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Quadrupolar Benzobisthiazole-Cored Arylamines as Highly Efficient Two-Photon Absorbing Fluorophores

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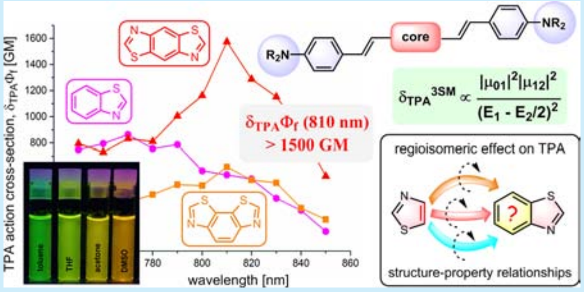
Supporting Information

ABSTRACT: A computer-aided design of novel D−π−A−π−D styrylamines containing five isomeric benzobisthiazole moieties as the electron-accepting core has revealed the linear centrosymmetric benzo[1,2-*d*:4,5-*d*′]bisthiazole as the most promising building block for engineering chromophores displaying high two-photon absorption (TPA) in the near-IR region, as also confirmed experimentally. The ease of synthesis of quadrupolar derivatives thereof, combined with extraordinarily high TPA action cross sections ($\delta_{\mathrm{TPA}}\Phi_f$ > 1500 GM), makes these heteroaromatic systems particularly attractive as diagnostic agents in 3D fluorescence imaging.



Thiazole and thiazole-annulated scaffolds are among the most prominent building blocks in chromophores with potential applications in fields such as nonlinear optics (NLO),[1−4] organic light-emitting diodes,[5] organic field-effect transistors,[6] and dye-sensitized solar cells.[7] Most of these applications rely on the electron-withdrawing ability of the thiazole ring, which is frequently used as the edge substituent. Recently, we demonstrated use of the 1,3-benzothiazole moiety as an electron-accepting core in quasi-quadrupolar fluorophores with the D−π−A−π−D setup, which display high two-photon absorption (TPA).[2] This feature enables the activation of chemical and photophysical processes by low-energy near-IR excitation, which is beneficial in deeper light penetration through materials or living tissues as compared to excitations by visible or UV light (lower-energy photons are also less likely to cause damage outside the focal volume). Dependency of the TPA rate on the square of the incident laser light intensity allows for better control and higher spatial resolution, which is exploited in microfabrication, high-resolution imaging and 3D data storage. To fully benefit from the advantages of the TPA process and to meet specific application requirements, a quest for dyes possessing larger TPA cross sections (δ_{TPA}) in a suitable excitation window, in conjunction with additional properties, such as high emission quantum yields, excelent photostability, and good cell permeability (keeping the molecular size as small as possible), is still a hot topic in material science.[8] In this respect, we were curious as to whether the introduction of a second thiazole ring onto photochemically stable, π-deficient benzothiazole might offer a useful design strategy for enhancing TPA.

While a reasonable number of benzobisthiazole dyes has been reported to date, predominantly in the form of variously substituted 2,6-di(hetero)arylbenzo[1,2-*d*:4,5-*d*′]bisthiazoles,[6,9] TPA properties of these derivatives have remained unexplored. To the best of our knowledge, there was only one attempt to characterize a benzobisthiazole-containing polymer (trans-PBT), which was however unsuccessful due its limited solubility.[10] Synthesis and spectral properties of bis(styryl)benzobisthiazole dyes, which may be viewed as analogues of the previously characterized benzothiazole fluorophores and could thus allow a direct comparison of these systems, were not reported so far. Additionally, two thiazole rings could be connected to the central benzene in several different ways, resulting in five constitutional isomers (Scheme 1), namely, benzo[1,2-*d*:5,4-*d*′]bisthiazole (**1**), benzo[1,2-*d*:4,5-*d*′]bisthiazole (**2**), benzo[1,2-*d*:4,3-*d*′]-bisthiazole (**3**), benzo[2,1-*d*:3,4-*d*′]bisthiazole (**4**), and benzo-[1,2-*d*:3,4-*d*′]bisthiazole (**5**).

