



Efficient Light-Induced pK_a Modulation Coupled to Base-Catalyzed Photochromism

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Abstract: Photoswitchable acid–base pairs, whose pK_a values can be reversibly altered, are attractive molecular tools to control chemical and biological processes with light. A significant, light-induced pK_a change of three units in aqueous medium has been realized for two thermally stable states, which can be interconverted using UV and green light. The light-induced pK_a modulation is based on incorporating a 3-*H*-thiazol-2-one moiety into the framework of a diarylethene photoswitch, which loses the heteroaromatic stabilization of the negatively charged conjugate base upon photochemical ring closure, and hence becomes significantly less acidic. In addition, the efficiency of the photoreactions is drastically increased in the deprotonated state, giving rise to catalytically enhanced photochromism. It appears that protonation has a significant influence on the shape of the ground- and excited-state potential energy surfaces, as indicated by quantum-chemical calculations.

Coupling orthogonal thermal and photochemical equilibria allows for light-gated ground-state reactivity as well as chemically gated photochromism, which can be combined in multistate reaction cycles to construct functional molecular systems that are controlled and driven by light.^[1] We have targeted the remote modulation of acid–base equilibria as one of the most fundamental chemical reactions highly relevant for the materials and life sciences. Beyond changing chemical reactivity and related catalytic activity,^[2] reversible control over the pK_a value of a compound should have profound influence on key properties, such as solubility, intermolecular interactions,^[3] as well as bioavailability,^[4] that are critical for

drug design. To induce a sufficient light-induced acidity change, defined here by interconverting 95 % of a protonated species (acid) into 95 % of a deprotonated species (conjugate base), would require a (reversible) pK_a modulation of at least 2.5 units.^[5] A variety of reversible^[6] photoacids have been developed over the past 50 years, in particular by exploiting the acidity difference between ground and excited states to realize large pK_a shifts, which, however, were associated with very short lifetimes only.^[7] Much longer lifetimes have been achieved by photoisomerization between two metastable ground-state species.^[8] For this purpose, various spiro-pyran,^[8a–d] azobenzene,^[8e–i] and diarylethene (DAE)^[8j–m] derivatives have been investigated (Figure 1a), but these either exhibited thermal instability^[8a–i,9] or insufficient pK_a modulation.^[8j–m] Hence, the development of photoswitchable acids that can efficiently be interconverted between thermally stable states with sufficiently large acidity modulation ($\Delta pK_a \geq 2.5$) remains an important objective in this field.

We focused here on the use of DAE photoswitches in analogy to work by Lehn and co-workers, who pioneered their use to modulate acid–base properties.^[8j] In contrast to other classes of photochromic molecules, optimized DAE derivatives display efficient, (nearly) quantitative, and robust

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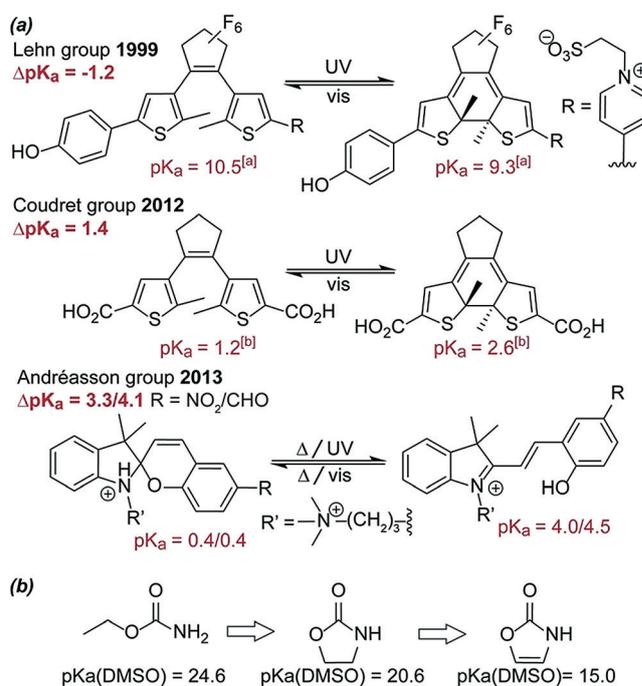


