

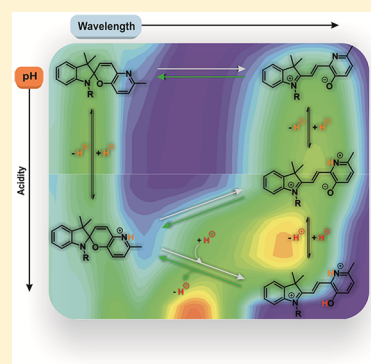
Pyridine–Spiropyran Derivative as a Persistent, Reversible Photoacid in Water

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S Supporting Information

ABSTRACT: A highly versatile water-soluble pyridine–spiropyran photoswitch is reported which functions as photoacid in a wide pH range. Under neutral conditions, the open-ring merocyanine (MC[−]) exists to 48% and closes quantitatively by irradiation with visible light, while the reverse reaction occurs rapidly in the dark or by irradiation at 340 nm. The different pK_a of the pyridine nitrogen in the closed spiropyran (4.8) and open merocyanine form (6.8) leads to a reversible proton release in a pH range of 3–7. Only negligible hydrolytic decomposition was observed in the pH range from 1 to 12. The application of potentially harmful UV light can be circumvented due to the fast thermal ring-opening except for pH values below 3. Its photoacidic properties make this compound an effective pH-regulating photoswitch in water and enable controlled proton-transfer processes for diverse applications. Additionally, all of the involved protonated states of the compound exhibit discriminative fluorescence features within certain pH ranges, which even expands its utility to a light-controllable, pH-sensitive fluorophore.



1. INTRODUCTION

Proton-transfer reactions are of fundamental importance in nature and can be used to regulate chemical reactivity,^{1–3} photochemical features,^{4–6} biological functions,^{7–9} as well as material properties.^{10,11} Photoacidic compounds release a proton upon optical excitation and can be used to control protonations and deprotonations. With commercially available technology, light as an external trigger can be applied with high precision of location, timing, and dosage.^{12–18} Possible side reactions can be minimized if the wavelengths for operation are cleverly chosen. Recently, we have shown that even processes triggered by near-UV light are possible in living mice.¹⁹

In recent years, effective reversible photoacids have become the focus of current research. Molecular motors,^{20–22} memory hydrogels,^{23,24} as well as acid-catalyzed reactions²⁵ are only a few research areas where photoacids are studied.

In the majority of examples, “photoacid” refers to a compound where the electronically excited state has a lower pK_a compared to the ground state.^{26,27} Therefore, the duration of the proton release is correlated with the lifetime of the excited species. Typically, after pico- to nanoseconds the proton reassociates. Thus, the liberated proton is too short-lived to catalyze a chemical process or to alter a macroscopic property.

Reversible photoswitches are compounds that exist in two photoisomeric states that can be interconverted by light of different wavelengths. In some cases, the isomerization in one of the directions can occur thermally. If the process is fast enough, this can even be an advantage in cases where this isomerization direction would involve UV light or leads to photodegradation.

The two isomeric states can have different acidic properties. In such a case, the proton transfer effect is as persistent as the stability of the photoisomers. There are only very few examples in which such types of persistent photoacids have been shown to work in water (and are hence compatible with biological applications): In a seminal study, Liao et al. presented a “long-lived photoacid” using a spiropyran/merocyanine photoswitch (1, Scheme 1a).^{28,29} They achieved a light-induced pH shift from 5.5 to 3.3 in water. In a follow-up study in which the term “metastable-state photoacid” was used they presented a new system (2, Scheme 1b) that could also operate in a more neutral pH range.³⁰ After light irradiation, the pH of an unbuffered aqueous solution (with 10% DMSO) shifted from 6.0 to 4.3. The process was thermally reversible in the dark over the course of 8–48 h.

