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Synthesis of Triazole-Coupled Quinoline-Based Fluorescent Sensor

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Abstract: Fluorescent sensor is one of the most important chemical sensors and is a powerful tool for imaging target molecules and ions in the living organism. Because it has high sensitivity and simultaneous imaging. In this work, fluorescence chemosensor was designed based on ionophore-bridge-fluorophore approach. In the structure of the designed chemosensor, anthracene unit was used as fluorophore. The receptoric hydroxy quinoline group to interact with the metal ion were incorporated into the structure by the triazole bridge which has high coordination properties. Detection of a specific type of a metal is very important in terms of biouse of the related compound. In addition to the synthetic approach, the metal coordination propertiess of the novel chemosensors will be investigated theoretically at the level of Density Functional theory with the application of B3LYP/6-31++G(d,p), which is a combination of hibrit exchange function and basis set.

Keywords: Fluorescent Sensor, Anthracene, Triazole

Introduction

In recent years, more and more attentions have been drawn to devise ingenious fluorescent sensors capable of selective recognition and effectively detecting the presence of alkali, alkaline earth and transition metal ions because of their importance in biological systems as well as to environmental concerned [1,2]. However, among different chemosensors, fluorescence-based ones present many advantages as fluorescence measurements are usually very sensitive, low cost, easily performed and versatile, offering subnanometer spatial resolution with submicron visualization and submillisecond temporal resolution [3,4].

8-Hydroxyquinoline is one of the widely used chelating moieties for metal ion coordination, and quite a number of chemically modified 8-hydroxyquinoline derivatives have been used as metal binding probes [5-9]. 8-HQ was introduced into fluorescent probes acting as a metal ion chelating agent for metal ions detection. Triazole substituted 8-HQ could furnish an extra binding site, and might inhibit the possible excited-state intramolecular proton transfer (ESIPT) event.

The chemistry of 1,2,3-triazole derivatives has gained interest over the past few years due to their wide range of applications in chemical, biological, medicinal, and materials science. The Huisgen 1,3-dipolar cycloaddition of azides and alkynes is the most efficient pathway for the synthesis of substituted 1,2,3-triazoles as chemotherapeutic agents [10-11], synthetic intermediates for bioactive compounds, agrochemicals, optical brighteners, photostabilizers, anticorrosive agents, and metal chelators [12-14]. The extraordinary stability toward metabolic transformations and aromatic nature of the triazole ring along with its high dipole moment and H-bonding capability, makes it an important functionality as a connecting group [15-18].

In the present study, the synthetic typical motif consist of a core fluorescent signaling unit of anthracene, which is well connected with oxyquinoline through triazole bridge, to generate a suitable ionophore site that has great affinity to coordinate with a metal ion.

- Selection and peer-review under responsibility of the Organizing Committee of the Conference

Method

General

All the chemicals used in the biologic assay studies were purchased from Sigma (Sigma-Aldrich GmbH, Sternheim, Germany). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Agilent NMR spectrometer (400 MHz). ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ and the chemical shifts are expressed in ppm relative to $CDCl_3$ (δ 7.26 and 77.0 for ^{1}H and ^{13}C NMR, respectively) as the internal standard.

Flash column chromatography was performed by using thick-walled glass columns and silica gel (60-mesh; Merck). The reactions were monitored by thin-layer chromatography (TLC) using Merck 0.2-mm silica gel 60 F254 analytical aluminium plates, visualized by UV light.

Synthesis of Fluorescent Sensor

8-(prop-2-ynyloxy)quinoline-2-carbaldehyde, **2.**

8-hydroxyquinoline-2-carbaldehyde (1.0 g, 5.7 mmol) was dissolved in 30 mL THF. K_2CO_3 (2.0 g, 15 mmol) was added and the mixture was refluxed for 30 min. Then, propargyl bromide (1 mL, 6.8 mmol) was added slowly. Reaction mixture was refluxed overnight. After TLC control, reaction mixture was cooled and filtered. Solvent was evaporated under vacuum and crude product was purified by flash column chromatography (EtOAc: Hexane 1:4).

White solid. (1.03 g, 86% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.28 (s, 1H), 8.27 (dd, *J*=0.7 and 8.5 Hz, 1H), 8.04 (d, *J*=8.5 Hz, 1H), 7.63-7.59 (m, 1H), 7.50 (dd, *J*=1.2 and 8.3 Hz, 1H), 7.34 (dd, *J*=1.2 and 7.8 Hz, 1H), 5.08 (d, *J*=2.4 Hz, 2H), 2.57 (t, *J*=2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.6, 153.7, 151.6, 140.0, 137.3, 131.4, 129.4, 120.6, 117.9, 111.0, 77.8, 76.6, 56.9.

