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Optical control of pH *via* chromoselective photodosimetry†

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The dynamic regulation of pH *via* an external stimulus is an attractive technique to gate chemical transformations. Applying photons of different energy, we preferentially address either a photoacid or a photobase donor in the same solutions and thus, present a technique to regulate the pH of a solution through light pulses.

The pH of a given system in both chemistry and biology is a crucial parameter to optimise the kinetics of a molecular transformation.[1,2] Moreover, the absence or presence of protons can serve as a gatekeeper and facilitate or inhibit a (bio)chemical reaction from proceeding.[3] Naturally, adjusting the pH became a straightforward approach to obtain stimulus-responsive control over natural and artificial systems. To additionally achieve a means of external control through a traceless reagent, the stimulation with photons *via* light-responsive small molecules became highly attractive.[4,5] Consequently, photoacid and photobase generators have found their application there where physical access is restricted, such as in polymer chemistry and biomedicine.[6–8]

These advancements underscore the significance of light-triggered reversible pH modulation. As an example, Irie demonstrated the reversible change in pH using triphenylmethane leucohydroxide (**1**) under UV-light irradiation, followed by thermal reconciliation.[9] Capitalizing on this fundamental work, Yucknovsky and Amdursky recently optimised the system, combining **1** with a second photobase generator **2**, that serves as a hydroxide (OH^-) ion donor, enabling reversible pH control with two excitation wavelengths (Fig. 1a).[10]

In parallel, the emergence of so-called photocages has provided an alternative means for the light-controlled, yet irreversible, release of small organic acids and bases.[11] In contrast, photoswitchable systems allowed for reversible control. For example, in 2021, both the groups of Beves and Pezzato introduced merocyanine photoswitches capable of modulating the bulk pH upon exposure to 450 nm or 500 nm light irradiation, respectively (Fig. 1b).[12–15]

While the examples mentioned above showcase the reversible modulation of pH triggered by light irradiation, the reverse reaction occurs spontaneously, lacks temporal control, and the

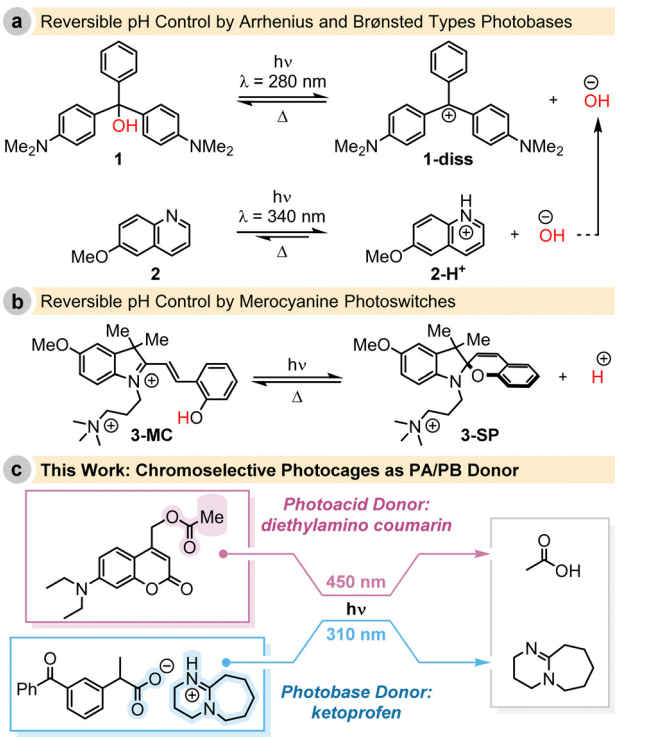

Fig. 1 (a) Reversible pH control by Arrhenius and Brønsted types photobase generator; (b) reversible pH control by Merocyanine photoswitches; (c) our approach: chromoselective pH regulation by photocages as photoacid/photobase donors.

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direction of pH change with respect to the initial state can only proceed in one direction due to the inherent reactivity of the molecule. Inspired by these advancements, our work aims to achieve complete spatiotemporal and reversible control of pH in a solution using chromoselective light irradiation, incorporating bimodality into our approach (Fig. 1c).