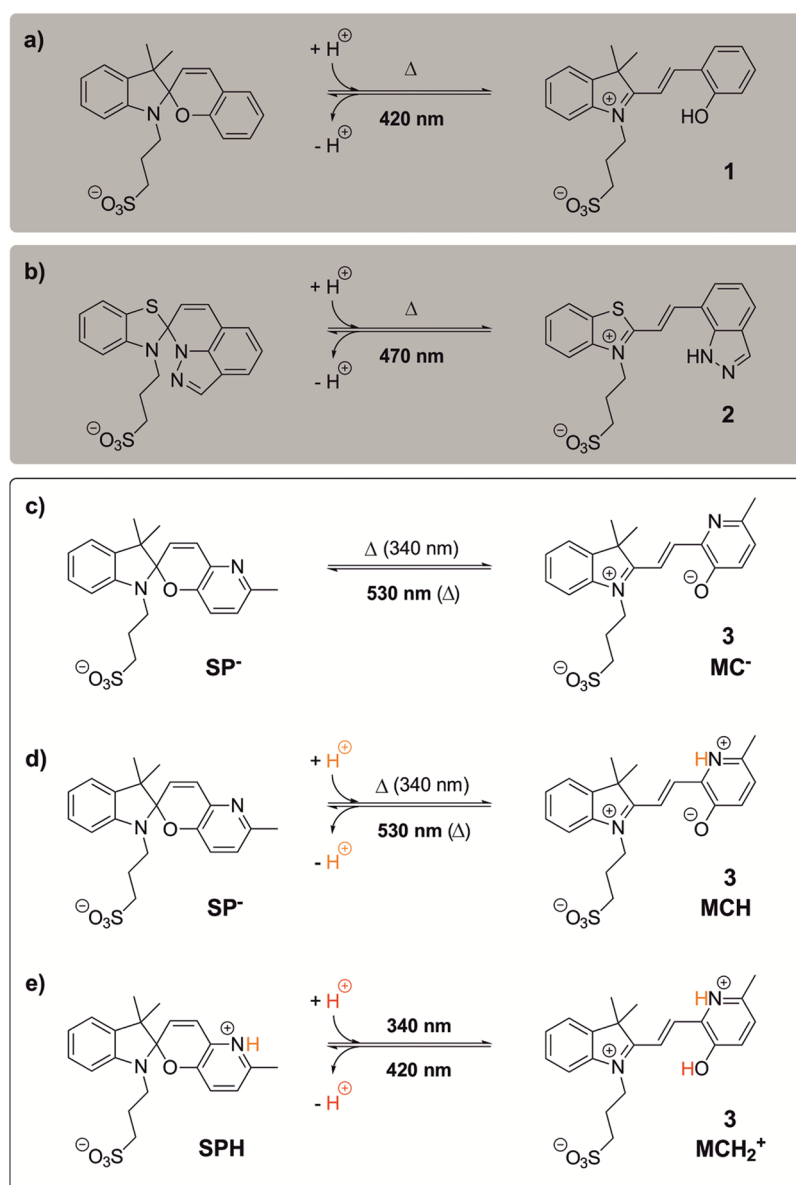
For example, Klajn et al. used the approach of long-lived spiropyran photoacids for the light-controlled self-assembly of nanoparticles.¹⁰ Aprahamian et al. used spiropyran 1 for the proton-induced switching of a hydrazone-based actuator in methanol.³¹

In general, spiropyran derivatives are very interesting photoswitches for diverse applications because the two photoisomers differ strongly in many properties, such as, for example, dipole moment and structure.^{32–34} They can be switched reversibly between the closed-ring, nonpolar spiropyran (SP) structure and the open-ring merocyanine (MC), which adopts a zwitterionic or a quinoidal mesomeric resonance structure.

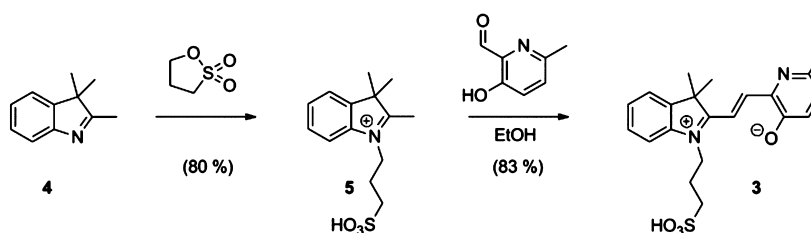
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Scheme 1. (a, b) Metastable-State Photoacids 1 and 2, Respectively, Used in Previous Studies.^{28,30} (c–e) Isomerization Reactions of the Spiropyran/Merocyanine Compound 3 of This Study at pH 7–12 (c), pH 3–7 (d), and pH 1–3 (e)



Scheme 2. Overview of the Synthesis of the Water-Soluble Spiropyran Photoacid 3



Here, it has to be considered that merocyanines can exist as an equilibrium of different *cis-trans* isomers due to the central chain of three double bonds. The TTC (*trans-trans-cis*) isomer is supposed to be the most stable conformation and therefore dominates the visible absorption band of MC.^{35,36}

In many studies, “nitro-BIPS” is used which has an additional nitro group in *para* position of the phenolic OH group in compound 1.^{34,37–40} However, despite its frequent use, the

photochemical properties are suboptimal.⁴¹ We had previously shown that “Py-BIPS”, a spiropyran derivative with a methylpyridinium ring, has many favorable properties. These include, for example, a singlet-only photoswitching mechanism and a high solubility of 28 mM in PBS buffer.^{12–14}

For this study we wondered if the nonmethylated Py-BIPS derivative 3 (Scheme 1c–e) could also photoswitch and found that it functions as a metastable-state photoacid with properties

which are better than the ones of previous examples. The sulfonic acid side chain was installed for water solubility. The compound can exist in five photochromic states depending on the pH value (Scheme 1c–e).

