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REGULAR ARTICLE

Radiationless decay of excited states of tetrahydrocannabinol through the S_1–S_0 (conical) intersection

**Gábor J. Halász · Andrzej L. Sobolewski ·
Ágnes Vibók**

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Abstract The ground and electronically excited singlet states of tetrahydrocannabinol have been studied theoretically using density functional and time-dependent density functional methods. The vertical excitation energies, the equilibrium geometries as well as the adiabatic excitation energies have been determined. Opening of the six-membered ring between the oxygen and carbon atoms has been considered as photochemical reaction path. This mechanism leads to a typical excited-state intramolecular hydrogen-transfer process and produces low-lying S_0–S_1 intersection (possible conical intersection, CI) which provides a channel for effective radiationless deactivation of the electronically excited state.

Keywords Ground and excited electronic states · Conical intersections · Radiationless decay · Tetrahydrocannabinol

Dedicated to Professor Sandor Suhai on the occasion of his 65th birthday and published as part of the Suhai Festschrift Issue.

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G. J. Halász
Department of Information Technology, University of Debrecen,
PO Box 12, 4010 Debrecen, Hungary

A. L. Sobolewski
Institute of Physics, Polish Academy of Sciences,
02668 Warsaw, Poland

Á. Vibók (✉)
Department of Theoretical Physics, University of Debrecen,
PO Box 5, 4010 Debrecen, Hungary
e-mail: vibok@phys.unideb.hu

1 Introduction

Cannabinoids have been the subjects of several studies since 1960s when Mechoulam, Gaoni and Edery first isolated, delta-1-tetrahydrocannabinol (Δ^1-THC) [1, 2], the main psychoactive component in the Cannabis plant. Over the years more than 300 cannabinoids have been synthesized and tested. It has also been revealed that several cannabinoid compounds possess a series of therapeutic properties (antibiotic, antitumoral, etc.) [3–6] and can play an important role as possible analgesic agents [7]. Despite these positive medicinal values found in cannabinoids, the application of these materials as therapeutic agents is hindered due to the fact they retain psychoactive effects. Nowadays, a lot of effort is taken to design molecular structures of cannabinoid compounds with desirable therapeutic properties but without possessing psychoactivity effects. Among others, several quantum chemical studies have been carried out to obtain valuable correlations between the chemical structure and the biological activity of these compounds [8–10]. Extensive theoretical work on this subject has been performed by Bodor and Huang [11]. Using semiempirical methods they have investigated the activity differences between the stereoisomers of tetrahydrocannabinols. Huang and Leszczynski [12] also performed a series of ab initio Hartree–Fock (HF) and density functional theory (DFT) calculations to study the stereoisomers of tetrahydrocannabinols (THC) and compared their geometric features with the electronic properties. Recently, theoretical results combining molecular mechanics, electronic structure and chemometric methods have been presented by Silva and co-workers [13] to determine the most significant molecular descriptors which could be correlated with the psychoactivity and psychoinactivity of cannabinoid compounds.

