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Theoretical investigation of N^C^N-coordinated Pt(II) and Pd(II) complexes for long-lived two-photon photodynamic therapy

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ABSTRACT

Transition metal complexes capable of near-infrared light triggered-cytotoxicity are actively being developed as potential photosensitizers (PS) for photodynamic therapy (PDT) of cancers. In the present work, the structures and photophysical properties of complexes Pt(N^C^N)Cl and Pd(N^C^N)Cl (N^C^N = 2,6-dipyrido-4-methyl-benzenechloride) are investigated with a theoretical approach. The features of low-lying singlet and triplet excited states are discussed in detail. Their potential therapeutic use as two-photon PS in PDT is proposed on the basis of their strong absorbance in near-infrared region (NIR), vertical triplet energies resulting higher than 0.98 eV, and the spin-orbit matrix elements lager than 0.24 cm^{-1}. Moreover, an evaluation of triplet excited states lifetime is presented. The longer lifetime of the triplet excited states would lead to higher $^1O_2$ yields for Pd(N^C^N)Cl compared to Pt(N^C^N)Cl. It is expected that the low-cost Pd(N^C^N)Cl will replace the reported Pt(N^C^N)Cl as a promising two-photon PS for improving clinical PDT efficacy.

1. Introduction

There are increasing evidences showing that photodynamic therapy (PDT) played a vital role in cancer treatment due to its minor systemic toxicity, high selectivity, and non-invasive characteristics [1,2]. This treatment option involves the administration of photosensitizers (PS) and exposure of the malignant tissue to light irradiation with appropriate wavelength to induce the formation of reactive oxygen species (ROS), to damage diseased tissue [3,4]. Under proper light excitation, an excited photosensitizer (PS*) can undergo type I (electron transfer) or type II (energy transfer) reaction to generate ROS [5–8]. Specifically, type I reaction generate radical and radical anion species ($O_2^{\bullet(-)}$ or HO•), while type II reactions can produce highly cytotoxic singlet oxygen ($^1O_2$) via transferring energy to nearby oxygen molecules to kill targeted cell [9,10]. Being an extremely powerful oxidant, the $^1O_2$ is the principal cytotoxic species in PDT [11,12]. Although the T_1 deactivating pathways are in competition among them, type II reactions generally predominate over the other. Obviously, the development of PS will create more opportunities for PDT applications. Actually, a variety of PDT agents have been approved for clinical use or undergoing clinical trials, including organic compounds and metal complexes [13–18].

The photophysical properties of many transition metal complexes make them as ideal PS candidates for PDT [15–17]. Transition metal complexes are particularly promising for many reasons. Firstly, this series usually can be synthesized versatilely. Secondly, the chemical and photophysical properties of them can be tuned easily, such as the range and the intensity of absorption spectra. Thirdly, the lifetime of triplet excited states (T_1) is comparatively longer than that of the singlet excited states (S_1) of organic compounds due to the formally spin-forbidden nature of triplet to singlet ($T_1 \rightarrow S_0$) transition. Finally, the intersystem crossing (ISC) between the singlet and triplet excited states ($S_m \rightarrow T_n$) is more efficient for metal complexes compared to the organic compounds because of the strong spin-orbit coupling promoted by the heavy metal atoms. Above all, transition metal complexes could offer many advantages over conventional organic dyes, and they will open up new horizons in biomedicine.

To successfully apply the transition metal complexes in PDT, the light must reach the tissue in depth. Therefore, long wavelengths of light (600–800 nm) are an ideal excited light source. This range of

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wavelengths can avoid injuring endogenous chromospheres within the body, and still improve the penetration depth in tissues [19,20]. However, currently available metal complexes are plagued by many issues, for example, the UV–vis region of the maximum absorption has limited their therapeutic applications. To tackle this drawback, two-photon PDT agents have been investigated over recent years as nice alternatives to the current PS irradiated by high-energy one-photon laser beam. The transition metal complexes with TPA properties have exhibited great advantages in the field of PDT. Contrary to one-photon PDT, two-photon PDT which use low-energy near-infrared (NIR) two-photon laser irradiation can provide deeper penetration in malignant tissues and sufficient energy to generate ROS [21–24].

Although two-photon PDT has attracted a great deal of interests, reports about transition metal complexes used as two-photon PDT agents are scarce and far less than those used as one-photon PS. In addition, there are few examples of metal complexes with both long wavelength and long-lived excited states. Recently, a platinum based compound, Pt(NˆCˆN)Cl (NˆCˆN = 2,6-dipyrido-4-methyl-benzenechloride) has been reported as an efficient photosensitizer for PDT [16]. Neither activating the photosensitizer by 405 nm light nor 780 nm light will cause significant cell death of cancers. The key advantages of the highly promising PDT agent are owing to the enhanced near-infrared (NIR) two-photon light absorption and the long-lived excited states, which are required to maximize the yield of ROS in the therapy. The Pt(NˆCˆN)Cl complex is proposed for the first time as a two-photon PDT agent among different reports about it [16,25–31]. However, from an economical viewpoint, the development of new two-photon PDT agents containing low-cost metals is desirable. In 2004, a Pd(NˆCˆN)Cl complex with tridentate NˆCˆN pincer ligand (NˆCˆN = 1,3-di(2-pyridyl)benzene) has been synthesized in experiment [32]. Unlike complex Pt(NˆCˆN)Cl, the excited properties of Pd(NˆCˆN)Cl are never been studied so far. But the Pd(NˆCˆN)Cl complex has a typical d^8 electronic configuration with dsp^2 hybridization and square-planar structure, like Pt(NˆCˆN)Cl. The conjugated π bond of aromatic ligand mixed with d_π(Pd) orbitals could facilitate charge migration and energy transfer. Moreover, metal Pd is much cheaper compared to metal Pt. So Pd(NˆCˆN)Cl is a good complex to do some valuable research.