2. RESULTS AND DISCUSSION

Synthesis of Photoacid 3. Scheme 2 depicts the synthetic route for photoacid 3 starting from 2,3,3-trimethylindoline which was alkylated with 1,3-propane sultone followed by an aldol condensation with the corresponding salicylic aldehyde. The obtained merocyanine derivative exhibits a high solubility (10 mM) at pH 7.4 in PBS buffer.

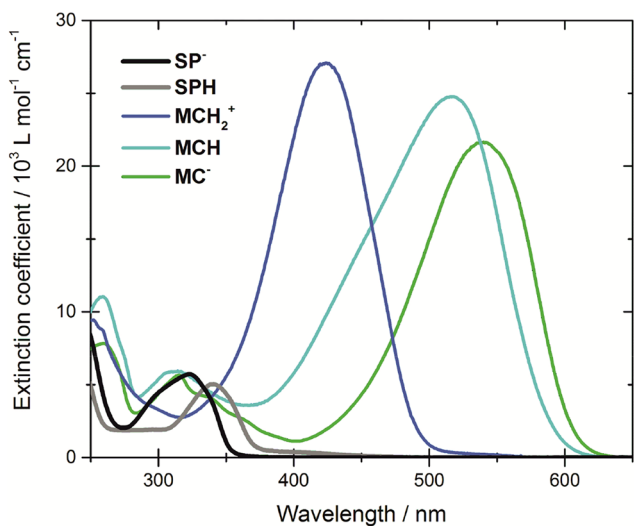


Figure 1. Pure absorption spectra in aqueous medium of the compounds shown in Scheme 1c–e.

Ground-State Properties of Photoacid 3 at Constant pH Values. The ground-state properties as well as the spectroscopic characteristics of compound 3 differ from most common spiroopyran derivatives^{12,14,42} since the thermal

equilibrium is substantially shifted to the open-ring form. Even in the solid state, photoacid 3 exists as dark purple merocyanine crystals. Dissolving photoacid 3 in aqueous PBS buffer (pH 7.4) results in an initially pure MC^- sample with a pronounced absorption band at 540 nm (Scheme 1c and Figure 1). The fraction of the open-ring isomer starts to decline due to the thermal equilibration in buffered solution. The MC^- concentration drops from 100% to 48% at pH 7.4 within a few minutes ($k_{\text{close}} = 0.32 \text{ min}^{-1}$), and this equilibrium is stable over several days (see Supporting Figure 5), unlike with other spiroopyrans in aqueous conditions^{42–44} (for a graphical overview of the (photo)switching properties, see Figure 3e). At pH 7–12, both isomers of photoacid 3 (SP^- and MC^-), however, remain relatively stable. Only in a pH range above 12 does the open-ring form hydrolyze. A freshly prepared solution of photoacid 3 at pH 5.5 leads to a sample consisting mostly of MCH , which bears a proton on its pyridine nitrogen (Scheme 1d) and adopts a major absorption band with a maximum at 515 nm (see Figure 1). From titration experiments, a pK_a value of this protonation step of 6.8 could be estimated. The initial sample composition in this pH regime changes rapidly from 100% to 70% of the MCH isomer ($k_{\text{close}} = 0.17 \text{ min}^{-1}$, see also Figure 5c).

At a pH of approximately 4.8, the pyridine nitrogen of the closed-ring isomer gets protonated, resulting in an absorption band at 340 nm assigned to SPH . Below pH 3, an additional absorption band with a maximum at 420 nm emerges that can be assigned to MCH_2^+ (Scheme 1e and Figure 1). When dissolved at a pH of 1, the solution remains a pure solution of MCH_2^+ .

A summarizing overview of the pH-dependent isomers that were detected by the titration experiment and the corresponding reaction pathways is provided in Figure 2. The detected absorption signals assigned to the open-ring isomers are likely a superposition of multiple *cis-trans* isomers that could additionally possess slightly different pK_a values.

Photoswitching and Fluorescence Properties of Photoacid 3 at Constant pH. All of the open-ring species

