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# Nonlinear Optical Chemosensor for Sodium Ion Based on Rhodol Chromophore

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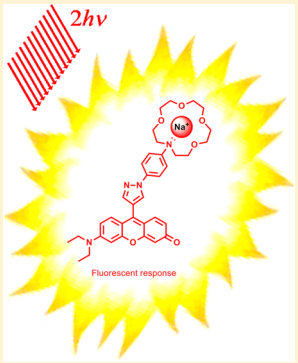
Supporting Information

**ABSTRACT:** As part of a strategy to identify good fluorescent probes based on two-photon excited fluorescence (TPEF), the sensor for sodium cation has been designed bearing a rhodol chromophore linked with an aza-crown ether. An efficient synthetic route to rhodol derivatives possessing five-membered heterocycles at position 9 and their precursors that contain xanthylium salt has been developed. The synthesis involves condensation of xanthylium salts bearing vinamidinium moiety at position 9, with phenylhydrazine derivatives as the key step. To accomplish the synthesis of derivatives bearing 1-aza-15-crown-5 and 1,10-diaza-18-crown-6, the Buchwald–Hartwig reaction has been employed in the final stage. Electronic spectra of all prepared rhodols display strong absorption in the range of 450–550 nm with well-resolved vibronic bands, which maintains its fine structure in a wide range of solvents. The most intensive two-photon absorption (2PA) band in the rhodol spectrum (165 GM), located at shorter wavelengths, matches well with the short-wavelength absorption band in the linear electronic spectrum and is most probably related to the two-photon allowed electronic transition $S_0 \rightarrow S_2$. The influence of cation binding on one- and two-photon spectroscopic properties of rhodol linked with 1-aza-15-crown-5 via the phenylpyrazole bridge has been investigated. This probe exhibits high sensitivity and good selectivity for $Na^+$ in $CH_3CN$. The mechanism involves the complexation of the $Na^+$ by 1-aza-15-crown-5 in the probe, which induces prominent fluorescence enhancement via quenching of electron-transfer. Interestingly, the complexation with $Na^+$ led to a significant increase of the 2PA band in the 750–800 nm region (corresponding to a two-photon allowed, one-photon forbidden transition) for rhodol bearing 1-aza-15-crown-5, which led to the overall enhancement of the TPEF signal (approximately an order of magnitude). Thus, a turn-on fluorescent probe for sodium ion, which does not respond to many other metal species, has been constructed.




## INTRODUCTION

Fluorescence sensing is one of the most widely used detection techniques because it can provide more sensitive and selective detection with remarkable spatial and temporal patterns over other analysis methods. Discovering new fluorescent metal ion sensors has been attracting considerable attention in recent decades due to the prospect of using them in a wide range of applications including the visualization of extra- and intracellular environment for medical purposes.[1−8] Among various ions, sodium cation is one of the most important targets because it is the most abundant monovalent metal ion in mammalian cells and a vital component of numerous enzymes.

At the same time, known fluorescent chemosensors usually based on classical linear chromophores such as cyanine and rhodamine dyes have some shortcomings since one-photon excitation mode uses the irradiation of higher energy and may cause increased risk of the damage of biological structures.[9−11] Moreover, using the two-photon excitation mode makes it possible to achieve higher spatial resolution in the bioimaging experiments.[12] Previously reported TPEF-sensors for $Na^+$ were constructed on the basis of photoinduced charge transfer.[13]

Thus, the objective of this study was to design and synthesize a $Na^+$-sensing system based on the following principles: (a) two-photon excitation; (b) electron-transfer quenching mechanism; (c) fluorescent platform possessing high $\Phi_{fl}$; (d) azacrown ether previously optimized for selective sodium binding.

There are some principles of the construction of NLO chromophores imposed by the selection rules for two-photon absorption (2PA), different than for one-photon absorption (1PA), which results in particular structure of 2PA systems.[9−11,14−16] Large 2PA cross-sections have often been associated with the extent of conjugation length (effective $\pi$-delocalization), which leads to an extended charge separation (a large $\pi$-conjugated system). Adding an electron donor D and acceptor A to the ends of a conjugated chromophore to give a D–$\pi$–A system enhances transition dipole moment as a consequence of the increase in the displacement of charge during the transition from HOMO to LUMO.[17−24] Although chromophores with longer and easily polarizable conjugation chains tend to have higher 2PA cross-section, using bulky dye molecules in the intracellular imaging experiments is rather problematic (although this is not impossible and branched two-photon absorbing dyes have been shown to allow imaging of specific compartment within cells).[25] Designing novel probes

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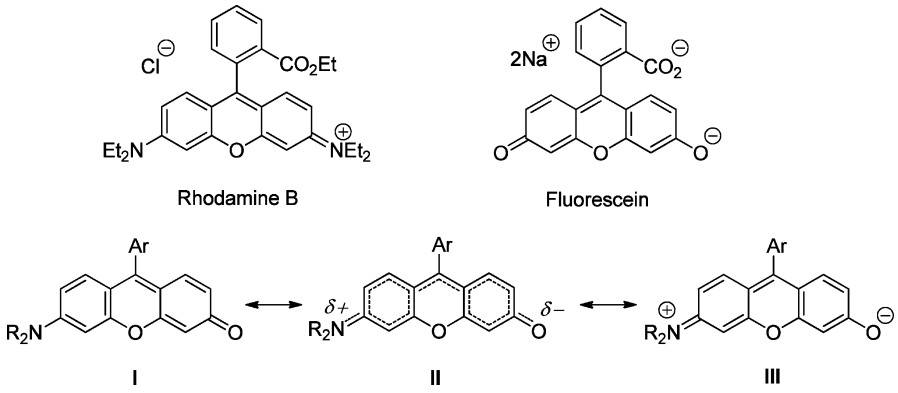


**Figure 1.** Resonance forms for the rhodol chromophores.

with reasonable molecular weight and combining large 2PA response *in the spectral range of interest* for biological imaging (700−1000 nm) with a high fluorescence quantum yield (Φ), thus yielding large two-photon brightness ($\sigma_2\Phi$), opens the way for two-photon imaging in bioenvironments by either reducing the excitation intensity (for reduced damages) or scanning more rapidly (for dynamic imaging) or alternatively to allow the detection of specific species in very low concentrations.[9−11,26−34]

We sought to design sensing molecular system based on the well-known principle of electron-transfer quenching. Photoinduced electron transfer, which takes place from amino groups to aromatic hydrocarbons/heterocycles, causes fluorescence quenching of the latter. When the amino group strongly interacts with a given cation, electron transfer is hindered and a large enhancement of fluorescence can be expected. A fluorescent chemosensor of such type generally consists of fluorophore and receptor parts linked by nonconjugated bridge.[35,36]

Rhodol chromophore occupies an intermediate position between the rhodamine and fluorescein. As the rhodamine chromophore contains a classical cyanine structure with the positive charge delocalized between terminal nitrogen atoms, the fluorescein chromophore possesses an oxonole structure.[37−39] Both rhodamines and fluoresceins have an electronically symmetrical structure bridged with the oxygen atom (Figure 1).

Rhodol chromophore, displaying intrinsically high fluorescence quantum yield, possesses the merocyanine character with the electronic structure depicted by two limiting forms: neutral (**I**) and zwitterionic (**III**), and the contribution of these forms depends on the solvent polarity.[40,41] When both resonance forms contribute equally to the ground-state structure, the molecule exhibits essentially no bond length alternation (so-called "cyanine limit", i.e., state **II**). Compared with polyene molecules (traditional 2PA chromophores), merocyanine dyes may have more efficient intramolecular charge transfer (ICT) between the donor and acceptor and hence higher dipole moment (or polarization) in the ground state as well as larger 2PA cross-section for the shorter conjugated chain.[23] Overall, only a few papers on merocyanine dyes in conjunction with two-photon absorption have been published.[42−47] Whereas rhodamine and fluorescein dyes have been widely studied, rhodol derivatives are more rarely mentioned in the literature.[48−59] Furthermore, to the best of our knowledge, no rhodol dyes were studied in terms of their 2PA properties. Thus, we resolved to use rhodol fluorophore bearing an additional heterocyclic unit at position 9, since (a) this position is the easiest to functionalize and (b) flexibility of the synthesis of five-membered aromatic heterocycles offers straightforward way to modify linker if necessary to fine-tune optical properties.

Among cation−receptor molecules, crown ethers have occupied a distinguished position due to their unique ability to strongly and selectively bind metal ions. This holds true especially for cations of two first groups of periodic table. The rationale behind the choice of 1-aza-15-crown-5 relies on the facts that 15-crown-5 is well-known to be optimized for sodium binding[60−62] and the presence of amine makes it possible to benefit from fluorescence modulation via photoinduced electron-transfer.

## RESULTS AND DISCUSSION

3-Diethylamino-6-hydroxy-substituted xanthylium salt **1**[63] was chosen as the key substrate for the synthesis of the rhodol-based chemosensor. In the first attempt, compound **1** was treated with the Vilsmeier reagent. It appeared that at room temperature salt **1** reacted with 1 equiv of the Vilsmeier reagent to form enamine **2** (according to ESI MS, signal 337.2). At the same time, at the higher temperature (80 °C) enamine **2** underwent the attack of the second equivalent of the Vilsmeier reagent to form vinamidinium derivative. The $^1$H and $^{13}$C NMR spectra of the latter showed a set of signals typical of 3,6-disubstituted xanthylium salts along with the signals corresponding with the vinamidinium moiety (see the Supporting Information); however, the mass spectrum (ESI) of that vinamidinium salt showed an intensive peak with mass 205.6. It seemed that under the conditions of the Vilsmeier reaction the hydroxyl group at position 6 is substituted with the chlorine atom to form disalt with the mass of the dication 411.2. The high-resolution mass spectrum confirmed the chemical formula of the compound **4** (Scheme 1). Attempts to substitute the chlorine by the oxygen atom were not successful: treating compound **4** with either sodium hydroxide or sodium carbonate for a short period of time gave rise to the hydrolysis of vinamidinium chromophore to form dialdehyde **5**. Performing the reaction for a longer period of time led to the decomposition of the product. In the case of using sodium acetate as an *O*-nucleophile, the dimethyliminium fragment hydrolyses into the formyl group, and subsequently the chlorine atom is substituted by the dimethylamino group, so that the salt **4** rearranges into rhodamine dye **6** (Scheme 1).

