From 2,5-Diformyl-1,4-dihydropyrrolo[3,2-b]pyrroles to Quadrupolar, Centrosymmetric Two-Photon-Absorbing A–D–A Dyes

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ABSTRACT: An original approach has been developed for the insertion of formyl substituents at positions 2 and 5 of 1,4-dihydropyrrolo[3,2-b]pyrroles by conversion of thiazol-2-yl substituents. The synthetic utility of these formyl groups was investigated, and a series of centrosymmetric A–π–D–π–A frameworks were constructed. The two-photon absorption of the quadrupolar pyrrolo[3,2-b]pyrrole possessing two dicyanovinylidene flanking groups is attributed to an S0 → (S1) → S3 transition which has a large TPA cross-section (1300 GM) for a molecule of this size.

This transformation proceeds via quaternization of the azole nitrogen atom followed by reduction and finally cleavage of the N,S-acetals with mercury or silver salts. Given that recent synthetic breakthroughs have enabled the preparation of 2,5-bis(thiazol-2-yl)pyrrolo[3,2-b]pyrroles in reasonable quantities, and the fact that TAPPs are in general compatible with alkylating/reducing agents, we came to the conclusion that the above reaction sequence could provide access to formyl-substituted pyrrolo[3,2-b]pyrroles, which in turn could open the door for further derivatization via Knoevenagel condensation, Wittig reaction, etc. To test this hypothesis, we synthesized TAPP 4 from 2-formylthiazole (Scheme 1). Its quaternization with methyl triflate proceeded quantitatively. In addition, the reduction to double N,S-acetal using NaBH4 did not pose any major problems. However, hydrolysis using copper(II) chloride or mercury(II) chloride gave 5% and 28% yields, respectively. Because of the low yield of the former and toxicity of the latter, we decided to test silver nitrate. A short optimization of the conditions led to cleavage in an acceptable 41% yield.

With the crucial dialdehyde 5 in hand, we attempted Knoevenagel condensation with malononitrile, which afforded the expected product 6 in high yield (Scheme 1). Unfortunately, condensation with other nucleophiles did not proceed as smoothly, apparently due to the low reactivity of...
the formyl groups. This was anticipated, as the pyrrolo[3,2-b]pyrrole core is extremely electron rich, and while the reaction with the first formyl group was relatively efficient due to the electron-withdrawing nature of the neighboring formyl group, the subsequent reaction of the second formyl group was much slower due to the absence of an activating functional group. Namely, attempts at condensation of dialdehyde 5 with dimethyl malonate, dimedone, 1,3-indandione, 2,2-dimethyl-1,3-dioxane-4,6-dione or 1,2,3,3-tetramethyl-3H-indolium perchlorate, triphenyl phosphonium ylides (Wittig reagents), and N-methyl-4-picolinium bromide failed to give the expected products.

We next considered the transformation of dialdehyde 5 into 2,5-bis(ethynyl)pyrrolo[3,2-b]pyrrole. Such transformations have been achieved with good yields for electron-rich aromatic aldehydes using the Bestmann−Ohira reagent (BOR), which is a 10% solution of dimethyl(1-diazo-2-oxopropyl)phosphonate in acetonitrile. When used for transformation of 5, the progress of the reaction was again hampered by the low reactivity of the aldehyde, and 6 equiv of BOR was needed in order to obtain satisfactory conversion to the desired 2,5-bis(ethynyl)pyrrolo[3,2-b]pyrrole (Scheme 2). Because of the light sensitivity of this material, it was used directly in the Sonogashira reaction to further expand the \( \pi \)-system leading to dyes 7 and 8.

The photophysical properties of pyrrolo[3,2-b]pyroles 6–8 were measured in cyclohexane, toluene, dichloromethane, tetrahydrofuran, and acetonitrile (Figure 1, Table 1, and Table S5). As expected, newly synthesized dyes 7 and 8 have their absorption and emission bathochromically shifted compared to traditional tetraaryl derivatives as a result of expansion of their
The emission spectra of the ground state. More spectacular changes are observed on the figures S11, respectively, when going from cyclohexane to acetonitrile, which can be attributed to rotational relaxation of the excited state. Quantum-chemical calculations (see the Supporting Information) successfully reproduced the main features of the OPA and TPA spectra for 6–8 (Figures S5–S7) with the usual level of overestimation of the transition energy by 0.24–0.28 eV. The decomposed TPA spectra by destination state showed that the main TPA bands for 7 and 8 were assigned to the transition to S2 excited state, while that for 6 was assigned to the transition to S1 (Figure S8). The drastic increase at wavelengths shorter than the peak of 6 can be explained by the strong TPA transition to S0 together with a weaker one to S2. For all dyes, the lowest energy OPA band is assigned to the transition to S4 (Figure S8). The transition dipole moments from S0 to S1, S1 to S2, S2 to S3, and S3 to S4 are given in Table S2. The electronic configuration of all the TPA excited states of 6 and 8 in DMSO was found to be HOMO → LUMO+. Two-photon transition to S2 for 7 and 8 is solely mediated by S1 as an intermediate state (S0 → S1 → S2). The transition dipole moments from S0 to S1 (μ10) and S1 to S2 (μ21) are μ10 = 16.3 D and μ21 = 17.2 D with the crossing angle.