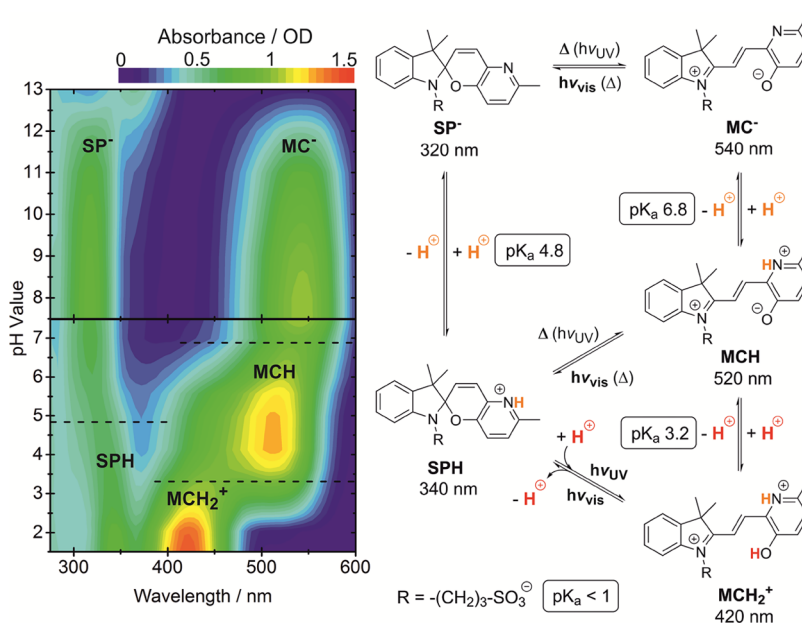


Figure 2. pH-dependent absorption spectra of photoacid 3 obtained from a titration experiment.

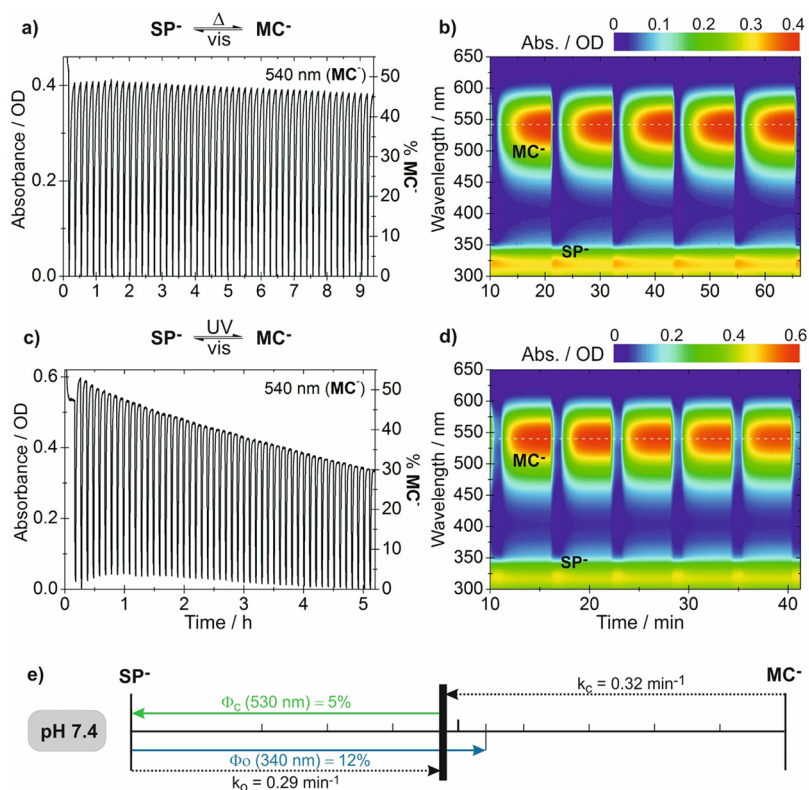


Figure 3. Reversible switching cycles of photoacid 3 in PBS buffer (pH 7.4). (a, b) Irradiation with 530 nm for 1 min (7.3 mW), then 15 min reaction in the dark. (c, d) Irradiation with 530 nm for 1 min (7.3 mW), then with 340 nm for 5 min (0.6 mW). (e) Graphical overview of the (photo)switching properties of photoacid 3 at pH 7.4.

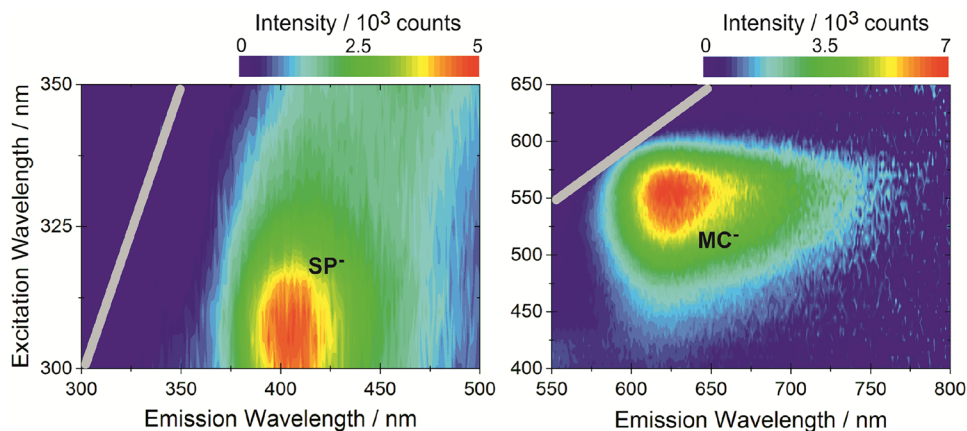


Figure 4. Excitation wavelength-dependent fluorescence contour plots of SP^- (left, $\Phi_f = 3.1\%$) and MC^- (right, $\Phi_f = 8.9\%$) of compound 3 at pH 7.4.

