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COMMUNICATION

Three-stage pH-Switchable Organic Chromophores with Large Nonlinear Optical Responses and Switching Contrasts

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Accepted 00th January 20xxStein van Bezouw,^{†,a} Min-Jeong Koo,^{†,b} Seung-Chul Lee,^b Seung-Heon Lee,^b Jochen Campo,^a O-Pil Kwon^{*,b} and Wim Wenseleers^{*,a}

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Three-stage pH-switchable organic second-order nonlinear optical (SO NLO) chromophores are synthesized and characterized by wavelength-dependent linear and nonlinear spectroscopy. The chromophores exhibit huge SO NLO responses in their “on” stages, and large switching contrasts between adjacent stages in both SO NLO response and fluorescence quantum yield, with moreover different “on/off” sequences for closely related compounds.

Second order nonlinear optical (SO NLO) compounds with large first hyperpolarizability β are highly interesting for wavelength conversion, electro-optical modulation, and second harmonic generation bio-imaging.^{1,2} Large β values can be obtained for π -conjugated systems that are asymmetrically substituted with strong electron donor and acceptor groups.^{1,3} For some compounds, β is highly dependent on the pH of the environment, as protonation changes their electronic structure, and in that way also the asymmetry of the molecule. Such pH-switchable SO NLO compounds have been investigated for their use as pH probes and in bio-imaging.^{4,5,6,7} For fluorescence imaging, multistage pH-switchable compounds (exhibiting at least two pK_a values) have also found interest for some time, for instance as “on-off-on” compounds that probe a pH window of interest where the fluorescence is suppressed.^{8,9} Moreover, multiple stages extend the pH range that can be probed beyond that around a single pK_a value. Recently, multistage SO NLO compounds were reported, requiring both pH change and light to switch fast and reversibly between the different stages,¹⁰ yet, to the best of our knowledge, no purely pH-switchable, multistage SO NLO compounds have appeared in literature so far. In this research, we investigate a series of multi-stage, pH-switchable compounds with a high contrast in both SO NLO

response and fluorescence quantum yield, and with a large SO NLO response in their “on” stages. The compounds (DA-NHQ, HM-NHQ, and OH-NHQ; see Fig. 1) consist of a two-stage pH-sensitive quinolinium (NHQ) electron-withdrawing group that is connected through a π -conjugated styryl bridge with a two-stage pH-sensitive electron-donating group (dimethylamino-phenyl (DA), methoxyphenol (HM) and phenol (OH), respectively), resulting in an efficient *push-pull* system with three-stage pH-sensitivity. The electron-donating strength follows the order of DA > HM > OH.^{6,11} The details of the synthesis are described in the Electronic Supplementary Information (ESI).[†] The three-stage pH-switching behaviour of the compounds is clearly visible in their absorption and

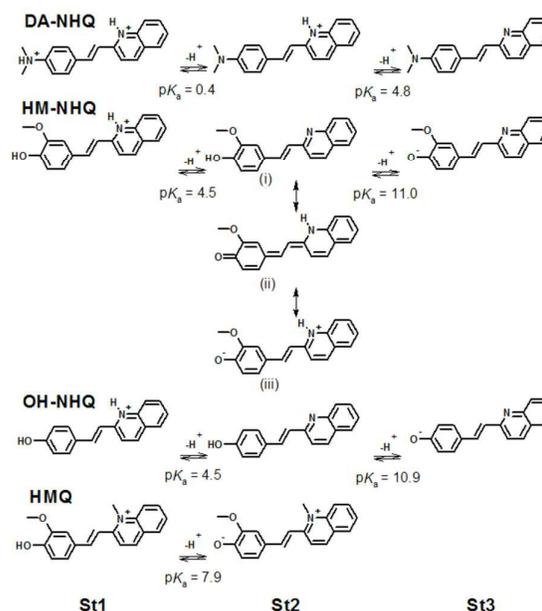


Fig. 1. Chemical structures of (the three pH stages of) the styryl quinolinium chromophores investigated in this work, shown together with the stages of the two-stage pH switchable chromophore HMQ-T from ref. 6. Out of the three possible ground state structures ((i)-(iii)) for HM-NHQ St2, (i) is determined to be the actual structure, as discussed in the main text. The pK_a values as determined for the transitions between the different stages (see section D in ESI) are also given. All compounds have a tosylate counter anion (not drawn).