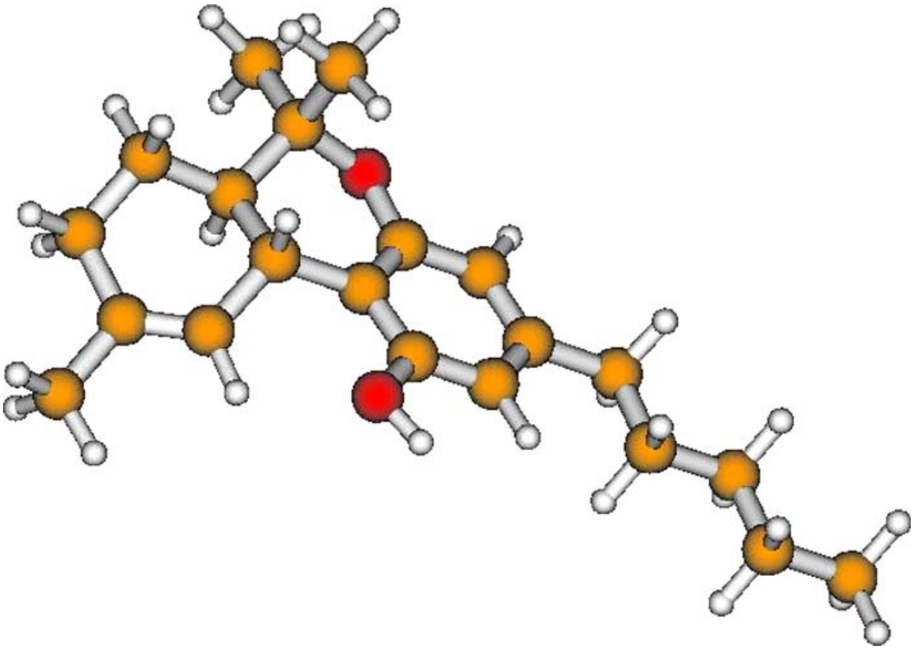

Fig. 1 Equilibrium geometry of Δ^9-tetrahydrocannabinol (THC)

Concerning the photochemical and photophysical features of the THC molecule, Pate [14] and Lydon et al. [15, 16] published very important experimental results. Their experiments demonstrate that under conditions of high UV/vis exposure, (a) the cannabis plant produces significantly greater quantities of THC than other compounds and (b) separated THC compound is not destroyed by this radiation. Nevertheless, these experimental findings are more than 20 years old, but there are still no available theoretical results supporting the photostability of this compound.

The aim of the present work is to investigate the photochemical and photophysical behaviours of the THC molecule using quantum chemical methods. Accordingly, potential-energy profiles of the ground and first excited states, vertical excitation energies and oscillator strengths have been calculated in this work. An intersection (possible conical intersection, CI) between the ground and first excited singlet states has been localized showing the existence of an efficient funnel for ultrafast nonradiative decay of electronic excitation back to the ground state[1] [17–19].

In the present work, we focus on the photophysical properties of Δ^9-THC molecule (Fig. 1) which are strongly correlated with the structure of the six-membered central ring containing oxygen atom. Based on our preliminary investigation, we simply remove the tail (4 carbon and 8 hydrogen atoms) of this molecule [remaining truncated THC and denoted as (t)THC] because this part has a very minimal effect on the photophysical behaviour of this system (Fig. 2).

Herein, for the calculation of the ground-state structures of (t)THC, the DFT has been used while for the excited electronic states the time-dependent DFT (TDDFT) method has been employed. The TDDFT method represents an efficient general approach to treat large molecular systems. Several previous works [20–22] have shown that TDDFT is suitable for the accurate prediction of vertical excitation energies with respect to those states which are singly-excited relative to the ground state. There remains some controversy regarding the ability of TDDFT to describe states with doubly excitation character [23]. Although recently several efforts have been made to improve the quality of the exchange and correlation functionals [24], the most widely used functionals still do not allow to describe accurately the excited states including long range charge transfer character. At adiabatic level, the linear response implementation of the TDDFT approach cannot inherently describe excited states with a significant contribution of double and higher electron excitation. Therefore, the localization of CIs between the ground and excited electronic states in adiabatic TDDFT scheme has been questioned [25, 26]. In spite of these known deficiencies, the TDDFT method has already been tested against accurate complete active space self-consistent field (CASSCF) and complete active space multiconfigurational second-order perturbation theory (CASPT2) results for several systems in the calculation of excited states energy profile [27]. According to these calculations, the TDDFT method appears to be a very promising tool for the

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[1] Conical intersections (CIs), geometries where two electronic states are truly degenerate, providing a very efficient channel for nonradiative relaxation processes to the ground state on an ultrafast time scale with the extra energy being transformed into heat.