To evaluate the influence of an additional thiazole ring and the effect of positional isomerism on TPA properties, a series of linear and V-shaped quadrupolar benzobisthiazole-derived dyes, bearing *N*,*N*-dialkylaniline and triphenylamine moieties as the electron-donating groups, have been investigated in this work (Scheme 1).

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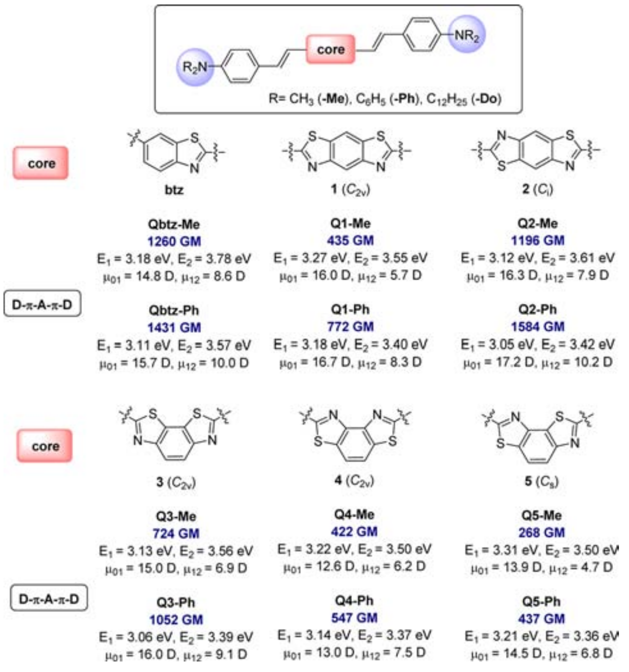
Scheme 1. Structure of the Parent Benzobisthiazoles (1−5) and Quadrupolar Chromophores Q1−Q5[a]



[a] R substituents in the arylamine part are indicated by the suffix at the end of the dye label. TPA cross sections, δ_{TPA} ($S_0 \rightarrow S_2$) given in GM (1 GM = 1×10^{-50} cm^4·s·photon^{-1}), excitation energies E_n, and ground-to-excited and excited-to-excited state transition dipole moments μ_{01} and μ_{12}, respectively, were computed at the CAM-B3LYP/6-311++G** level using a PCM solvation model (toluene as the solvent).

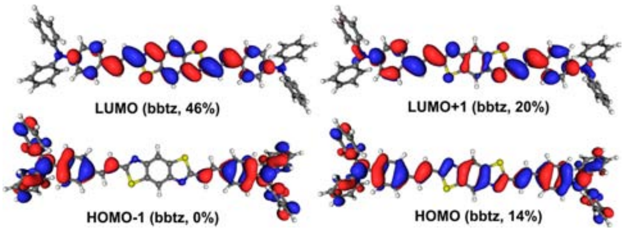


Figure 1. Frontier molecular orbitals in **Q2-Ph**.

A computer-aided prescreening of chromophores with the highest TPA activity has been done by means of the quadratic response time-dependent DFT method, employing the CAM-B3LYP functional and a polarizable continuum model (PCM) accounting for bulk solvent effects, as implemented in the Dalton program.[11] δ_{TPA} associated with the five lowest excitations are collected in Supporting Information, SI. Since we found a strong dependency of the TPA cross sections on the conformation of the two styryl branches with respect to a heteroaromatic core (*s-cis* and/or *s-trans* arrangement), all low-energy conformers were included in our calculations, and the results were Boltzmann-averaged.[12] Note that δ_{TPA} values for different conformers of the same molecule vary, in some cases, by several hundreds of GM, underlining the necessity to consider conformational flexibility in rational design of TPA-active materials.[13]