Dialdehyde **5** easily formed pyrazole **7** by the condensation with the phenylhydrazine hydrochloride. Attempts to replace the chlorine atom with the hydroxyl group in the pyrazole **7**


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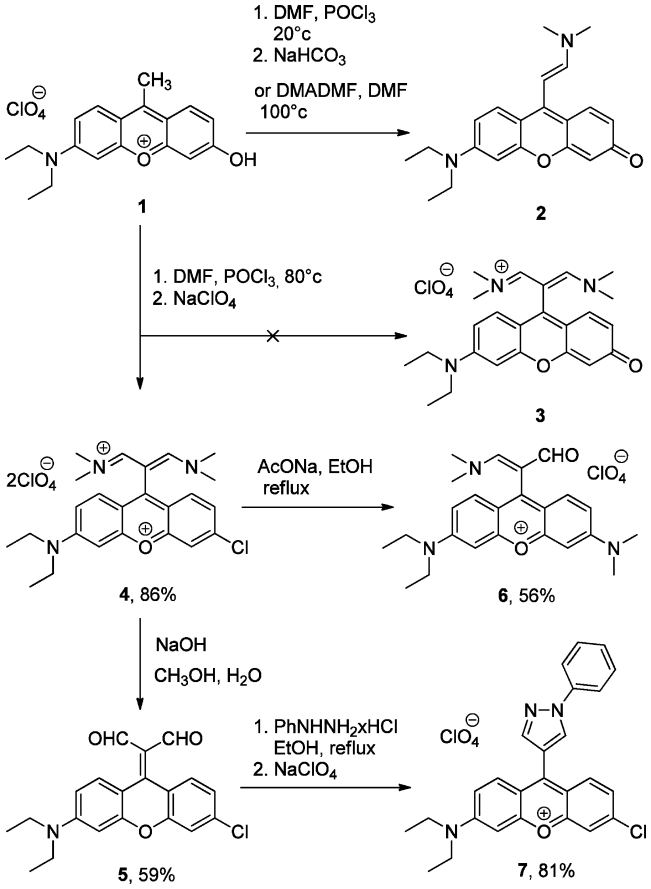
**Scheme 1**




also failed. Upon addition of either sodium hydroxide or sodium carbonate into the ethanol solution of pyrazole **7**, the latter immediately decolorized. After heating for several hours no conversion was observed, while the acidification of the reaction mixture brought back the initial color. We hypothesize that the xanthylium system undergoes the addition of the hydroxide anion at the position 9 to form the neutral intermediate which is much less reactive toward the nucleophiles (Figure 2).

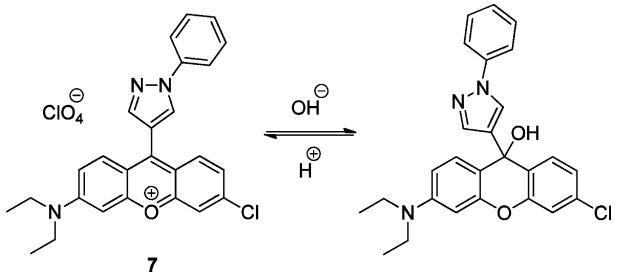
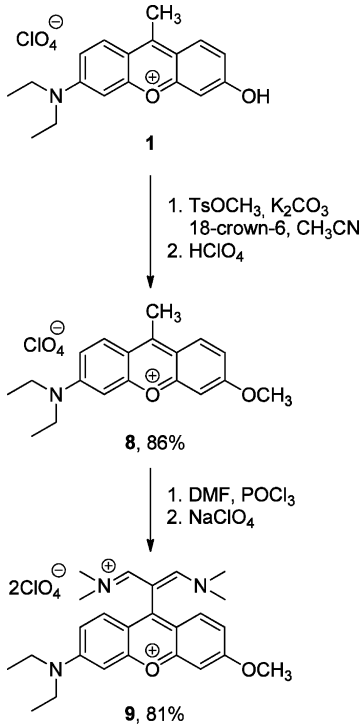



**Figure 2.** Addition of the hydroxide anion to the xanthylium salt **7**.

To avoid the substitution with the chlorine atom we switched to *O*-protected xanthylium salts. Compound **1** was alkylated with methyl 4-toluenesufonate according to the known procedure.[63] Methoxyxanthylium salt **8** was transformed into vinamidinium derivative **9** following the strategy described for dye **1** (Scheme 2).

Vinamidinium salt **9** was hydrolyzed into dialdehyde **10** in the same manner as in the case of chloro derivative **4**.

**Scheme 2**




Compound **10** was subsequently reacted with phenylhydrazine hydrochloride to give pyrazole **11a** serving as the model rhodol (Scheme 3).

Meanwhile, we examined the reactivity of the vinamidinium chromophore toward 1,2-binucleophiles as a latent form of malonaldehyde functionality with dimethylamine leaving groups. It appeared that disalt **9** in the presence of sodium acetate easily reacted with phenylhydrazine hydrochloride to afford *N*-phenylpyrazole **11a** in high yield. Subsequently, the methoxy group was cleaved with the mixture of hydrobromic and acetic acids to give rhodol **12a**. Rhodol derivative bearing bromoaryl functionality (**12b**) was synthesized in the similar manner (Scheme 3).

It is worth noting that, prior to our study, rhodols substituted with heterocycles at the central position were mentioned only in one patent in which the rhodol derivatives were synthesized by another, more complicated method.[64] A similar method for the introduction of heterocycles at the central position was used in the case of rhodamine dyes.[65]

Subsequently, we proceeded to the synthesis of planned chemosensor molecules via the modification of rhodol **12b** with azacrown ethers fragments possessing a high affinity for $Na^+$ and $K^+$ ions.[66−68] It is known that cyclic oligo(ethyleneglycol) chains of azacrown ether molecules hinder the nitrogen atom for the *N*-arylation, thus decreasing the conversion and the reaction yield. In the literature there are several examples of Buchwald−Hartwig reductive amination of simple aromatic halides with azacrown ethers,[69−72] which are carried out using predominantly $Pd_2(dba)_3$−DavePhos as the catalyst system and *t*-BuONa as a base.[73−75]

In order to find suitable conditions for the amination of rhodol **12b** with diazacrown ether **13** a set of experiments have been performed (Table 1). In the case of using SPhos as a ligand in the reductive amination no products were monitored. When DavePhos was used as a ligand (entry 4), formation of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**Scheme 3**

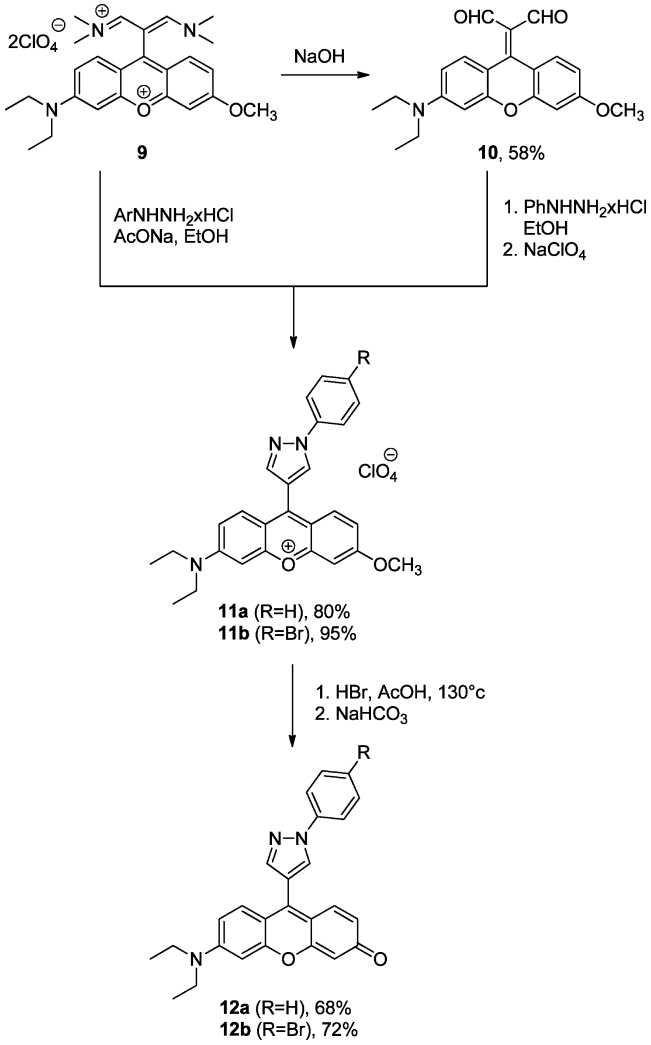



**Table 1. Reductive Amination of Dye 12b with Diazacrown Ether 13**[a]

| entry | catalyst/ligand | base | solvent | product (yield, %)[b] |
|---|---|---|---|---|
| 1 | $Pd(OAc)_2$/SPhos | $Cs_2CO_3$ | toluene | |
| 2 | $Pd(OAc)_2$/SPhos | *t*-BuONa | dioxane | |
| 3 | $Pd(OAc)_2$/SPhos | *t*-BuONa | toluene | |
| 4 | $Pd(OAc)_2$/ DavePhos | *t*-BuONa | toluene | monocoupling (2) |
| 5 | $Pd(OAc)_2$/ DavePhos | *t*-BuONa | dioxane | |
| 6 | $Pd_2dba_3$/DavePhos | *t*-BuONa | toluene | monocoupling (traces) |
| 7 | $Pd(OAc)_2$/ DavePhos | $Cs_2CO_3$ | toluene | |
| 8 | $Pd_2dba_3$/DavePhos | *t*-BuONa | dioxane | |
| 9 | $Pd(OAc)_2$/*t*-$Bu_3P$ | *t*-BuONa | dioxane | **14** (15) |

[a]The experiments were performed at 100 °C for 24 h. [b]Yield of isolated products.

the new compound with low conversion was observed, which after isolation (trace amount) according to the mass spectrum was identified as the product of the monoamination (Figure 3). Nevertheless, the experiment with the catalytic system $Pd(Ac)_2$/*t*-$Bu_3P$ gave rise to the formation of rhodol **14** in 15% yield (Scheme 4).