### Table 1. Spectroscopic Properties of Dyes 6–8 in Different Solvents

| compd | solvent | λ_{abs,max} (nm) | ε_{max} (M⁻¹ cm⁻¹) | λ_{em,max} (nm) | Stokes shift (cm⁻¹) | φ_d | 2λ_{abs,max} (nm) | λ_{TPA,max} (nm) | σ_{TPA,max} (GM) | σ_{TPA,max} (GM) |
|-------|---------|------------------|---------------------|-----------------|-------------------|-----|-----------------|-----------------|----------------|------------------|
| 6     | CHX     | 501              | 92200               | 509             | 314               | 0.009 | 1032            | 648             | 505 ± 95 (1340 ± NA) | 6.6             |
|       |         | 472              | 59700               |                 |                   |      |                 |                 |                 |                  |
|       | DCM     | 516              | 73000               | 540             | 861               | 0.013 | 962             | 577             | 17              |                  |
|       |         | 481              | 56000               |                 |                   |      |                 |                 |                 |                  |
|       | ACN     | 505              | 59100               | 540             | 1280              | 0.007 | 822             | 721             | 1050 ± 190       | 63              |
|       |         | 481              | 52100               |                 |                   |      |                 |                 |                 |                  |
| 7     | CHX     | 443              | 116800              | 451             | 400               | 0.51  | 910             | 770             | 825 ± 160        | 17              |
|       |         | 419              | 84800               |                 |                   |      |                 |                 |                 |                  |
|       | DCM     | 441              | 81700               | 486             | 2100              | 0.06  | 882             | 721             | 1050 ± 190       | 63              |
|       |         | 435              | 68600               |                 |                   |      |                 |                 |                 |                  |
| 8     | CHX     | 459              | 92200               | 469             | 564               | 0.53  | 1032            | 648             | 505 ± 95 (1340 ± NA) | 6.6             |
|       |         | 435              | 68600               |                 |                   |      |                 |                 |                 |                  |
|       | DCM     | 455              | 71000               | 566             | 4310              | 0.02  | 910             | 770             | 825 ± 160        | 17              |
|       |         | 442              | 66200               | 581             | 5410              | 0.003 |                 |                 |                 |                  |

*Determined with fluorescein in 0.1 M NaOH as a standard. *Determined with coumarin 153 in ethanol as a standard. CHX = cyclohexane, DCM = dichloromethane, ACN = acetonitrile.

$\pi$-electron system. A noticeable, >100 nm red-shift is shown by compound 6 bearing strongly electron-withdrawing cyano substituents when compared to parent TAPP 4. The fluorescence quantum yields (φ_d) of dyes 7 and 8 exceed 40%, which correspond very well to those reported earlier for this class of dyes. In the case of dye 6, however, φ_d is ca. 1%, which can be attributed to rotational relaxation of the excited state. All prepared dyes exhibit moderate solvatochromism, with 13 and 17 nm hypsochromic shifts registered for 7 and 8, respectively, when going from cyclohexane to acetonitrile (Figures S11–S13).

Inspection of the results suggests a polarized character of the ground state. More spectacular changes are observed on the emission spectra of 7 and 8, with strong positive solvato-fluorochromism expressed by an over 100 nm bathochromic shift observed for compound 8. Altogether, this results in an increase of Stokes shift by a factor of ca. 10 when going from nonpolar cyclohexane to polar acetonitrile.

TPA properties of 6–8 were studied by experimental and quantum-chemical calculations (see the Supporting Information for details). The measurements showed that pyrrolo[3,2-b]pyrrole dyes 7 and 8 have a reasonably large TPA cross-section at wavelengths around 750 nm (Figure 1). The peak values observed are 1050 ± 190 GM for 7 at 720 nm and 825 ± 160 GM for 8 at 770 nm. These TPA peaks have transition energies (i.e., twice the photon energies) located at lower energies than those of one-photon absorption. A weaker but non-negligible TPA was observed at twice the wavelength of the OPA peak (800–900 nm for 7 and 850–950 nm for 8). These weak TPA bands can be explained by partial relaxation of forbidden TPA transition to the OPA-allowed excited states due to vibronic coupling.