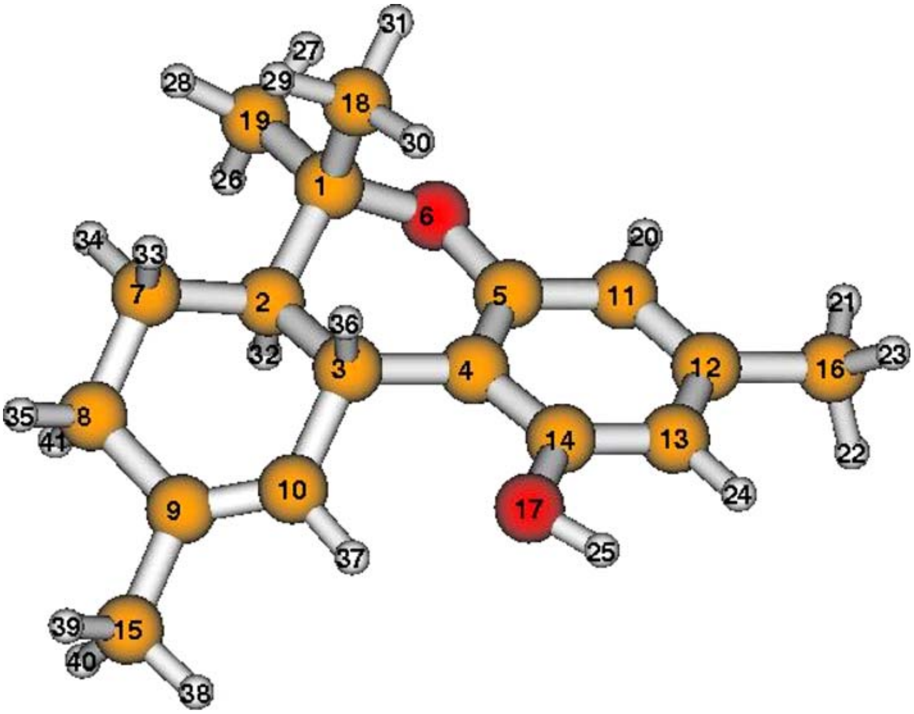


Fig. 2 Equilibrium geometry of truncated tetrahydrocannabinol (t)THC

investigation of excited state potential-energy functions of large systems for which the CASSCF and CASPT2 methods are not feasible.

This paper is organized as follows: the computational details of the calculations are explained in Sect. 2. In Sect. 3, the results are presented and discussed. A summary and conclusions are given in the final section.

2 Computational details

The standard DFT and TDDFT calculations were performed with the TURBOMOLE program package [28]. Molecular structures and orbitals were visualized using Molden [29]. The ground-state equilibrium geometries of (t)THC were optimized with the DFT methods. The lowest excited singlet state equilibrium structures of the molecule were determined with the TDDFT method. The def2-SV(P) basis set [30] and B3-LYP functional [31] were used in these calculations. The vertical excitation energies and oscillator strengths were determined at the ground-state equilibrium geometry using the same basis set.

The relaxed scan (RS) along the photophysically relevant reaction coordinates in the lowest excited singlet state was calculated with the TDDFT method. It was found that the photophysically relevant reaction path is related to the opening of the central six-membered ring containing the oxygen atom. Therefore, for the ground state calculations, we have to consider two minimum energy conformers of this system, one for the initial closed form and the other is the open structure of the molecule as the product of the excited state relaxation mechanism. For the construction of the reaction path suitable driven coordinates have been chosen, and for the given values of these driving coordinates all remaining coordinates were optimized.

To check the existence of the intersection between the ground and first excited singlet states (S_0–S_1), additional CASSCF type calculations were performed at the estimated geometry of the CI determined using the TDDFT method.

The calculations were carried out in Warsaw on a Linux Cluster of the Institute of Physics, at the Leibniz Rechenzentrum of the Bavarian Academy of Sciences on a Linux Cluster and at the Jülich Supercomputing Centre on an IBM p6 575 Cluster JUMP.

