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On-off-on Control of Molecular Inversion Symmetry via Multi-stage Protonation: Elucidating Vibronic Laporte Rule

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Abstract: The Laporte rule dictates that one- and two-photon absorption spectra of inversion-symmetric molecules should display alternatively forbidden electronic transitions; however, for organic fluorophores, drawing clear distinction between the symmetric- and non-inversion symmetric two-photon spectra is often obscured due to prevalent vibronic interactions. We take advantage of consecutive single- and double-protonation to break and then reconstitute inversion symmetry in a nominally symmetric diketopyrrolopyrrole, causing large changes in two-photon absorption. By performing detailed one- and two-photon titration experiments, with supporting quantum-chemical model calculations, we explain how certain low-frequency vibrational modes may lead to apparent deviations from the strict Laporte rule. As a result, the system may be indeed considered as an on-off-on inversion symmetry switch, opening new avenues for two-photon sensing applications.

Inversion-symmetric organic chromophores commonly feature, in the singlet manifold, alternating-parity electronic states, where a *gerade* (*g*) or *ungerade* (*u*) parity S_0 ground-state connects via one-photon allowed but two-photon forbidden electric dipole transition to opposite-parity (*u* or *g*) lowest-energy S_1 excited state.[1] Bonding of a proton may disrupt ground-state inversion symmetry, such that the above exclusion, commonly called Laporte rule, no longer applies, and two-photon absorption (2PA) efficiency of the $S_0 \rightarrow S_1$ transition may drastically increase. Monitoring 2PA variations has been suggested for studying pH,[2,3] ion sensing,[4–8] redox reactions,[9] and solvent polarity.[10] However, unambiguous spectroscopic evidence for Laporte rule controlling the 2PA remains scarce. This is, in part, because presence of spectrally-overlapping species, e.g. different protonation forms, makes acquiring reliable 2PA cross section

spectra an arduous task; and even if such spectra are obtained, for room temperature and condensed phases, both linear (1PA) and 2PA transitions are often of electronic-vibrational (vibronic) origin, making interpretation of this data debatable. To make matters worse, while quantum-chemical calculations deliver reliable vibronic features of 1PA spectra, predicting analogous vibronic spectra for 2PA, especially for complex chromophores, remains extremely challenging.[11] It is therefore of significant fundamental- and practical interest to elucidate how attaching a proton changes vibronic 2PA of a nominally inversion-symmetric chromophore. Moreover, if a second proton binds at a symmetric site, then that should revive the Laporte rule, thus shedding further light on the origin of vibronic 2PA transitions.
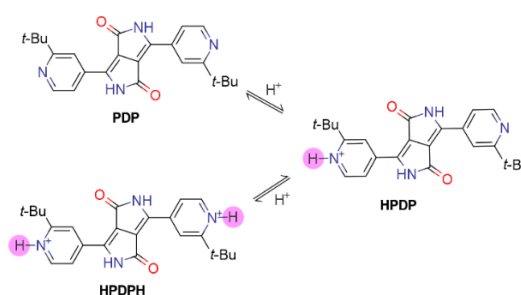
Scheme 1. Structure of neutral (PDP), single-protonated (HPDP) and double-protonated (HPDPH) chromophore.

Here, we synthesize a novel inversion-symmetric 3,6-bis-(2-*tert*-butylpyridin-4-yl)-diketopyrrolopyrrole (PDP), which combines a diketopyrrolopyrrole (DPP) core with two flanking pyridyl moieties,

