

An Unusual Addition Reaction for Constructing a Novel pH-Controlled Fluorescence Switch

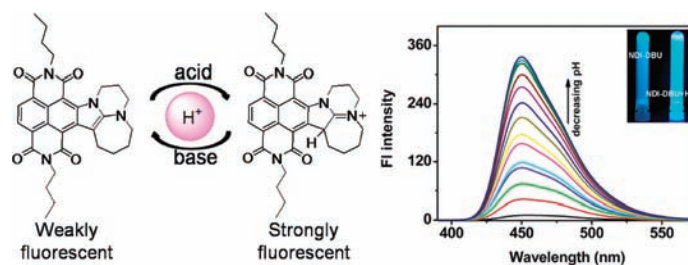
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ABSTRACT



A pH-controlled fluorescence switch based on a core-substituted naphthalenediimide compound (NDI-DBU) was constructed. The novel pentacyclic compound (NDI-DBU) was derived from naphthalenediimide (NDI) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in only one synthetic operation, catalyzed by CuI.

The development of a molecular fluorescent sensor for in vivo and in vitro analysis has drawn particular interest,¹ as fluorescent sensors have general advantages of high sensitivity, real-time screening, and high throughput. Despite the multitude of available fluorophores, new fluorophoric systems with more challenging properties are still hotly sought.²

The electron-deficient naphthalenediimides (NDIs) have attracted much attention in the fields of materials and supramolecular chemistry in recent years.³ Functionalization through the diimide nitrogens or core substitution (substituted on the ortho position of the imide) makes absorption and fluorescence properties of analogues variable.⁴ Core-substituted NDIs, especially with electron-donor groups, are rapidly emerging in supramolecular and materials chemistry,

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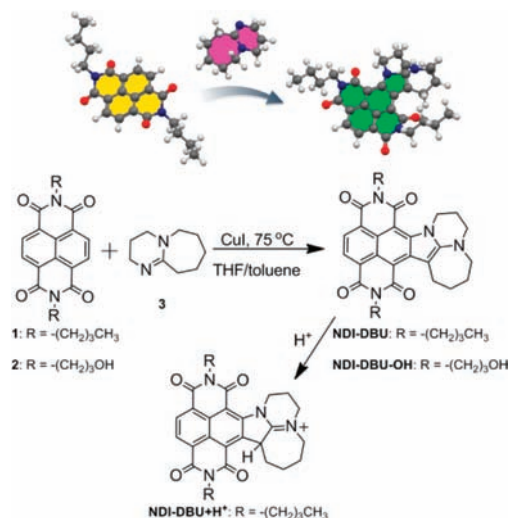
creating highly colored, fluorescent, and conducting functional materials.⁵

Herein, we report an unusual cyclocondensation reaction for the construction of a heterocyclic scaffold from the naphthalenediimide (NDI) in only one synthetic operation. Furthermore, we surprisingly found that the core-substituted NDI compound (**NDI-DBU**) was pH-sensitive. Its absorption and emission spectra dramatically changed upon the addition of trifluoroacetic acid (TFA) in MeCN solution, while recovering on further addition of triethylamine (TEA).

During the course of our recent research on the “click” reaction⁶ of *N,N'*-dipropargyl-1,4,5,8-tetracarboxylic diimide using DBU as base and CuI as catalyst, we encountered the formation of a green byproduct unexpectedly. The mass spectrometry (MALDI-TOF) indicated that this byproduct might result from the addition of DBU and the desired product. This led us to suppose that it could be the NDI moiety that reacted with DBU. Hence we synthesized another simple NDI compound (**1**)⁷ to react with DBU in the same condition. A green product with blue fluorescence was also detected when compound **1** reacted with a large excess of DBU, catalyzed by CuI in THF/toluene at 75 °C. After straightforward purification, the green product (**NDI-DBU**) was obtained in 20% yield. **NDI-DBU** is readily dissolved in common organic solvents, such as tetrahydrofuran (THF), CH₂Cl₂, toluene, MeCN, MeOH, and *N,N*-dimethylformamide (DMF). The temperature dependence of the reaction was also studied (as shown in Table S1, SI). When the temperature was raised, the yield increased. Hence, the refluxing temperature (75 °C) was chosen for the reaction.