3 Results and discussion

3.1 Ground-state equilibrium structures and the reaction path

The equilibrium structures of the lowest energy ground state conformers for the closed and open forms of (t)THC have been determined by unconstrained DFT geometry optimizations using the def2-SV(P) basis set and the B3-LYP functional. The Cartesian coordinates obtained for both structures are presented in the Supporting Information.

The TDDFT vertical excitation energies, oscillator strengths and dipole moments obtained at the optimized

Table 1 Vertical excitation energies (ΔE), given in eV, oscillator strengths (f), and dipole moments (μ) of (t)THC molecule calculated with the TDDFT/def2-SV(P) method at the DFT/def2-SV(PT) ground state equilibrium geometries

State	Closed form			Open form		
	ΔE (eV)	f	μ (debye)	ΔE (eV)	f	μ (debye)
S_0	0	–	1.04	0.85[a]	–	2.57
S_1	4.89	0.018	1.00	4.91	0.016	0.95
S_2	5.44	0.018	0.93	5.02	0.001	0.22
S_3	5.67	0.010	0.68	5.18	0.002	0.37
S_4	5.74	0.028	1.12	5.44	0.051	1.58
S_5	5.86	0.023	1.04	5.51	0.084	2.00

[a] Relative to the global minimum (closed form)

geometry of both forms are presented in Table 1. The optical transition to the lowest excited singlet state of both forms has moderate oscillator strength in the UV range of the spectrum ($f = 0.018$, $\Delta E = 4.89$ eV) and ($f = 0.016$, $\Delta E = 4.91$ eV), respectively. However, there is a significant difference between the second excited states of these two forms. This state is essentially dark in absorption from the ground state ($f = 0.001$) in open form, while in closed one it absorbs moderately strongly ($f = 0.018$). The calculated UV absorption spectra of closed-form (full line) and open-form (dashed-line) of (t)THC are additionally shown in Fig. 3. It shows that the absorption values are absolutely in the UV spectrum for both conformers.

The results show that there are two important processes along the reaction path between the two conformers. One of them is the stretching and breaking of the CO bond in the six-membered central ring containing oxygen atom and the other one is the hydrogen transfer from the methyl group to the oxygen atom. The C_1–O_6 distance was used to characterize the former and the C_{18}–H_{31} and O_6–H_{31} distances to describe the later process (see Fig. 2 for the numbering of the atoms). Table 2a summarizes these parameters and the corresponding energies for the three stationary points of the reaction path on the S_0 surface. The energetic barrier that separates the two local minima from each other clearly shows that thermal relaxation cannot drive the system from one form to the other.

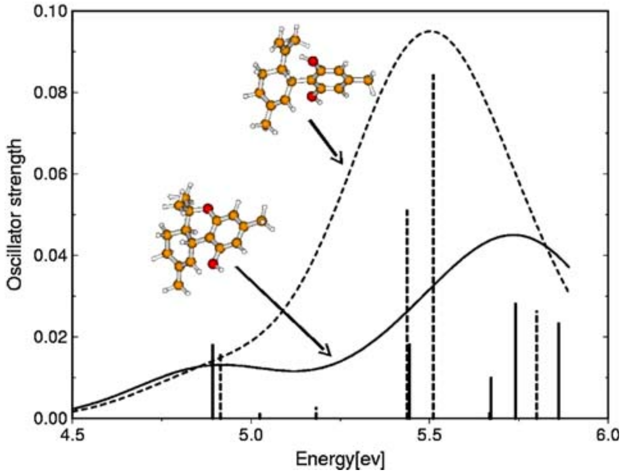


Fig. 3 Absorption spectra of (t)THC (closed form, *solid line*) and (t)THC (open form, *dashed line*) calculated with the TDDFT/def2-SV(P) method at the DFT/def2-SV(P) ground state equilibrium geometry. The spectral envelopes were determined by convolution of the stick spectra with a Gaussian function of 1.5 eV full-width-at-half-maximum

