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Donor–π-acceptor benzothiazole-derived dyes with an extended heteroaryl-containing conjugated system: synthesis, DFT study and antimicrobial activity

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ABSTRACT

A series of novel derivatives containing an electron-donating *N*,*N*-dimethylaminophenyl ring connected to an electron-withdrawing benzothiazole or benzothiazolium moiety via a heteroaryl system (furan, thiophene or *N*-methylpyrrole) and up to two ethenylene groups have been synthesized and characterized. Furthermore, their nonlinear optical (NLO) properties have been investigated at the theoretical level using DFT and time-dependent DFT methods, and their antimicrobial activities were evaluated against a standard set of unicellular organisms. Both benzothiazole and benzothiazolium systems are predicted to exhibit large NLO responses, based on the calculated static molecular quadratic hyperpolarizabilities β_0 as well as intramolecular charge transfer (ICT) transition characteristics. Moreover, the 3-alkyl-benzothiazolium salts were found to display high toxicity against several tested microbes.

1. Introduction

Organic molecules containing both an electron-donating group (donor) and an electron-withdrawing group (acceptor) at opposite ends of a conjugated π-electron system (often referred to as push–pull systems) are of fundamental importance in materials chemistry since they serve as critical components for many advanced technologies, such as nonlinear optical (NLO) devices,[1] organic light-emitting diodes (OLEDs),[2] photovoltaic cells,[3] etc. In such donor–π-acceptor systems, the donor and acceptor moieties provide the necessity of ground-state charge asymmetry, whereas the π-conjugated bridge provides a pathway for the redistribution of electron density under the influence of external electric fields.[4] For the practical application of second-order NLO materials, not only a high molecular quadratic hyperpolarizability β but also a good thermal, chemical and photochemical stabilities are required. It is well known that additional stability of a NLO chromophore can be gained by substitution of the polyene segments by aromatic ones along the conjugation path between a donor and an acceptor. However, such modification leads to a decrease of β values (aromatic rings disfavour an intramolecular charge transfer since it requires them to adopt quinoidal-like structure). Theoretical as well as experimental studies revealed that good thermal and photochemical stabilities of NLO chromophores with preserved high hyperpolarizabilities can be achieved by replacement of an aromatic ring with easily delocalizable heteroaromatics.[5–8]

In respect of these findings, benzothiazole-derived dyes with a donor–π-acceptor setup are promising candidates for NLO applications.[9] Several such systems containing benzothiazole as an (auxiliary) electron-withdrawing group have already been synthesized, and relatively high values of hyperpolarizability β have been reported for them.[10,11] However, a further improvement in β values can be achieved by proper introduction of donor and acceptor substituents onto the benzothiazole core due to its non-symmetric character,[9,10] or by quaternization of the benzothiazole nitrogen.[12,13]

To date, only a few organic salts have been studied for NLO properties, because their electric charge prohibits their use in a poling process. However, donor–π-acceptor organic salts exhibit extremely large NLO responses, substantially higher stabilities and greater chromophore number densities in comparison with organic poled NLO polymers.[14] Furthermore, changing of the counterion

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can influence the crystal packing, with the aim of producing non-centrosymmetric bulk structures, which are a prerequisite for macroscopic second-order NLO effects. Thus, with the progress in fabrication processes of materials, push–pull organic salts also become applicable in NLO devices and could even replace contemporary NLO polymers.

Over the last few years, our research group synthesized a large number of push–pull 3-alkyl-benzothiazolium salts **1** with different number of ethenylene units in a π-conjugated bridge and various donor and alkyl substituents (Fig. 1).[15a–c] As some benzothiazole-derived cyanine dyes were recognized to exhibit interesting biological activities (like e.g., commercially available *dithiazanine*, which is used as an anthelmintic and antiparasitic drug),[16] benzothiazolium salts **1** were primarily studied for their antimicrobial toxicities. Those were analyzed by means of QSAR methods to identify structural blocks responsible for high biological activity.[17] It was shown that the length of the π-conjugated bridge between electron-donating group and benzothiazolium moiety as well as the donor ability have a significant influence.

Recently, Coe et al.[12] reported the results of Hyper-Rayleigh scattering (HRS) measurements for 3-methyl-benzothiazolium salts **1** (n=1–4; R=R′=CH_3) in comparison with the analogous 1-methylpyridinium salts. Experimental measurements revealed that the static molecular quadratic hyperpolarizability β_0 increases with the length of polyene chain, and the benzothiazolium salts exhibit larger NLO responses than their pyridinium analogues.

Aware of above mentioned results, we decided to extend our series of push–pull 3-alkyl-benzothiazolium salts **3** as well as the corresponding non-ionic benzothiazole derivatives **2**, by incorporation of five-membered electron-rich heteroaromatics, namely furan, thiophene or *N*-methylpyrrole, into a π-conjugated bridge (Fig. 2). Such setting could lead to enhanced chemical, photochemical and thermal stabilities, compared to derivatives with a polyenic π-bridge, and even to higher molecular quadratic hyperpolarizabilities β_0.