9-(azidomethyl)anthracene, **4.**

9-(Chloromethyl)anthracene (227 mg, 1 mmol) ve NaN_3 (130 mg, 2 mmol) were dissolved in 20 mL CH_3CN and refluxed overnight at 85 °C. After all starting compounds were consumed, reaction mixture was filtered and solvent was evaporated under vacuum. Crude product was purified by flash column chromatography by EtOAc:Hexane mixture (1:15).

Yellow solid. (228 mg, 98% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.51 (s, 1H), 8.32-8.28 (m, 2H), 8.07-8.06 (m, 1H), 8.05-8.04 (m, 1H), 7.62-7.58 (m, 2H), 7.54-7.50 (m, 2H), 5.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 131.4, 130.7, 129.3, 129.0, 126.8, 125.8, 125.2, 123.5, 46.3.

8-((1-(anthracen-9-ylmethyl)-1H-1,2,3-triazol-4-yl)methoxy)quinoline-2carbaldehyde, **5.**

8-(prop-2-ynyloxy)quinoline-2-carbaldehyde, **2** (211 mg, 1 mmol) and 9-(azidomethyl)anthracene, **4** (233 mg, 1 mmol) were dissolved in 5 mL THF:H_2O (4:1). $CuSO_4.5H_2O$ (25 mg, 0.1 mmol) and sodium ascorbate (40 mg, 0.2 mmol) were added and reaction mixture was mixed overnight at room temperature. After the reaction was complete, water was added and extracted with EtOAc. Product was purified by flash column chromatography by EtOAc:Hexane (1:1) .

Yellow solid. (360 mg, 81% yield); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.98 (s, 1H), 8.57 (s, 1H), 8.30-8.28 (m, 2H), 8.21-8.19 (m, 1H), 8.08-8.06 (m, 2H), 7.96 (d, *J*=8.5 Hz, 1H), 7.60-7.50 (m, 5H), 7.43-7.40 (m, 2H), 7.36-7.34 (m, 1H), 6.55 (s, 2H), 5.41 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 193.6, 154.6, 151.3, 143.7, 140.0, 137.2, 131.4, 131.2, 130.7, 130.0, 129.7, 129.5, 127.7, 125.4, 123.5, 123.0, 122.9, 120.2, 117.7, 111.3, 63.5, 46.5.

Computational Method

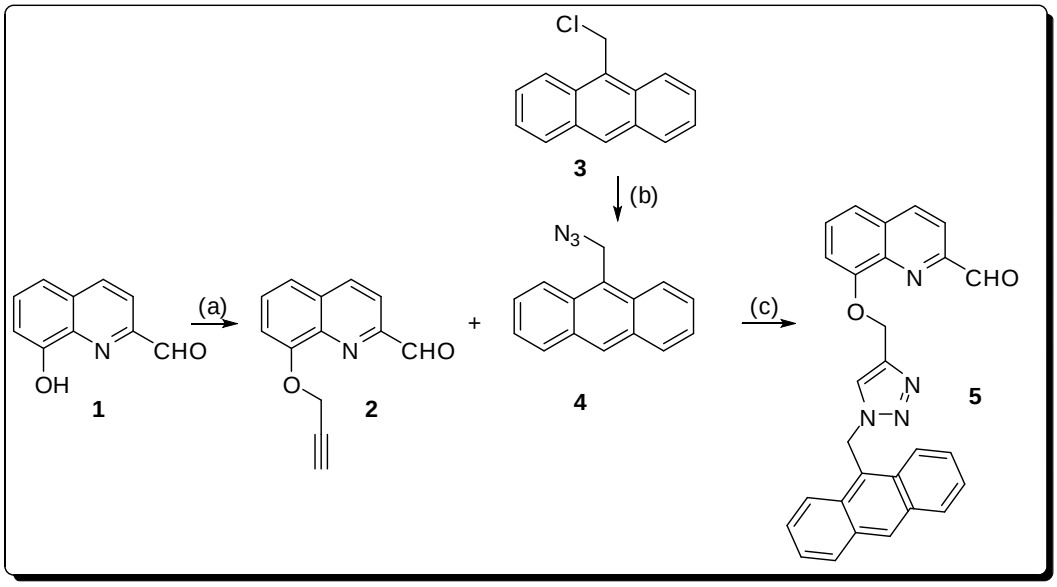
The three-dimensional ground state (S_0) geometry of the compound was geometry optimized using Density Functional Theory (DFT) by using the Gaussian 09W package program and the hybrid functional B3LYP. The B3LYP is composed of Becke's three parameter exchange functional (B3) and the nonlocal correlation functional by Lee, Yang, and Parr (LYP). The basis set used for all atoms was 6-31++G(d,p) in both DFT and time-dependent density functional theory (TD-DFT) method. We have applied default G09 grid for computations.

For the nonel compound, vibrational analyses were carried out using the same basis set employed in the corresponding geometry optimizations. The frequency analysis of none of the compounds yielded any imaginary frequencies, indicating that the structure of each molecule corresponds to at least a local minimum on the potential energy surface. The normal mode analysis was performed for 3N-6 vibrational degrees of freedom, N being the number of atoms in the molecule.