^a Department of Physics, University of Antwerp, Campus Drie Eiken (CDE), Universiteitsplein 1, B-2610 Wilrijk, Belgium.

E-mail: Wim.Wenseleers@uantwerp.be

^b Department of Molecular Science and Technology, Ajou University, Suwon 443-749, Korea. E-mail: opilkwon@ajou.ac.kr

[†] These authors contributed equally to this work.

‡ Electronic Supplementary Information (ESI) available: Details of synthesis, hyper-Rayleigh scattering, fluorescence quantum yield and pK_a measurements, summary table of linear and nonlinear optical properties, pH-dependent absorption and fluorescence spectra, solvatochromic data. See DOI: 10.1039/x0xx00000x

fluorescence spectra as a function of pH (see Figs. 2 and 3), revealing pronounced changes in both shape and intensity (see section C in ESI on the fluorescence quantum yields of the compounds). The first hyperpolarizabilities of the compounds in their various pH stages (Fig. 1) are measured accurately over a wide range of laser wavelengths (setup described in ESI, and ref. 12), both on and off resonance, in order to allow for accurate β dispersion models¹³ to be applied. This is not only needed to extrapolate reliably to the static (zero frequency) limit β_0 , and make a meaningful comparison between different compounds (and the different stages of the same compound), but also allows for optimizing the β contrast.

The investigation of compound HM-NHQ was motivated by the very promising SO NLO results for a two-stage pH probe (HMQ, also included in Fig. 1) that was investigated before by our groups.⁶ HMQ combines a broad range of β ratios within a wavelength range that is easily reached with standard Ti:sapphire lasers with the highest β values reported for any switchable SO NLO compound so far. A third stage was now added by removing the methyl group on the nitrogen atom, opening it up for protonation, resulting in HM-NHQ (Fig. 1). The shift in pK_a from 7.9 for the two-stage compound to 2.15 for the first transition of the multistage compound HM-NHQ indicates a change in ground state structure, which is further investigated using optical spectroscopy. Further tunability of the pK_a and SO NLO properties was studied by removal of the methoxy group, which results in compound OH-NHQ. The third compound under investigation, DA-NHQ, is based on a known fluorescent “on-off-on” type probe.^{9,14} The combination of the very strongly electron-donating N,N-dimethylamino group, and very strong, positively charged acceptor group in stage St2 of this compound, make this stage very interesting for SO NLO

applications, especially because at the same time the compound maintains an interesting switching behaviour in both SO NLO and fluorescence (see Tables S1 and S3 in ESI), even though the pK_a value of the first transition shifts to a somewhat impractical range. The experimental β values and fitted β dispersion models for the different stages of the compounds are shown in Fig. 3 (see section E in ESI for details on the modelling, which involves only a single shape-determining fit parameter). In all cases, a very good description of the experimental data is obtained. Also given are the dispersions of the β ratios (β contrast) between St1 and St2, and between St2 and St3. The corresponding calculated static values β_0 and β_0 contrasts, as well as peak β values, are summarized in Table 1.

At first sight, the SO NLO results for HM-NHQ St1 and St2 should be comparable to those for the acidic (St1) and basic (St2) stages of the two-stage pH-switchable compound HMQ, because, compared to HMQ, the methyl group is exchanged for a proton without further structural modifications. This indeed is the case for the stages St1, for which both the β dispersion and β_0 are comparable for HM-NHQ and HMQ. However, for the stages St2, the situation is completely different: the β_0 for HM-NHQ St2 is 5.5 times lower than that of the basic stage of HMQ. As a result, although for HM-NHQ, β strongly decreases upon switching from stage St1 to St2 ($\beta_{0,St1}/\beta_{0,St2} = 2.5$), β for HMQ changes in the opposite sense, resulting in an inverted contrast ($\beta_{0,St1}/\beta_{0,St2} = 0.4$). This result is complemented by the absorption spectra that show the main charge transfer band of HMQ St2 redshifted compared to that of HMQ St1, while that of HM-NHQ St2 is blueshifted from HM-NHQ St1, in accordance with the two-level model for push-pull systems that predicts an inverse dependence of the first hyperpolarizability on transition energy.¹⁵