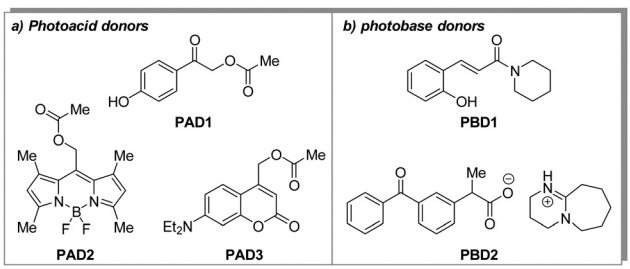
Thus, we selected a series of photoacid donors (**PAD**s) and photobase donors (**PBD**s) to identify suitable **PAD** and **PBD** pairs, in which each component can be addressed chromoselectively to obtain a tool that allows to bidirectionally affect the pH from a given initial state. Specifically, we equipped UV- and visible-light sensitive photocages with an organic acid (**PAD1**, **PAD2**, and **PAD3**, Scheme 1a), and a UV-light sensitive photocage with an organic base (**PBD1** and **PBD2**, Scheme 1b). Irradiation with UV- and/or visible light is expected to lower the observed pH, whereas irradiation with UV-light should increase the pH. Most visible-light sensitive photocages are also susceptible to UV-light, but since the quantum yield of release can vary, a global change in pH is still foreseen. The **PAD**s and **PBD**s displayed in Scheme 1 were successfully synthesised following the procedures given in the ESI.†

Fig. 2 shows the UV-vis spectra of the selected **PAD**s and **PBD**s (30 μM, 50% methanol in water). However, to generate a pronounced, global change in pH, higher concentrations of both **PAD** and **PBD** are required (see ESI†). Successively, the photochemical release of cargo was assessed. Irradiation of **PAD1** with 310 nm light for 5 minutes reduces the pH by 1 unit, from 6.25 to 5.25 (Fig. 3). Similarly, irradiation of **PAD3** with 365 nm light in 5 steps of 2 minutes reduces the pH stepwise from 5.7 to 4.9 (Fig. 4).

Irradiation of **PAD2** with 505 nm light did not result in an observed change in pH (Fig. S1, ESI†), potentially due to a combination of low solubility and low quantum yield of release, both of which are known issues for fluorinated BODIPY-photocages.[16–18]

Next, we turned towards the **PBD**s. Although the addition of piperidine increases the pH in a methanol/water mixture (Fig. S2, ESI†), photochemical release of piperidine from **PBD1** (λ = 310 nm) did not result in a concerted increase in pH (Fig. S3, ESI†). However, irradiation of **PBD2** in methanol/water at 365 nm does change the pH of the solution from pH 6 to ultimately pH 8 (Fig. 4). Addition of a small amount of buffer changes the initial pH but does not influence the observed behaviour (see ESI†). Furthermore, the dose-dependent response observed was encouraging.

We thus identified suitable molecules that allow us to both up- and downregulate the pH by irradiation with light in a dose-dependent manner, albeit both at 365 nm (Fig. 4). To obtain



Scheme 1 (a) Photoacid and (b) photobase donors are tested in the current study.

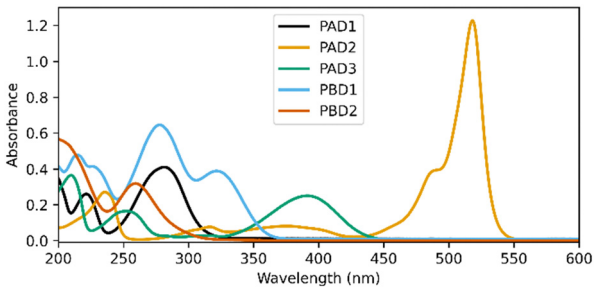


Fig. 2 UV-vis spectra of **PAD**s and **PBD**s in 50% methanol in water at a concentration of 30 μM.

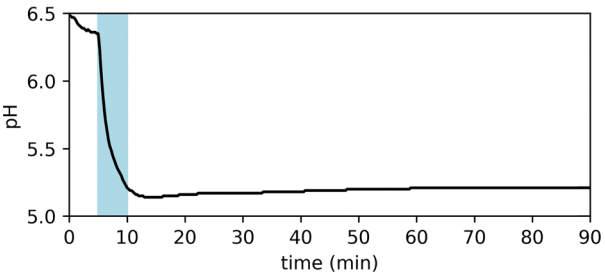


Fig. 3 Observed pH of a solution of **PAD1** (1.8 mM, 50% methanol in water) upon irradiation with 310 nm light for 5 min.