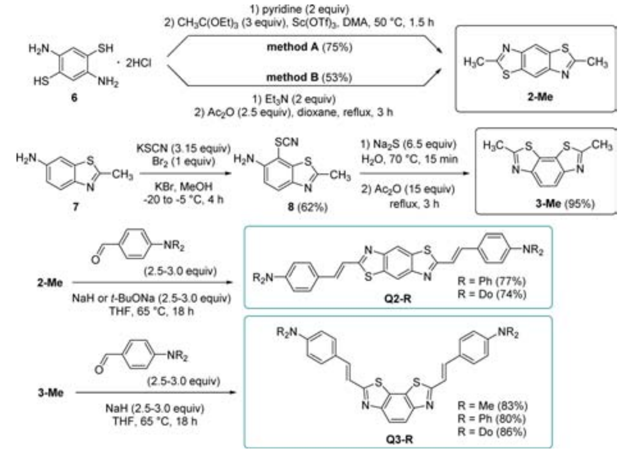
In all cases, the highest δ_{TPA} with maxima positioned in the red and near-IR region ($E_n < 4.0$ eV) are related to the excitation from the ground state to the second excited state ($S_0 \rightarrow S_2$), and the corresponding TPA cross sections are reported in Scheme 1. The $S_0 \rightarrow S_2$ transition takes place from both HOMO−1 and HOMO to the LUMO and LUMO+1 (Figure 1 and Table S3) and corresponds to a charge transfer from the arylamine edges to the π-deficient heteroaromatics. Although all five benzobisthiazoles possess stronger electron-accepting ability than the parent benzothiazole, as indicated by NPA charge analysis (Table S4), this feature does not necessarily guarantee a higher NLO response, and no relationship between δ_{TPA} and the acceptor strength of the π-deficient core can be established. Instead, the relative position of two thiazole rings on the central benzene plays a key role.

Irrespective of the R substituent, benzobisthiazole dyes are ranked according to increasing TPA cross sections as follows: **Q5** < **Q4** < **Q1** < **Q3** < **Q2**, with a difference of >900 GM between the least and the most efficient TPA dye! The additional thiazole ring has a beneficial effect only in the case of **Q2-Ph**, whereas δ_{TPA} of **Q2-Me** is virtually identical with its benzothiazole analogue. Using a three-state model,[14] the great variation of δ_{TPA} within the isomeric benzobisthiazole series and the strikingly lower TPA cross sections of **Q1** and **Q3**−**Q5** as compared to the benzothiazole congeners can be primarily attributed to the differerent excited-to-excited state transition moments μ_{12} and the somewhat larger detuning energies ($E_1 - E_2/2$) in the former series (cf. Table S5, Figure S1 in SI for more detailed analysis of the observed trends). In contrast, the superiority of dyes derived from benzobisthiazole **2** over its isomers is related to a favorable combination of all parameters involved in the three-state model (the highest transition dipole moments μ_{01} and μ_{12} and the reduced detuning energy). This results from the most efficient coupling between two branches connected to the heteroaromatic ring with two nitrogen and two sulfur atoms in mutual *para* position, respectively. The lowest μ_{12} values are computed for dyes derived from **1** and **5**, where two N and two S atoms, respectively, are in unfavorable *meta* position. Benzobisthiazoles **3** and **4** are intermediate cases, where one of the N,N or S,S couples is positioned *para*, while the other one is placed in the *ortho* position. Substantially higher δ_{TPA} of **Q3** over **Q4** indicate more important placement of two azole N atoms into a mutual *para* position, compared to the two sulfur atoms.

To prove these findings, quadrupolar chromophores containing benzobisthiazoles **2** and **3** as the central moiety were prepared and subjected to measurements of δ_{TPA} via a two-photon excited fluorescence (TPEF) method with femtosecond laser excitation at wavelengths of 750−850 nm. The synthesis of other isomers was not attempted due to their anticipated lower TPA activity.