Extensive analysis of **NDI-DBU** was performed to elucidate the structure. The mass spectrometry indicated that this product resulted from the elimination of 4 equiv of H atoms between DBU and NDI. Elemental analysis confirmed this. Besides the typical signals derived from the *n*-butyl group, the ¹H NMR spectrum exhibited seven typical resolved signals ascribed to methylene groups and two coupling doublets derived from the aromatic group of NDI core. According to the ¹H–¹H COSY spectrum, the connectivity of these groups corresponded to four isolated spin systems with two *n*-butyl groups, two aromatic protons, and three and four methylene groups, respectively. The green color, blue fluorescence, and all the facts along with the ¹³C NMR spectrum led us to propose the pentacyclic structure (as shown in Scheme 1). The two-dimensional NMR spectroscopy, such as TOCSY, HMBC, and HSQC spectra, confirmed this structure. Additionally, the FTIR spectrum, with the red-shift of the absorption of carbonyl from 1701 to 1681 cm⁻¹ and the new absorption derived from aromatic rings around 1500 cm⁻¹, confirmed the formation of the pentacyclic structure. The presence of the three conjugated aromatic

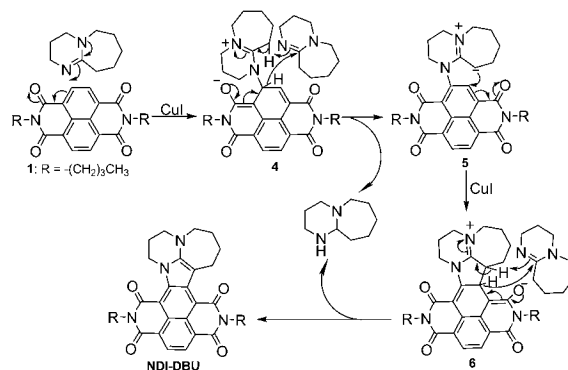
Scheme 1. Synthesis of **NDI-DBU**



rings along with the inclusion of the electron-donating amino group would be responsible for the strong absorption band in the visible region.

There are a lot of examples concerning the use of DBU as a C- and N-nucleophile in organic reactions with diethyl maleate, α-chloroacids, dimethyl acetylenedicarboxylate, heptafluorobut-2-ene, and 2,3-dichloropyrazine and its ana-

Scheme 2. Proposed Mechanism of **NDI-DBU** Formation



logues.⁸ According to the literature, we proposed that the Michael addition⁹ is responsible for the formation of the pentacyclic structure (Scheme 2). Moreover, when perform-

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ing the similar reaction of the NDI and DBU without CuI as catalyst, we only detected the molecular ion peak (m/z) of **NDI-DBU** through mass spectrometry (MALDI-TOF). However, the ^1H NMR spectrum of the only isolated product did not verify the formation of **NDI-DBU** in this condition. As shown in Figure S1 (SI), only a few weak signals which is typical for **NDI-DBU** showed some possibility of the formation of **NDI-DBU**. Hence we proposed that CuI, which is often used to catalyze the conjugate addition of organometallic reagents to α,β -unsaturated compounds,¹⁰ promoted the 1,4-addition of the NDI core over the 1,2-addition. Thus, the mechanism regarding the formation of **NDI-DBU** could be rationalized as follows: DBU first added by a Michael addition on compound **1** via its N-8 nitrogen atom and afforded the ammonium salt **4** (Scheme 2). And CuI led to a 1,4-addition instead of 1,2-addition when DBU added on compound **1**. Subsequent abstraction of a H-6 proton, along with the H atom of the NDI core by another molecule of DBU led to an intermediate ylide **5** that is susceptible to react with the NDI core by another Michael addition to give five-membered-ring **6**. During the second Michael addition, CuI also performed as catalyst, which promoted the 1,4-addition over 1,2-addition. Finally, **NDI-DBU** was generated from the abstraction of the acidic H-6 proton, along with the H atom of NDI core by another molecule of DBU. Hence, except for acting as a reactant to construct the pentacyclic structure, DBU would also act as an oxidant and a base to capture the protons. And CuI promoted the 1,4-addition over 1,2-addition during both of the Michael additions, acting as catalyst. A set of comparative experiments were carried out to support the proposed mechanism: when performed with a 3-fold excess of DBU, similar reaction failed in producing the **NDI-DBU** adduct; upon the addition of another additional stronger base (2 equiv of Schwesinger's P_1 base¹¹) for deprotonation, **NDI-DBU** adduct was formed.