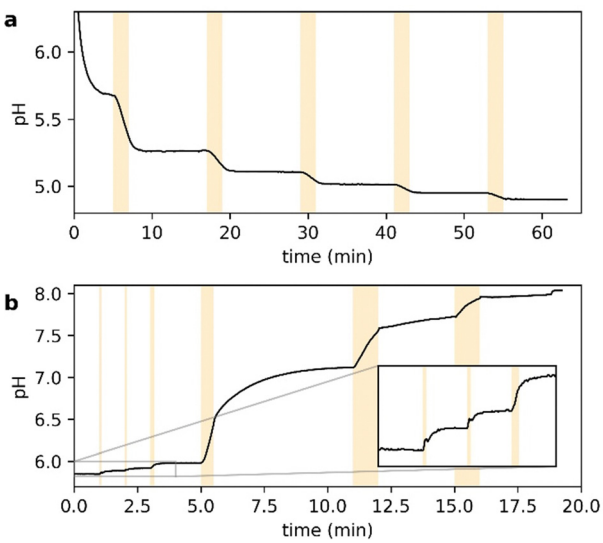


Fig. 4 (a) A saturated solution of **PAD3** (<2 mM) in 50% methanol in water is irradiated 5 times with 365 nm light for 120 s, as indicated by the yellow shading, while simultaneously the pH is measured. (b) A solution of **PBD2** (2.5 mM) in 50% methanol in water is irradiated with 365 nm light for 5, 5, 10, 30, 60, and 60 s.

wavelength-selective preferential release of one over the other, the rate of release of acid at a selected wavelength must be higher than the release of base, and *vice versa* at a different wavelength.

Since **PBD2** has an exceptionally high quantum yield of release (0.75) upon irradiation with UV-light,[19,20] and the quantum yield of release of acid from **PAD3** is only moderate at those wavelengths,[21] a solution of **PBD2** and **PAD3** is expected to basify upon irradiation with UV-light. Moreover, the UV-vis absorption spectrum of **PAD3** extends into the visible spectrum, while **PBD2** does not absorb in this range. Hence, we expected that irradiation with visible light would decrease the pH. Furthermore, the activation maximum of a comparable photoactive base generator was recently shown to be close to 310 nm.[22]

Indeed, when a solution of **PAD3** and **PBD2** (0.63 and 0.40 mM, respectively) is irradiated alternatively with 310 and 450 nm light, the observed pH fluctuated as expected (Fig. 5). In contrast to photoacids and photobases reported earlier, both up- and downregulation of pH is possible at a given starting point. Furthermore, pH recovery is not influenced by thermal backreactions, but is actively initiated by irradiation with the opposing wavelength of light.

Unfortunately, reduction of the pH below 5.5 was not yet accessible with **PAD3**/**PBD2**. For this reason, the same chromophore was equipped with more acidic leaving groups resulting in **PAD4** and **PAD5** (*cf.* Table 1).[23] While **PAD4** readily dissociates in water, **PAD5** is stable and able to reduce the pH similar to **PAD3**. However, **PAD5** does not reduce the pH further than 5.5, and due to the lower solubility compared to **PAD3**, in further experiments, **PAD3** was employed. The inaccessibility of highly acidic solution was attributed to the buffering qualities of **PBD2**, which does not release at a pH below 5.5 (Fig S4, ESI†).

Many chemical reactions are governed by the pH of the medium, and thus we were interested to employ our **PBD2**/**PAD3** pair to control the pH-dependent chemical equilibrium in a chemical system in solution. Specifically, we selected bromocresol purple (**BCP**) as the equilibrium between its singly ($\mathbf{BCP}^-$) and its doubly deprotonated form ($\mathbf{BCP}^{2-}$) is sensitive to pH and an optical read-out is feasible (Scheme 2).[24]

Addition of **BCP** (final concentration 13 μM) to a solution of **PBD2** and **PAD3** (0.56 and 0.91 mM resp.) irradiated with 310 nm light for 1–3 min shows an increase of $\mathbf{BCP}^{2-}$, as

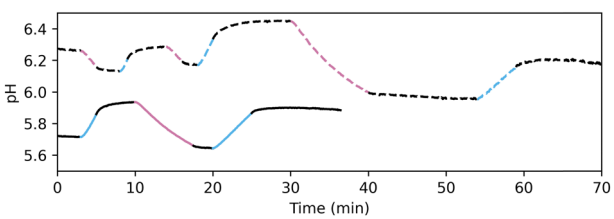
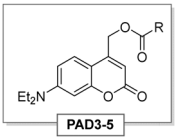


Fig. 5 A solution of **PBD2** (0.40 mM) and **PAD3** (0.63 mM) in 50% methanol in water was alternatingly irradiated with 450 nm (pink) and 310 nm (blue) light. A black line indicates no irradiation. The initial pH (6.05) was adjusted by the addition of small amounts of acetic acid and triethylamine.