Theoretical investigation is known to become indispensable to obtain the relationship between structures and properties of the excited states. Hence, we intend to provide a theoretical study on photophysical properties of Pd(NˆCˆN)Cl to seek cancer therapeutic agents which is cheaper than Pt(NˆCˆN)Cl. In this work, the PDT effect of Pt(NˆCˆN)Cl and Pd(NˆCˆN)Cl complexes (NˆCˆN = 2,6-dipyrido-4-methyl-benzenechloride) (Fig. 1) is investigated and compared. Herein, the one-photon and two-photon absorption wavelengths, two-photon absorption cross-sections, electronic transitions properties, lowest triplet excited states properties and spin-orbit coupling constants are calculated by Density Functional Theory (DFT) and its Time-Dependent Density Functional Theory (TD-DFT). It is expected that this study would provide an in-depth understanding of the optical and electronic properties of these complexes, and provide some useful information for the experimentalist.

2. Methodology

Nowadays, Density Functional Theory (DFT) and Time-Dependent Density Functional Theory (TD-DFT) have emerged as effective instrument to calculate the structures and properties of the ground and excited states. Thanks to Yang and co-workers, much theoretical work has been accomplished with Pt(NˆCˆN)Cl compounds [29,30]. For this series of Pt(II) complexes, PBE0 [33,34] has been proved to outperform other functionals to optimize structures in the ground states (S_0), while TPSSh [35] functional is found to be the most appropriate to calculate absorption properties. So, in this article, geometry optimizations are carried out for M(NˆCˆN)Cl (M = Pt and Pd) using a density functional theory (DFT) method at the level of PBE0. Stable configurations of these complexes are confirmed by the vibrational frequency analysis, in which no imaginary frequency is found for all configurations at the energy minima. Meanwhile, the absorption spectral properties are explored using TDDFT method under TPSSh level. In order to be consistent with the experimental measurements, the geometry optimization and absorption calculation are both performed in dichloromethane (CH_2Cl_2) solution using the popular polarizable continuum model (PCM) [36,37]. In all the calculations, 6–31G(d) and 6-311 + G(d) basis sets are adopted for C, N and H atoms and Cl atom, respectively, and the SDD basis sets [38] associated with the pseudo potential are adopted for metal atoms (Pt and Pd) as the previous jobs [29,30]. The lowest triplet excited geometries (T_1) are also computed by DFT with unrestricted PBE0 (UPBE0) functional. All of the above computations are performed using the Gaussian09 program package running on the high-performance computing clusters [39].

In order to probe the two-photon PDT applicability of the presented Pt(NˆCˆN)Cl and Pd(NˆCˆN)Cl complexes, the two-photon absorption cross-section which can represent the TPA characters are evaluates by means of quadratic response theory in DALTON program [40]. Meanwhile, the spin orbit coupling matrix elements ($\hat{H}_{SO}$) between the lowest singlet and low-lying triplet states and the lifetimes of the first triplet excited states are also computed by using the DALTON code [40]. Because of few hybrid functionals available in DALTON, B3LYP functional [41,42] is selected on these calculations through comprehensive consideration of all results. The two-photon absorption is calculated based on the previously PBE0 optimized structures at S_0 states, while the $\hat{H}_{SO}$ values and T_1 lifetimes are calculated based on the UPBE0 optimized structures at T_1 states. In addition, all the calculations have been carried out by using the Breit-Pauli method.

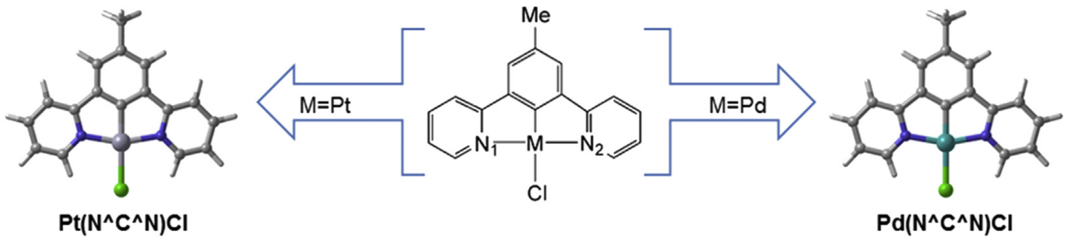

Fig. 1. Sketched map and optimized S_0 structures of complexes Pt(NˆCˆN)Cl and Pd(NˆCˆN)Cl.