The electrochemical properties of **NDI-DBU** were examined by using cyclic voltammetry (CV). **NDI-DBU** undergoes two reversible one-electron reductions which occurred at -0.69 and -1.10 V, along with one irreversible oxidation that occurred at 0.77 V versus SCE (Figure S2, SI). The first reduction could be ascribed to formation of radical anions, with the second reduction relating to formation of dianions.¹² The irreversible oxidation corresponds to the dialkylamino group.

The UV-vis absorption spectra of **NDI-DBU** were measured in toluene, THF, MeCN, and MeOH. As shown in Figure S3 (SI) (spectra in MeCN also see the dark line in Figure 1A), all the optical spectra of **NDI-DBU** in different solvents showed a broad, strong, and structureless visible absorption band between 500 and 770 nm, along with a

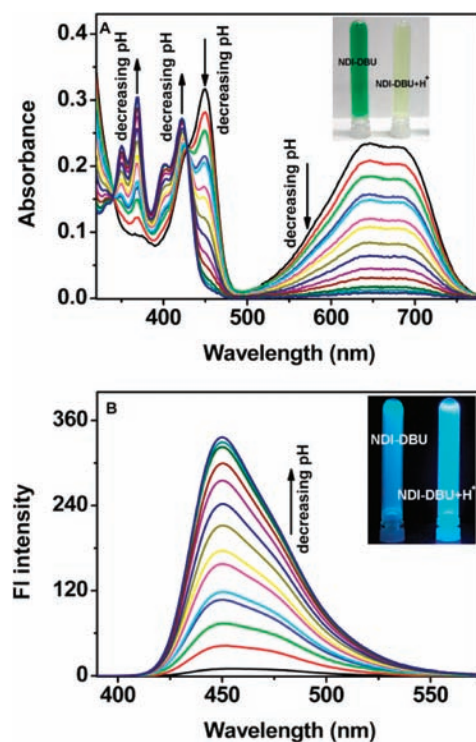


Figure 1. UV-vis absorption spectra (A), and fluorescence spectra excited at 340 nm (B) of **NDI-DBU** in the presence of different concentrations of TFA in MeCN solution ($[\text{NDI-DBU}] = 20 \mu\text{M}$, $[\text{TFA}] = 3.0, 4.5, 6, 7.5, 9, 10.5, 12.0, 13.5, 15.0, 16.5, 18.0, 19.5, 21 \mu\text{M}$). Inset of A and B: Color change and fluorescence color change of **NDI-DBU** in MeCN solution in the presence of TFA.

strong absorption maximum around 450 nm. The broad absorption band between 500 and 770 nm could be attributed to a charge transfer (CT) transition (${}^1\text{CT} \leftarrow \text{S}^0$) involving the dialkylamino group and the pyrrolo-extended NDI chromophore. Hence, it shows a strong positive solvatochromism with solvent polarity increasing, which corresponds to the stabilization of the CT state. Apparently, the strong absorption maximum around 450 nm is not typical of unsubstituted NDIs.

Similar characteristics also have been observed in other NDI compounds substituted by electron-donating groups.^{4,13} According to the studies by Würthner and co-workers⁴ on alkylamino-substituted naphthalene diimide compounds, a similar new absorption band was also observed. Therefore, the strong absorption maximum around 450 nm showed weak charge transfer character. For this absorption band, the solvatochromism was not that observable, which is coincident with literature.^{4,13}

Figure 1 shows the UV-vis absorption and fluorescence spectra of **NDI-DBU** and those in the presence of different amounts of TFA in MeCN solution. The absorption coefficient of **NDI-DBU** (ϵ_{max}) was calculated as 14250 from an absorption titration experiment in MeCN solution. Upon

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addition of TFA to **NDI-DBU** in MeCN solution, the absorbance of the CT band and that at 450 nm of **NDI-DBU** decreased following the formation of three new bands centered at 422, 370, and 350 nm, respectively. Concomitantly, the emission intensity at 450 nm gradually increased with the addition of TFA to **NDI-DBU** in MeCN solution. The fluorescence quantum yields (Φ_F) were calculated as 0.11 (**NDI-DBU**) and 0.74 (**NDI-DBU+H⁺**), respectively, by the steady-state comparative method using anthracene ($\Phi_F = 0.36$, MeCN)¹⁴ as standard material.