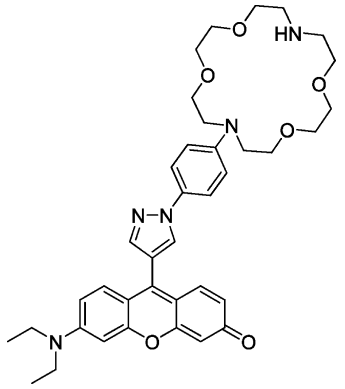
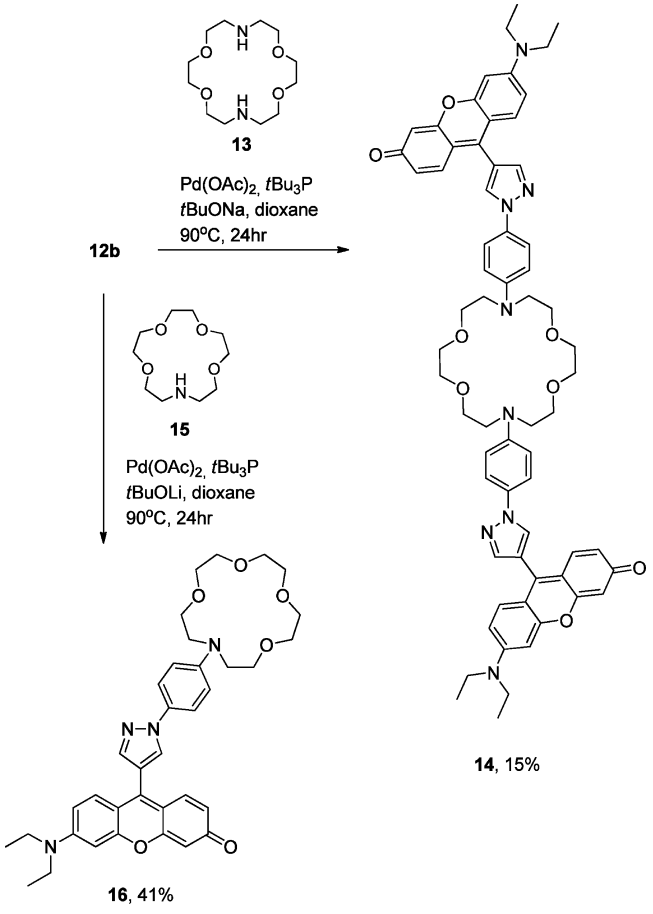



**Figure 3.** Product of the reductive monoamination of rhodol **12b**.

**Scheme 4**




Rhodol **16** was synthesized in 41% yield, analogously to dye **14** using *t*-BuOLi as base (Scheme 4).

**Optical Properties.** Xanthylium dyes substituted with vinamidinium chromophore (**4**, **9**) in their absorption spectra show two pronounced absorption bands: the short-wavelength one localized within vinamidinium chromophore system and the long-wavelength localized within the xanthylium chromophore. In the case of the methoxy derivative **9**, the long-wavelength band is more intense due to its more electron-symmetrical structure (Table 2, Figure 4). The product of rearrangement **6** can be considered as the electron analogue of rhodamine B substituted with a diethylaminoacroleine system. In its electronic spectrum, dye **6** exhibits a strong, narrow rhodamine-like absorption band and the Stokes shift also is


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**Table 2. Optical Properties of Dyes Synthesized**

| compd | solvent | $\lambda_{abs}$ (nm) | $\varepsilon$ $10^{-3}$ ($M^{-1}$ $cm^{-1}$) | $\Delta S$ ($cm^{-1}$) | $\lambda_{em}$ (nm) | $\Phi$ (%) |
|---|---|---|---|---|---|---|
| **4** | $CH_3CN$ | 556 | 17 | 260 | 564 | 0.77 |
| | | 514 | 21 | | | |
| | | 307 | 34 | | | |
| **5** | $CH_3CN$ | 569 | 15 | | nd[a] | |
| | | 479 | 20 | | | |
| **6** | $C_2H_5OH$ | 560 | 95 | 600 | 580 | 28 |
| **7** | $CH_3CN$ | 536 | 22 | 140 | 540 | 2.8 |
| | | 502 | 26 | | | |
| | | 408 | 12 | | | |
| **9** | $CH_3CN$ | 549 | 31 | 900 | 577 | 0.42 |
| | | 512 | 32 | | | |
| | | 305 | 36 | | | |
| **10** | $CH_3CN$ | 543 | 16 | | nd[a] | |
| | | 477 | 29 | | | |
| **11a** | $CH_3CN$ | 528 | 35 | 1500 | 574 | 0.70 |
| | | 498 | 31 | | | |
| | | 380 | 14 | | | |
| **11b** | $CH_3CN$ | 527 | 43 | 1600 | 577 | 0.60 |
| | | 498 | 39 | | | |
| | | 382 | 19 | | | |
| **12a** | $C_2H_5OH$ | 528 | 81 | 800 | 551 | 74 |
| | | 362 | 12 | | | |
| | $CH_2Cl_2$ | 528 | 50 | 760 | 550 | 66 |
| | | 494 | 40 | | | |
| | | 352 | 9.6 | | | |
| | DMSO | 532 | 49 | 1000 | 561 | 85 |
| | | 498 | 36 | | | |
| | | 357 | 9.0 | | | |
| **12b** | $C_2H_5OH$ | 529 | 73 | 800 | 552 | 70 |
| | | 495 | 31 | | | |
| | | 360 | 11 | | | |
| **14** | DMSO | 532 | 98 | 1000 | 561 | 3.0 |
| | | 497 | 77 | | | |
| **16** | $CH_3CN$ | 524 | 53 | 1000 | 552 | 2.0 (10)[b] |
| | | 490 | 42 | | | |
| | | 297 | 34 | | | |

[a]Fluorescence was not measured due to low S/N ratio. [b]In the presence of the excess of $NaClO_4$.

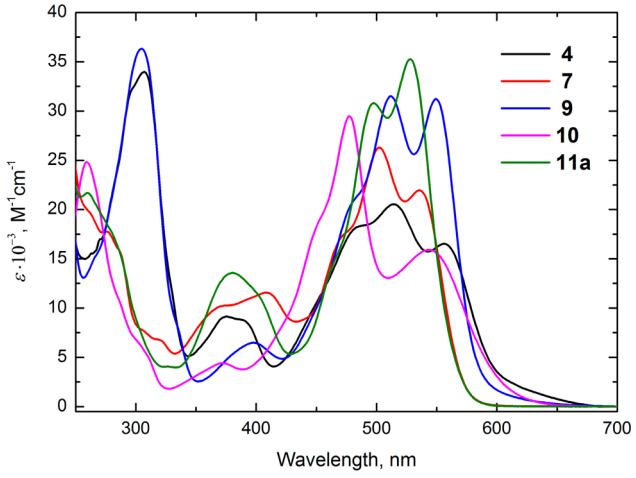


**Figure 4.** One-photon absorption spectra of dyes **4**, **7**, **9**, **10**, and **11a** in $CH_3CN$.

typical of rhodamines, although fluorescent quantum yield is lower compared with rhodamine B (Table 2, Figure 4).[76]

Electronic spectra of all prepared rhodols display strong absorption in the range of 450−550 nm with a well-resolved vibronic structure, which maintains its fine structure in a wide range of solvents as well as subtle absorption bands around 400 nm (Figure 5, Table 2). Examination of the linear absorption

