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Emission Pathway Switching by Solvent Polarity: Facile synthesis of Benzofuran-Bipyridine Derivatives and Turn-on Fluorescence Probe for Zinc Ions

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Benzofuran

Bipyridine

Solvatochromism

Emission pathway switching

Turn-ON fluorescence

ABSTRACT

Bipyridine attached benzofuran derivatives were prepared by the cyclization of alkyne *ortho*-substituted phenols. Electronically different substituents, *N,N*-dibutylamino vs *tert*-butyl group, were attached on benzofuran rings. Depending on the polarity and pH of solvent environment, *N,N*-dialkylamino group participates in two distinctively different roles in emissive properties, i.e., ICT-type and PET-type behaviors. Upon capturing lone-pair electrons of *N,N*-dialkylamino groups by protonation, ratiometric blue-shift and complete turn-on behaviors were observed in THF and MeCN solution, respectively. Such peculiar behavior was further utilized to show turn-on sensing of zinc ions.

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Introduction

Small luminescent molecules have been widely used as molecular probes for detecting various ions of interest such as toxic metal ions and anions.^{1–5} Such detection strategy can be categorized into two major schemes, chemical reactions and physical environmental factors.⁶ Both detection schemes are associated with dramatic color changes and/or fluorescence changes (more desirably, fluorescence turn-on responses). In some cases, sophisticated chemical functionalization of the probe molecules is required to reach the most favorable responses in terms of reactivity, selectivity and sensitivity toward the target analyte. For instance, the insertion of electron-donating/withdrawing (push–pull) groups is one of the widely accepted strategies because the electronic push–pull components can provide further control to adjust absorption and emission properties of molecular probes.

On the other hand, bipyridine is a well-known bidentate ligand for many metal ions. Unlike other transition metal ions which typically quench the fluorescence upon binding to the fluorophore, when *d*¹⁰ metal ions such as zinc, cadmium, or mercury bind to bipyridine moiety (or another fluorophore attached bipyridine), the fluorescence often remains unquenched so that binding event can be monitored by shift of emission bands.^{7–12} Among various fluorescent molecules, a benzofuran moiety has been utilized as a skeleton of many fluorophores presumably due to its strong emission with high quantum yield and facile synthesis.^{13–17} In general, elongated conjugation was required to further bring the absorption and emission maximum to the visible region. Therefore, direct functionalization of benzofurans with electronic components can be beneficial to facilitate adjustment of their photophysical properties. Based on

previous research, we envisioned that direct conjunction between bipyridine and benzofuran can potentially be used for fluorescent detection of metal ions. Herein we disclose our work on the synthesis of bipyridine attached benzofuran derivatives and their photophysical properties, which show highly sensitive behaviors relative to local electronic environment, such as solvent polarity.

Results and Discussion

One-pot synthesis of benzofuran derivatives

Historically, there are multiple synthetic pathways of benzofuran derivatives.^{18–25} One of recent major approaches is utilizing a transition metal catalyzed cross-coupling reaction of *ortho*-halogenated phenol, followed by cyclization,^{26–31} including inter-^{32–35} and intramolecular^{36–40} annulation. Amongst these, cyclization reactions of *ortho*-substituted phenols mediated by various catalysts including palladium, copper, and zinc have been widely utilized to prepare benzofuran derivatives.

As shown in Scheme 1, the efficient and modular one-pot synthesis of benzofurans was performed using the Sonogashira cross-coupling reaction,¹² followed by 2-ethynylphenol cyclization under mild conditions. While optimizing the cyclization reaction conditions, we found that acetic anhydride can be directly used to facilitate the *in-situ* protection of phenols during the Sonogashira coupling with 6,6'-diethynyl-2,2'-bipyridine. The corresponding dialkynyl bipyridines were then subjected to cyclization with neighboring phenol groups under reflux conditions to furnish compounds **1** and **2**, which have *tert*-butyl and *N,N*-dibutylamino functional groups, respectively (Scheme 1). We inserted dialkylated-amino groups to probe the functional roles of lone-pair electrons of nitrogen in emissive

behaviors whereas the analogous compound with *tert*-butyl groups serve as control.

Scheme 1. Synthetic route of bipyrindine-benzofuran derivatives.

Absorption spectra and Computational Results

Geometry optimized structure of compound **2** is shown in Figure 1. As anticipated, the core of the entire molecule, including bipyrindine and benzofuran moieties, is in the same plane. All four hetero atoms, two nitrogens on the bipyrindine and two oxygens on the benzofurans, show *transoid*-type arrangement due to the lone-pair electron repulsion.

Figure 1. Ground state optimized geometry of compound **2** at B3LYP/6-31G(d) level of theory.

