

Highly solvatochromic fluorescent naphthalimides: Design, synthesis, photophysical properties and fluorescence switch-on sensing of ct-DNA

Subhendu Sekhar Bag*, Manoj Kumar Pradhan, Rajen Kundu, Subhashis Jana

Bioorganic Chemistry Laboratory, Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781039, India

ARTICLE INFO

Article history:

Received 11 September 2012

Revised 11 October 2012

Accepted 2 November 2012

Available online 12 November 2012

Keywords:

Propynyl naphthalimides

Fluorophores

Solvatochromic

Intra molecular charge transfer (ICT)

Probes of ct-DNA

Switch-on sensing

ABSTRACT

We report the design, synthesis and photophysical properties of highly solvatochromic donor/acceptor substituted naphthalimide based fluorophores. The synthesized naphthalimides containing propargyl ends showed highly solvatochromic intramolecular charge transfer (ICT) feature as was revealed from the UV–visible, fluorescence photophysical properties of these fluorophores and DFT/TDDFT calculation. Fluorescence life times for the imide fluorophores were also measured in different solvents. The solid state photophysical property of donor substituted naphthalimide **1** showed promising for future application in material sciences. Furthermore, both the donor/acceptor substituted naphthalimide fluorophores **1–2** were exploited in sensing calf-thymus DNA via switch-on fluorescence response. The propargyl linker containing naphthalimides can further be exploited for the synthesis of labeled biomolecular building blocks.

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Solvatochromic fluorescent molecules are widely known to serve as extremely sensitive probes in biological systems for the detection and probing of structures, dynamics, micropolarity around a biomolecule and interbiomolecular interactions.¹ Therefore, the development of such fluorescent molecules is a very important research target for understanding biological events associated with interbiomolecular interactions. As for example, highly solvatochromic fluorescent probes and fluorescently labeled biomolecular building blocks such as solvofluorochromic nucleosides/amino acids have been successfully utilized for the sensing and detection of biomolecular microenvironment/biomolecules.² However, many of such explored fluorophores emitted at a short wavelength region, possessed low emission intensity and/or suffered from a quenching incidence rendering them unsuitable for practical use.³ Therefore, bright and long-wavelength emissive fluorescent molecules with emission in the visible region have attracted great interest in recent time as new fluorescent probes for the detection and sensing of biomolecules without any interference by the background signal generated from the autoabsorption and autofluorescence of biomolecules.

As a part of our ongoing program for the design and synthesis of highly solvatochromic fluorophores with a linker unit for possible future use in labeling of biomolecular building blocks and taking into consideration of the importance of naphthalimide derivatives⁴ in biological applications, we were thus very much interested in

the possibility of synthesizing 1,8-naphthalimide derivatives with donor/acceptor substituents as new potential solvatochromic fluorophores. Naphthalimide derivatives aroused the interest of chemists, physicists and biologists for various reasons. The 4-amino and/or alkyl amino-1,8-naphthalimide chromophore or their analogues have been reported for their several interesting photophysical properties and utilized for chemosensory applications.⁴ⁱ Because of the 'push–pull' nature of its internal charge transfer (ICT) excited state, they have been utilized in several biological applications.⁴ Naphthalenimides show a diversified reactivity towards biological substrates including DNA and proteins. Furthermore, because of their potential anti-tumor activity upon electronic excitation with UV light 1,8-naphthalimides have attracted much attention in the fields of biology and medicine. 4-Amino-1,8-naphthalimide also have been utilized in supramolecular fields as well as DNA targeting molecule. Troger's base compounds as well as metal complexes of naphthalimides have been developed and found to interact strongly with DNA.^{4i–1} However, there is no report of 1,8-naphthalimide in which 4-position is conjugated to donor/acceptor substituted phenylacetylenes to achieve much longer absorption wavelength.

Therefore, in this particular we report the syntheses and photophysical properties of donor/acceptor containing 1,8-naphthalimide derivatives **1–2** in which chromophores have free acetylene arms which can be exploited further for future applications such as for the synthesis of labeled biomolecular building blocks. We explored the sensitivity in fluorescence response upon changing the solvent polarity of these fluorophores. We also wanted to examine

* Corresponding author. Fax: +91 361 258 2324.

E-mail address: ssbag75@iitg.ernet.in (S.S. Bag).

the ability of the fluorophores **1–2** in possible sensing of biomolecule like ct-DNA.

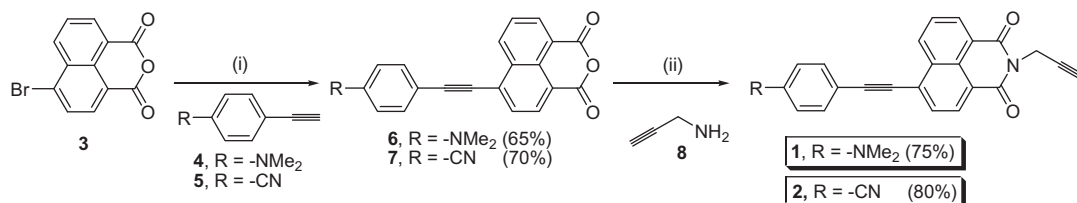
Therefore, we have chosen 4-bromo-1,8-naphthalic anhydride as our starting material. The reason behind our choice was to achieve charge transfer fluorescence response upon incorporating a donor unit by a substitution at 4-bromo functionality. Thus, there might be a possibility of getting emission at longer wavelength region because of the conjugation between the donor substituent and the acceptor naphthalimide core leading to a long range charge transfer (CT) process and hence we expectedly would observe an excellent solvofluorochromicity.^{4,5} On the other hand we also wanted to know the effect of an acceptor substituent and compare the photophysical behavior with that of the donor substituted one. Therefore, the fluorophores might show high solvatofluorochromicity which could be utilized for probing of biomolecular microenvironment.