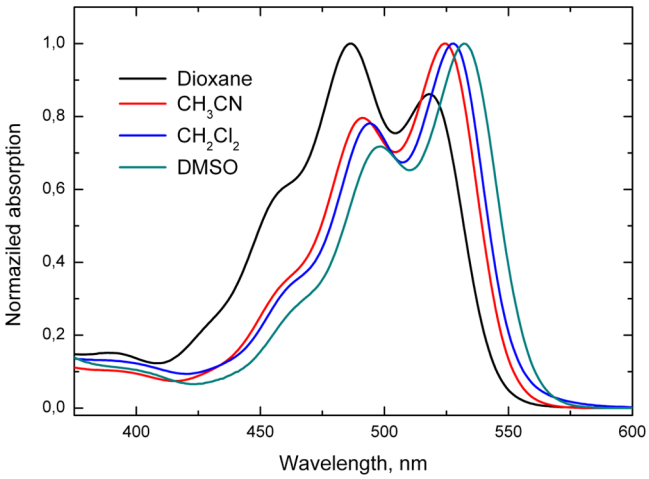


**Figure 5.** Normalized absorption spectra of rhodol **12a** in DMSO, $CH_3CN$, $CH_2Cl_2$, and 1,4-dioxane.

spectra of rhodols reveals some regularities within the absorption bands. Analysis of solvent effects can be interpreted according to the Franck−Condon principle, the smaller bond length alternation (BLA) in the polymethine chain in the ground state, and the smaller bond lengths change in the excited state. Consequently, absorption spectra of dyes possessing electron-symmetrical structure should exhibit strong 0−0 bands at the expense of vibronic transitions.[77,78]

Increasing solvent polarity tends to increase the contribution of the charge-separated limiting forms to the electronic ground state and thus increased $\pi$-charge density alternation. Similar to the report[77] for the DMSO model, rhodol **12a** demonstrated the lowest intensity ratio between 0−1 and 0−0 subbands ($I_{0-1}/I_{0-0}$ = 0.72), whereas in 1,4-dioxane the 0−1 subband is more intensive compared with the 0−0 subband ($I_{0-1}/I_{0-0}$ = 1.16). Thus, the solvatochromic effect is indicated by the change of the intensity of vibronic transition and the small shift of the absorption maxima (Figure 5).

Rhodol **12a** displays strong fluorescence properties in both nonpolar ($CH_2Cl_2$), polar aprotic (DMSO), and protic (EtOH) solvents, with fluorescent quantum yield reaches 66%, 74%, and 85%, respectively.

The optical properties of the rhodol chromophore modified with the azacrown ether **16** are similar to the model dye **12a** (Table 2, Figure 1 in the Supporting Information). The only difference is that the rhodol **16** has much weaker fluorescent ability. Quenching the fluorescence occurs due to the photoinduced electron transfer (PET) from the nitrogen atom of the azacrown ether to the HOMO of the rhodol chromophore.

The absorption properties of diazacrown ether-modified rhodol **14** are somewhat different compared with model dye **12a** (Figure 2, Supporting Information). Though the addition of the diazacrown ether should not affect the absorption properties, the electronic spectrum in acetonitrile displays well


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**Table 3. Two-Photon Absorption of Rhodol 12a in DMSO, $C_2H_5OH$, and $CH_2Cl_2$**

| solvent | $2\lambda_{OPA}^{max}$ (nm) | $\lambda_{TPA}^{max1}$ (nm) | $\sigma_2^{max1}\Phi$ (GM) | $\sigma_2^{max1}$ (GM) | $\lambda_{TPA}^{max2}$ (nm) | $\sigma_2^{max2}.\Phi$ (GM) | $\sigma_2^{max2}$ (GM) | $\lambda_{TPA}^{max3}$ (nm) | $\sigma_2^{max3}.\Phi$ (GM) | $\sigma_2^{max3}$ (GM) |
|---|---|---|---|---|---|---|---|---|---|---|
| $CH_2Cl_2$ | 1056 | 1060 | 20 | 30 | 920 | 51.7 | 78.7 | 790 | 109 | 165 |
| $C_2H_5OH$ | 1056 | 1060 | 35 | 47 | 980 | 68 | 92 | 820 | 85 | 115 |
| DMSO | 1064 | nd[a] | | | ≥920 | ≥37.6 | ≥44.1 | 820 | 100 | 117 |

[a]2PA was not measured for 1000−1200 nm range.

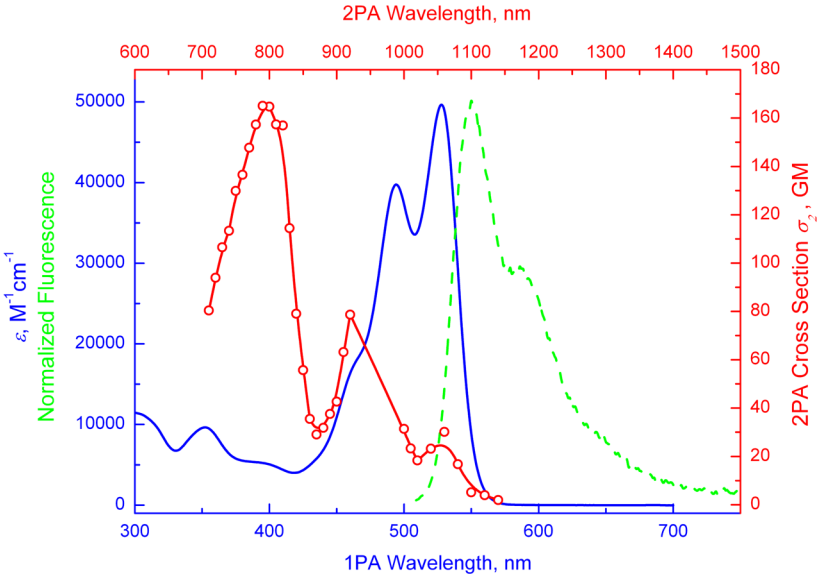


**Figure 6.** 1PA (blue), 2PA (red), and normalized fluorescence spectra (green) of dye **12a** in $CH_2Cl_2$.

resolved 0−1 and 0−0 subbands with the commensurate intensity. We assume that in acetonitrile solution two rhodol chromophores can approach each other, which can lead to the interaction between the electronic levels of two chromophores.

The two-photon absorption spectrum of model rhodol **12a** in methylene chloride consists of three bands. The weakest long-wavelength band has the absorption maximum at 1056 nm, which corresponds with the 0−0 subband in the 1PA spectrum, typical of D−$\pi$−A chromophores.[14,15,19−21,49] For better comparison, the 2PA spectrum is shown on the same graph as 1PA by multiplying the wavelength scale by 2, with separate axes (Table 3, Figure 6). Moreover, 2PA spectrum of the rhodol molecule shows weak absorption band (25 GM) somewhat hypsochromically shifted as compared with the maximum of the $S_0 \rightarrow S_1$ transition. The latter can probably be attributed to the vibrational coupling between the first excited state $S_1$ and its vibrational modes.[49] The most intensive 2PA band in rhodol spectrum (165 GM), located at shorter wavelengths, matches well with the subtle short-wavelength absorption band in the linear electronic spectrum and is most probably related to the two-photon allowed electronic transition $S_0 \rightarrow S_2$. 2PA cross-section is only slightly lower in solvents mimicking intracellular environment (EtOH) and cell membrane (DMSO) (Table 3). While the value of $\sigma_2$ of the rhodol chromophore is rather moderate, two-photon brightness ($\sigma_2^{max}\Phi$) of this dye is sufficient for two-photon excited fluorescence microscopy purposes.[79,80]

**Metal Ion Binding Properties.** Dye molecule **16** which featured crown ether moieties demonstrates properties of selective two-photon fluorescent probe for alkali metal ions sensing. When alkali metal ion is complexed with crown ether the free electron pair of the nitrogen atom is partly shifted toward metal ion, thus blocking PET and consequently giving rise to an increase in fluorescence. While compound **14** showed no changes in fluorescence properties upon addition of $Na^+$-, $K^+$-, $Li^+$-, and $Mg^{2+}$-containing salts, compound **16** demonstrated marked response upon addition of $Na^+$, weak response for $K^+$ and no response upon addition of $Mg^{2+}$ or $Li^+$ containing salts. (Figure 7). The reason why compound **14** failed to show a response upon the addition of metal ions is probably because of only partial quenching of electron transfer upon complexation. As reported by Mateeva et al., 1,10-diaza-18-crown-6 derivatives show more pronounced fluorescence changes in the presence of divalent cations.[13c] The presence of