A key step in the synthesis of **Q2** and **Q3** was a double aldol-type condensation between 4-donor-substituted benzaldehydes and benzobisthiazoles with two active methyl groups (**2-Me** or **3-Me**) under strongly basic conditions (Scheme 2). The starting **2-Me** was prepared by a condensation of the commercially available 2,5-diaminobenzene-1,4-dithiol dihydrochloride (**6**) with acetic anhydride in the presence of triethylamine as a cosolvent. Ac_2O was efficient enough in the one-step formation of a benzobisthiazole scaffold and the use of orthoesters and rare-earth metal triflates as catalysts was not necessary, albeit the latter method provides the desired product in somewhat higher yield.[15] **3-Me** was prepared from 6-amino-2-methylbenzothiazole (**7**),[2] which was first reacted with KSCN and Br_2 to afford the thiocyanate **8**. This was consequently transformed in one pot to **3-Me** via reduction with Na_2S and ring-closing reaction between

Scheme 2. Synthetic Routes to Fluorophores Q2 and Q3



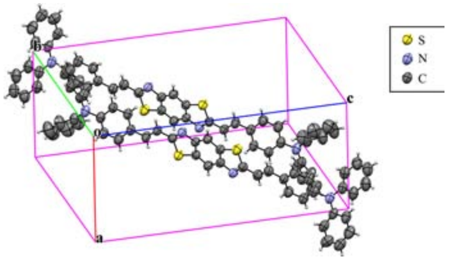


Figure 2. Intermolecular $\pi-\pi$ stacking in the unit cell of **Q2-Ph**·2CHCl$_3$ (solvent molecules are omitted for clarity, and the displacement ellipsoids are drawn at 50% probability level). The benzobisthiazole molecules are mutually π-stacked with interplanar distance of 3.502(3) Å and slippage of 0.812 Å (see SI for more details).

Table 1. Photophysical Properties of Quadrupolar Dyes in Toluene

dye	λ_{abs} [nm]	ε_{max} [M^{-1}cm^{-1}]	λ_f [nm]	Φ_f	λ_{TPA} [nm]	$\delta_{TPA}\Phi_f$ [GM]	δ_{TPA} [GM]
Qbtz-Me	417	68500	493	0.17	750	232	1365
Qbtz-Ph	431	72400	491	0.56	770	864	1543
Q2-Ph	445	83900	496	0.94	810	1575	1676
Q2-Do	451	85800	499	0.48	810	871	1815
Q3-Me	440	62300	492	0.20	790	195	975
Q3-Ph	442	74600	493	0.50	810	619	1238
Q3-Do	448	77200	497	0.31	810	503	1622

Ac$_2$O and the intermediately formed 6-amino-2-methylbenzothiazol-7-thiol.[16]

The presence of a second thiazole ring allows avoiding metal-catalyzed cross-coupling reactions to attach the second styryl arm to the central ring, making the synthesis more convenient, cost friendly, and amenable to large-scale production as compared to that of the **Qbtz** series. **Q2-Me** was not isolated due to its high insolubility in common organic solvents, presumably due to $\pi-\pi$ stacking interactions (see Figure 2). No insolubility issue occurred when preparing **Q3-Me** and all the other derivatives with phenyl (Ph) and dodecyl (Do) substituents at the periphery. All double bonds in the target chromophores formed under the Knoevenagel condensation were *trans*-configured, as confirmed by the coupling constants of the vinyl protons ($^3J_{H,H} \approx 16$ Hz) in ^{1}H NMR spectra and the X-ray structure of **Q2-Ph**.

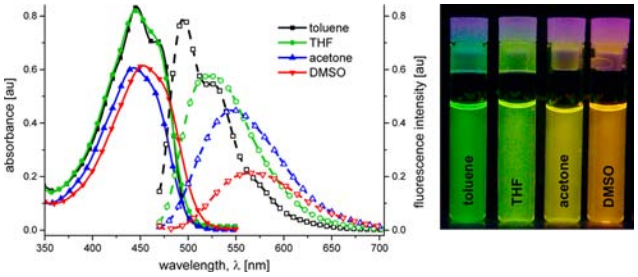


Figure 3. UV−vis absorption (solid line) and emission (dashed line) spectra of **Q2-Ph** (c = 10 μM) in toluene, THF, acetone, and DMSO (left). Fluorescence of **Q2-Ph** in various organic solvents (right).