The low-lying triplet (T) and singlet excited states (S) of the compounds were relaxed to obtain their minimum energy geometries using the TD-DFT as implemented in G09 package program. The vertical excitation energies and oscillator strengths were obtained for the lowest triplet and singlet transitions at the optimized ground state equilibrium geometries by using TD-DFT at the same hybrid functional and basis set [22]. Optimized ground state structures were utilized to obtain the electronic absorption spectra, including maximum absorption wavelengths, oscillator strengths, and main configuration assignment by using TD-DFT.

Results and Discussion

The present molecular probe containing quinoline and anthracene fluorophores has been synthesized. The synthetic route adopted for preparation of **5** is shown in Scheme 1. Click chemistry, serving as a linking strategy for the 1, 3 dipolar cycloaddition of alkynes and azide by generating 1, 2, 3-triazoles, has been exploited in the wide variety of areas including bio conjugation, drug design and material chemistry. Meanwhile, the 1,2,3-triazole linker could be exploited for the binding of cations which might be useful in the recognition of metal ions. Based on this statement, the probe **5** was designed (Scheme 1). This could be easily synthesized using the anthracene azide **4** and alkyne of 8-oxyquinoline, **2** in the presence of $CuSO_4$ as a catalyst.



Scheme 1. (a) Propargyl bromide, K_2CO_3, THF; (b) NaN_3, THF; (c) $CuSO_4$, sodium ascorbate

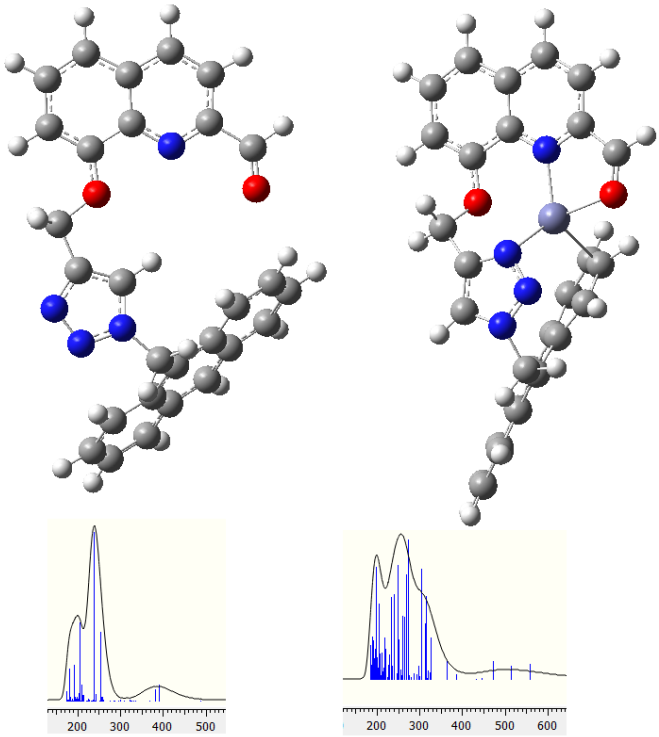


Figure 1. Geometry optimized structures and corresponding UV-VIS spectra of the compounds

Geometry optimizations of the compounds have been performed by the aforementioned method and corresponding UV-VIS spectra have been obtained by the application of TDDFT calculations. Metal coordination has been proven by the change in the UV-VIS spectra since some of the bands faced a red-shift. Upon coordination with the metal (Zn^{2+}) the triazole moiety moved toward the metal to make the coordination stronger.

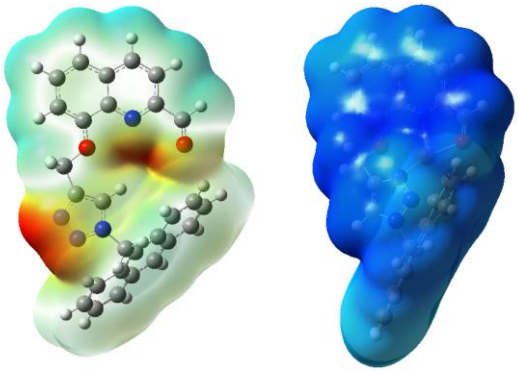


Figure 2. 3D electrostatic potential map for the present compounds.

3D electrostatic potential maps for the compounds indicate that upon coordination of the +2 charged metal cation the charge distribution in the compound changed completely a more uniform charge distribution has been obtained.

Conclusion

In conclusion, propargyl unit was attached to 8-OH of quinoline by O-propargylation and alkyne derivative was obtained. Then, anthracene azide was coupled with this quinoline-alkyne derivative in the presence of Cu(I) catalyst by forming triazole bridge and a novel fluorescent sensor was isolated in good yield. Computational calculations proved the coordination of the metal cation through changes in the electronic spectra and charge distribution in the system.

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