are capable of photoisomerization. Therefore, we studied their photochromic behavior at first under different but constant pH conditions. Irradiation at a pH of 7.4 with 530 nm converts the MC^- isomer quantitatively to the SP^- isomer with a quantum yield of $\Phi_{\text{close}} = 5\%$. From the pure SP^- state, isomerization was possible either thermally within minutes (Figure 3a,b, $k_{\text{open}} = 0.29 \text{ min}^{-1}$) or by irradiation at 340 nm (Figure 3c,d, $\Phi_{\text{open}} = 12\%$). In the former case, photoacid 3 is highly stable over 50 switching cycles. In the latter case, the initial photostationary state contained slightly more MC^- than the thermal equilibrium. However, a gradual photodegradation was observed over the switching cycles. For a graphical overview of the switching behavior, see Figure 3e.

Spiropyran derivatives are known for their fluorescence properties in the open-ring form.^{45–47} Figure 4 shows the fluorescence signals of the SP^- and the MC^- isomers at pH 7.4. The open-ring MC^- has an emission maximum at 625 nm while the ring-closed SP^- fluoresces around 405 nm. The latter is attributed to the pyridine fragment of the molecule.

At a pH of 5.5, a similar photochromic behavior was observed. After irradiation with 530 nm, a quantitative ring-closing reaction to SP^- is detectable ($\Phi_{\text{close}} = 7\%$). The ring-opening reaction again occurs thermally and rapidly in the dark, producing the protonated MCH (Figure 5a,b, $k_{\text{open}} = 0.22 \text{ min}^{-1}$). The ring-opening reaction was also initiated by irradiation with UV light at 340 nm at pH 5.5 (Figure 5c,d,

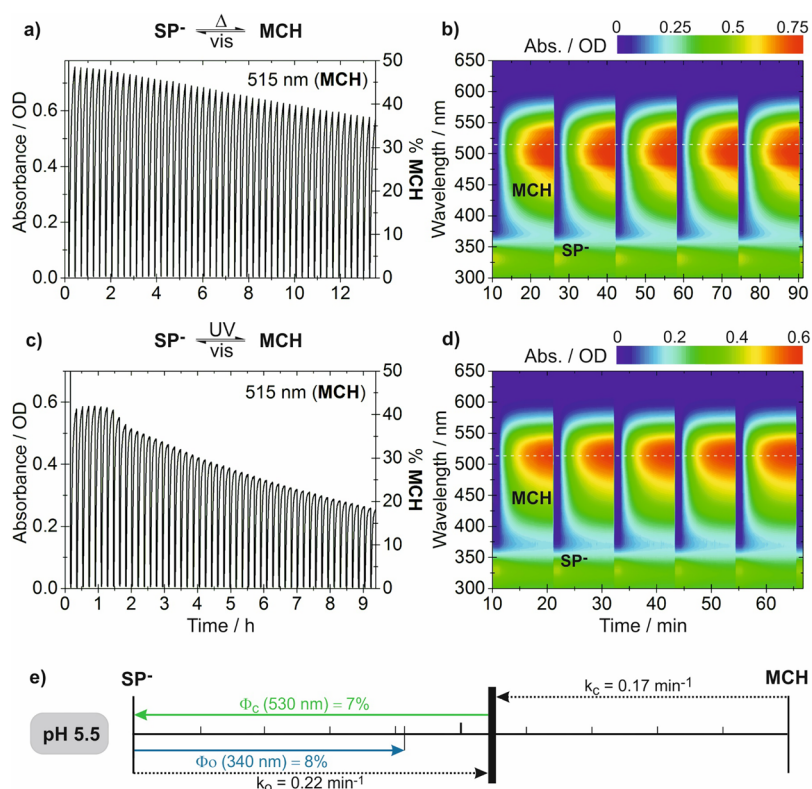


Figure 5. Reversible switching cycles of photoacid 3 in PBS buffer (pH 5.5). (a, b) Irradiation with 530 nm for 5 min (7.3 mW), then 15 min reaction in the dark. (c, d) Irradiation with 530 nm for 5 min (8.5 mW), then with 340 nm for 10 min (0.6 mW). (e) Graphical overview of the (photo)switching properties of photoacid 3 at pH 5.5.

$\Phi_{\text{open}} = 8\%$). The photostationary state contained slightly less **MCH** than the thermal equilibrium. Photodegradation over 50 cycles was slightly more pronounced compared to pH 7.4.

