (D)	1.27		
$M_z$ (D)	-0.0384		
$M^2$ (D <sup>2</sup> )	67.7		

Abbreviation: BER, berberine.

**FIGURE 6** The calculated bond lengths between heavy atoms in ground (A) and equilibrium excited (B) states of berberine (BER) molecule

## 4 | CONCLUSIONS

1. The absorption of BER in the visible region of the spectrum is due to the transitions (HOMO-1) → LUMO and HOMO → (LUMO+1).
2. The vibronic coupling and Boltzmann distribution play a significant role in the BER absorption spectrum.
3. The best agreement with the experimental spectrum gives the O3LYP functional.
4. Functionals with long-range correction show poor agreement with experiment.
5. Upon photoexcitation, a significant electron transfer occurs from the outer di-oxygen five-membered heterocycle to the center of the BER chromophore.

## CONFLICT OF INTEREST

The author declares no conflicts of interest.

## AUTHOR CONTRIBUTIONS

Lyudmila O. Kostjukova: Project administration; resources; software; visualization.

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