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as shown in Scheme 1. The pyridyl substituents offer the opportunity for reversible single- and double-protonation, while their small, ≤ 7°, dihedral angle with the DPP core suggests a single π-conjugated system, whereas *tert*-butyl groups secure suitable solubility.[12] The inherent rigidity of the dyes' backbone limits symmetry-lowering conformations and promotes photo-stability in organic solvents, while also leading to pronounced $S_0 \rightarrow S_1$ vibronic transitions along with efficient one- and two-photon excited fluorescence (2PEF).[13]
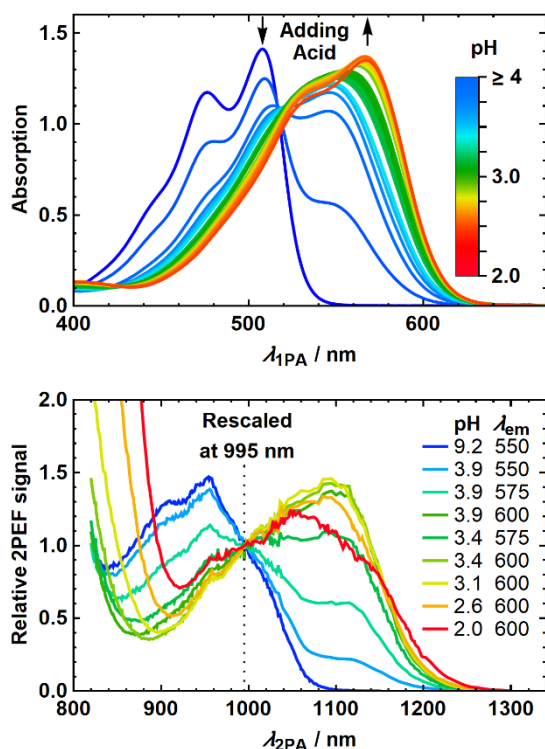

Figure 1. pH-dependence of 1PA (top) and 2PEF excitation (bottom) spectra for PDP in methanol upon addition of triflic acid. The two-photon profiles are rescaled for convenience at 995 nm (dotted line), as raw maximum signals varied by a factor of ~40.

Figure 1 (upper panel) shows changes of 1PA spectrum of PDP in methanol (dark blue curve) upon titration with triflic acid. Initially, at pH > 4, one observes an isosbestic point at $\lambda_{1PA} = 517$ nm, whereas at pH < 2.7, there appear two secondary isosbestic points at $\lambda_{1PA} = 555$ and 434 nm. This behavior indicates presence, in addition to the neutral form, of single-protonated (HPDP) and double-protonated (HPDPH) forms of PDP. To isolate these overlapping 1PA spectra, we use a multivariate curve resolution-alternating least squares (MCR-ALS) decomposition method,[14] detailed in the Supporting Information. The resulting individual 1PA spectra are shown with solid lines in Figure 2 (1PA wavelength - upper horizontal scale). Single-protonation red-shifts the 1PA maximum, from the neutral PDP value at $\lambda_{1PA} = 508$ nm, to 546 nm, while double-protonation shifts the maximum even further to the red, to 569 nm. Based on our quantum-chemical calculations (see below), and similarity to other pyrrolopyrroles,[15] we attribute the highest-intensity 1PA band in PDP and HPDPH to the 0-0 vibronic component of the $S_0 \rightarrow S_1$ transition. For HPDP, the calculations show that 1PA maximum is also due to $S_0 \rightarrow S_1$

transition, however, significant spectral broadening characteristic to dipolar systems complicates more detailed assignment of accompanying vibronic features.

The MCR-ALS model of 1PA titration data also results in experimental pK_{aH} (the pK_a of the protonated base) for the first- and second-protonation steps of 4.6 and 3.2, respectively. Comparative calculations by linear regression of energies obtained with COSMO-RS method and pK_{aH} values of other pyridines[16] give pK_{aH} values of 5.9 and 4.2, respectively. The ~1 pH unit mismatch between the experimental and theoretical values is within typical uncertainties of computational and experimental calibrations;[17] while both methods support a ~1.5 pH interval between the two protonation stages.