Table 1 Structure and pK_a of released acid of **PAD3–5**



	R	pK_a of RCO_2H
PAD3	CH_3	4.76
PAD4	CF_3	0.23
PAD5	*o*-ClC_6H_4	2.94

determined spectroscopically (Fig. 6a). Similarly, the amount of $\mathbf{BCP}^{2-}$ drops linearly by up to 30% upon irradiation with 1–3 min of 445 nm light (Fig. 6b). Furthermore, Fig. 6 clearly shows the dose-dependency of the pH change.

Taken together, we could show the reversible up- and downregulation of pH using two individual chromophores and could use the global change in pH to affect the equilibrium of a chemical reacting in the same solution. A current limitation of this proof-of-principle system is, on the one hand, the necessity of UV-light to address **PBD2**. On the other hand, both photocages were not yet optimised towards full aqueous solubility. This will be the natural next step and could be achieved by, for instance, employing water-soluble chromophores previously described by the Southan and Tovar group.[25]

Despite these challenges, we demonstrated for the first time the chromoselective dynamic regulation of pH in the same solution. Transforming **PAD**/**PBD** into an all-visible-light-responsive, water-soluble system could enable its application in biochemical enzymatic reactions in the future.

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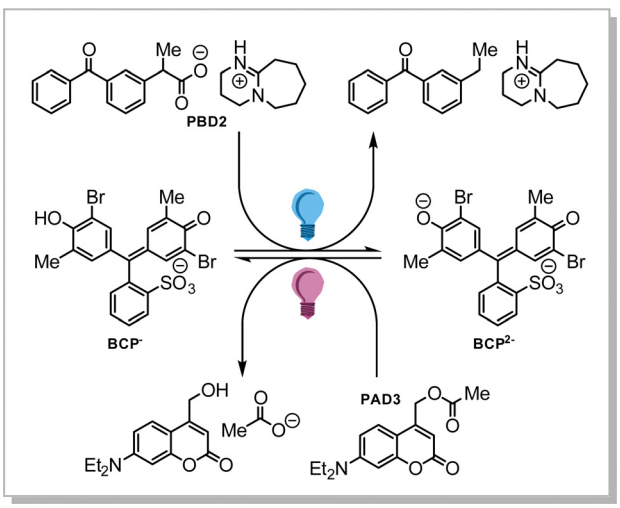

Scheme 2 Change in protonation state of bromocresol purple (**BCP**) from $\mathbf{BCP}^-$ to $\mathbf{BCP}^{2-}$.

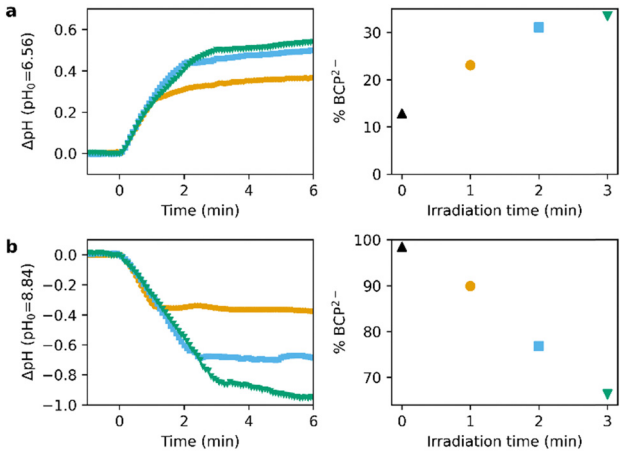

Fig. 6 (a) A solution of **PBD2** (0.49 mM) and **PAD3** (0.59 mM) in 50% methanol in water was irradiated with 310 nm light for 1–3 min. Initial pH (5.65) was adjusted by addition of small amounts of acetic acid and triethylamine to 6.56. **BCP** was added after irradiation (final concentration 0.013 mM). (b) A solution of **PBD2** (0.56 mM) and **PAD3** (0.91 mM) in 50% methanol in water was irradiated with 445 nm light for 1–3 min. Initial pH (5.65) was adjusted by addition of small amounts of acetic acid and triethylamine to 8.84. **BCP** was added after irradiation (final concentration 0.013 mM).

Data availability

Experimental details and compound characterisation data can be found in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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