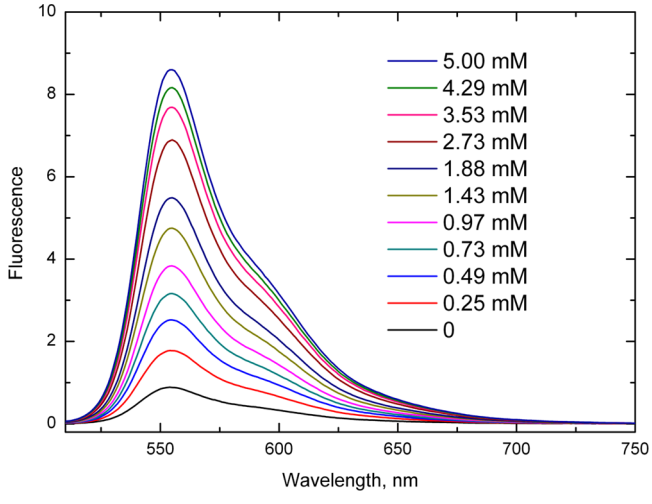


**Figure 7.** Emission spectra of dye **16** at different [$Na^+$] in $CH_3CN$.


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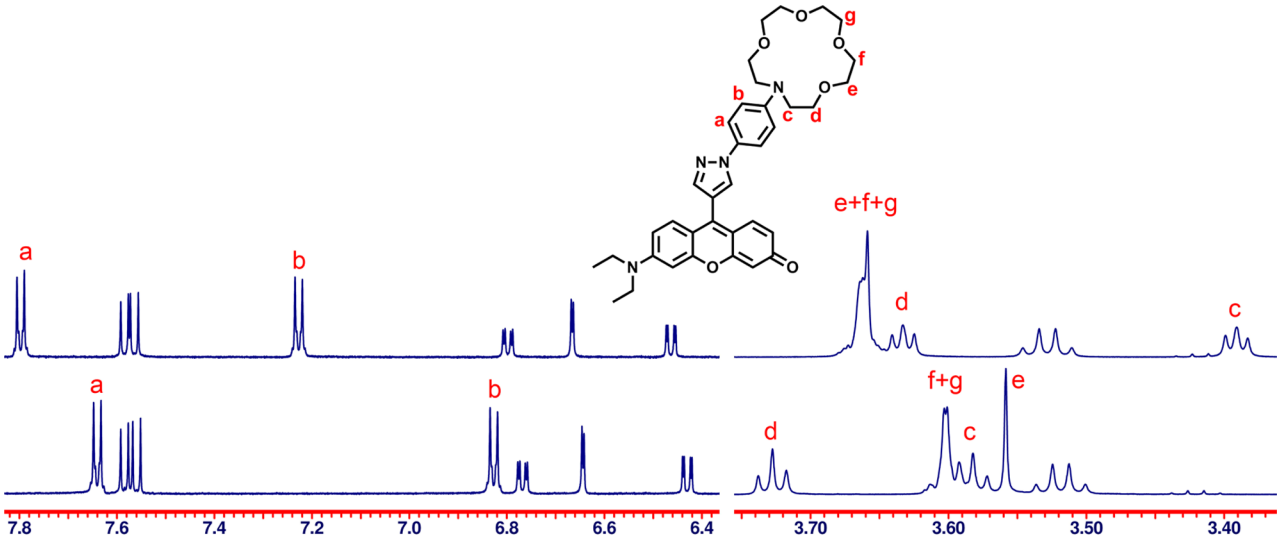


**Figure 8.** $^1$H NMR spectra of free rhodol **16** (below) and the complex of **16** with $Na^+$ (above) in $CD_3CN$.

**Table 4. 2PA Properties of Dyes 14 (in DMSO) and 16 (in $CH_3CN$) upon Complexation with Metal Cations**

| compd | $2\lambda^{max}_{OPA}$ (nm) | $\lambda^{max1}_{TPA}$ (GM) | $\sigma_2^{max1}\cdot\Phi$ (GM) | $\sigma_2^{max1}$ (GM) | $\lambda^{max2}_{TPA}$ (nm) | $\sigma_2^{max2}\cdot\Phi$ (GM) | $\sigma_2^{max2}$ (GM) | $\lambda^{max3}_{TPA}$ (GM) | $\sigma_2^{max3}\cdot\Phi$ (GM) | $\sigma_2^{max3}$ (GM) |
|---|---|---|---|---|---|---|---|---|---|---|
| **14** | 1064 | nd[a] | | | nd[a] | | | 790 | 5.8 | 193 |
| **14** + $KPF_6$ | 1050 | nd[a] | | | nd[a] | | | 790 | 5.5 | 267 |
| **16** | 1048 | 1080 | 2.2 | 110 | 970 | 1.7 | 86 | 770 | 1.4 | 72 |
| **16** +$NaClO_4$ | 1050 | 1060 | 6.3 | 63 | 970 | 21.6 | 216 | 770 | 18 | 176 |
| **16** + $LiClO_4$ | 1050 | 1080 | 3.1 | 102 | 970 | 3.7 | 125 | 820 | 4.3 | 144 |
| **16** + $Mg(ClO_4)_2$ | 1048 | 1080 | 2.9 | 147 | 970 | 1.7 | 86 | 820 | 3.0 | 151 |
| **16** + $KPF_6$ | 1046 | 1060 | 2.8 | 138 | 970 | 7.1 | 353 | 820 | 6.7 | 335 |

[a]TPA was not measured in this spectral range.

two rhodol moieties can also interfere with typical mechanism of fluorescence modulating.

The formation of the sodium ion complex with dye **16** is also demonstrated by NMR spectroscopy. The addition of sodium perchlorate into the solution of rhodol **16** in $CD_3CN$ gives rise to the shift of the crown ether moiety peaks along with the peaks of phenyl ring adjacent to the crown ether (Figure 8). Peaks assignment was performed on the basis of HSQC and HMBC experiments.

The addition of the crown ether fragment (dye **16**) also affects the nonlinear properties of the rhodol chromophore (Table 4). Compared with the model dye **12a** the addition of monoazacrown ether fragment decreases the short-wavelength absorption band and increases the intensity of the bands corresponding with the one-photon allowed transition in its 2PA spectrum (Figure 9, Table 4). At the same time, the presence of metal salts affects both 2PA properties and the fluorescence ability. Furthermore, the 2PA spectrum displays different effects for the low energy and high energy bands. The presence of $Li^+$ ion causes an almost 2-fold increase of short-wavelength band, a somewhat increase of the band located at 970 nm and hardly influences the long-wavelength band. Compared with free derivative **16** the fluorescence does not change. The presence of $Mg^{2+}$ ion has no influence on the band located at 970 nm but increases the intensity of low energy and high energy bands with no influence on the fluorescence. The addition of $K^+$ ion into the solution of **16** gives rise to a significant increase of the second (970 nm) and the high energy (820 nm) bands; however, there are no changes in the fluorescence properties (Figures 9 and 10).

The addition of $Na^+$ ion decreased the intensity of the low energy band however the intensity of the second and the high energy bands are significantly increased. The fluorescence ability in the presence of sodium ion is also increased. It appears that the second band located at 970 nm (which is both one and two-photon allowed) is more selective and sensitive to the presence of $Na^+$ (2PA increases by more than 2) following the trend of fluorescence. Hence the TPEF signal is increased by more than 1 order of magnitude (Figures 9 and 10, Table 4), demonstrating the ability of new dye **16** to act as sensitive two-photon probe for sensing the presence of $Na^+$ ion in acetonitrile. Yet, for application of such rhodol-based chemosensors in aqueous media, modifications should be made to further increase their two-photon absorption cross-section as well as their solubility in aqueous environments.

## ■ CONCLUSIONS

The method of heterocyclization at the 9-position of the rhodol chromophore was developed. The strategy presented herein enables transformation of 4-dimethylamino-2-hydroxyacetophenone into pyrazolylrhodols in five steps (36−45% overall yields). It was shown that direct transformation of **1** into **3** cannot be successful due to concomitant chlorination resulting in chlororhodol **4**, which is not prone to further transformations.


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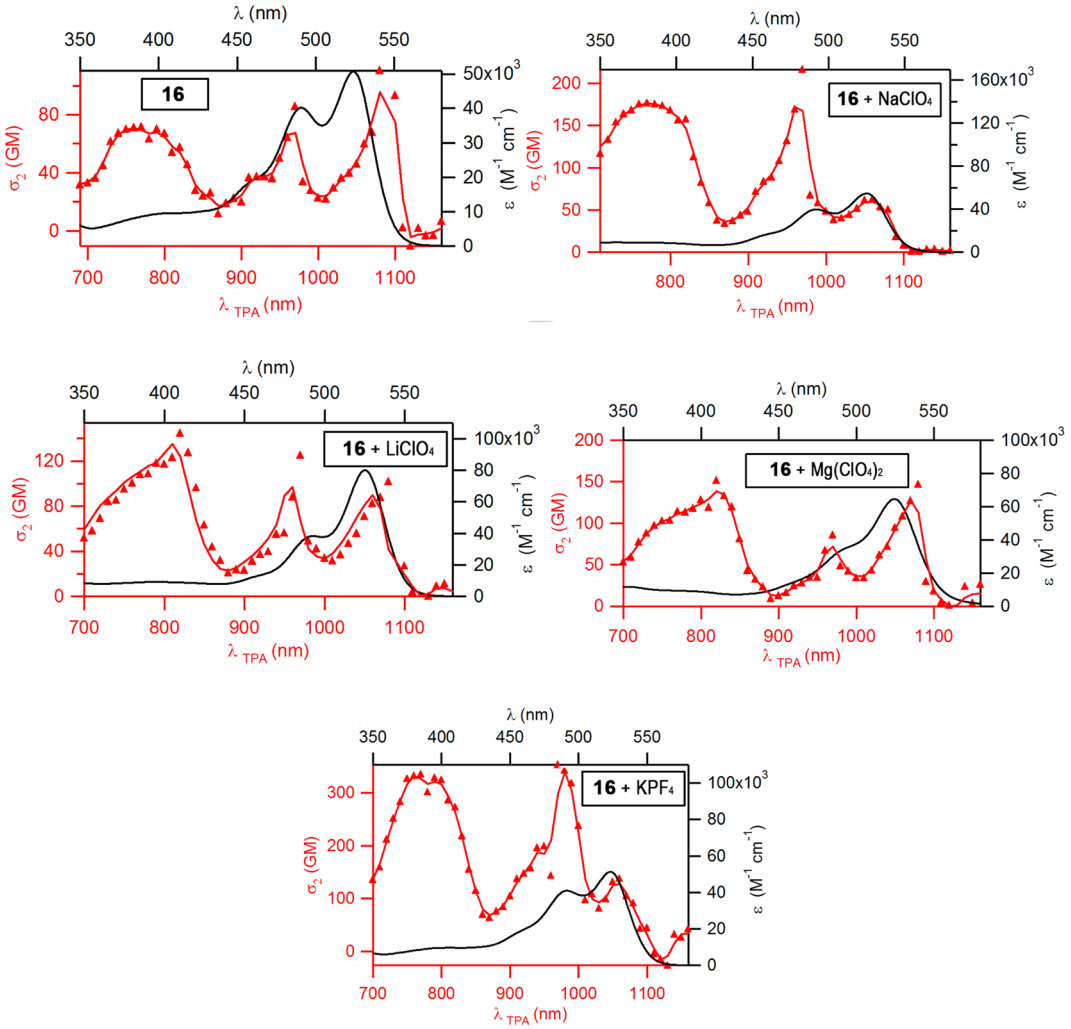


**Figure 9.** Two-photon properties of the dye **16** upon addition of metal salts in acetonitrile.

Linear absorption spectra of dyes synthesized consist of two bands, an intense long-wavelength one with a well-resolved vibronic structure and a weak short-wavelength one. The two-photon absorption spectrum of model rhodol consists of three bands. The weakest long-wavelength band has the absorption maximum that well corresponds with the 0−0 subband in 1PA spectrum, typical of D−$\pi$−A chromophores, somewhat hypsochromically shifted weak absorption band attributed to the vibrational coupling between $S_1$ state and its vibrational modes. The strongest 2PA band located at shorter wavelengths is most probably related to the two-photon allowed electronic transition $S_0 \rightarrow S_2$.

