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A fluorescence turn-on and colorimetric probe based on a diketopyrrolopyrrole–tellurophene conjugate for efficient detection of hydrogen peroxide and glutathione

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ABSTRACT

A reversible probe based on diketopyrrolopyrrole–tellurophene conjugate for the detection of reactive oxygen species has been designed and synthesized. The probe utilizes the redox properties of the tellurium atom for the detection of reactive oxygen species and exhibits high selectivity and sensitivity towards H_2O_2; the presence of which is demonstrated by a fluorescent signal. In addition to fluorescence signal, the probe displayed a color change from light blue to light purple upon oxidation by H_2O_2 in aqueous media. The generated tellurophene-1-oxide may be quickly reduced by glutathione to regenerate the original diketopyrrolopyrrole–tellurophene conjugate. The probe can be applied to monitor the concentration of H_2O_2 in aqueous solution over an approximate pH range 3.8–8.0.

1. Introduction

Reactive oxygen species (ROS) play significant roles in cell signaling and various biological processes in normal cells [1,2]. However, they also pose a threat to cell structures when their overproduction occurs under environmental stress. Therefore, the selective detection and removal of these species from the biological system is an issue of medicinal and ecological importance [3–5]. Hydrogen peroxide (H_2O_2) is one of the main ROS produced during the activity of almost all oxidases [6,7] can lead to diverse physiological and pathological events in aerobic organisms. Usually, it is embedded in all aerobic cells in balance with biochemical antioxidants. At normal physiological concentrations (<20 nM), H_2O_2 serves as a second messenger for normal cellular growth and proliferation [8]. However, due to oxidative stress an imbalance occurs between the production of H_2O_2 and antioxidant defence systems. Generally living cells are protected from oxidative stresses by intracellular redox systems, such as glutathione (GSH) and thioredoxin [9,10]. As a result, intracellular levels of either H_2O_2 or GSH can be strongly attributed to the degree of oxidative stress in living cells.

Several types of probes are available for the detection of H_2O_2 and other ROS, including analogs of fluorescein and rhodamine as well as lanthanide coordination complexes [11–17] that generate fluorescent products whose emissive behavior is generally irreversible. Recently, Han and Nagano et al. reported a near-infrared (NIR) fluorescence probe for the detection of ROS that was operated by employing the redox properties of the Te atom [18,19]. Also, Oba et al. reported the conversion of diaryl telluride to diaryl telluroxide by singlet oxygen ($^1O_2$) [20].

Herein, we present the design and synthesis of an electron deficient diketopyrrolopyrrole (DPP)-based compound **3** linked with a tellurophene moiety. Compound **3** can respond to both H_2O_2 (by using the redox properties of S and Te) [21] and thiol (*via* the bicyclic lactam chromophore unit of DPP) [22]. DPP unit has been used for designing organic semiconducting materials for field effect transistors [23,24] and photovoltaics devices [25–27]. Recently, a variety of fluorescent molecular probes based on DPP have been developed for the detection of various analytes such as Zn^{2+}, F^-, CN^-, cysteine and DNA in addition to its use as a pH sensor [28–40]. However, DPP–tellurophene based small organic molecules have not been reported for detecting important species such as H_2O_2 and

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GSH in biological conditions. Our approach to perform reversible detection of ROS with compound **3** is illustrated in Scheme 1.

2. Experimental

2.1. Materials and instruments

All solvents used were of analytical grade. Solvents were dried according to standard procedures. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using Spectrochem GF254 silica gel-coated plates. Chromatography was performed with silica 100–200 mesh. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury NMR spectrometer (300 MHz and 400 MHz) using deuterated chloroform purchased from Cambridge Isotope Laboratories; chemical shifts are given in ppm with tetramethylsilane (TMS) as an internal reference. Coupling constants (J) are given in hertz (Hz). Signals are abbreviated as follows: singlet, s; doublet, d; double-doublet, dd; triplet, t; multiplet, m. Elemental analyses were performed using an EA1112 (Thermo Electron Corp.) elemental analyzer. Thermal properties were studied under a nitrogen atmosphere on a Mettler DSC 821^{e} instrument. Mass spectra were recorded on a Shimadzu LCMS-2020 (Liquid Chromatograph Mass Spectrometer). UV–vis absorption spectra were obtained using a UV–vis absorption spectrometer (HP 8453, photodiode array type) in the wavelength range of 190–1100 nm. The fluorescence spectra were recorded with a Hitachi F-7000 fluorescence spectrophotometer with a slit width of (10 nm) used for excitation and emission. Compounds **1** and **2** were synthesized according to literature procedures [41–43]. Density functional theory (DFT theoretical calculations) was studied by using the Spartan program ('10) with basis set (B3LYP/6-31G*) for compound **5**. For compound **3**, calculations of the highest-occupied molecular orbital (HOMO), lowest-unoccupied molecular orbital (LUMO) energy levels, and triplet energy were performed using density functional theory (DFT) with the B3LYP functional. The 6-31G(d) basis set was used for the calculation of molecular orbital energy levels and total energies of molecules. All calculations were performed using DMol3 implemented in the Materials Studio 6.0 package (Accelrys, Inc.).