Lower panel of Figure 1 shows results from two-photon pH experiments, normalized to unit value at 995 nm. The 2PEF excitation profiles were measured in the range, $\lambda_{2PA} = 820 - 1300$ nm, thus encompassing the whole $S_0 \rightarrow S_1$ transition of all three forms, using ~150 fs duration pulses from a 6 kHz pulse rate, wavelength-tuned optical parametric amplifier. Each spectrum was shape corrected, and absolute 2PA cross section determined, by comparison to suitable reference standards,[18–20] discussed in the Supporting Information. In neutral methanol solution, PDP shows 2PA maximum at, $\lambda_{2PA} = 954$ nm. Upon addition of small amounts of triflic acid (pH ~3.5), the maximum red-shifts to ~1100 nm, whereas at lower pH < 2.5, the peak undergoes a slight hypsochromic shift to, ~1060 nm.

In contrast to the 1PA titration, the raw 2PEF data shows no clear isosbestic points, likely a result of largely varying fluorescence quantum yields and 2PA cross sections of the simultaneously excited different forms. Nevertheless, by applying the MCR-ALS technique to the measured excitation-emission matrix (the latter was obtained by recording, at each excitation wavelength, the emission spectrum spanning, $\lambda_{em} = 450 - 804$ nm, using a CCD-spectrometer, see Supporting Information for details), the relevant 2PA spectra and 2PA cross sections were reliably evaluated, as shown by symbols (2PA wavelength - lower horizontal scale) in the Figure 2. The 2PA peaks of PDP, HPDP and HPDPH are respectively at, $\lambda_{2PA} = 954$, 1086 and 1066 nm, with corresponding peak cross section values, $\sigma_{2PA} = 0.81$, 7.7 and 2.0 GM (1 GM = 10^{-50} cm⁴ s⁻¹ photon⁻¹). To highlight where 2PA transitions match or deviate from the corresponding 1PA transitions, we plotted in Figure 2 the 2PA vs 1PA profile ratios for all three species (black lines in Figure 2).

In case of HPDP (middle panel), we observe that the 2PA profile follows very closely that of the 1PA, which results in nearly constant ratio over the entire $S_0 \rightarrow S_1$ transition wavelength range (black line). The fact that the ground- and excited vibronic levels appear to be contributing, on average, in the same manner to the 2PA as they do for the 1PA, suggests that the 2PA cross section should be adequately described by the two essential states model, meaning that any third-level (intermediate-level) contributions may be neglected. To estimate the value of permanent electric dipole moment change ($\Delta\mu$) in the $S_0 \rightarrow S_1$ transition, we use the relation,[21]

$$\left| \Delta\vec{\mu} \right| = \sqrt{\frac{\hbar c^2 N_A}{\pi 10^2 \ln 10} \frac{5}{(1+2\cos^2\beta)} \frac{n}{f^2} \frac{\sigma_{2PA}}{\lambda_{2PA}\varepsilon}} \qquad (1)$$

where σ_{2PA} is the 2PA cross section (cm⁴ s photon⁻¹), ε is the molar extinction coefficient (M⁻¹ cm⁻¹), λ_{1PA} is the 1PA transition wavelength (cm), c is the speed of light in vacuum (cm s⁻¹), h is the Planck constant (erg s), $f = (n^2+2)/3$ is the optical field