Although the addition of crown ether fragments gives rise to the almost 2-fold decrease in 2PA compared with the model rhodol, the addition of metal salts into solutions of chemosensor molecules increases the 2PA. Moreover, the rhodol-modified with monoazacrown ether demonstrates a good fluorescence response on the addition of $Na^+$ and weak response for $K^+$, thus resulting in the significant increase of two-photon brightness for $Na^+$.

## EXPERIMENTAL SECTION

All chemicals were used as received unless otherwise noted. Reagent-grade $CH_2Cl_2$ was distilled prior to use. All reported $^1H$ NMR spectra were collected using 400, 500, and 600 MHz spectrometers. Chemical shifts ($\delta$ ppm) were determined with TMS as the internal reference; $J$ values are given in hertz. Chromatography was performed on silica gel (230−400 mesh) or neutral aluminum oxide (70−230 mesh). Preparative size-exclusion chromatography (SEC) was carried out using BioRad Bio-Beads SX-1. The mass spectra were obtained via electrospray ionization (ESI-MS). For the complexation experiments $10^{-3}$ M solutions of $LiClO_4$, $NaClO_4$, $Mg(ClO_4)_2$, and $KPF_6$ in acetonitrile were used. All photophysical studies have been performed with freshly prepared air-equilibrated solutions at room temperature (298 K). TPEF cross sections of $10^{-4}$ M solutions were measured relative to fluorescein in 0.01 M aqueous NaOH for 700−800 nm,[81] using the well-established method described by Xu and Webb[81b] and the appropriate solvent-related refractive index corrections.[82] Reference values between 700 and 715 nm for fluorescein were taken from literature.[83] The quadratic dependence of the fluorescence intensity on the excitation power was checked for each sample and all wavelengths. To span the 700−980 nm range, a Nd:YLF-pumped Ti:sapphire oscillator was used generating 150 fs pulses at a 76 MHz rate. To span the 1000−1400 nm range, an OPO (PP-BBO) was added to the setup to collect and modulate the output signal of the Ti:sapphire oscillator.

**3-Chloro-6-diethylamino-9-(1-dimethylamino-3-(dimethyliminio)prop-1-en-2-yl)xanthylium Perchlorate (4).** Compound **1** (2.9 g, 7.6 mmol) was dissolved in 20 mL of dry DMF, and phosphorus oxychloride (4.66 g, 30 mmol, 2.8 mL) was added dropwise with stirring so that the internal temperature did not rise above 50 °C. After addition, the reaction was heated at 80 °C for 1 h. On cooling, the mixture was poured on ice and neutralized with a water solution of $NaHCO_3$ followed by extraction with $CH_2Cl_2$ and


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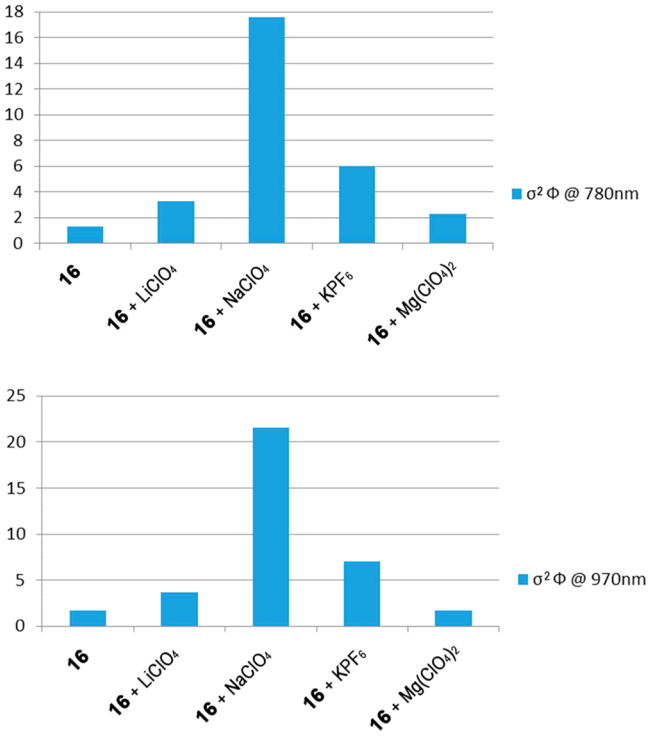


**Figure 10.** Bar diagram with the TPEF signal of dye **16** in the presence of salts for excitation at 780 nm (upper panel) and 970 nm (lower panel).

drying over $Na_2SO_4$. The solvent was evaporated, and the residue was recrystallized from ethanol to give 3.99 g (86%) of the pure product. Mp: 228−229 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): 8.19 (s, 2H), 8.05 (s, 1H), 7.92 (d, *J* 8.7 Hz, 1H), 7.84 (d, *J* 9.8 Hz, 1H), 7.73 (d, *J* 8.6 Hz, 1H), 7.58 (d, *J* 9.9 Hz, 1H), 7.28 (s, 1H), 3.95−3.85 (m, 4H), 3.32 (s, 6H), 2.45 (s, 6H), 1.35−1.26 (m, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): 164.6, 158.7, 157.8, 152.8, 148.9, 141.6, 132.4, 130.7, 127.3, 122.0, 121.0, 120.7, 117.9, 97.5, 91.3, 48.9, 47.1, 46.9, 40.0, 13.4, 12.4. HRMS (ESI-TOF) calcd for $[C_{24}H_{30}ClN_3O]^{2+}$ 205.6039 $[M^{2+}]$, found 205.6042. Anal. Calcd for $C_{24}H_{30}Cl_3N_3O_9$ (610.87): C, 47.19; H, 4.95; N, 6.88; Cl, 17.41. Found: C, 47.28; H, 4.99; N, 6.84; Cl, 16.85. $\lambda_{abs}$ ($CH_3CN$, $\varepsilon \times 10^{-3}$): 307 (34), 514 (21), 556 (17) nm.

**2-(3-Chloro-6-diethylamino-9*H*-xanthen-9-ylidene)-malonaldehyde (5).** A solution of xanthylium salt **4** (0.61 g, 1 mmol) and NaOH (0.4 g, 10 mmol) in 20 mL of 50% mixture of $CH_3OH$ and water was heated at reflux for 5 min. On cooling, the mixture was diluted with water and AcOH (0.75 mL) was added followed by the extraction with $CH_2Cl_2$ and drying over $Na_2SO_4$. The solvent was evaporated off, and the residue was eluted through a silica column ($CH_2Cl_2$−$CH_3OH$ 14:1) to give 0.21 g (59%) of compound **5**. Mp: 146−148 °C. $^1$H NMR (600 MHz, $CD_3CN$): 9.38 (s, 2H), 8.10 (d, *J* 8.8 Hz, 1H), 7.91 (d, *J* 9.7 Hz, 1H), 7.64 (s, 1H), 7.38 (d, *J* 8.7 Hz, 1H), 7.08 (d, *J* 9.9 Hz, 1H), 6.74 (s, 1H), 3.67 (q, *J* 7.2 Hz, 4H), 1.29 (t, *J* 7.1 Hz, 6H). $^{13}$C NMR (150 MHz, $CD_3CN$): 186.2, 159.0, 158.5, 157.5, 153.8, 140.5, 135.6, 133.2, 124.8, 119.8, 117.5, 117.1, 114.6, 95.3, 46.0, 11.9. HRMS (ESI-TOF): calcd for $C_{20}H_{18}ClNO_3$ 356.10480 $[M + H^+]$, found 356.10477. Anal. Calcd for $C_{20}H_{18}ClNO_3 \cdot 0.5H_2O$ (364.82): C, 65.84; H, 5.25; N, 3.84. Found: C, 66.11; H, 5.48; N, 4.01. $\lambda_{abs}$ ($CH_3CN$, $\varepsilon \times 10^{-3}$): 479 (20), 569 (15) nm.

**3-Diethylamino-6-dimethylamino-9-(1-dimethylamino-3-oxoprop-1-en-2-yl)xanthylium Chloride (6).** Xanthylium salt **4** (0.24 g, 0.5 mmol) and sodium acetate (0.05 g, 0.61 mmol) in ethanol (4 mL) were heated at reflux for 2 h. On cooling, the precipitated product was filtered and washed with ethanol to give 0.12 g (56%) of compound **6**. Mp: 235 °C. $^1$H NMR (400 MHz, $CD_3CN$): 9.18 (s, 1H, CHO), 7.65−7.56 (m, 3H), 7.08−7.00 (m, 2H), 6.76 (d, *J* 2.8 Hz, 1H), 6.73 (d, *J* 2.4 Hz, 1H), 3.62 (q, *J* 7.2 Hz, 4H), 3.24 (s, 6H), 3.20 (br s, 3H), 2.43 (br s, 3H), 1.26 (t, *J* 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CD_3CN$): 187.3, 162.0, 158.6, 158.3, 158.2, 156.8, 156.3, 133.1, 132.6, 115.7, 115.5, 115.1, 114.9, 105.0, 97.0, 96.8, 47.4, 46.6, 41.2, 40.2, 12.8. HRMS (ESI-TOF): calcd for $[C_{24}H_{30}N_3O_2]^+$ 392.2338 $[M^+]$, found 392.2329. $\lambda_{abs}$ ($C_2H_5OH$, $\varepsilon \times 10^{-3}$): 560 (95) nm.