In a pH range between approximately 5 and 7, the interconversion occurs between **MCH** and **SP⁻** as depicted in Figure 2. If the solvent acidity increases to pH 3–5, the ring-closed isomer exists in its protonated **SPH** state. The respective open-ring species also exhibits a fluorescence emission at 610 nm (Figure 6) that is slightly blue-shifted in comparison to **MC⁻** at pH 7.4. The peculiar shape of the observed emission signal with its two maxima hints at the presence of different conformational **MCH** isomers adopting inherent fluorescent properties.

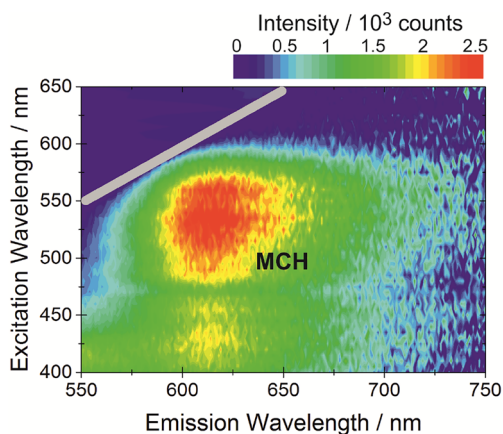


Figure 6. Excitation wavelength-dependent fluorescence contour plot of **MCH** ($\Phi_f = 3.5\%$) of compound 3 at pH 5.5.

After compound 3 is dissolved at pH 1, **MCH₂⁺** is initially formed quantitatively and remains if the sample is not exposed to visible light. Furthermore, **MCH₂⁺** appears to be thermally stable toward hydrolysis. After irradiation at 420 nm, **SPH** is formed with an absorbance maximum of 340 nm ($\Phi_{\text{close}} = 10\%$) and can be reversibly switched back to the open merocyanine form by irradiation at 310 nm (Figure 7, $\Phi_{\text{open}} = 11\%$, no thermal opening rate detected).

Compared to **MC⁻** and **MCH**, this second protonation step accounts for a substantially blue-shifted fluorescence signal of **MCH₂⁺** around 470 nm (Figure 8).

pH Switching Behavior of Photoacid 3. As mentioned previously, the pK_a of the pyridine nitrogen of compound 3 changes from 4.8 in the closed form to 6.8 in the open form. This should allow for a photoreversible release of a proton, switching between the two photoisomers. As an example, we prepared a 100 μM solution of compound 3 in 0.01 \times PBS (step 1 in Figure 9) and adjusted the starting pH to ca. 6.8 or 5.5 (green and red curve in Figure 9, respectively) with 0.1 M NaOH. Then the solution was irradiated at 530 nm (5 min, 8.5 mW) and left in the dark. These steps were repeated, and the resulting end pH values obtained are shown in Figure 9. pH jumps of 0.6–0.7 units were obtained in every step under these conditions. Then a saturated solution of compound 3 was treated similarly after the initial pH was adjusted to 6.8. In these experiments, a pH jump of 1.5 was obtained. In all cases, a reversible switching performance was observed, and the starting pH value was recovered within 15 min.

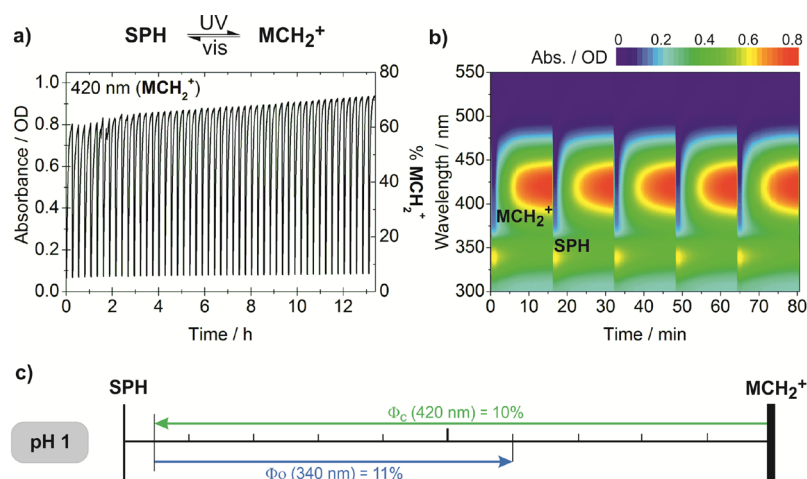


Figure 7. Reversible switching cycles of photoacid 3 in PBS buffer (pH 1). (a b) Irradiation with 420 nm for 1 min (11.7 mW), then with 340 nm for 15 min (0.6 mW). (c) Graphical overview of the (photo)switching properties of photoacid 3 at pH 1.