To find out what is happening, more information is needed on the electronic structure of HM-NHQ St2. Three *a priori* possible ground state structures ((i)-(iii)) are given in Fig. 1. In order to distinguish between these different possibilities, we studied the solvatochromism of this stage, *i.e.* relating its absorption energy in a range of solvents to their polarity, using both dielectric constant and Reichardt's empirical E_T^N scale^{7,16} as polarity measures (see Figs. 3 and S8-9). Although previously for HMQ St2, a negative solvatochromism was found,⁶ indicating that it has a larger dipole moment in its ground state than in its excited state and hinting at a zwitterionic ground state structure similar to (iii) in Fig. 1 with a negatively charged oxygen as strong donor group and a positively charged nitrogen as strong acceptor group, HM-NHQ St2 is found to have a positive solvatochromism. Thus, it appears that HM-NHQ St2 has a predominantly neutral ground state. Although a neutral ground state can be reached by an electron movement compared to HMQ St2 (and HM-NHQ St2 (iii)), resulting in HM-NHQ St2 (ii), with the proton at the same position as the methyl group in HMQ, this is not plausible as structurally, both molecules HM-NHQ and HMQ are very similar: a change from methyl to proton at the nitrogen does not explain such a drastic change in electronic ground state structure. More likely is that the proton at the nitrogen is removed first on

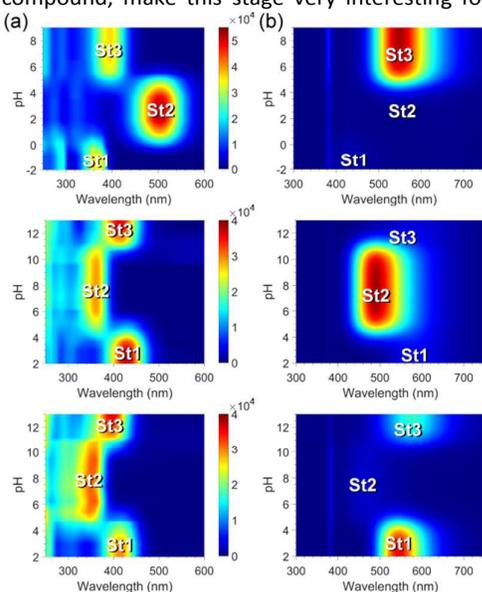


Fig. 2. Contour plots of the (a) absorption (extinction coefficient ϵ in $10^4 \text{ M}^{-1} \text{ cm}^{-1}$; from spectra taken at small pH intervals), and (b) fluorescence (arb. units; interpolated from spectra of the pure stages (see ESI) using the well-known Henderson-Hasselbalch equation) of DA-NHQ (top), HM-NHQ (middle) and OH-NHQ (bottom) in methanol solution as a function of pH (1D spectra can be found in Figs. S2 and S3 in ESI). The regions associated with the three pH-stages shown in Fig. 1 are indicated by St1-St3.