Figure 1. a) Selected pK_a photoswitches in water or [a] in methanol/water (5:2) or [b] in acetonitrile. b) The pK_a –structure relationship of linear and cyclic carbamates.

photoconversion in both photoisomerization directions.^[10] In view of this advantageous photochemical behavior and the absence of thermal interconversion (P-type photochromism),^[11] for DAEs, the system can be precisely adjusted between two distinct and temporally independent forms. This property has been successfully used to modulate chemical reactivity,^[12] most frequently taking advantage of relocating double bonds during a light-induced 6π electrocyclic ring opening/closure.^[13] Inspired by the pK_a dependence observed for 2-oxazolidinones and oxazolones (Figure 1b),^[14] we herein explore this powerful concept to control the acidity of an integrated 3*H*-thiazol-2-one moiety by photochemically removing and reinstalling an internal carbon–carbon double bond, thus tuning the aromatic stabilization of its conjugate base (Figure 2).

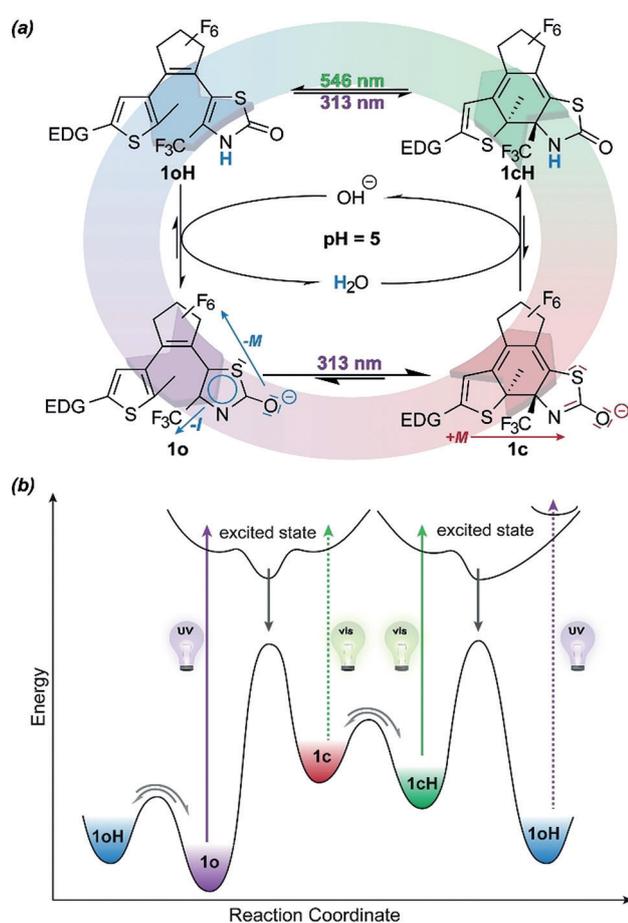


Figure 2. Light-induced pK_a modulation. a) Four-state reaction cycle involving photoisomerization (**1oH**→**1cH**, **1o**→**1c**) and thermal acid-base (**1oH**⇌**1o**, **1cH**⇌**1c**) equilibria of a thiazolone-based diarylethene (EDG = electron-donating group, here: 4-methoxyphenyl) at pH 5. Deprotonation of the open isomer **1oH** leads to aromatic and thus stable negatively charged **1o**, which undergoes ring closure upon UV irradiation with a high quantum yield. The negative charge in the closed form **1c** is isolated, leading to protonation and thus formation of **1cH**, which undergoes cycloreversion to **1oH** upon irradiation with visible light to close the catalytic cycle. Inductive (I) and mesomeric (M) effects of the substituents attached are indicated with arrows visualizing their directionality. b) Schematic potential energy diagram for an ideal pK_a switch.