With this background and aim we have first synthesized the fluorophores **1–2**. The routes adopted for the synthesis of target compounds **1–2** is shown in Scheme 1. Thus, a Pd(0)-mediated 'click-reagent version' of Sonogashira coupling^{4b,6} of anhydride **3** with 4-ethynyl-*N,N*-dimethylaniline and 4-ethynylbenzonitrile, respectively, in dry DMF at 80 °C for 4 h, yielded 4-substituted-1,8-naphthalic anhydrides, **6–7**. After recrystallization from hot toluene pure naphthalic anhydride derivatives **6–7** in 65% and 70% yields, respectively, were afforded. Next, conjugated anhydrides **6–7** were allowed to react with propargyl amine in dry ethanol under reflux for 50 h to afford 4-(4-*N,N*-dimethylamino-phenylethynyl)-*N*-(2-propynyl)-1,8-naphthalimide (**1**, **4-DMAPENI**) and 4-(4-cyanophenylethynyl)-*N*-(2-propynyl)-1,8-naphthalimide (**2**, **4-CPENI**), respectively, with good yields (Scheme 1). Washing the products in water and ethanol and recrystallization gave pure

compound **1** as red crystalline solid and **2** as yellow powdered solid in very good yields. The structures of the final products were characterized by NMR, mass spectrometry, and by X-ray single crystal analysis of compound **1**.

The crystal structure of fluorophore **1** showed a very interesting arrangement (Fig. 1). Thus, the donor substituted planar naphthalimide with the pendent propargyl arm crystallized in a layered sheet-like arrangement. The planar sheets are layered on top of each other, with slip-stacked ArCH- π -bonding (3.29 Å) between internal alkyne and aromatic C-H of naphthalimide core. The layers are held by C-C- π (3.37 Å) bonding between donor/acceptor aromatics and π -stacking between the donor unit in one layer and the acceptor naphthalimide core of the other layer (Fig. 1a). Head-to-tail arrangements of donor *N,N*-dimethylanilino unit of one molecule in one layer and acceptor naphthalimide core of a separate molecule in second layer makes the system stable by forming a strongly π -stacked and charge transfer stabilized stacked layer like structure.⁷ The layers are so arranged that the donor-*N,N*-dimethylphenyl moiety interacts via π -stacking and charge transfer interactions with the acceptor naphthalimide ring in the molecule in the layer above and below with an average interlayer distance being 3.31 Å. The pendant terminal acetylenic-H involved in H-bonding with C=O of naphthalimide group (2.37 Å) of a molecule in a different layer giving rise to a bent-stair-like arranged third stacked layer (Fig. 1a and b).

After getting all the compounds in hand in very pure form we turned our attention to study their photophysical properties. Thus, the UV-vis absorption spectra of the naphthalimide fluorophores **1–2** were studied in various solvents of different polarity. The longest wavelength absorption of compound **1** was characterized by a broad band with the maxima appearing between 450 and 467 nm



Reagents and conditions: (i) Pd(PPh₃)₄/Et₃N/DMF/CuSO₄/Na-ascorbate/80 °C, 4 h; (ii) EtOH/Reflux, 50 h.

Scheme 1. Synthesis of donor/acceptor labeled naphthalimide fluorophores **1–2**.

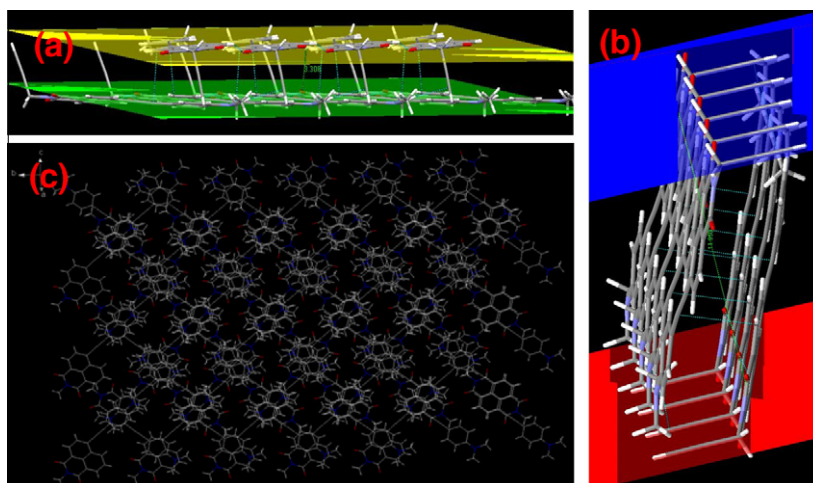


Figure 1. Crystal structure (a–b) showing inter planar distance and the two planes formed by two pendent acetylenic arms. (c) Crystal network of the molecule **1** (the CCDC number is CCDC 882241).

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