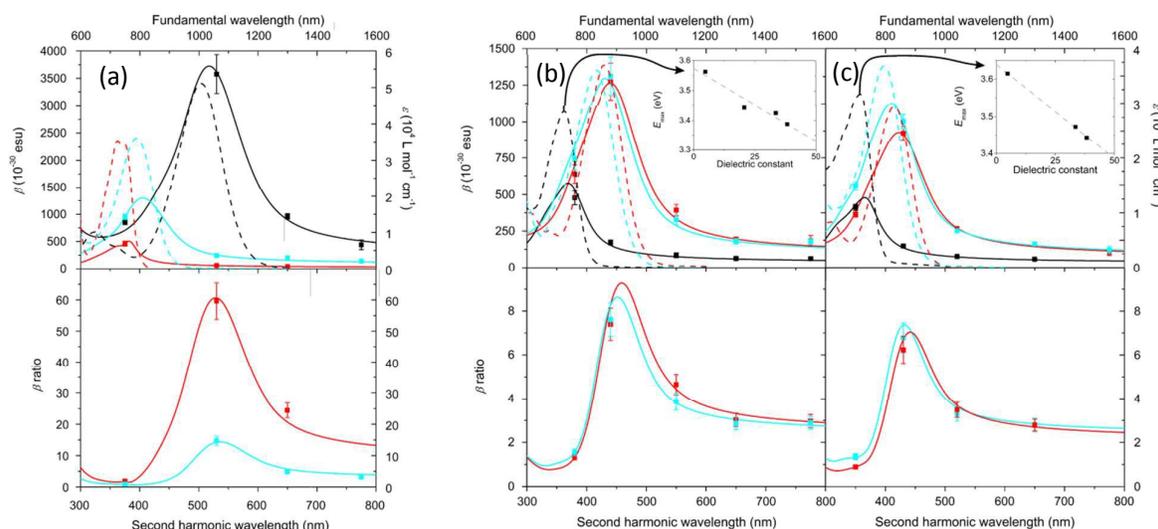


Fig. 3. Absorption spectra (dashed lines), experimental HRS data (symbols) and fitted β dispersion model curves (solid lines) in upper panels (with St1=red, St2=black, and St3=cyan) and experimental (symbols) and fitted (lines) β ratios in lower panels (St2/St1=red, St3/St1=cyan in lower panel of (a), and St1/St2=red, St3/St2=cyan in lower panel of (b) and (c)), of the different stages of the pH-switchable multistage compounds (a) DA-NHQ, (b) HM-NHQ, and (c) OH-NHQ, in methanol solutions. Note that the definitions of the contrasts in the lower panels are sometimes inverted, *i.e.* to always represent “on” vs. “off” mode. Insets show the positive solvatochromism of St2 of HM-NHQ (b) and OH-NHQ (c) (see ESI, Figs. S8–S11), which strongly contrasts with the negative solvatochromism of St2 of HMQ.⁶

deprotonation before the proton at the oxygen, resulting in the neutral ground structure HM-NHQ St2 (i). This is further supported by semi-empirical calculations using the PM7 Hamiltonian and the conductor-like screening model,¹⁷ with a dielectric constant for methanol of 32.7. Indeed, the energy of the ground state structure HM-NHQ St2 (i) is calculated to be 29 kJ/mol lower than for HM-NHQ St2 (ii). The compensation of the charges severely weakens both the donor and acceptor capacities that cause the large β value for HMQ St2, resulting in a low β value for HM-NHQ St2. Finally, HM-NHQ St3, with a strong donor and weak acceptor, has a very similar β and β dispersion as HM-NHQ St1, which has a weak donor and a strong acceptor. Indeed, this exchange of donor/acceptor strength induces a remarkably small difference of only <15% over the whole β dispersion. On the other hand, their β ratio with HM-NHQ St2 reaches over eight on resonance, effectively resulting in a striking “on-off-on” switching behaviour.

As an additional handle to tune the donor-acceptor strength, the SO NLO properties of compound OH-NHQ were investigated. Compared to compound HM-NHQ, OH-NHQ lacks a methoxy group in the phenol ring, so that the electron density in the phenyl ring is reduced. This is shown by a ~15% decrease in static hyperpolarizability compared to that of HM-NHQ due to a reduction in donor strength of the phenyl ring for all three stages, which also confirms that structure (i) (and not (ii), in which case the phenyl-ring would be the acceptor group so that β_0 should increase due to the relative electron deficiency) is the ground state structure of HM-NHQ St2, and similarly of OH-NHQ but without the methoxy-group. On the other hand, the pK_a of St1 to St2 is not altered beyond experimental error, although a reduction for OH-NHQ could be anticipated due to the lower electron density also on the –OH/O– group that is bound to the phenyl group so that the group is more easily deprotonated. Clearly, the pK_a (which is influenced by changes in ground-state electronic structure) is

less sensitive to a slight change in electron density than β_0 (which also depends on the excited-state structure; indeed the absorption spectrum is also redshifted for HM-NHQ compared to OH-NHQ).