Target molecule **1oH** (Figure 2a; see the Supporting Information for its synthesis) is composed of a 4-(4'-methoxyphenyl)-2-methylthien-3-yl residue connected to the commonly used hexafluorocyclopentene bridge,^[15] which also carries a 4-trifluoromethyl-3*H*-thiazol-2-on-5-yl substituent serving as the acidic site. Deprotonation leads to negatively charged **1o**, which is primarily stabilized because of its aromatic character. The strongly electron-accepting hexafluorocyclopentene bridge^[16] and the adjacent trifluoromethyl group also help stabilize anion **1o**. This is supported by the fact that the HOMO of **1o** is located on the thiazole moiety whereas it is centered on the thiophene ring in **1oH** (see Figure S16 in the Supporting Information). Upon UV-light-induced ring closure and the resulting double bond migration, the acidity and hence the stability of **1c** should be significantly lower than that of **1o** for several reasons: 1) loss of aromatic stabilization, 2) cross-conjugation with the electron-withdrawing bridge, and 3) decoupling from the inductively electron-withdrawing effect (“-I effect”) of the trifluoromethyl group (Figure 2a). In addition, the electron-donating methoxy group attached to the opposite terminus of the DAE becomes π -conjugated and thus further reduces the acidity of the closed isomer **1cH**. Irradiation with visible light should induce ring opening and therefore reverse these effects.

Titration of **1o** (Figure 3a) in an aqueous 0.15 M KCl solution containing 30 vol% acetonitrile with 0.7 M HCl (in the same solvent composition) gave a solvent-mixture-specific^[17] s_pK_a value of 4.0 ± 0.1 ($\Delta G_a = 5.0 \text{ kcal mol}^{-1}$) whereas titration of isomer **1c** gave a s_pK_a value of 6.8 ± 0.1 ($\Delta G_a = 8.5 \text{ kcal mol}^{-1}$). This corresponds to a pK_a shift of 2.8 units, consistent with DFT calculations that had predicted a change of 2.6 units (see Section S5 in the Supporting Information). Therefore, complete protonation and deprotonation of both isomers can be achieved by using 0.1 M HCl and KOH solutions, respectively. Both open compounds (**1oH** and **1o**) strongly absorb in the UV region up to $\lambda = 330 \text{ nm}$ (Figure 3b), which was attributed to a combination of high-lying states according to time-dependent (TD) DFT calculations.

In **1oH**, the lower-energy $S_0 \rightarrow S_1$ transition is much less intense, which is a consequence of the small overlap between the HOMO and the LUMO, whereas it has significant intensity in **1o** (band at $\lambda \approx 360 \text{ nm}$) as a result of the stronger overlap (see Figure S16). Irradiation with UV light (313 nm) leads to an intense absorption band at $\lambda = 500 \text{ nm}$ in both cases owing to the formation of the protonated and deprotonated closed isomers (**1cH** and **1c**), which present similar orbital topologies. Irradiation with green light ($\lambda = 546 \text{ nm}$) induces quantitative ring opening and thus leads to complete reversion. Spectral analysis of both cyclization and cycloreversion showed clean photoreactions for the protonated as well as the deprotonated forms (Figure S7). Photokinetic analysis of the ring closure and ring opening revealed a strong dependence of the rate and conversion of the photoreaction on the protonation state (Figure 3c).

Whereas the conversion of the protonated form **1oH** is low and the rate of the reaction is also low, the conversion and rate of deprotonated **1o** are much higher. In both cases, cycloreversion is complete (owing to selective excitation of the closed isomers), yet again the photoinduced ring opening