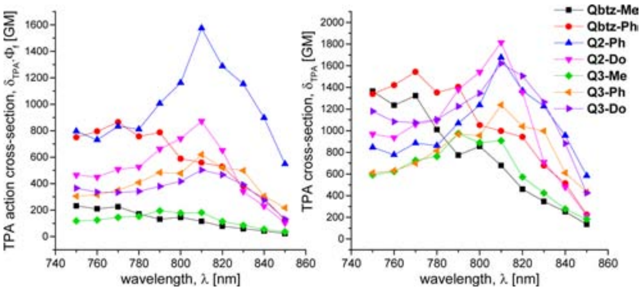


Figure 4. TPA action cross sections $\delta_{TPA}\cdot\Phi_f$ (left) and TPA cross sections δ_{TPA} (right) of the quadrupolar dyes in toluene.

The absorption spectra of benzobisthiazole dyes in toluene (Table 1, Figure 3, Figure S5) feature one intense band in the visible region with maxima λ_{abs} in the range of 440−451 nm (11−23 nm bathochromically shifted compared to the **Qbtz** series), with one shoulder peak on the low-energy side. This multicomponent pattern is also seen in emission spectra (Figure S5) and can be related to the vibronic coupling. The fluorescence in toluene is observed in the blue-green spectral region with the most intense peaks at 490−500 nm. While λ_{abs} remains essentially unchanged upon increasing solvent polarity, a pronounced red shift is observed for fluorescence maxima λ_f (Figure 3).

TPEF spectra of the prepared dyes are in toluene shown in Figure 4. All benzobisthiazole chromophores exhibit moderate to excellent TPA cross sections (975−1815 GM), with maxima λ_{TPA} positioned at 790−810 nm (Table 1). This is substantially less than twice that of the single-photon absorption λ_{abs} ($S_0 \rightarrow S_1$), implying a $S_0 \rightarrow S_2$ transition as expected for quadrupolar dyes due to parity selection rules. λ_{TPA} of **Qbtz-Me** and **Qbtz-Ph** are blue-shifted to 750 and 770 nm, respectively, consistent with the somewhat higher second excitation energies E_2 calculated for these derivatives. The highest δ_{TPA} (>1600 GM) are observed for **Q2-Do**, **Q2-Ph**, and **Q3-Do**.

The efficiency of central heteroaromatic rings is assessed by comparing δ_{TPA} of triphenylamine end-capped derivatives, establishing the following order: **Q3-Ph** < **Qbtz-Ph** < **Q2-Ph**. This is in agreement with our computations and confirms (a) a slight superiority of the linear centrosymmetric benzobisthiazole **2** over benzothiazole and (b) lower TPA activity of dyes derived from angular benzobisthiazole **3** compared with its linear congener **2** and benzothiazole analogue (this is also evident from comparing **Q3-Do** to **Q2-Do** and **Q3-Me** to **Qbtz-Me**). Although the difference between δ_{TPA} of **Q2-Ph** and **Qbtz-Ph** is rather small, the former exhibits a fluorescent quantum yield more than twice as large, resulting in substantially higher TPA action cross section, $\delta_{TPA}\cdot\Phi_f$ (Figure 4, left). Since the latter quantity is vital in TPEF microscopy, where both strong TPA and one-photon emission are required, **Q2-Ph** is an excellent candidate for two-photon imaging.

Similar to our previous findings, derivatives decorated with a diphenylamino group exhibit larger NLO response than their dimethylamino analogues (**Qbtz-Me** vs **Qbtz-Ph**, **Q3-Me** vs **Q3-Ph**). TPA enhancement is even more pronounced when employing a didodecylamino group (**Q2-Ph** vs **Q2-Do**, **Q3-Ph** vs **Q3-Do**). This somewhat counterintuitive behavior is confirmed by our calculations[17] and can be rationalized by involving additional optical channels in triphenylamine series, which to some extent reduce the δ_{TPA} values obtained from the three-state model (cf. Table S6). Both the elongation of pendant alkyl chains and the extension of π-conjugation using a diarylamino moiety offer thus a useful strategy not only to increase the solubility but also to amplify δ_{TPA}, where the latter modification is revealed as more suitable for engineering highly emissive fluorophores.

