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A theoretical study of a series of water-soluble triphenylamine photosensitizers for two-photon photodynamic therapy

Xin Wang^{a,b}, Xue Yin^a, Xiao-Yong Lai^a, Ying-Tao Liu^{a,*}^a State Key Laboratory of High-efficiency Coal Utilization and Green Chemical Engineering, College of Chemistry and Chemical Engineering, Ningxia University, Yinchuan 750021, China^b International Joint Research Laboratory of Nano-Micro Architecture Chemistry, Institute of Theoretical Chemistry, Jilin University, Changchun 130023, China

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ABSTRACT

In this study, the therapeutic activity of a series of water-soluble triphenylamine (TP) photosensitizers (Ps) was explored by using theoretical simulations. The key photophysical parameters which determined the efficiency of Ps, such as absorption electronic spectra, singlet-triplet energy gaps and spin-orbit matrix elements were calculated at density functional theory and its time-dependent extension (DFT, TD-DFT). The calculated results showed that these TP photosensitizers possessed large two-photon absorption cross-section in the near-infrared region (NIR), efficient intersystem crossing (ISC) transition from the first singlet excited state to the low lying triplet excited states and sufficient energy for generating reactive oxygen species (ROS). These suitable features made these TP series holding great promise for applications in two-photon photodynamic therapy (PDT). These TP photosensitizers studied here in principle extended the application range of two-photon PDT in water solution.

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1. Introduction

Photodynamic therapy (PDT) emerged as a non-invasive medical technique for treating cancer has received increasing attention over the last years [1–4]. The drugs used in PDT were photosensitizers (Ps) which could be activated at the photo exposed malignant tissues, generating reactive oxygen species (ROS), such as singlet oxygen (1O_2), to damage tumours [5–7]. The PDT could be carried out by the following three steps [8]. Firstly, the photosensitizer was excited from the ground state (S_0) to its first singlet excited state (S_1) by a specific light. Secondly, the S_1 state of photosensitizer decayed to its triplet excited state (T_1) through efficient intersystem crossing (ISC) transition, and the spin-orbit coupling (SOC) constants should be greater than 0.24 cm^{-1} [9,10]. Thirdly, the energy of T_1 state was transferred to molecular oxygen (3O_2), and then the ROS was formed. This phenomenon could occur only if the triplet state of the used photosensitizer lied above 0.98 eV [11].

To efficiently generate ROS, a good photosensitizer must possess an electronic absorption peak falling in the near-infrared (NIR) region (the so-called therapeutic window that ranged from 600 to 900 nm), which allowing light easily permeate into the tissues [8,12]. However, if the NIR light beyond 750 nm was directly used in the one-photon excitation mode, the energy of the triplet states for singlet oxygen production would be insufficient [13]. Fortunately, an alternative two-photon

activated photodynamic therapy and efficient two-photon absorption (TPA) molecules have been widely reported [14–16]. In two-photon absorption, two photons were simultaneously absorbed to an excited state, and the total energy of two absorbed photons matched well with the energy gap between the excited state and the ground state. In contrast to traditional one-photon activated PDT, two-photon activated PDT had a good performance in increasing the treatment depth by using a near-infrared two-photon laser. Besides increasing light penetration, the two-photon activated PDT ensured a sufficient energy for ROS production to establish PDT for cancer treatment. Additionally, a desired result may be obtained by precisely addressing two-photon excitation potentially where a potential damage of tissue surrounding treated area can be minimized. Therefore, the two-photon activated PDT would be a promising approach to the treatment of cancer. However, the development of therapeutic applications of two-photon activated PDT also suffered from several limitations, such as the photosensitive drugs had low two-photon absorption cross-section, low water solubility and poor photostability.

As we known, the triphenylamine (TP) compounds represented a new class of water-soluble organic photosensitizers with direct two-photon absorption, which could be used as two-photon Ps in cancer cells [17,18]. These TP compounds (TPs) usually had 2 or 3 vinyl branches with pyridinium (Py) or *N*-methyl benzimidazolium (Bzim) as electron-acceptor groups. Since more rigid 2, 5-diaryloxazoles were known as efficient two photon absorbers, a series of oxazole (Ox) ring TP derivatives were achieved [19]. It was worth noting that the Ox ring was more prone to isomerization. When the Ox ring was tethered

* Corresponding author.

E-mail address: liuyingtao2004@126.com (Y.-T. Liu).

to the triphenylamine core with different connections, two analogous TP-Ox2Py and TP-Ox5Py sets could be synthesized. Since the Bzim group was proven to be more effective than the pyridinium in the two-photon PDT, a TP-Ox5Bzim set was also synthesized [17,18,20]. The substitution of the vinylic bond by an oxazole ring was expected to increase the two-photon absorption properties of the TP scaffold photosensitizers in water solution. In order to get two-photon absorption materials with improved two-photon absorption property, the conjugated links between the electron-rich TP donor core and the electron-acceptor Py and Bzim branches has been further modified by ethynyl (Ey) on the basis of the previous works [21–25]. This series of TP compounds were named TP-2EyPy, TP-3EyPy, TP-2EyBzim and TP-3EyBzim to distinguish from the previous TP series with vinyl bond or oxazole (Ox) ring linker (see Fig. 1), and some of these TP compounds were either known to be, or could be two-photon PDT photosensitizers [24,25].