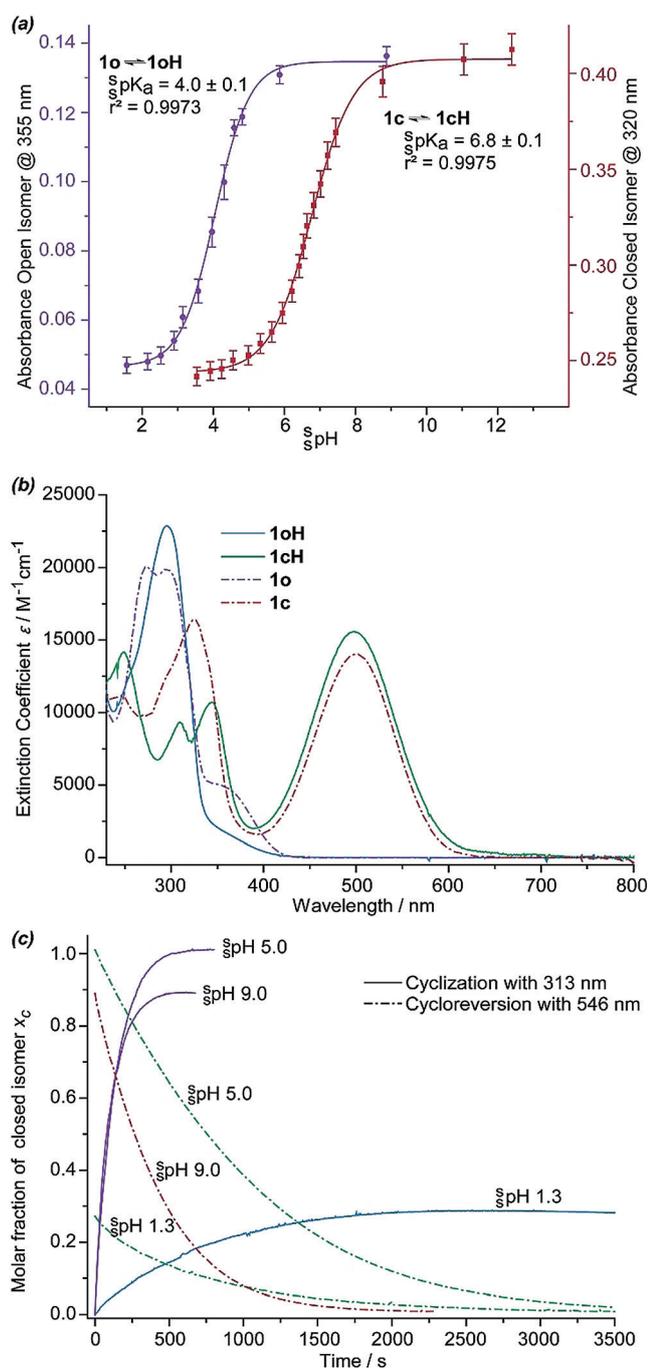


Figure 3. UV/Vis experiments with compound **1** in aqueous 0.15 M KCl solution (30 vol% MeCN). a) Titration of open and closed isomers with aqueous 0.7 M HCl solution (30 vol% MeCN). b) UV/Vis spectra of all four species. c) Photokinetic data obtained at different pH values.

is faster for deprotonated **1c** than for protonated **1cH**. Evaluation of these photokinetic data (Table 1) showed that the quantum yields for cyclization differ by more than one order of magnitude between the deprotonated and protonated forms ($\Phi_{1o \rightarrow 1c} = 47 \pm 5\%$ vs. $\Phi_{1oH \rightarrow 1cH} = 2.1 \pm 0.2\%$; Table 1). Note that the quantum yields of the ring opening depend not only on the protonation state but also on the irradiation wavelength, as reported for DAEs in the liter-

ature.^[18] The interplay of the differences in quantum yields and extinction coefficients is consequently reflected in the composition of the photostationary states (PSSs) after UV irradiation, which show much higher conversions in the deprotonated state (amount of closed isomer $\chi_c(\text{PSS}) = 85 \pm 5\%$) than in the protonated state ($\chi_c(\text{PSS}) = 35 \pm 5\%$). It is important to point out that no thermal ring opening was observed, neither in the protonated nor in the deprotonated form. At this point, we underline that according to DFT calculations, **1o** should show a strong preference for adopting the antiparallel conformation (98% estimated population), which is very favorable for DAEs as the photochemical ring closure proceeds solely from this conformation. In addition to the thermal stability, the photochemical fatigue was investigated as well; photodegradation was observed upon $\lambda = 313$ nm irradiation under strongly basic conditions whereas only marginal fatigue occurred in an acidic milieu (Figures S10). Furthermore, a rather slow thermal side reaction of the closed, deprotonated form **1c** with water was noticed.^[8j,m,19]