To conclude, the fusion of the additional π-deficient heteroaromatic ring to the central electron-accepting core must not necessarily lead to TPA enhancement, as intuitively expected, and may even have a detrimental effect on the NLO response (**Qbtz** vs **Q1**, **Q3**−**Q5**). To benefit from this structural modification, the relative position of heteroaromatic moieties attached to the central ring has to be optimized to ensure an efficient electronic coupling, which results in favorable one-photon absorption parameters and an enhanced TPA response. In this respect, the **Q2** series with excellent TPA cross sections ($\delta_{\text{TPA}} > 1600$ GM), high emission quantum yields, and a facile method for synthesis provides a low-cost and very efficient alternative to many TPA fluorophores currently used.[18] In addition, all benzobisthiazoles have further possible points of attachment, allowing for more modifications to modulate and improve TPA cross sections using the same building block, for example, by introducing auxiliary electron donor or acceptor substituents on the heteroaromatic ring or by building multi-branched structures via coordination of heterocyclic nitrogen atoms to metal ions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental and computational details, computed TPA cross sections and one-photon absorption characteristics, detailed quantum-chemical analysis, synthetic procedures, and crystal structure data for **Q2-Ph**$\cdot 2\text{CHCl}_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Breitung, E. M.; Shu, C. F.; McMahon, R. J. *J. Am. Chem. Soc.* **2000**, *122*, 1154. (b) Hrobárik, P.; Zahradník, P.; Fabian, W. M. F. *Phys. Chem. Chem. Phys.* **2004**, *6*, 495. (c) Hrobárik, P.; Sigmundová, I.; Zahradník, P.; Kasák, P.; Arion, V.; Franz, E.; Clays, K. *J. Phys. Chem. C* **2010**, *114*, 22289. (d) Ma, X. H.; Ma, F.; Zhao, Z. H.; Song, N. H.; Zhang, J. P. *J. Mater. Chem.* **2010**, *20*, 2369. (e) Raposo, M. M. M.; Castro, M. C. R.; Belsley, M.; Fonseca, A. M. C. *Dyes Pigm.* **2011**, *91*, 454. (f) El-Shishtawy, R. M.; Borbone, F.; Al-Amshany, Z. M.; Tuzi, A.; Barsella, A.; Asiri, A. M.; Roviello, A. *Dyes Pigm.* **2013**, *96*, 45.

(2) Hrobáriková, V.; Hrobárik, P.; Gajdoš, P.; Fitilis, I.; Fakis, M.; Persephonis, P.; Zahradník, P. *J. Org. Chem.* **2010**, *75*, 3053.

(3) Hrobárik, P.; Hrobáriková, V.; Sigmundová, I.; Zahradník, P.; Fakis, M.; Polyzos, I.; Persephonis, P. *J. Org. Chem.* **2011**, *76*, 8726.

(4) Belfield, K. D.; Morales, A. R.; Kang, B. S.; Hagan, D. J.; Van Stryland, E. W.; Chapela, V. M.; Percino, J. *Chem. Mater.* **2004**, *16*, 4634.

(5) Yu, G.; Yin, S. W.; Liu, Y. Q.; Shuai, Z. G.; Zhu, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 14816.

(6) (a) Ando, S.; Murakami, R.; Nishida, J.; Tada, H.; Inoue, Y.; Tokito, S.; Yamashita, Y. *J. Am. Chem. Soc.* **2005**, *127*, 14996. (b) McEntee, G. J.; Vilela, F.; Skabara, P. J.; Anthopoulos, T. D.; Labram, J. G.; Tierney, S.; Harrington, R. W.; Clegg, W. *J. Mater. Chem.* **2011**, *21*, 2091. (c) Lin, Y. Z.; Fan, H. J.; Li, Y. F.; Zhan, X. W. *Adv. Mater.* **2012**, *24*, 3087.

(7) (a) Zhang, W. Y.; Feng, Q. Y.; Wang, Z. S.; Zhou, G. *Chem.—Asian J.* **2013**, *8*, 939. (b) Saeki, A.; Tsuji, M.; Yoshikawa, S.; Gopal, A.; Seki, S. *J. Mater. Chem. A* **2014**, *2*, 6075.