3.2 Excited-state equilibrium structures and potential-energy profiles

The optimization of the geometry of the first excited singlet S_1 state of the closed form (t)THC was performed at the TDDFT/def2-SV(P) level using the B3-LYP functional. The Cartesian geometry parameters of the S_1 equilibrium structure can be found in the Supporting Information. The potential-energy profiles for the ground and for the first excited states are determined along the RS (see in Fig. 4, full curves with circle and squares). Furthermore, the vertical potential-energy profile of the ground state obtained along the RS given in the first excited singlet state (dashed curve with triangles) is also shown.

Our calculations on the (t)THC molecule have revealed the existence of an intersection between the ground and first excited singlet states (S_0–S_1). In Fig. 4, the crossing between the first excited state and the ground state potential-energy functions is a true intersection as both curves are obtained at the same geometry (numerically, the energy difference between the two surfaces at that geometry is ~0.006 eV at TDDFT level and ~0.197 eV at CASSCF level, respectively).

CI space for a system with n degrees of freedom is a $n - 2$ dimensional subspace; therefore, it could be unexpected that our one-dimensional scan of the PES hits this subspace. The potential-energy profiles for the S_1 excited state clearly display an avoided crossing at $R_{1,6} \simeq 1.7$ Å. Studying the first excited electronic state of (t)THC, it was found that for C_1–O_6 distances larger than this value the main contribution (>98%) for the first excited state is coming from a single electron excitation from the HOMO molecular orbital to the LUMO one. Figure 5a shows these orbitals for the open form of (t)THC. In the first exited state of (t)THC, these molecular orbitals are singly occupied clearly demonstrating the biradical nature of the S_1 state. We have also displayed in Fig. 5b the HOMO and LUMO orbitals of the system at a geometry with the smallest $R_{1,6}$ among the calculated ones in the region of interest. Similar pictures could be seen for other geometries in the large C_1–O_6 distance region. For the case of the intersection, the

Table 2 Some parameters of the stationary points of the reaction path

	$R_{1,6}$ (Å)	$R_{18,31}$ (Å)	$R_{6,31}$ (Å)	ΔE (eV)	E_{vib} (eV)	$\Delta E_{\mathrm{total}}$ (eV)
(a) The three most relevant distances to describe the opening of the ring (C_1–O_6) and the intermolecular hydrogen transfer (C_{18}–H_{31} and O_6–H_{31})						
Closed form	1.449	1.104	2.688	0	9.59	0
Transition state	2.411	1.273	1.428	2.64	9.38	2.43
Open form	3.450	2.362	0.977	0.85	9.52	0.79

	$\Theta_{4,3,2,1}$ (deg)	$\Theta_{5,4,3,2}$ (deg)	$\Theta_{18,1,2,3}$ (deg)	$\Theta_{19,1,2,18}$ (deg)
(b) Some dihedral angles important for describing the relative spatial position of the two subsystems holding the HOMO and LUMO molecular orbitals after breaking the C_1–O_6 bond				
Closed form	−44.7	13.3	−59.3	−126.6
Transition state	−80.0	66.4	−47.5	−178.2
Open form	−63.4	102.9	−67.9	−179.7