Herein, we report the synthesis and characterization of title systems **2** and **3**. Furthermore, the structure/NLO–activity relationships in selected systems are investigated using density functional theory (DFT) and time-dependent DFT methods. Calculated hyperpolarizabilities β_0 as well as intramolecular charge transfer (ICT) transition characteristics are confronted with those of the analogous benzothiazolium salts **1aM–dM** (n=1–4; R=R′=CH_3). Also, antimicrobial activities of all compounds prepared in this work are evaluated against a standard set of unicellular organisms.

2. Results and discussion

2.1. Synthesis of target structures

The synthesis of our target structures can be divided into two separate tasks: (a) preparation of neutral (in the sense of non-ionic) chromophores **2a–d** with a direct connection between the benzothiazole and the heteroaryl moiety, and (b) preparation of neutral derivatives **2e–j** and benzothiazolium salts **3**, where these two

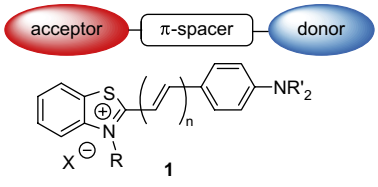


Figure 1. Structure of push–pull 3-alkyl-benzothiazolium salts with a polyenic π-bridge: **1a** (n=1), **1b** (n=2), **1c** (n=3), **1d** (n=4). The *N*-alkyl substituents R are indicated as capitals (M=methyl, A=allyl, P=prop-2-ynyl) appended to the label of corresponding compounds.

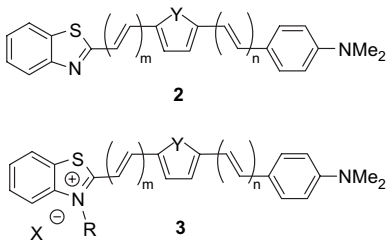
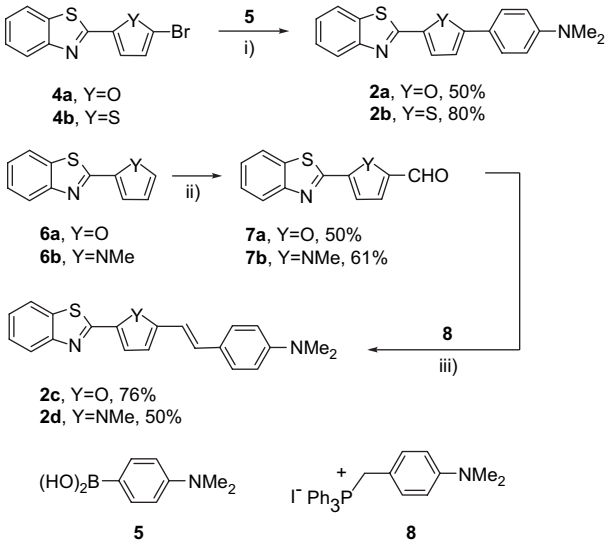


Figure 2. Structures of target compounds. Y=O, S, NMe; R=methyl (M), allyl (A), prop-2-ynyl (P); X=I, Br; m=0, 1; n=0, 1.

structural units are connected via an ethenylene spacer. In the first class, the synthetic approach starts with 2-heteroaryl-benzothiazoles, readily available via condensation of the corresponding heteroaryl-2-carbaldehydes with 2-amino-thiophenol to form the benzothiazole ring.[18–20] The target compounds without any ethenylene groups in the bridge system were prepared by an aryl–aryl coupling reaction, starting from 2-(5-bromofuran-2-yl)benzothiazole **4a** or 2-(5-bromothiophen-2-yl)benzothiazole **4b**, which were reacted with 4-(dimethylamino)phenylboronic acid **5** under Suzuki-coupling conditions,[21] catalyzed by palladium acetate, to form **2a** and **2b**, respectively, in good yields (Scheme 1). Compounds **2c** and **2d** were built using Wittig olefination.[22] The starting 2-heteroarylbenzothiazoles **6a** and **6b** were formylated by the Vilsmeier–Haack protocol to give the corresponding carbaldehydes **7a** and **7b**.[23] Subsequently, the products smoothly underwent a Wittig reaction with phosphonium iodide **8** (Scheme 1), providing target compounds **2c** (*E*:*Z*=11:1) and **2d** (*E*:*Z*=16:1) in good yields. At this point, it is fitting to mention that the phosphonium iodide **8** can be easily prepared by one-pot reaction of *N*,*N*-dimethylaniline, formaldehyde, PPh_3 and NaI, an approach introduced by Roncali et al.[24] However, the extended reaction time needed (3 weeks) was easily reduced to 2 h, when the reaction was performed under microwave irradiation (see Section 4).



Scheme 1. Preparation of 2-(heteroaryl)benzothiazoles **2a–d**. Reagents and conditions: (i) $Pd(OAc)_2$, PPh_3, aq Na_2CO_3, THF, reflux; (ii) $POCl_3$, DMF, 0 °C to rt; (iii) Na, MeOH, reflux.

To access derivatives **2e–j** and **3a–f** of the second class, with an ethenylene spacer connecting the benzothiazole and the heteroaryl functionalities, an aldol-type condensation reaction between 2-methylbenzothiazole or 2-methyl-3-alkyl-benzothiazolium salts and suitable heteroaryl-2-carbaldehydes was proposed.[15a–c,25] The first set of aldehydes **10a–c** was prepared by aryl–aryl coupling