(8) (a) He, G. S.; Tan, L. S.; Zheng, Q.; Prasad, P. N. *Chem. Rev.* **2008**, *108*, 1245. (b) Pawlicki, M.; Collins, H. A.; Denning, R. G.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 3244. (c) Kim, H. M.; Cho, B. R. *Chem. Commun.* **2009**, 153.

(9) (a) Reinhardt, B. A.; Unroe, M. R.; Evers, R. C.; Zhao, M. T.; Samoc, M.; Prasad, P. N.; Sinsky, M. *Chem. Mater.* **1991**, *3*, 864. (b) Intemann, J. J.; Mike, J. F.; Cai, M.; Barnes, C. A.; Xiao, T.; Roggers, R. A.; Shinar, J.; Shinar, R.; Jeffries-EL, M. *J. Polym. Sci., Part A: Polym. Chem.* **2013**, *51*, 916. (c) Bon, J. L.; Feng, D. J.; Marder, S. R.; Blakey, S. B. *J. Org. Chem.* **2014**, *79*, 7766.

(10) Belfield, K. D.; Yao, S.; Morales, A. R.; Hales, J. M.; Hagan, D. J.; Van Stryland, E. W.; Chapela, V. M.; Percino, J. *Polym. Adv. Technol.* **2005**, *16*, 150.

(11) *DALTON*, a molecular electronic structure program, 2011 (available from http://www.daltonprogram.org). See SI for computational details.

(12) The *cis*-configured isomers are energetically disfavored by >26 kJ/mol, giving rise to a negligible Boltzmann weighting factor.

(13) Conformational dependence of δ_{TPA} has been recently reported also in: Silva, D. L.; Murugan, N. A.; Kongsted, J.; Rinkevicius, Z.; Canuto, S.; Agren, H. *J. Phys. Chem. B* **2012**, *116*, 8169.

(14) $\delta_{\text{TPA}}(S_0 \rightarrow S_2)$ of quadrupolar dyes is usually dominated by the three-state term, which is proportional to the product $|\mu_{01}|^2|\mu_{12}|^2$ and inversely proportional to the square of the detuning energy $(E_1 - E_2/2)$.

(15) (a) Mike, J. F.; Inteman, J. J.; Ellern, A.; Jeffries-El, M. *J. Org. Chem.* **2010**, *75*, 495. (b) Čibová, A.; Magdolen, P.; Fülöpová, A.; Zahradník, P. *Chem. Pap.* **2013**, *67*, 110.

(16) (a) Fridman, S. G.; Golub, D. K. *Chem. Heterocycl. Compd.* **1965**, *1*, 713. (b) Kiprianov, A. I.; Mikhailenko, F. A. *Chem. Heterocycl. Compd.* **1967**, *3*, 270.

(17) See Figure S2 for a dependence of δ_{TPA} on the pendant alkyl chain length in **Q2-R** series, where δ_{TPA} increases steadily to reach a plateau for the dioctylamino group. Despite the higher μ_{01} and μ_{12} values for the NPh_2 end-capped derivative, its TPA activity is comparable to that of the NHex_2 analogue.

(18) For recent examples of quadrupolar dyes with large δ_{TPA}, see: (a) Wilkinson, J. D.; Wicks, G.; Nowak-Król, A.; Łukasiewicz, Ł. G.; Wilson, C. J.; Drobizhev, M.; Rebane, A.; Gryko, D. T.; Anderson, H. L. *J. Mater. Chem. C* **2014**, *2*, 6802. (b) Belfield, K. D.; Bondar, M. V.; Yao, S.; Mikhailov, I. A.; Polikanov, V. S.; Przhonska, O. V. *J. Phys. Chem. C* **2014**, *118*, 13790. (c) Grzybowski, M.; Hugues, V.; Blanchard-Desce, M.; Gryko, D. T. *Chem.—Eur. J.* **2014**, *20*, 12493.