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correction factor, n is the solvent index of refraction and β is the angle between the $\Delta\mu$-vector and direction of the transition dipole moment μ-vector. Eq 1 gives the value, $\Delta\mu = 3.4$ Debye, which compares well with our theoretically calculated value, $\Delta\mu = 4.0$ Debye, obtained via linear and quadratic response TD-DFT using tuned CAM-B3LYP[22,23] density functional and a polarized continuum approximation of the methanol environment. Experimental and theoretical values for 1PA and 2PA parameters of PDP, HPDP and HPDPH are collected in Table 1.
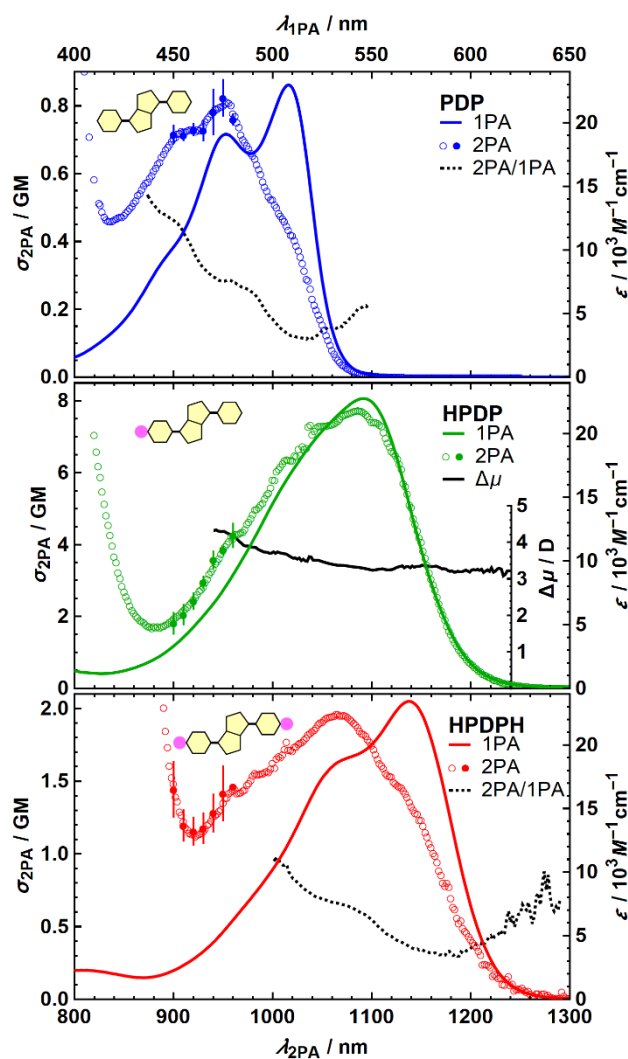

Figure 2. Decomposed 1PA and 2PA spectra for all PDP forms in methanol. 2PA cross section (circles) are shown as a function of the excitation wavelength (lower horizontal axis), while corresponding one-photon molar absorption (colored lines) are shown according to the 1PA wavelength (upper axis). Inset dashed black lines depict the ratio of 2PA to 1PA spectra, while the solid black line is the change in permanent dipole moment calculated from Eq 1.

For PDP and HPDPH, one may be tempted to interpret the low σ_{2PA} compared to HPDP, as well as the hypsochromically shifted maximum compared to respective 1PA, as confirmation of Laporte rule. However, as noted already, such approach may need to be revised, especially as it does not fully account for the vibronic nature of the underlying transitions. Indeed, the 2PA maxima of PDP and HPDPH approximately match the 478 nm

and 535 nm features in the corresponding 1PA spectra, and since our calculations indicate S_1 is the only electronic state in the λ_{2PA} = 900 – 1300 nm range, we tentatively assign these peak 2PA bands to vibronic components of the $S_0 \rightarrow S_1$ transition. According to formal C_{2h} molecular symmetry, this B_u electronic transition is 2PA forbidden, but can be allowed via Herzberg-Teller (HT) coupling with b_u or a_u vibrational modes, which match experimental frequency shifts, $\nu = 1200 – 1500$ cm^{-1}.[24] However, these potential vibronic couplings should be less effective in the 0-0 region, where experimental 2PA should vanish, especially in the red part of the spectrum. In contrast, the experimental 2PA versus 1PA ratio (dotted black curves in Figure 2) remain finite for both PDP and HPDPH in the 0-0 region, accompanied by a modest increase towards longer wavelengths, which could be perceived as a relaxed Laporte rule.

Table 1. Spectroscopic results of PDP forms in methanol

	PDP	HPDP	HPDPH
	Experiment		
ε, 10^3M^{-1}cm^{-1} (λ_{1PA}, nm)	22.9 (508)	22.8 (546)	23.4 (569)
σ_{2PA}, GM (λ_{2PA}, nm)	0.81 (954)	7.7 (1086)	2.0 (1066)
$\Delta\mu$, D	N.A.	3.4	N.A.
	Calculation		
ε, 10^3M^{-1}cm^{-1} (λ_{1PA}, nm)	34.6 (485)	32.5 (546)	31.3 (578)
σ_{2PA}, GM (λ_{2PA}, nm)	0 (969)	16 (1112)	0 (1157)
$\Delta\mu$, D	0.0	4.0 (5.0)[a]	0.06

[a] Permanent electric dipole moment change obtained from calculated linear electronic properties.