For DA-NHQ, stages with both very high and very low β values are observed. Indeed, for DA-NHQ St2, the N,N-dimethylamino donor group, which is regarded in comparative studies as one of the strongest among electron donor groups,¹⁸ is combined with a very strong acceptor, namely the electron deficient pyridinium. This results in a very large β_0 of 263×10^{-30} esu, and a peak value on resonance of about 3750×10^{-30} esu, which are among the largest β values ever observed for any switchable compound. On protonation of the N,N-dimethylamino donor group (DA-NHQ St1), the free π electrons are effectively trapped on the nitrogen in a σ bond, and the group loses its donor capacity. As a result, with a positive charge on both ends of the conjugated chain, and only an electron acceptor left without an electron donor, the resulting β values for DA-NHQ St1 are very low. This combination of very strong and very weak SO NLO properties for adjacent stages results in a static β_0 ratio of 9.1, and a huge on resonance β ratio of 61, which are by far the largest ratios ever reported (the largest ratio previously reported is, to the best of our knowledge, 26 on resonance for an indolinoxazolidine derivative by Mançois *et al.*)⁴ and corresponds to a (on resonance) contrast in signal ($\propto \beta^2$) of over 3700. Stage DA-NHQ St3, on the other hand, combines a strong donor with a weak acceptor, resulting in an intermediate first hyperpolarizability. As a result, compound DA-NHQ has three stages with very different SO NLO characteristics, resulting in multistage behaviour for the compound, where three different pH regimes can be distinguished. DA-NHQ, HM-NHQ and OH-NHQ hence respectively exhibit “off-off-on”, “off-on-off”, and “on-off-on” SO NLO switching modes (see Table S3 in ESI).

In addition to the SO NLO response, the quinolinium

Table 1. Static and peak first hyperpolarizabilities (in 10^{-30} esu), calculated from a fit of the HIV model to the experimental data, for the different stages of the investigated compounds. Values for the two-stage compound HMQ originate from reference [10]. Errors are estimated to be 5% based on a combination of experimental error and an error on the modeling of the β dispersion, except for DA-NHQ where errors reach 10%. Indicated wavelengths (λ) are given in nm.

	$\beta_{0,S11}$	$\beta_{0,S12}$	$\beta_{0,S13}$	$\beta_{max,S11}(\lambda)$	$\beta_{max,S12}(\lambda)$	$\beta_{max,S13}(\lambda)$	$\beta_{0,S11}/\beta_{0,S12}$	$\beta_{0,S13}/\beta_{0,S12}$	$(\beta_{S11}/\beta_{S12})_{max}(\lambda)$	$(\beta_{S13}/\beta_{S12})_{max}(\lambda)$
HM-NHQ	98	39	96	1264 (880)	574 (736)	1295 (860)	2.5	2.4	9.27 (916)	8.63 (904)
OH-NHQ	75	35	77	926 (844)	479 (732)	1127 (820)	2.1	2.2	7.04 (884)	7.37 (864)
DA-NHQ	29	263	92	507 (764)	3723 (1036)	1298 (812)	1/9.1	1/2.9	60.7 (1056)	14.4 (1072)
HMQ	88	214	-	996 (840)	2425 (1056)	-	0.4	-	0.11 (1125)	-

chromophores are also found to exhibit fluorescence switching with large intensity contrasts between the three stages, and following different switching modes (“off-on-on”, “on-off-on” and “on-off-on” for DA-NHQ, HM-NHQ and OH-NHQ, respectively; see Tables S1 and S3 in ESI). Although the quantum yield of the chromophores is low (in the range of 10^{-2} - 10^{-3}), it can still be high enough for practical applications,¹⁹ for instance as auxiliary probe to the SO NLO response. Moreover, NLO and fluorescence switching are complementary to each other for HM-NHQ. Comparable three-stage switching is also observed in water solution (see Fig. S4-S6, ESI), but the poor solubility of the neutral stages of the compounds in this medium hampers detailed characterization of this behaviour.

In conclusion, three different three-stage pH-switchable styryl quinolinium SO NLO chromophores have been synthesized by combining two-stage pH-sensitive electron-donating and -accepting groups, and have been characterized by linear and tuneable wavelength second-order nonlinear spectroscopy. The SO NLO responses of the ‘on’ stages of the chromophores are demonstrated to be very large (static first hyperpolarizability β_0 up to 263×10^{-30} esu for the most efficient push-pull system among the different pH stages), and huge contrasts in both β ratio (up to 9.1 in the static limit and up to 61 at resonance) and fluorescence intensity (up to 38) between adjacent pH stages are obtained. In one case, a very minor structural modification was found to result in an entirely different ground state structure with inverted β contrast.

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Table of contents entry (Graphical abstract)

First three-stage pH-switchable second-order nonlinear optical chromophores are synthesized and characterized by tunable-wavelength (non)linear spectroscopy, showing remarkably different on-off sequences.