2.2. Determination of binding constant

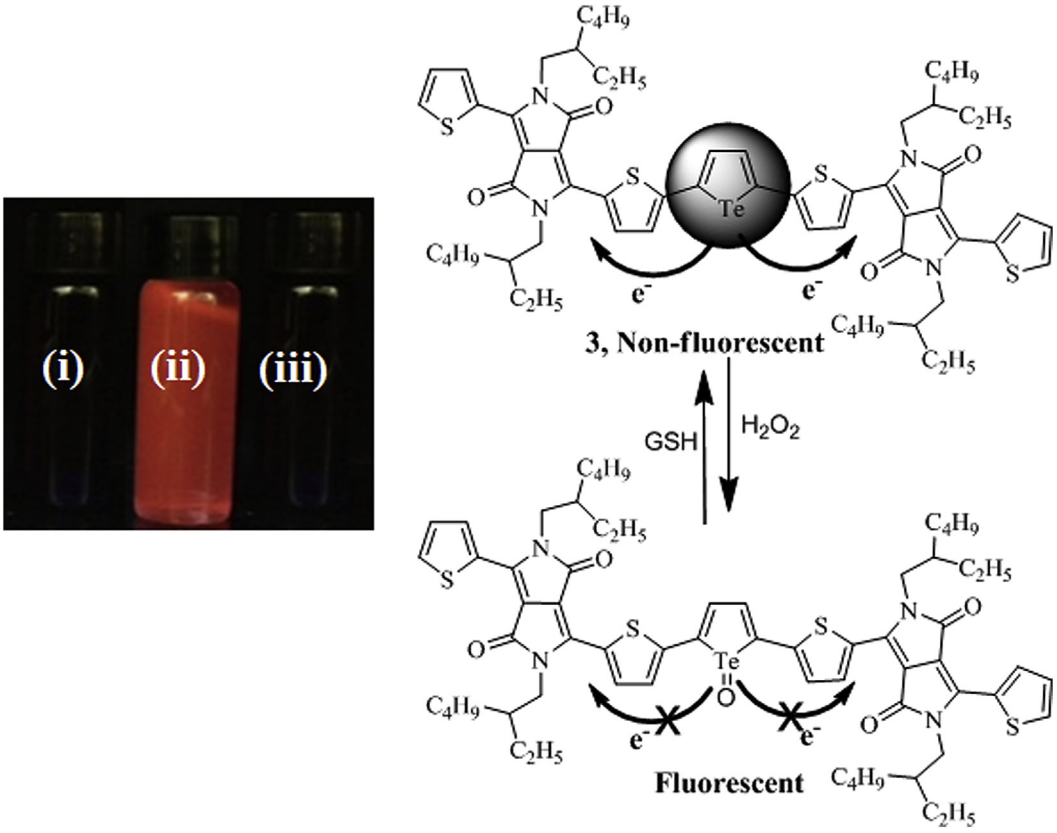
Binding constants for compound **3**-H_2O_2/GSH complex were calculated using Benesi–Hildebrand Equation [44].

$$1/\left(A_f - A_{obs}\right) = 1/\left(A_f - A_{fc}\right) + 1/K\left(A_f - A_{fc}\right)\,[\text{Ligand}]$$

where A_f is absorbance of free host, A_{obs} is absorbance observed, A_{fc} is absorbance at saturation, K is the binding constant.

2.3. Synthesis of compound **3**

A mixture of compound **1** (0.39 g, 0.656 mmol), compound **2** (0.17 g, 0.328 mmol) and catalyst $Pd(PPh_3)_4$ (0.019 g, 0.016 mmol) were placed in toluene (20 mL) and heated at 90 °C for 10 h. After completion of the reaction monitored by TLC, the solvent was evaporated under vacuum. The product was then purified by column chromatography (Hexane: CH_2Cl_2, 1:2 as eluent) to get dark blue solid in 88% yield (370 mg), mp = 166 °C, ν_{max} (KBr)/cm^{-1}: 2932–2864 (alkyl C–H stretch), 1660 (C=O), 1552 (C=C aromatic



Scheme 1. Design strategy based on redox properties of tellurium atom, structure, and detection mechanism of compound **3** and its oxidized form. Optical images under the illumination of UV light (λ = 366 nm): in HEPES buffer/DMSO (8:2, v/v, pH 7.4): (i) compound **3**; (ii) compound **3** with H_2O_2; (iii) GSH was added to the solution of compound **3** after oxidizing by H_2O_2.