It has been reported that the strong electronic interaction between the electron-rich core substituents and the naphthalene π -conjugated core of core-substituted NDIs (cNDIs) would result in highly colored and fluorescent NDI dyes.^{5,15} Accordingly, the **NDI-DBU** can be regarded as an aminopyrrolo-substituted naphthalene diimide. The three conjugated aromatic rings with electron-donating pyrrolo moiety and electron-withdrawing naphthalene diimide core endure the unique optical properties of cNDIs. Besides, the dialkylamino group substituted on the pyrrolo ring could act as another strong electron donor, while the naphthalene diimide core acted as an electron acceptor. The strong electronic interaction between them was responsible for the intense, structureless, and broad band of absorption between 500 and 770 nm. Upon protonation, the dialkylamino group changes from an electron donor to an acceptor, so that the strong excited state intramolecular charge transfer (ICT) interaction is suppressed. Consequently, the intense CT band disappeared in the absorption spectrum. Concomitantly, binding of a proton also inhibits the excited state intramolecular quenching, resulting in an increase of the fluorescence intensity of the pyrrolo-extended naphthalene diimide. Therefore, **NDI-DBU**, which is essentially weakly fluorescent in a highly polar environment, becomes strongly fluorescent in the presence of protons ($\lambda_{em} = 450$ nm).

The fluorescence switch can be turned off by releasing a proton from **NDI-DBU**. This can be achieved by the addition of TEA (see Figure S4, SI). Upon the addition of TEA to a mixed solution of TFA and **NDI-DBU** in MeCN solution, the absorbance of the intense CT band between 500 and 770 nm increased and the absorption spectrum resumed gradually. The fluorescence intensity at 450 nm decreased simultaneously. The ¹H NMR spectra showed that all the signal except that derived from the *n*-butyl group changed upon the addition of TFA to **NDI-DBU** in CD₃CN solution, and recovered after the addition of TEA to the mixed solution (see Figure S5, SI). Further switching on and off is affected

by the alternate addition of TFA and TEA (Figure 2). This can be reversibly performed at least for seven cycles.

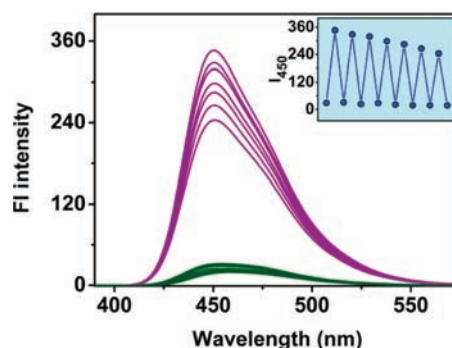


Figure 2. Fluorescence response of **NDI-DBU** (black line) in MeCN solution upon the alternate addition of TFA (purple lines) and TEA (green lines). Inset: Fluorescence changes at 450 nm. ($\lambda_{ex} = 340$ nm, [**NDI-DBU**] = 20 μ M, [TFA] = 20 μ M, [TEA] = 17.5 μ M).

To explore the scope of the discovered reaction, we employed another analogous substrate. When compound **1** was replaced by another NDI derivative (**2**)¹⁶ in a similar reaction, the analogous **NDI-DBU** adduct with pentacyclic structure (**NDI-DBU-OH**) was also formed.

In conclusion, we have shown a new pH-sensitive fluorophore derived from the NDI compound in only one synthetic operation. Further expansion of the mechanism of the discovered reaction is under way. The strong ICT interaction of **NDI-DBU** between the dialkylamino group and NDI core was suppressed by the protonation of **NDI-DBU**. As a result, **NDI-DBU**, which is essentially weakly fluorescent in a highly polar environment, becomes strongly fluorescent in the presence of protons ($\lambda_{em} = 450$ nm). The fluorescence switch can be reversibly turned off and on by alternating addition of TEA and TFA. Another analogous **NDI-DBU** adduct with hydroxy substituents (**NDI-DBU-OH**) was also formed by using a similar synthetic methodology. Therefore, the fluorophore could also be further used to establish novel energy transfer systems as covalent building blocks.

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Supporting Information Available: Synthesis, 2D NMR studies, and switching studies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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