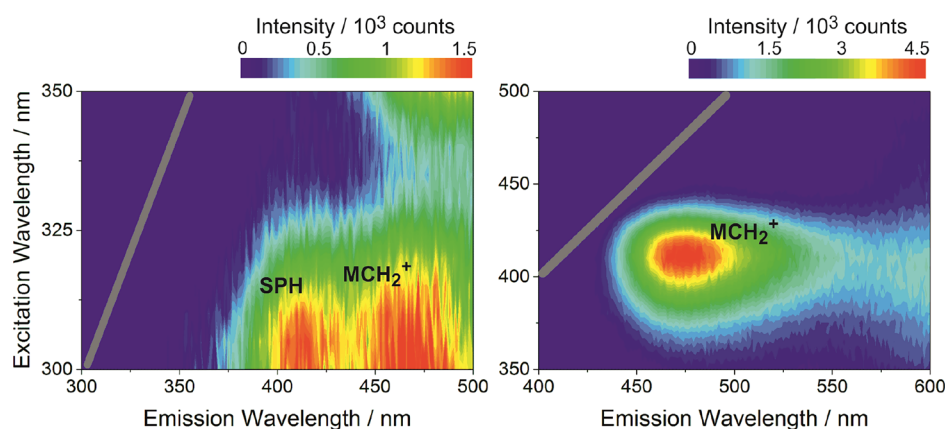


Figure 8. Excitation wavelength-dependent fluorescence contour plot of SPH (left, $\Phi_f = 2.5\%$) and MCH₂⁺ (right, $\Phi_f = 4.5\%$) of compound 3 at pH 1.

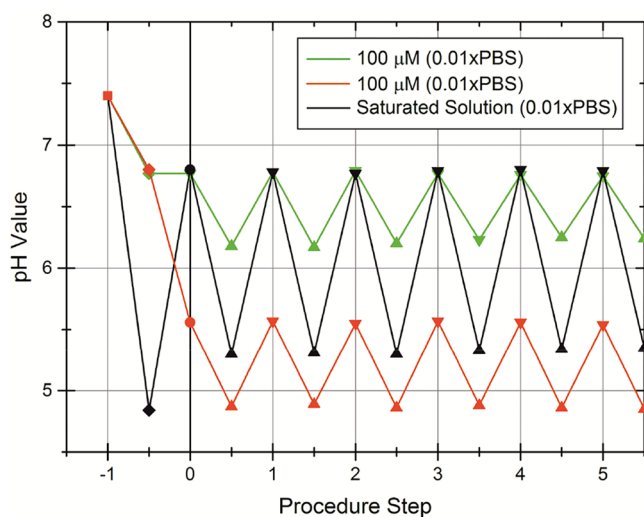


Figure 9. pH regulation experiments with photoacid 3. Key: squares, initial pH value of buffer; diamonds, pH after dissolving compound 3; circles, after addition of HCl or NaOH to adjust pH; down triangles, pH value upon irradiation with 530 nm (5 min); up triangles, pH recovered thermally in the dark (15 min).

3. CONCLUSION

The pH jump that can be obtained is determined by several factors. For a simulation of the effect of different properties on the maximally obtainable pH jump, see Supporting Figures 6–9. In general, the pH jump will become negligible with decreasing starting pH since then the maximally liberated amount of protons will become negligible compared to the one already available in solution. Toward basic starting conditions, the maximally obtainable pH jump will be determined by the difference of the acidic pK_a of MCH and SPH, respectively. A higher concentration of photoacid will lead to a higher pH jump, but the effect levels off. All of these effects will be reduced if the switching amplitude of the photoacid is reduced or, trivially, if buffer salts are present. The acidic pK_a of MCH₂⁺ will only play a role at very high concentrations of photoacid 3 or would play a more pronounced role if it were closer to the one of SPH.

In the case of compound 3, the solubility in water is very high (10 mM). With the three pK_a values being as they are, the actually obtained pH jump behavior is dominated by the ΔpK_a on the pyridine nitrogen. The jumps are relatively high and fully reversible as compound 3—unlike other spiropyrans—is surprisingly stable toward hydrolysis. Our photoacid can be operated in a comparably broad pH range. This characteristic can be used for a time-resolved and locally controlled

protonation in chemical reactions for biomedical applications, polymerization reactions, and material sciences. Compared to other spiroopyran compounds, the switching amplitude is quite high. This can be a problem with spiroopyrans if they are to be photoswitched in water. Andréasson and Pischel et al. had solved this problem for example applying supramolecular complexation.⁴⁸ In our system the use of UV light can be avoided due to the fast thermal ring-opening reaction. Apart from the changes in acidity the two photoisomers show distinct fluorescence properties. This photoswitchable fluorescence could make compound **3** interesting for biomedical imaging. Conversely, it is possible to use the molecule as a pH sensor, which functions in a pH range from 1 to 12 due to the different absorption and emission signals.