Compared to these two, the TPA peak for 6 was found to be significantly blue-shifted and with a relatively smaller magnitude of the peak cross-section (505 ± 95 GM at 648 nm). At short wavelengths below 600 nm, the spectral magnitude showed a drastic increase as incident wavelength was decreased and reached ca. 1300 GM at 577 nm.

The observed blue-shift of the TPA peak and red-shift of the OPA peak of 6 results in exceptionally wide separation of the transition energy between the OPA and TPA transitions as shown in Figure 1.

Table 2. Calculated Results of the Excited States (S_i) Involved in the Major Transitions of OPA and TPA for Dyes 6–8

| dye | S_i | E (eV) | λ (nm) | f | config (amplitude) |
|-----|-----|--------|--------|---|-------------------|
| 6   | 1   | 2.88   | 431    | 1.90 | H → L (0.689)     |
|     | 2   | 3.34   | 371    | 0.30 | H-1 → L (0.691)  |
|     | 4   | 4.26   | 291    | 0.00 | H → L + 1 (0.648) |
|     | 9   | 4.83   | 257    | 0.00 | H-6 → L (0.668)  |
| 7   | 1   | 3.17   | 391    | 3.03 | H → L (0.670)    |
|     | 2   | 4.00   | 310    | 0.00 | H → L + 1 (0.643) |
|     | 3   | 4.13   | 300    | 0.25 | H-1 → L (0.664)  |
|     | 8   | 4.96   | 250    | 0.00 | H-2 → L (0.437)  |
| 8   | 1   | 3.08   | 403    | 2.99 | H → L (0.663)    |
|     | 2   | 3.81   | 326    | 0.00 | H → L + 1 (0.647) |
|     | 5   | 4.08   | 304    | 0.22 | H-1 → L (0.657)  |
|     | 9   | 4.08   | 257    | 0.00 | H-2 → L (0.507)  |

*Transition energy E, transition wavelength λ, oscillator strength f, and electronic configuration (and its amplitude). H stands for HOMO and L stands for LUMO. Bold type represents the TPA excited state.
(7) of 1.7° for 7 and μ₁₀ = 16.5 D and μ₂₁ = 19.7 D with θ = 1.4° for 8. These large transition dipole moments with small angles result in efficient TPA. These properties originate from the large overlap of the molecular orbitals (HOMO → LUMO for μ₀ and LUMO → LUMO + 1 for μ₁), distributing in the same direction along the long axis of the molecule for both 7 and 8 (Figure 2). The same was observed for 6. The dominant intermediate was also found to be the S₁ state for its two-photon transition (i.e., S₀ → (S₁) → S₂).

Figure 2. Isosurface plots of selected molecular orbitals involved in the lowest one- and two-photon absorption excitations of 6–8.

The N-phenyl rings are twisted by 69° for 6 and 54° for 7 and 8 with respect to the pyrrolo[3,2-b]pyrrole plane (Figure S9). This gives virtually zero overlap between the orbitals and makes them a dark state for both OPA and TPA. In addition, the experimentally observed wide separation of the transition energy between the OPA (516 nm, 2.40 eV) and TPA (650 nm/2, 3.81 eV) peaks of 6 (by 1.41 eV) can be explained by the order of the excited states (where TPA occurs to S₄) and the shorter π-conjugation length.

In conclusion, thiazole is shown to be a CHO equivalent in the first ever synthesis of 2,5-diformylpyrrolo[3,2-b]pyrrole, which in turn is an excellent building block for the preparation of 2,5-diethylpyrrolo[3,2-b]pyrrole. Centrosymmetric, quadrupolar dyes prepared from these two building blocks have relatively large TPA cross sections such as 800–1000 GM at ca. 750 nm for phenylethynyl π-extended derivatives. As for the dicyanoethyl containing dye, the TPA bands were blue-shifted (680 nm) and showed a drastic increase to ca. 1300 GM. Quantum-chemical calculations revealed that the separation between excited states responsible for one-photon and two-photon absorption is exceptionally large in this case, which can be traced to bridging the strongly electron-withdrawing CH≡C(CN)₂ groups with the exceptionally electron-rich pyrrolo[3,2-b]pyrrole core.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c00718.

Data associated with this article, including experimental procedures, compounds characterization, steady-state absorption and emission along with the two-photon absorption details, electrochemical details and computational analysis details (PDF)

FAIR data, including the primary NMR FID files, for compounds 5–8 (ZIP)

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### Author Contributions

M.T. conceived the idea. M.T. and P.K. performed all synthetic experiments and wrote the manuscript. S.O. performed TPA experiments and wrote the formal analysis of that part of the manuscript. D.T.G. supervised the project, performed formal analysis, and wrote and reviewed the manuscript.

### Notes

The authors declare no competing financial interest.

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