Theoretical investigation of the photosensitization mechanisms of urocanic acid

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Abstract

The photosensitization mechanisms of urocanic acid (UA), the main skin chromophores of ultraviolet (UV) light, are investigated by means of theoretical calculations. The results indicate that the direct photooxidative damage to DNA bases by triplet state UA through electron transfer reaction is not favorable on thermodynamic grounds. However, UA can photogenerate various reactive oxygen species (ROS, e.g., $^1O_2$, O_2^{-}) theoretically and the ROS-generating mechanisms are illustrated as follows. Firstly, the $^1O_2$-generating pathway involves direct energy transfer between triplet state UA and $^3O_2$. Secondly, UA gives birth to O_2^{-} through two pathways: (i) direct electron transfer between triplet state UA and $^3O_2$; (ii) electron transfer between anion radical of UA (generated through autoionization reactions) and $^3O_2$.
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1. Introduction

In recent years, increasing evidences demonstrate that the reactive oxygen species (ROS) photogenerated by various endogenous photosensitizers play important roles in the skin photoaging and photocancinogensis [1]. Among the endogenous photosensitizers, urocanic acid (UA), the main degradation product of histidine metabolism in the skin, has attracted considerable attention [2–6]. UA is one of the main skin chromophores of ultraviolet (UV) light in the range of 290–320 nm and has been proved to be an efficient ROS-generator [4–6]. The direct relation between the photosensitization of UA and photoaging of the skin has been demonstrated [4]. Although numerous experimental and theoretical studies have investigated the photo-physicochemical properties of UA [7–10], to the best of our knowledge, there is no report devoting to illustrating the detailed photosensitization mechanisms of UA. Considering the great contributions of quantum chemical methods, especially time-dependent density functional theory (TD-DFT), in investigating the photosensitive properties of various photosensitizers [11–14], we attempt to explore the photosensitization mechanisms of UA using theoretical methods.

2. Methods

Considering the fact that UA exists in monoanion form generated by proton dissociation from the carboxyl group in solution at pH 7, the monoanion of both the *trans-* and *cis*-UA were taking as the starting points of the present study (Fig. 1) [15]. The calculation details are as follows. The molecular structures of UA and its derived anion or cation radicals were fully optimized by hybrid density functional theory (DFT) [16,17] and B3LYP functional [18–20] with 6-31+G(d,p) Gaussian basis set in water. Then, the lowest triplet excitation energy (E_{T_1}) of UA was calculated by TD-DFT formalism with the same basis set in water

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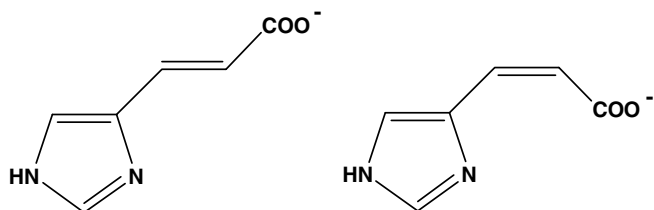 *E-mail address:* jhf@sdut.edu.cn (H.-F. Ji).

Fig. 1. Molecular structures of *trans*-urocanic acid (left) and *cis*-urocanic acid (right) at PH 7.0.

[21–23]. The effectiveness and accuracy of TD-DFT in estimating the E_{T_1} of various photosensitizers have been verified [11–14]. During the calculations, the self-consistent reaction field (SCRF) method with polarizable continuum model (PCM) of Tomasi and coworkers was employed to include the solvent (water) effect [24–26]. Based on the electronic parameters of the parent, anion and cation radicals of UA, the vertical electron affinity (VEA) and vertical ionization potential (VIP) in the ground (S_0) state and the triplet (T_1) state were estimated.

All the calculations were completed with Gaussian 03 package of programs [27].

3. Results and discussion

During the photosensitization, photosensitizers in S_0 state are initially excited to S_1 state and then intersystem cross to T_1 state, which is mainly responsible for the photosensitive reactions for its relatively long lifetime. The photosensitive reactions usually involve two mechanisms, namely, reacting directly with substrates (e.g., DNA bases) or damaging through intermediate of ROS.