4. EXPERIMENTAL SECTION

Synthesis of Photoacid 3. Scheme 2 shows the synthetic route. 2,3,3-Trimethylindoline **4** (3.00 g, 18.84 mmol, 1.0 equiv) and 1,3-propane sultone (2.30 g, 18.84 mmol, 1.0 equiv) were stirred at 120 °C for 1.5 h. Methanol was added to the reaction mixture and stirred at room temperature for 30 min. Ethyl acetate and cyclohexane were added. The white precipitate was filtered and washed with ethyl acetate. The solid was dried under reduced pressure to afford 3-(2,3,3-trimethyl-3H-indol-1-ium-1-yl)propane-1-sulfonate **5** (4.25 g, 15.12 mmol, 80%) as a white solid. ¹H NMR (500 MHz, DMSO-*d*₆): δ = 8.06–8.04 (m, 1H), 7.83–7.81 (m, 1H), 7.65–7.59 (m, 2H), 4.65 (t, *J* = 8.0 Hz, 2H), 3.51 (bs, 1H), 2.83 (s, 3H), 2.62 (t, *J* = 6.6 Hz, 2H), 2.18–2.12 (m, 2H), 1.53 (s, 6H) ppm. ¹³C NMR (125 MHz, DMSO-*d*₆): δ = 196.5, 141.9, 141.2, 129.3, 129.0, 123.4, 115.5, 54.1, 47.4, 46.6, 23.8, 22.1, 13.8 ppm. ESI-MS (+): *m/z* = 282.20 [M + H]⁺. HRMS: *m/z* calcd for C₁₄H₂₀NO₃S 282.11584 [M + H]⁺, found 282.11627 (Δ*m* = 0.00043, error 1.5 ppm).

3-(2,3,3-Trimethyl-3H-indol-1-ium-1-yl)propane-1-sulfonate (2.00 g, 7.11 mmol, 1.0 equiv) was dissolved in EtOH (20 mL), and 3-hydroxy-6-methylpicolinaldehyde **3** (0.98 g, 7.11 mmol, 1.0 equiv) was added. The reaction mixture was stirred at 80 °C for 8 h. The precipitate was filtered and dried under reduced pressure to afford 3-(3,3,6'-trimethylspiro[indoline-2,2'-pyrano[3,2-*b*]pyridin]-1-yl)-propane-1-sulfonic acid (2.37 g, 5.92 mmol, 83%) as a light red solid. ¹H NMR: (500 MHz, DMSO-*d*₆): δ = 8.48 (d, *J* = 15.8 Hz, 1H), 8.12–8.10 (m, 1H), 7.92 (d, *J* = 15.9 Hz, 1H), 7.89–7.88 (m, 1H), 7.67–7.63 (m, 2H), 7.40–7.36 (m, 2H), 4.75 (t, *J* = 7.7 Hz, 2H), 2.65 (t, *J* = 6.9 Hz, 2H), 2.51 (s, 3H), 2.23–2.17 (m, 2H), 1.77 (s, 6H) ppm. ¹³C NMR: (125 MHz, DMSO-*d*₆): δ = 181.6, 154.9, 150.0, 145.5, 143.6, 141.1, 136.6, 129.6, 129.2, 129.1, 126.0, 123.0, 115.6, 112.8, 52.3, 47.7, 46.3, 26.0, 24.7, 23.1 ppm. ESI-MS (+): 401.20 [M + H]⁺. HRMS: *m/z* calcd for C₂₁H₂₅N₂O₄S 401.15295 [M + H]⁺, found 401.15290 (Δ*m* = 0.00005, error 0.1 ppm). Mp: 200 °C dec.

NMR Spectra. For the characterization of the compounds were recorded on Bruker AVIII-HD 500 MHz instruments equipped with a N₂-cooled cryogenic probe head using *d*₆-DMSO as solvent. HRMS spectra were recorded using a Thermo Scientific MALDI LTQ Orbitrap (see the Supporting Information).

Photometric Measurements. The photometric studies with compound **3** were performed with either a Jena Analytik Specord S600 spectrometer or an Ocean Optics DH-mini UV–vis–NIR light source with an USB 4000 fiber spectrometer. For photoswitching experiments, the spectrophotometers were equipped with modular ThorLabs cuvette holders and mounted LEDs with wavelengths of 340, 420, and 530 nm.

pH Measurements. The pH value of the sample solutions was measured with a Mettler Toledo InLab Nano pH electrode. The light-induced pH regulation experiments were performed in 0.01× PBS buffer by use of the above-described spectrometers with ThorLabs LEDs attached.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01268.

¹H and ¹³C NMR spectra of compounds **5** and **3**. Data for optical spectroscopy: determination of pure spectra of all particular isomers of compound **3**, thermal reaction rates and stability, calculation of photoreaction as well as fluorescence quantum yields. Simulated data: calculations of maximum obtainable pH jumps in dependence of the particular p*K*_a as well as starting pH values for different sample concentrations (PDF)

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Notes

The authors declare no competing financial interest.

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