**3-Chloro-6-diethylamino-9-(1-phenyl-1*H*-pyrazol-4-yl)-xanthylium Perchlorate (7).** Dialdehyde **5** (71 mg, 0.2 mmol) and phenylhydrazine hydrochloride (30 mg, 0.2 mmol) in ethanol (4 mL) were heated at reflux for 15 min. On cooling, a solution of $NaClO_4 \times H_2O$ (56 mg, 0.4 mmol) in ethanol (4 mL) was added to the reaction mixture. The precipitate was filtered and washed with ethanol to give 85 mg (81%) of the product. Mp: 138−139 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): 9.28 (s, 1H), 8.32 (s, 1H), 8.19 (d, *J* 9.2 Hz, 1H), 8.1−8.0 (m, 4H), 7.69 (dd, *J* 8.8 Hz *J* 2.0 Hz, 1H), 7.62 (t, *J* 8.0 Hz, 2H), 7.54 (dd, *J* 10.0 Hz *J* 2.0 Hz, 1H), 7.46 (t, *J* 7.6 Hz, 1H), 7.24 (d, *J* 2.0 Hz, 1H), 3.87 (br s, 4H), 1.4−1.2 (m, 6H, $CH_3$). $^{13}$C NMR (100 MHz, DMSO-$d_6$): 158.6, 158.0, 153.6, 148.4, 142.9, 141.1, 138.9, 133.7, 131.5, 129.8, 127.7, 126.7, 119.3, 119.2, 119.1, 118.0, 117.5, 113.7, 96.9, 46.8, 46.6, 13.4, 12.4. HRMS (ESI-TOF): calcd for $[C_{26}H_{23}ClN_3O]^+$ 428.15242 $[M^+]$, found 428.15258. $\lambda_{abs}$ ($CH_3CN$, $\varepsilon \times 10^{-3}$): 408 (12), 502 (26), 536 (22) nm.

**3-Diethylamino-9-(1-dimethylamino-3-(dimethyliminio)-prop-1-en-2-yl)-6-methoxyxanthylium Diperchlorate (9).** Compound **9** was prepared identically to **4**. Yield: 81%. Mp: 216 °C. $^1$H NMR (400 MHz, $CD_2Cl_2$): 8.14 (s, 2H), 7.95 (d, *J* 9.6 Hz, 1H), 7.90 (d, *J* 8.8 Hz, 1H), 7.37 (dd, *J* 9.6 Hz *J* 2.4 Hz, 1H), 7.28 (dd, *J* 8.8 Hz *J* 2.4 Hz, 1H), 7.24 (d, *J* 2.4 Hz, 1H), 6.95 (d, *J* 2.4 Hz, 1H), 4.06 (s, 3H), 3.85−3.70 (m, 4H), 3.40 (s, 6H), 2.48 (s, 6H), 1.45−1.30 (m, 6H). $^{13}$C NMR (100 MHz, $CD_2Cl_2$): 168.9, 165.4, 158.4, 158.0, 156.1, 132.7, 131.3, 119.4, 118.2, 116.9, 101.4, 97.4, 92.4, 57.2, 49.8, 47.5, 47.3, 39.8, 13.2, 12.1. HRMS (ESI-TOF): calcd for $[C_{25}H_{33}N_3O_2]^{2+}$ 203.6287 $[M^{2+}]$, found 203.6291. Anal. Calcd for $C_{25}H_{33}Cl_2N_3O_{10}$ (606.45): C, 49.51; H, 5.48; N, 6.93; Cl, 11.69. Found: C, 49.44; H, 5.54; N, 6.87; Cl, 11.54. $\lambda_{abs}$ ($CH_3CN$, $\varepsilon \times 10^{-3}$): 305 (36), 512 (32), 549 (31) nm.

**2-(3-Diethylamino-6-methoxy-9*H*-xanthen-9-ylidene)-malonaldehyde (10).** Compound **10** was prepared identically to **5**. Yield: 58%. Mp: 198 °C (dec). $^1$H NMR (400 MHz, $CDCl_3$): 9.39 (s, 2H), 8.12 (d, *J* 9.2 Hz, 1H), 8.03 (d, *J* 9.6 Hz, 1H), 7.03 (dd, *J* 9.2 Hz *J* 2.4 Hz, 1H), 6.96 (d, *J* 2.8 Hz, 1H), 6.92 (dd, *J* 9.6 Hz *J* 2.4 Hz, 1H), 6.62 (d, *J* 2.8 Hz, 1H), 3.97 (s, 3H), 3.60 (q, *J* 7.2 Hz, 4H), 1.33 (t, *J* 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): 187.4, 167.0, 161.6, 159.0, 156.9, 156.4, 135.8, 134.2, 116.2, 115.6, 115.2, 114.9, 113.6, 99.4, 95.1, 56.3, 46.0, 12.8. HRMS (ESI-TOF): calcd for $C_{21}H_{22}NO_4$ 352.1549 $[M + H^+]$, found 352.1551. Anal. Calcd for $C_{21}H_{21}NO_4 \cdot 0.5H_2O$ (360.40): C, 69.98; H, 6.15; N, 3.89. Found: C, 70.17; H, 6.14; N, 4.04. $\lambda_{abs}$ ($CH_3CN$, $\varepsilon \times 10^{-3}$): 477 (29), 543 (16) nm.

**3-Diethylamino-6-methoxy-9-(1-phenyl-1*H*-pyrazol-4-yl)-xanthylium Perchlorate (11a).** Vinamidinium salt **9** (0.82 g, 1.34 mmol), phenylhydrazine hydrochloride (0.27 g, 1.9 mmol), and sodium acetate (0.33 g, 4 mmol) in ethanol (20 mL) were heated at reflux for 2 h. On cooling, the product precipitated was filtered and washed with ethanol to give 0.56 g (80%) of the pure product. Mp: 126−127 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): 9.27 (s, 1H), 8.31 (s, 1H), 8.13 (d, *J* 9.2 Hz, 1H), 8.08−8.00 (m, 3H), 7.65−7.57 (m, 2H), 7.48−7.40 (m, 3H), 7.28 (dd, *J* 9.2 Hz *J* 2.4 Hz, 1H), 7.16 (d, *J* 2.0 Hz, 1H), 4.06 (s, 3H), 3.9−3.7 (m, 4H), 1.27 (br s, 6H). $^{13}$C NMR (100 MHz, DMSO-$d_6$): 167.0, 158.5, 156.9, 156.3, 149.8, 142.8, 138.9, 133.2, 131.8, 131.3, 129.8, 127.6, 119.2, 117.5, 116.4, 115.3, 114.4, 113.9, 100.6, 96.3, 57.0, 46.2, 46.0, 13.2, 12.1. HRMS (ESI-TOF): calcd for $[C_{27}H_{26}N_3O_2]^+$ 424.20195 $[M^+]$, found 424.20355. $\lambda_{abs}$ ($CH_3CN$, $\varepsilon \times 10^{-3}$): 380 (14), 498 (31), 528 (35) nm.

**Method for the Preparation of Compound 11a from Compound 10.** Dialdehyde **10** (175 mg, 0.5 mmol) and phenylhydrazine hydrochloride (75 mg, 0.52 mmol) in ethanol (7 mL) were heated at reflux for 15 min. On cooling, a solution of $NaClO_4 \cdot H_2O$ (140 mg, 1.0 mmol) in ethanol (5 mL) was added to the reaction mixture. The precipitate was filtered and washed with ethanol to give


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220 mg (85%) of the product. Spectral data are identical to the previous experiment.

**9-(1-(4-Bromophenyl)-1*H*-pyrazol-4-yl)-3-diethylamino-6-methoxyxanthylium Perchlorate (11b).** Compound **11b** was prepared identically to **11a**. Yield: 95%. Mp: 258 °C (dec). $^1$H NMR (500 MHz, DMSO-$d_6$): 9.26 (s, 1H), 8.33 (s, 1H), 8.12 (d, *J* 9.0 Hz, 1H), 8.03 (d, *J* 9.8 Hz, 1H), 8.00 (d, *J* 8.9 Hz, 2H), 7.82 (d, *J* 8.9 Hz, 2H), 7.45−7.40 (m, 2H), 7.28 (dd, *J* 9.2 Hz *J* 2.6 Hz, 1H), 7.17 (d, *J* 2.4 Hz, 1H), 4.06 (s, 3H), 3.83−3.77 (m, 4H), 1.28 (br s, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): 167.5, 159.0, 157.4, 156.8, 150.1, 143.5, 138.6, 133.6, 133.0, 132.2, 131.8, 121.6, 120.5, 117.9, 116.8, 115.9, 114.8, 114.6, 101.1, 96.8, 57.5, 46.7, 46.5, 13.6, 12.6. HRMS (ESI-TOF): calcd for $[C_{27}H_{25}BrN_3O_2]^+$ 502.1130 [M$^+$], found 502.1127. Anal. Calcd for $C_{27}H_{25}BrClN_3O_6$ (602.86): C, 53.79; H, 4.18; N, 6.97. Found: C, 53.76; H, 4.32; N, 6.97. $\lambda_{abs}$ ($CH_3CN$, $\varepsilon \times 10^{-3}$): 382 (19), 498 (39), 527 (43) nm.