Our system describes a four-state reaction cycle, which allows for unidirectional operation (counterclockwise in Figure 2 a) owing to the wavelength selectivity of the photochemical ring-closure and ring-opening steps and the thus altered acid–base equilibrium. If the pH is adjusted to a value in between the two different pK_a values of the open and closed isomers, a catalytic cooperative interconnection can be achieved in which the efficiency of the photoisomerization is significantly enhanced by coupling it to the thermal acid–base equilibrium. Indeed, irradiation of the solution with UV light ($\lambda = 313$ nm) at pH 5 leads to complete conversion and a reaction rate comparable with that for the ring closure of the deprotonated form, that is, **1o** \rightarrow **1c** (see Figure 3 c as well as the PSS compositions and effective quantum yields given at the bottom of Table 1). At pH 5, cycloreversion occurs with the rate of reaction of the protonated species, **1cH** \rightarrow **1oH**, as confirmed by calculations of the corresponding effective quantum yield (see Table 1). Thus our four-state system can be described in terms of a catalytic cycle where the photoisomerization of compound **1** (at 10^{-5} M concentration) is catalyzed by the presence of base, that is, small amounts of hydroxide (ca. 10^{-9} M), in aqueous medium at pH 5 in this case.

To obtain an in-depth understanding of the energetics of this process (Figure 4), calculations to map critical points on the ground- and excited-state energy surfaces in acetonitrile solution were carried out (note that the photochromism shows the same trends in pure acetonitrile as in acetonitrile containing 30 vol% water, investigated above; see Figure S6). In agreement with a thermally forbidden conrotatory ring opening/closure, the computational results indicate that the conversion between the closed and open isomers is prevented in the ground state by large barriers for the neutral molecules ($\Delta G^\ddagger = 52.5$ kcal mol $^{-1}$ for **1cH** \rightarrow **1oH**) as well as the deprotonated switch ($\Delta G^\ddagger = 51.1$ kcal mol $^{-1}$ for **1c** \rightarrow **1o**). In both cases, the open isomer is thermodynamically more stable, in the neutral form by $\Delta G_r = -7.6$ kcal mol $^{-1}$ (**1cH** \rightleftharpoons **1oH**) and in the deprotonated form by $\Delta G_r = -4.0$ kcal mol $^{-1}$ (**1c** \rightleftharpoons **1o**). Both protonated forms (**1oH** and **1cH**) as well as the closed,

Table 1: Spectroscopy and photochemistry in dependence of the pH value in aqueous 0.15 M KCl solution (30 vol% MeCN).

	s_pK_a	λ_{max} [nm] (ϵ_{max} [$M^{-1} cm^{-1}$])	$\epsilon_{313 nm}$ [$M^{-1} cm^{-1}$] ($\epsilon_{546 nm}$ [$M^{-1} cm^{-1}$])	$\Phi_{313 nm}$ [%] ($\Phi_{546 nm}$ [%])	$\chi_c^{PSS[c]}$ [%] (λ_{irrad} [nm])
1oH	1.3	295 (22900 ± 460)	16900 ± 340 (8600 ± 430)	2.1 ± 0.2 (3.6 ± 0.4)	35 ± 5 (313 ± 6 ^[a])
1cH	1.3	497 (15600 ± 780)	9000 ± 450 (8600 ± 430)	8.3 ± 1 (3.6 ± 0.4)	3 ± 5 (546 ± 6 ^[a])
1o	9.0	295 (19900 ± 400)	15600 ± 310 (7500 ± 380)	47 ± 5 (9.6 ± 1)	85 ± 5 (313 ± 6)
1c	9.0	500 (14000 ± 700)	15200 ± 760 (7500 ± 380)	5.2 ± 0.5 (9.6 ± 1)	0 ± 5 (546 ± 6 ^[a])
	5.0			34 ± 3 ^[b]	100 ± 5 (313 ± 6 ^[a])
	5.0			(4.0 ± 0.4) ^[b]	0 ± 5 (546 ± 6 ^[a])

[a] Monochromator bandwidth. [b] Effective quantum yields. [c] Molar fraction of **1cH**, **1c**, or their mixture.