In order to eliminate the possibility that these features may result from inversion symmetry-breaking conformations,[25–27] we have performed theoretical calculations showing that although rotation of pyridyl moieties along the linking single-bond can lead to slightly higher energy asymmetric conformers, the 2PA 0-0 band from such conformations remains negligible for both PDP and HPDPH. As an alternative mechanism, one might consider symmetry breaking as a result of excited state bistability,[28,29] however, PDP doesn't show the associated solvent-dependent Stokes-shift (see Supplementary Information for a detailed discussion of the bistability model).

While seeking an explanation of why 2PA for PDP and HPDPH is far from entirely suppressed in the 0-0 region, we turn our attention to potential coupling between electronic levels and low-energy vibrational modes, < 500 cm^{-1}. Unfortunately, evaluation of HT terms involve calculating derivatives of the second-order moments over vibrational coordinate space, for which computational methods are still under development.[30–34] One approach applied previously to dipolar molecules models molecular distortion along select ground-state vibrational mode eigenvectors and then calculates corresponding effective 2PA cross section.[11] We extend this non-Condon 2PA calculation to select high- and low-frequency modes for symmetric PDP, encompassing several b_u modes, which introduce an in-plane asymmetric distortion, as well as for a_g modes, which are also

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Franck-Condon active in 1PA. We omitted a_u modes as they would not lead to nonvanishing in-plane dipoles due to their out-of-plane displacement vectors. While a_g modes contribute to low-energy 1PA vibronic transitions, they show negligible 2PA effect. In contrast, certain 1PA inactive b_u modes significantly boost the $\Delta\mu$ value, leading to the 2PA cross sections in the range (Table S2), $\sigma_{2PA} = 0.06 - 0.75$ GM. Even though our current model lacks desired quantitative accuracy, it does qualitatively reproduce our key experimental observations, including the apparent violation of Laporte Rule.

In conclusion, we have shown, for the first time, that multi-stage protonation in a nominally inversion-symmetric dye not only facilitates large changes in 2PA, but also provides direct experimental proof of on-off-on control of the molecular inversion symmetry. While the marked 2PA effects may be used for molecular sensing, careful analysis of the experimental 1PA and 2PA titration spectra, reveals that neutral- and double-protonated forms both retain non-vanishing 2PA in the 0-0 region, even though such transitions should be strictly forbidden. Theoretical model calculations clarify that this is due to non-Condon coupling of the electronic transition to matching-symmetry low-energy molecular vibrations, thus restoring the Laporte rule's canonical status. Our results also suggest that symmetry switching of 2PA could be used in novel analytical applications including quantitative monitoring of pH as well as establishing reliable pK_a values, or extended to elucidate similar binding effects in more complex molecular symmetries, including star-shaped (octupolar) and dendritic structures.

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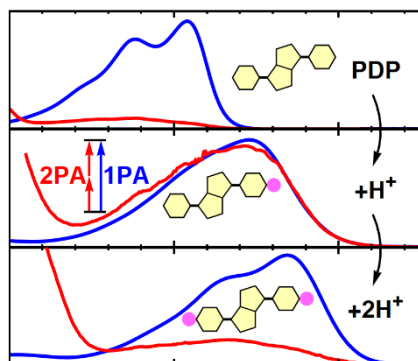
The Laporte selection rule dictates that inversion-symmetric molecules have alternately forbidden one- and two-photon electronic transitions, although in reality, vibronic interactions often interfere with applying this principle. Using single- and double-protonation to break and reconstitute inversion symmetry of a single chromophore, we can model these vibronic interactions, and demonstrate two-photon absorption switching via the Laporte rule.