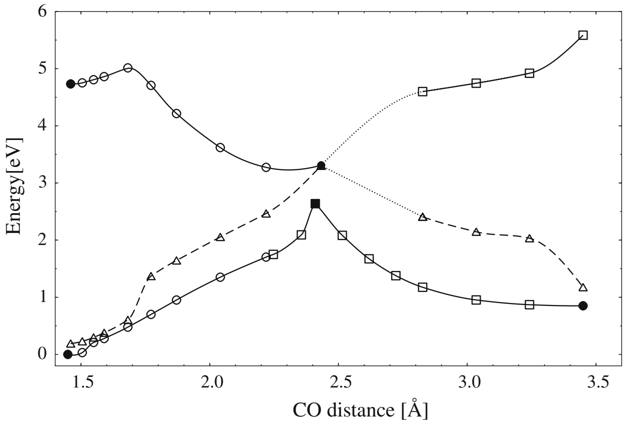


Fig. 4 Energy profiles of (t)THC in the ground S_0 state and in the first exited singlet S_1 state calculated along the minimum energy path at the DFT/def2-SV(P) and TDDFT/def2-SV(P) levels, respectively. Markers denote the way geometry optimization was performed: unrestricted geometry optimizations (*filled circle*), unrestricted search for transition state (*filled square*), geometry optimizations with fixed C_1–O_6 distance (*unfilled circle*), geometry optimizations with fixed C_1–O_6 and C_{18}–H_{31} distance (*unfilled square*). The *dashed line* with *triangles* represents the energy of the S_0 state determined along the minimum energy path of the S_1 state

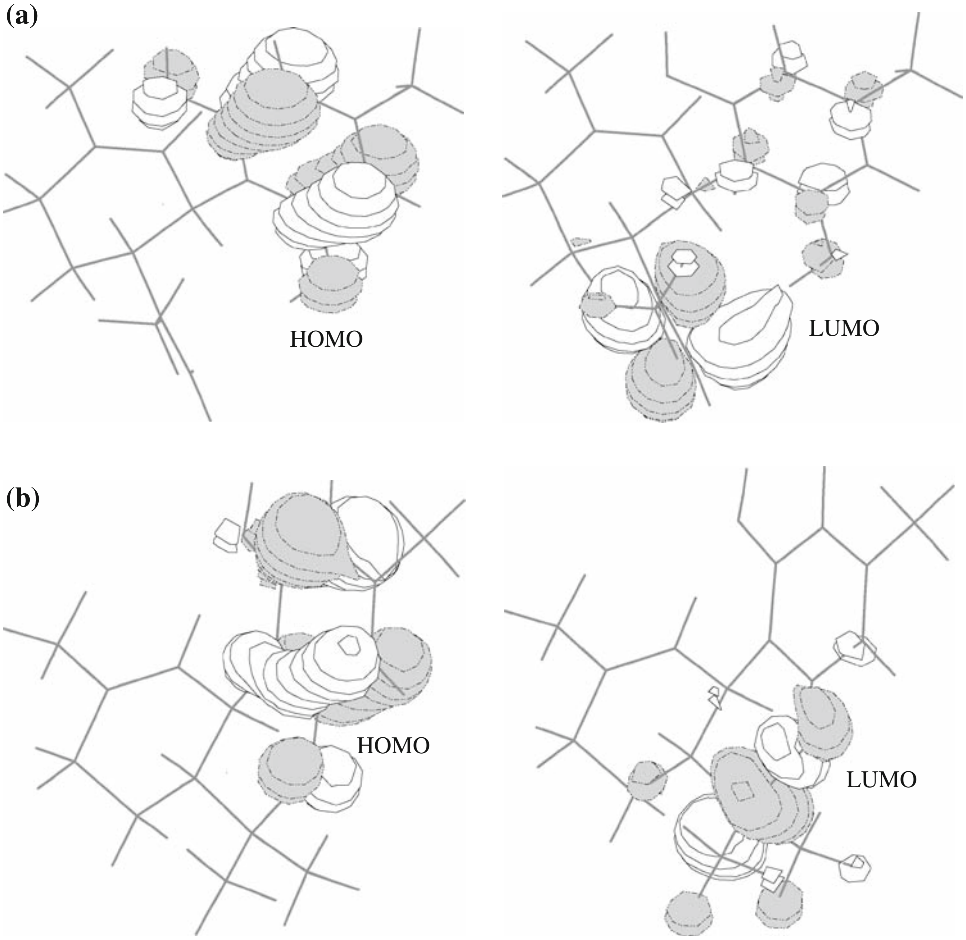
main contribution (99.2%) to the S_1 state comes from a single excitation of a similar kind. Here, we also performed a calculation at the CASSCF level. At this level we have a multireference wavefunction with a single dominating configuration for both of the states. For the ground state, the dominating configuration (91%) contains 69 doubly occupied orbitals and two singly occupied ones. For the S_1 state the main contribution (94%) is a closed shell configuration. According to the results of [32–34] (S_0–S_1), CIs in organic molecules are usually found along reaction paths which result from the feature of biradical structures. So, our result of hitting the intersection space with a one-dimensional scan could be unexpected in some sense but it is not surprising. It is a consequence of the biradical feature of the S_1 state in a wide region around the transition state geometry of the system. Table 2b displays some dihedral angles important to specify the relative spatial position of the two subsystems holding the singly occupied molecular orbitals of the first excited state.