The development of conjugated organic molecules with large two-photon absorption cross-sections were interest of broad researchers [26,27]. The basic strategy they used to improve two-photon absorption cross-section was to increase the degree of conjugation and the length of charge transfer during excitation. Therefore, to get a new and efficient two-photon TP photosensitizer for PDT, it was worth while studying the relationship between the structures and properties of these alkene, alkyne and oxazole branched TP sensitizers. We hoped this study would be aid of interpreting experimental data in one aspect, and predict which molecules were more likely to be valuable photosensitizers and worth extensive efforts to synthesis in another aspect.

2. Computation Method

Ground state molecular optimizations were performed at the B3LYP/6-31G(d) [28] level of density functional theory (DFT) which could regularly predict the performances of organic molecules. The frequency calculations were carried out to confirm that all the optimized structures were real minima on the respective potential energy surfaces. The time-dependent DFT (TD-DFT) method was employed for the frontier molecular orbitals properties and absorption spectra calculation. To mimic the experimental environment, the calculations have been performed in aqueous solution by means of the polarizable continuum model (PCM) [29,30]. Different TD-DFT methods were employed for one-photon absorption (OPA) calculation at the B3LYP optimized geometries. Selecting an appropriate functional for the OPA calculation was extremely important to ensure correct prediction results. Here the TP-2Py was taken as an example, the performance of different exchange correlation functionals, namely PBE0 [31,32], B3LYP [33,34], M06 [35], BHandHLYP [36], M062X [37], CAMB3LYP [38] and ω B97XD [39] functionals were compared. The calculated OPA results obtained from different functionals were shown in Table S-1. It can be seen from Table S-1 that the maximum absorption wavelength obtained by

M062X (467.0 nm) functional was closer to the experimental data (474.0 nm) than other tested functional models. Hence, the M062X functional was employed to calculate the OPA properties in this paper. The calculations present above were accomplished in the Gaussian09 software package [40].

Moreover, the two-photon absorption (TPA) cross-section which could represent the TPA characters was evaluated by means of quadratic response theory in DALTON program [41]. Meanwhile, the spine orbit coupling matrix elements (ξ) between the lowest singlet and low lying triplet states were also computed by using the DALTON code [41]. Due to few hybrid functionals could be available in DALTON program, typical B3LYP and CAMB3LYP functional were selected to be used in the calculation of TPA properties and spine orbit coupling matrix elements. After comprehensive consideration of all results, we found that CAMB3LYP function in the DALTON program was more suitable for these TP compounds. The functional comparison in the DALTON program is also listed in Table S-1.

3. Results and Discussion

3.1. Molecular Geometries

The optimized geometries of the investigated TP photosensitizers were reported in Fig. 2. By deliberately combining the electron-rich TP core with two or three cationic electron-acceptor groups via a conjugated link, the TP scaffold allowed building of V-shaped structures with a strong quadrupolar character for the two-branched derivatives and octupolar structures for the three-branched derivatives. These TP compounds could be divided into three parts, the electron-rich TP core, the cationic electron-acceptor groups, and the conjugated link between the donor core and the electron-acceptor branches. To get better photophysical properties for the TP photosensitizers, we set out to explore the effect of the conjugated link and the electron-acceptor branches for the TPs structures.

As show in Fig. 2, the TP-OxPy and TP-EyPy series were achieved through changing the vinyl bond by oxazole (Ox) ring and ethynyl (Ey) bond in the part of the conjugated link. Moreover, two different analogous TP-Ox2Py and TP-Ox5Py series were presented due to the different possible connection of the Ox group. On the other hand, the TP-Bzim, TP-OxBzim and TP-EyBzim series were obtained through replacing the Py group by Bzim group in the electron-acceptor units. In this work, the ammonium groups appeared in electron-acceptor branches to ensure better water solubility. In addition, the photo physical properties of three-branched TPs would be different from those of the two-branched ones. Hence, the different spectra features, induced by different conjugated structures and different electron-acceptor moieties, would be discussed in detail in the following sections.

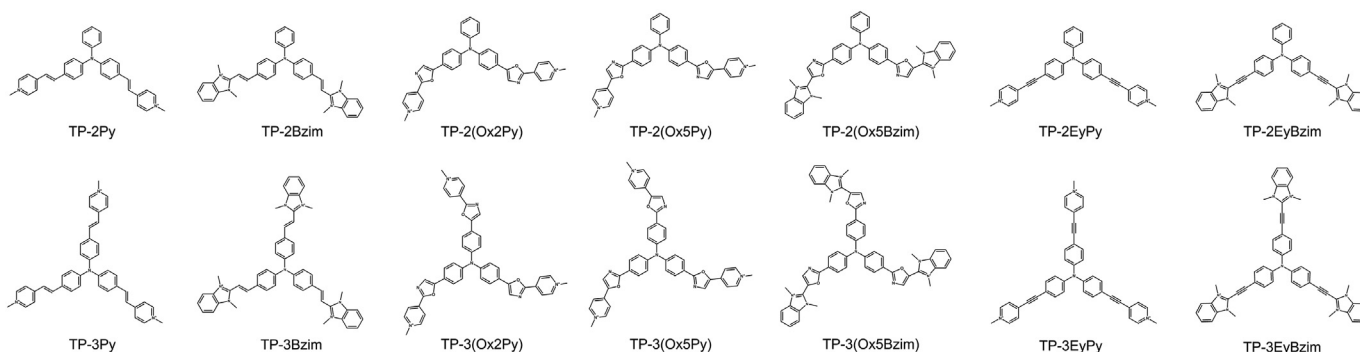


Fig. 1. The chemical structures of all the TP compounds investigated in this work.

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