**6-Diethylamino-9-(1-phenyl-1*H*-pyrazol-4-yl)-3*H*-xanthen-3-one (12a).** Compound **11a** (0.26 g, 0.5 mmol) was dissolved in a mixture of 5 mL of glacial acetic acid and 3 mL of 48% hydrobromic acid and heated at 130°c for 10 h. On cooling, the reaction mixture was diluted with water and neutralized with a solution of $NaHCO_3$ followed by extraction with $CH_2Cl_2$ and drying over $MgSO_4$. The solvent was evaporated, and the residue was eluted through an $Al_2O_3$ column ($CH_2Cl_2$−$CH_3OH$ 96:4) to give 0.14 g (68%) of rhodol **11a**. Mp: 137−138 °C. $^1$H NMR (400 MHz, $CDCl_3$): 8.20 (s, 1H), 7.90 (s, 1H), 7.82−7.78 (m, 2H), 7.57−7.43 (m, 4H), 7.39 (tt, *J* 7.6 Hz *J* 1.6 Hz, 1H), 6.68−6.62 (m, 2H), 6.60 (d, *J* 2.8 Hz, 1H), 6.48 (br s, 1H), 3.50 (q, *J* 7.2 Hz, 4H), 1.27 (t, *J* 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$): 159.0, 156.1, 152.6, 142.0, 139.6, 130.4, 129.9, 128.1, 128.0, 127.6, 119.5, 115.4, 115.3, 110.6, 110.4, 105.4, 96.9, 45.3, 12.7. HRMS (ESI-TOF): calcd for $C_{26}H_{23}N_3O_2$ 410.18630 [M + H$^+$], found 410.18786. Anal. Calcd for $C_{26}H_{23}N_3O_2{\cdot}H_2O$ (427.50): C, 73.05; H, 5.89; N, 9.83. Found: C, 72.87; H, 5.70; N, 9.85. $\lambda_{abs}$ ($C_2H_5OH$, $\varepsilon \times 10^{-3}$): 362 (12) 494 (36) 527 (87) nm.

**9-(1-(4-Bromophenyl)-1*H*-pyrazol-4-yl)-6-diethylamino-3*H*-xanthen-3-one (12b).** Compound **12b** was prepared identically to **12a**. Yield: 72%. Mp: 256−257 °C. $^1$H NMR (400 MHz, $CDCl_3$): 8.14 (s, 1H), 7.89 (s, 1H), 7.72−7.62 (m, 4H), 7.45−7.38 (m, 2H), 6.65−6.58 (m, 3H), 6.43 (d, *J* 2.0 Hz, 1H), 3.49 (q, *J* 7.2 Hz, 4H), 1.27 (t, *J* 7.2 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$,): 185.3, 182.9, 159.0, 155.9, 152.4, 142.3, 141.0, 138.6, 132.9, 130.3, 129.6, 128.5, 127.8, 120.9, 115.9, 115.5, 110.4, 110.1, 105.6, 97.0, 45.2, 12.7. HRMS (ESI-TOF): calcd for $C_{26}H_{22}BrN_3O_2$ 488.0974 [M + H$^+$], found 488.0971. Anal. Calcd for $C_{26}H_{22}BrN_3O_2$ (488.38): C, 63.94; H, 4.54; N, 8.60; Br, 16.36. Found: C, 63.87; H, 4.75; N, 8.58; Br, 16.35. $\lambda_{abs}$ ($C_2H_5OH$, $\varepsilon \times 10^{-3}$): 360 (11), 495 (31), 529 (73) nm.

**9,9′-(1,1′-(4,4′-(1,4,10,13-Tetraoxa-7,16-diazacyclooctadecane-7,16-diyl)bis(4,1-phenylene))bis(1*H*-pyrazole-4,1-diyl))-bis(6-diethylamino-3*H*-xanthen-3-one) (14).** Rhodol **12b** (0.49 g, 1 mmol), diazacrown ether **13** (0.13 g, 0.5 mmol), sodium *tert*-butoxide (0.16 g, 1.7 mmol), and palladium diacetate (9 mg, 0.04 mmol) were placed into a dried Schenk flask. The flask was capped, subsequently degassed several times, and filled with argon. Then a 0.25 M toluene solution of tri-*tert*-butylphosphine (0.13 mL, 0.032 mmol) and 7 mL of dry degassed dioxane were added to the inert atmosphere. The stirred reaction mixture was heated at 90 °C for 24 h. On cooling, the mixture was diluted with $CH_2Cl_2$ (30 mL), and solid material was filtered off. Solvents were evaporated off, and the residue was eluted through the silica column ($CH_2Cl_2$−$CH_3OH$ 85:15). The fraction consisted of compound **14** and was evaporated. The crude product (100 mg) was purified on SEC in $CHCl_3$ to give 80 mg (15%) of the title compound. Mp: 174 °C. $^1$H NMR (400 MHz, $CDCl_3$): 7.99 (s, 2H), 7.79 (s, 2H), 7.58−7.49 (m, 6H), 7.47 (d, *J* 10.0 Hz, 2H), 6.74 (d, *J* 9.2 Hz, 4H), 6.70−6.62 (m, 4H), 6.56 (d, *J* 2.4 Hz, 2H), 6.50 (br s, 2H), 3.74 (t, *J* 5.6 Hz, 8H), 3.70−3.60 (m, 16H), 3.51 (q, *J* 7.2 Hz, 8H), 1.27 (t, *J* 7.2 Hz, 12H). $^{13}$C NMR (100 MHz, $CDCl_3$): 182.9, 158.8, 156.3, 153.0, 147.6, 141.3, 130.6, 130.1, 129.3, 128.0, 126.9, 121.2, 114.7, 114.4, 112.2, 110.8, 105.1, 96.8, 71.3, 69.2, 51.8, 45.5, 12.8. HRMS (ESI-TOF): calcd for $C_{64}H_{68}N_8O_8$ 1077.5238 [M + H$^+$], found 1077.5245. Anal. Calcd for $C_{64}H_{68}N_8O_8{\cdot}2H_2O$ (1113.30): C, 69.05; H, 6.52; N, 10.06. Found: C, 69.08; H, 6.40; N, 10.11 $\lambda_{abs}$ (DMSO, $\varepsilon \times 10^{-3}$): 497 (77), 532 (98) nm.

**9-(1-(4-(1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-yl)-phenyl)-1*H*-pyrazol-4-yl)-6-diethylamino-3*H*-xanthen-3-one (16).** Rhodol **12b** (0.44 g, 0.82 mmol), azacrown ether **15** (0.22 g, 1 mmol), lithium *tert*-butoxide (0.16 g, 2 mmol), and palladium diacetate (20 mg, 0.09 mmol) were placed into a dried Schenk flask. The flask was capped, subsequently degassed several times, and filled with argon. Then a 0.25 M toluene solution of tri-*tert*-butylphosphine (0.3 mL, 0.075 mmol) and 5 mL of dry degassed dioxane were added to the inert atmosphere. The stirred reaction mixture was heated at 90 °C for 24 h. On cooling, the mixture was diluted with $CH_2Cl_2$ (30 mL) and solid material was filtered off. Solvents were evaporated, and the residue was eluted through the silica column ($CH_2Cl_2$−$CH_3OH$ 9:1). The fraction consisting of compound **16** was evaporated. The crude product was purified on SEC in THF to give 0.21 g (41%) of the title compound. Mp: 200−201 °C. $^1$H NMR (500 MHz, $CDCl_3$): 8.00 (s, 1H), 7.84 (s, 1H), 7.57 (d, *J* 9.2 Hz, 2H), 7.52 (d, *J* 9.2 Hz, 1H), 7.50 (d, *J* 9.7 Hz, 1H), 6.76 (d, *J* 9.2 Hz, 2H), 6.66−6.61 (m, 2H), 6.60 (d, *J* 2.6 Hz, 1H), 6.44 (d, *J* 1.9 Hz, 1H), 3.80 (t, *J* 6.2 Hz, 4H), 3.73−3.60 (m, 16H), 3.49 (q, *J* 7.3 Hz, 4H), 1.27 (t, *J* 7.1 Hz, 6H). $^{13}$C NMR (125 MHz, $CDCl_3$): 159.0, 155.8, 152.2, 147.2, 141.8, 141.0, 130.4, 129.8, 129.1, 128.2, 127.7, 121.2, 115.1, 114.4, 111.8, 110.4, 109.8, 105.3, 96.8, 71.3, 70.3, 70.1, 68.4, 52.7, 45.1, 12.6. HRMS (ESI-TOF): calcd for $C_{36}H_{42}N_4O_6$ 627.3183 [M + H$^+$], found 627.3190. Anal. Calcd for $C_{36}H_{42}N_4O_6$ (626.74): C, 68.99; H, 6.75; N, 8.94. Found: C, 68.73; H, 6.69; N, 8.83. $\lambda_{abs}$ ($CH_3CN$, $\varepsilon \times 10^{-3}$): 297 (34), 490 (42), 524 (53) nm.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Normalized absorption spectra for dyes **14** and **16**, two-photon absorption spectrum of compound **12a** in DMSO, as well as $^1$H NMR and $^{13}$C NMR spectra for compounds **4**−**7**, **9**, **10**, **11a**,**b**, **12a**,**b**, **14**, and **16**. This material is available free of charge via Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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