Calculated absorption wavelengths (λ_{max}) of compounds **1**, **2** and $[\mathbf{2}+\text{H}]^+$ in THF are 332, 334, and 319 nm, respectively. These absorption bands are in excellent agreement with experimentally collected UV-vis absorption spectra. The TD-DFT and UV-Vis computed data for all three compounds is given in the Supplementary Information. The most intense absorption band (63% contribution) of compound **2** can be assigned to $S_0 \rightarrow S_1$ excitation (339.2 nm) while the least intense absorption band (37% contribution) can be assigned to $S_0 \rightarrow S_5$ excitation (324.4 nm). Figure 2 reveals that both $S_0 \rightarrow S_1$ and $S_0 \rightarrow S_5$ excitations consist of HOMO-3 to LUMO, HOMO-2 together with HOMO-1 ($\frac{1}{2}$ electron each) to LUMO, HOMO to LUMO+1, and HOMO to LUMO+2 transitions. Based on Kohn-Sham frontier orbitals, transitions from HOMO-3, HOMO-2 and HOMO-1 can be classified as $n \rightarrow \pi^*$, while transitions from HOMO are $\pi \rightarrow \pi^*$. For compound **2**, the electron density of HOMO-3, HOMO-2 and HOMO-1 orbitals is concentrated on the nitrogen atom of NBu_2 groups, while the electron density of LUMO orbitals is concentrated on the bipyrindine moiety. Unlike compound **2**, compounds **1** and $[\mathbf{2}+\text{H}]^+$ show a more uniform distribution of electron density over the four ring system. Such distinct electron contribution in compound **2** strongly suggests that tertiary amine functional group would play a pivotal role in emissive behavior at the excited state.

Figure 2. Kohn-Sham orbitals and excited state electron configurations of compound **2** in THF; contribution of each excited state is given as a percentage. (Note: HOMO-2 and HOMO-1 show $\frac{1}{2}$ electron excitations, small arrow illustrations.)

Emissive properties of benzofuran derivatives

Upon Sonogashira coupling, internal cyclization reaction generates corresponding benzofurans which commonly show very intense fluorescence in visible ranges. Absorption and emission spectra of synthesized compounds are shown in Figure 3. When excited at 310 nm in THF solution, compound **1** shows a strong emission at 380 nm.

In striking contrast, compound **2** shows a much red-shifted emission at 465 nm in THF solution when excited at 310 nm. In comparison with the UV-vis spectra, the Stokes shift of compound **2** ($\lambda_{\text{abs}} - \lambda_{\text{em}} = 135$ nm) is much larger than that of compound **1** ($\lambda_{\text{abs}} - \lambda_{\text{em}} = 50$ nm) under the identical conditions (Figure 3). As described by electron density distribution (Figure 2), the large Stokes shift in compound **2** can best be explained by charge separation in the excited state where *N,N*-dibutylamine and bipyrindine act as electron-donating and electron-deficient groups, respectively.

Figure 3. Normalized (a) absorption and (b) emission spectra of compound **1** and **2** in THF (20 μ M, λ_{ex} = 310 nm, T = 298 K). Black, red and blue line indicate compound **1**, **2**, and $[\mathbf{2}+\text{H}]^+$, respectively.

It should be noted that, although emissive behavior of benzofuran has been known, its application as a fluorophore has been limited due to shorter wavelength emission in the UV-visible region. By directly introducing electron-donating *N,N*-dibutylamino groups in the phenyl rings, however, the emission wavelength could be brought to the further visible region without compromising its high quantum yield. In order to compare with the *tert*-butyl analogue, protonation of compound **2** was conducted. Upon addition of an excess amount of $\text{CF}_3\text{CO}_2\text{H}$ solution, the lack of available lone-pair electrons induced a dramatic hypsochromic shift where the emission maximum became $\lambda_{\text{em, max}} = 355$ nm, which is similar to that of the *tert*-butyl analogue. Unlike emission, UV-vis spectrum does not show any significant change upon protonation (Figure S1). Those distinct behaviors in absorption and emission spectra upon protonation further imply the existence of a charge-separated excited state in compound **2**.

Such excited-state intramolecular charge transfer (ICT)-type interaction can best be explained by solvent dependent behaviors in fluorescence, since differences in solvent polarity result in changes of emission wavelength and/or lifetime. As anticipated, while UV-vis absorption does not show any significant shift in different solvents (Figure S2), emission spectra of compound **2** display strong solvent dependency. Emission maximum is systematically red-shifted as solvent polarity is increased (Figure 4).

Figure 4. Solvent dependent emission spectra of compound **2**. (20 μ M, λ_{ex} = 310 nm, T = 298 K). Insert: Wavenumber of $\lambda_{\text{em, max}}$ vs $E_{\text{T}}(30)$ of solvents. Solvents: hexane, cyclohexane, benzene, toluene, diethyl ether, THF, ethyl acetate, and dichloromethane (from left to right). $E_{\text{T}}(30)$ value of solvent was taken from reference.