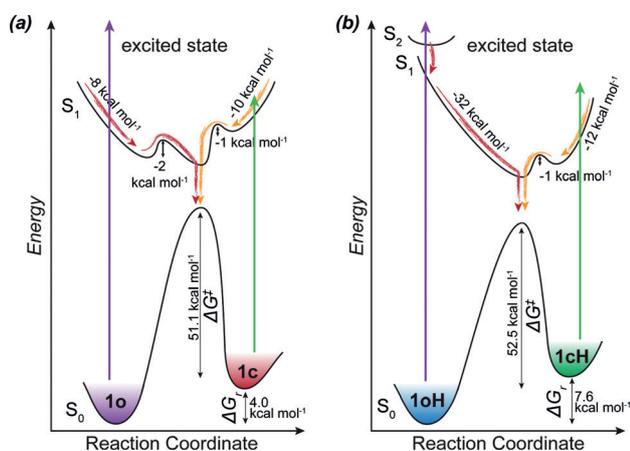


Figure 4. Qualitative potential energy diagrams of a model compound. a) The deprotonated isomers **1o** and **1c** with $\Delta G^\ddagger = 51.1 \text{ kcal mol}^{-1}$ and $\Delta G_r = 4.0 \text{ kcal mol}^{-1}$. b) The protonated isomers **1oH** and **1cH** with $\Delta G^\ddagger = 52.5 \text{ kcal mol}^{-1}$ and $\Delta G_r = 7.6 \text{ kcal mol}^{-1}$.

deprotonated form (**1c**) exhibit excited-state energy diagrams (see Sections S5) similar to those of already characterized DAEs.^[20] The irradiation of **1oH** results in excitation to the S_2 state. Direct excitation to S_1 is less likely owing to its very low oscillator strength (TD-DFT: $f = 0.02$), and thus it is mostly populated indirectly by internal conversion. The S_1 state relaxes in a barrier-free fashion towards a conical intersection. In agreement with previous reports on DAEs,^[11a,18a,21] small barriers were found along the cycloreversion path in the excited state for both acidic as well as basic milieus. In contrast, the calculations suggest that the excited-state energy surface for photocyclization of the deprotonated form (**1o** → **1c**) differs from those of other DAEs as an additional local minimum was found between the Franck–Condon point and the conical intersection, separated by a small barrier. This might seem counterintuitive considering the observed quantum yield, but the reaction dynamics of DAEs are known to be complex, and a local minimum might indeed be able to

“focus” the reaction as a smaller portion of the potential energy surface is explored. Excitation of **1o** results in direct population of its S_1 state, which exhibits a much higher oscillator strength than that of **1oH**.

The herein presented four-state system (Figure 2a) enabled us to realize two important and interwoven functions: On the one hand, we were able to establish a light-induced pK_a modulation of $\Delta_s pK_a = 2.8 \pm 0.2$ units between two thermally stable isomers. On the other hand, we described the base-catalyzed photochemical ring closure of DAE **1**, thereby expanding the area of pH-gated photochromism^[81,22] towards acid/base catalysis. Our design is based on the coupling of multiple thermal

and photochemical equilibria,^[1] which, in the present cyclic system, allows for the light-driven and wavelength-selective modulation of acidity as well as a catalytic enhancement of photoisomerization by the resulting charge state at the operating pH value. Based on our experimental and computational data, it appears that deprotonation indeed seems to affect the excited-state energy surface and thus the dynamics of the system. Currently, we are trying to decipher the underlying reasons for the accelerated photocyclization of the deprotonated species (**1o**). Future work will be devoted to further maximizing the extent of light-induced pK_a modulation and to shift the operating pH value to physiological conditions to be able to harness these systems for the control of biological processes. Furthermore, the use of **1o** as a photoactive buffer to modulate the pH value of an aqueous solution will be investigated.

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Conflict of interest

The authors declare no conflict of interest.

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