The first mechanism occurs through the electron transfer reaction between the T_1 state photosensitizer and DNA base (Eq. (1)).

$$UA(T_1) + D \rightarrow UA^{\cdot -} + D^{\cdot +} \qquad (1)$$
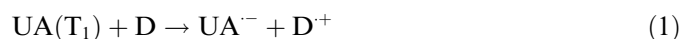
The precondition of the reaction is that the summation of the VEA for T_1 state UA (VEA_{T_1}) and the VIP of DNA bases is negative. The VEA_{T_1} of UA is calculated to be -4.11 eV for *trans*-UA and -3.63 eV for *cis*-UA, respectively, indicating that the T_1 state *trans*-UA has relatively stronger electron affinity compared with the T_1 state *cis*-UA. According to previous study, the VIP of guanine, the most easily oxidized base, is about 5.49 eV [11]. Therefore, based on the present results, the electron transfer reaction between the T_1 state UA and DNA bases is not favorable on thermodynamic grounds. DNA photodamage and photogenerated ROS have been proved to be the initial molecular events resulting in most of the typical histological and clinical manifestations of chronic skin photodamage [28]. Therefore, compared with the direct photooxidative damage to DNA bases by excited state UA, the ROS-photogenerating pathway is more likely responsible for the photosensitizing activity of UA during the deleterious biological processes.

In addition, T_1 state UA may undergo a series of phototoxic reactions with molecular oxygen to give birth to various ROS. The first important ROS-photogenerating pathway involves the direct energy transfer between the T_1 state UA and $^3O_2$ to give birth to $^1O_2$ (Eq. (2)), one of the most important ROS.

$$UA(T_1) + {}^3O_2 \rightarrow UA(S_0) + {}^1O_2 \qquad (2)$$
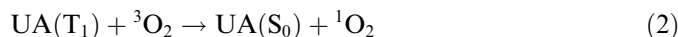
It can be seen from Table 1 that the E_{T1} of UA (2.84 eV for *trans*-UA and 3.08 eV for *cis*-UA) is higher than the excited-state energy of $^1O_2$, 1.05 eV $(^3\sum_g^- \rightarrow \Delta_g^1)$ or 1.65 eV $(^3\sum_g^- \rightarrow {}^1\sum_g^+)$ in water [11], indicating that UA can photo-generate $^1O_2$ in principle through direct energy transfer pathway (Fig. 2). This is in good agreement with the experimental report that UA is an efficient $^1O_2$ generator when irradiated with UV light [4–6].

Secondly, T_1 state UA may react with $^3O_2$ to generate superoxide anion radical ($O_2^{\cdot -}$) through direct electron transfer (Eq. (3)) with the prerequisite that the summation of VIP_{T_1} of UA and the adiabatic electron affinity of $^3O_2$ (AEA_{O2}) is negative.

$$UA(T_1) + {}^3O_2 \rightarrow UA^{\cdot +} + O_2^{\cdot -} \qquad (3)$$
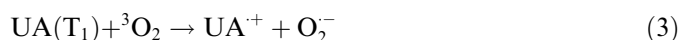
According to the calculated results, the summation of VIP_{T1} (2.94 eV for *trans*-UA and 2.33 eV for *cis*-UA, Table 1) and AEA_{O2} (-3.81 eV) [29] is negative, suggesting that $O_2^{\cdot -}$ can be generated in principle through this pathway in water (Fig. 2). This provides deeper insight into the photogenerating mechanism of $O_2^{\cdot -}$ by UA [2]. The occurrence of the direct electron transfer pathway benefits to a large ex-

Table 1
Lowest triplet excitation energies (E_{T1}, in eV), vertical electron affinity (VEA, in eV) and vertical ionization potential (VIP, in eV) of urocanic acid in monoanion form in ground (S_0) state and triplet (T_1) state in water