While solvent dependency of compound **1** was also investigated, no significant change was observed in both absorption and emission (Figure S3). Therefore, it seems that ICT-type behavior of compound **2** comes primarily from the electron-rich *N,N*-dibutylamino groups. Correlation plot of emission energy (cm^{-1} in unit) also shows a nice linearity in a wide range of $E_{\text{T}}(30)$ values (Figure 4)⁴¹.

Protonation of amine groups

As discussed in previous section, the ICT-type interaction can further be modulated and restored to initial local emission (LE) by capturing the lone-pair electrons of nitrogen, i.e., by protonation of NBu_2 groups in compound **2**. We then conducted a more systematic approach on the emissive behaviors of compound **2** upon protonation in two different solvent systems. As shown in Figure 3b, emission maximum of compound **2** in THF solution is $\lambda_{\text{em, max}} = 465$ nm with a quantum yield of $\Phi_{\text{F}} = 16\%$. Upon acidification, the intensity of this emission band decreases and, at the same time, a new band at $\lambda_{\text{em, max}} = 365$ nm shows an increased intensity (Figure 5a). In sharp contrast to the ratiometric behaviors observed in THF, compound **2** shows a negligible fluorescence ($\Phi_{\text{F}} = < 1\%$) under identical conditions (2 μ M, $\lambda_{\text{ex}} = 310$ nm, T = 298 K) in MeCN. Addition of TFA, however, results in the intense emission band at $\lambda_{\text{em, max}} = 365$ nm with a quantum yield of $\Phi_{\text{F}} = 31\%$ (Figure 5b). It is interesting finding that the compound **2** behaves in two distinct manners (ratiometric vs turn-on) upon solvent polarity changes as well as acidity of solution.⁴² Often local (micro- and macro-) environmental dependent behaviors of molecule are very useful for chemical sensing and especially for biological imaging applications. Local environment parameters include pH, solvent polarity, viscosity, hypoxia, and temperature.⁴³⁻⁴⁶ Accordingly, there is an increasing interest in studying such sensitive behaviors of molecules, which could be utilized as chemosensors toward environment. To our knowledge, switching of emission pathway of the molecule (or dual mode emission), however, is relatively rare.^{47, 48}

Figure 5. Protonation of compound **2** in (a) THF and (b) MeCN. Excess amount of $\text{CF}_3\text{CO}_2\text{H}$ was added to the solution of compound **2** (20 μ M), λ_{ex} = 310 nm. T = 298 K.

Such striking difference in emissive behaviors of compound **2** toward different solvent polarity and acidity indicates that the lone-pair electrons of dibutylamino functional groups play a different role in each case. For compound **2** in THF, dibutylamino group participates in the ICT-type emission, but protonation inhibits the ICT behavior while generating an intense local emission. In MeCN solution, however, the lone-pair

electrons participate in a photoinduced electron transfer (PET)-type quenching process of fluorescence,⁴⁹ in which the molecule shows negligible fluorescence.⁵⁰⁻⁵³ Upon addition of CF₃CO₂H to the solution, the lone-pair electrons are captured and the PET-type de-excitation process becomes no longer available, which in turn, restores the inherent emission of the benzofuran fluorophore.

Turn-ON fluorescence toward Zinc

Turn-ON fluorescence has been an attractive research area where sensory molecules respond to the anion or cation of interest. PET-type quenched (or “masked”) fluorophore has been widely utilized to induce the desirable “Turn-ON” behavior, in which metal binding captures the lone-pair electrons and restores the fluorescence as a signal read-out. Similarly, the protonation study of compound **2** in MeCN steered us to further investigate the possibility of using this molecule as a metal probe. As expected, the addition of zinc ions to compound **2** in MeCN solution exhibits gradually growing emission bands at $\lambda_{\text{em, max}} = 395$ nm (Figure 6).

Figure 6. Emission spectra of compound **2** upon zinc ion addition (1, 3, 5, 10 and 60 equiv.) in MeCN (20 μ M, $\lambda_{\text{ex}} = 310$ nm, T = 298 K).

Conclusion

Highly fluorescent benzofuran derivatives were prepared by direct cyclization of alkyne ortho-substituted phenols. We found that lone-pair electrons of *N,N*-dibutylamino group can play dramatically distinct roles in emissive behavior depending on the solvent polarity. Upon the addition of protons, compound **2** shows a ratiometric blue-shift of the emission band in THF solution while a large increase of fluorescence is seen in MeCN solution. Such turn-on fluorescence behavior may be utilized to detect zinc ion sensing in MeCN. Further investigation of more fundamental photophysical properties and modification toward metal sensing ability of benzofuran derivatives are currently underway in our lab.

Acknowledgments

Financial support for this work from Pennsylvania State University is acknowledged. This research was also supported in part by the National Science Foundation through XSEDE resources, provided by San Diego Supercomputing Center, under grant number TG-CHE160074.

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Supplementary Material

Experimental procedures for all compounds generated through this work, and spectroscopic, and computational data.