Turning to the reaction path we have identified three important nuclear coordinates which play an essential role for the relaxation mechanism from the first excited singlet state potential-energy surface of the (t)THC towards the intersection with the ground state surface. These are: stretching of the (C_1–O_6) bond which leads to the opening of the six-membered central ring and moving the H_{31} atom from C_{18} to O_6. This process can be considered as the well-known excited-state intramolecular hydrogen transfer (ESIHT) process, which is one of the fastest photochemical reaction studied [27, 35, 36]. The RS on the S_1 state leads in an almost barrierless fashion (~0.2 eV) from the Franck–Condon geometry of the system to the intersection with the ground state.

4 Conclusions

Equilibrium structures, saddle points, and reaction paths on the potential-energy surface of the ground and the lowest excited singlet state of (t)THC molecule have been determined at the DFT and TDDFT levels, respectively. Our results reveal possible important nuclear degrees of freedom involved in the photophysics of (t)THC, and the most relevant in the mechanism we have investigated in our work here. These coordinates are very important in the Franck–Condon region since there is no (or very small) barrier to reach the (S_0–S_1) intersection. It has been shown that the (t)THC is a typical excited-state intramolecular hydrogen transfer (ESIHT) system, and the calculated potential-energy profile (surface) of the first excited singlet state along the ESIHT reaction pathway leads to the intersection

Fig. 5 The HOMO and LUMO molecular orbitals of (t)THC at two different geometries with large C_1–O_6 distance. **a** Equlibrium geometry of the open form of the system. **b** Optimized geometry at the S_1 PES with $R_{1,6}$ = 1.77 Å



with the ground state potential-energy surface, possibly a CI. This provides a possible pathway for ultrafast radiationless decay back to the ground state and ensures the photostability of the (t)THC molecule over a wide range of UV excitation energies. The qualitative model of the photophysics of (t)THC is similar to previous theoretical results for 5,6-dihydroxyindole (DHI) [37]. Although the TDDFT method is a popular and inexpensive method for the excited-state investigation of truly large system, it is not sufficiently accurate to provide quantitatively correct values for excitation energies. Sometimes it provides extremely flat and barrierless energy profiles along the reaction path for hydrogen transfer reactions [38, 39]. Therefore, our present results primarily supply a qualitative picture for modelling the relaxation mechanism of (t)THC. Additionally, TDDFT, as a single-reference method cannot quantitatively correctly describe the CI between the excited and the ground state. In the near future we plan to perform a more detailed investigation for the photochemical properties of this system using more advanced electronic structure methods as CASSCF and CC2 (a simplified and cost-efficient variant of singles and doubles coupled cluster theory). The ab initio calculations of accurate multi-dimensional potential-energy surfaces enable extension of our electronic structure studies to dynamical ones. Using time-dependent quantum wave packet or quasi classical trajectory methods for the description of the photon-induced reaction dynamics, a more complex study can be obtained for the photocycle of (t)THC. Experimental spectroscopic results obtained from ultrafast time-resolved spectroscopy are not available for this system at the moment, but would offer a useful means of calibrating our theoretical approach.

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