	E_{T_1}	VEA_{S_0}	VEA_{T_1} [a]	VIP_{S_0}	VIP_{T_1} [b]
trans-UA	2.84	-1.27	-4.11	5.78	2.94
cis-UA	3.08	-0.55	-3.63	5.41	2.33

[a] $VEA_{T_1} = VEA_{S_0} - E_{T_1}$.
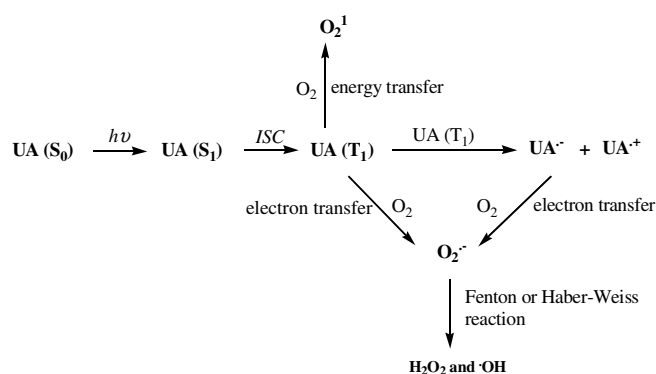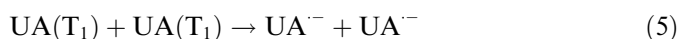[b] $VIP_{T_1} = VIP_{S_0} - E_{T_1}$.

Fig. 2. Theoretically proposed photosensitization mechanisms of urocanic acid.

tent from the strong electron-donating ability of the T_1 state UA in its anion form. Similar photosensitization mechanisms have also been observed for some photosensitizers existing in anion form in solution in our previous studies [14,29].

Moreover, the T_1 state UA may also react with neighboring S_0 state (Eq. (4)) or T_1 state (Eq. (5)) UA to give birth to corresponding anion-cation radical couples, termed autoionization reactions. Then, the anion radical could then pass it's extra electron to $^3O_2$, forming O_2^- and regenerating ground state UA (Eq. (6)).

$$UA(T_1) + UA \rightarrow UA^{\cdot-} + UA^{\cdot-} \qquad (4)$$

$$UA(T_1) + UA(T_1) \rightarrow UA^{\cdot-} + UA^{\cdot-} \qquad (5)$$

$$UA^{\cdot-} + {}^3O_2 \rightarrow UA + O_2^- \qquad (6)$$

According to the theoretically estimated VEA and VIP of UA in S_0 and T_1 states (Table 1), the probability of each reaction is explored. As to reaction (4), the summation of the VEA_{T_1} (−4.11 eV for *trans*-UA and −3.63 eV for *cis*-UA) and the VIP_{S_0} (5.78 eV for *trans*-UA and 5.41 eV for *cis*-UA) of UA is positive, implying that this reaction is unfavorable from the thermodynamic point of view. In comparison, reaction (5) is permitted owing to its negative total reaction energy (VEA_{T_1} (−4.11 eV for *trans*-UA and −3.63 eV for *cis*-UA) + VIP_{T_1} (2.94 eV for *trans*-UA and 2.33 eV for *cis*-UA)), which results in the formation of $UA^{\cdot-}$. Our calculations suggest that $UA^{\cdot-}$ can then easily pass the extra electron to $^3O_2$ to generate O_2^- for the negative reaction energy (AEA_{O2} (−3.81 eV) − VEA_{S_0} (−1.27 eV for *trans*-UA and −0.55 eV for *cis*-UA)). This accounts for the second O_2^--photogenerating pathway of UA besides the direct electron transfer reaction between T_1 state UA and $^3O_2$ as proposed above (Fig. 2). Once O_2^- is generated, through Fenton reaction [30] or Haber-Weiss reaction [31], other ROS (e.g., H_2O_2 and $^\cdot OH$) can be produced subsequently, which will amplify the photosensitizing activity of UA.

To summarize, the present study gains some deeper insights into the mechanisms of the ROS photochemical generation by UA (Fig. 2), which will be helpful to understand the photosensitizing activity of UA during the deleterious biological processes.

Acknowledgements

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