2,3-Diarylmaleate salts as a versatile class of diarylethenes with a full spectrum of photoactivity in water

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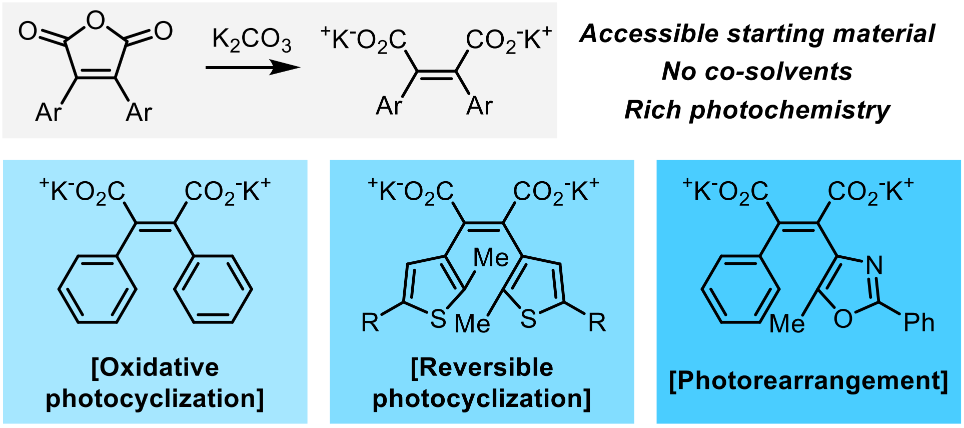


Accessible starting material
No co-solvents
Rich photochemistry

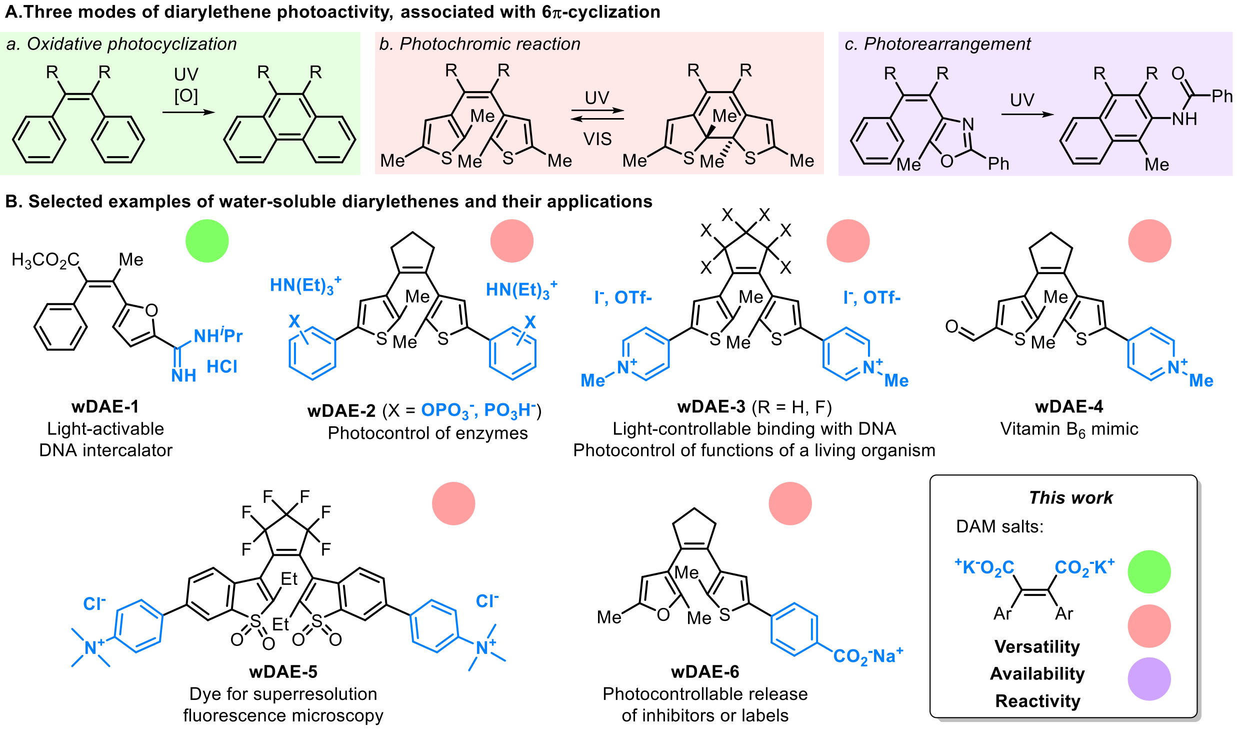
Pushing the diarylethene photochemistry to water!

Abstract

There is an incessant interest in transfer of common chemical processes from organic solvents to water, which is vital for the development of bioinspired and green chemical technologies. Diarylethenes feature a rich photochemistry, including both irreversible and reversible reactions that are in demand in organic synthesis, materials chemistry, and photopharmacology. Herein, we introduce the first versatile class of diarylethenes, namely, potassium 2,3-diarylmaleates (DAMs), that show excellent solubility in water. DAMs obtained from highly available precursors feature a full spectrum of photoactivity in water and undergo irreversible reactions (oxidative cyclization to phenanthrenes or rearrangement) or reversible photocyclization (switching), depending on their structure. This finding paves a way towards wider application of DAEs in photopharmacology and bioinspired technologies that require aqueous media for photochemical reactions.

Light is a unique energy source for chemical reactions providing the opportunity to induce them in a selected volume within the selected period of time.[1–4] Varying the properties of a molecule by its reversible or irreversible chemical transformation is of great interest for the development of new methods and technologies in materials chemistry, biology and medicine.[5,6] Solubility of photoactive organic molecules in water is a crucial requirement in many bio-related applications.[7,8] For example, the bioimaging beyond the diffraction limit with high-resolution fluorescence microscopy became possible in aqueous solutions using appropriate photoswitchable dyes as labels.[9–13] Among photoactive molecules, diarylethenes (DAEs) became one of the most powerful molecular tools for photochemical applications. There are three modes of DAE's chemical activity associated with light-induced cyclization (Scheme 1A): reversible switching between initial and closed-ring isomers,[14] irreversible oxidative cyclization towards tricyclic aromatics (Mallory reaction);[15] irreversible photorearrangement to bicyclic aromatics.[16] The classical Mallory reaction is used mainly for building polyaromatic compounds that contain a fragment of phenanthrene or its analogues (Scheme 1Aa).[17–21] The photoswitching of DAEs finds application in the development of stimuli-responsive materials and light-controllable processes (Scheme 1Ab).[22–27] The photorearrangement with formation of bicyclic aromatics is a recently discovered transformation (Scheme 1Ac) that is promising for various applications, including organic synthesis,[28–30] photopharmacology[31] and click-chemistry.[32]

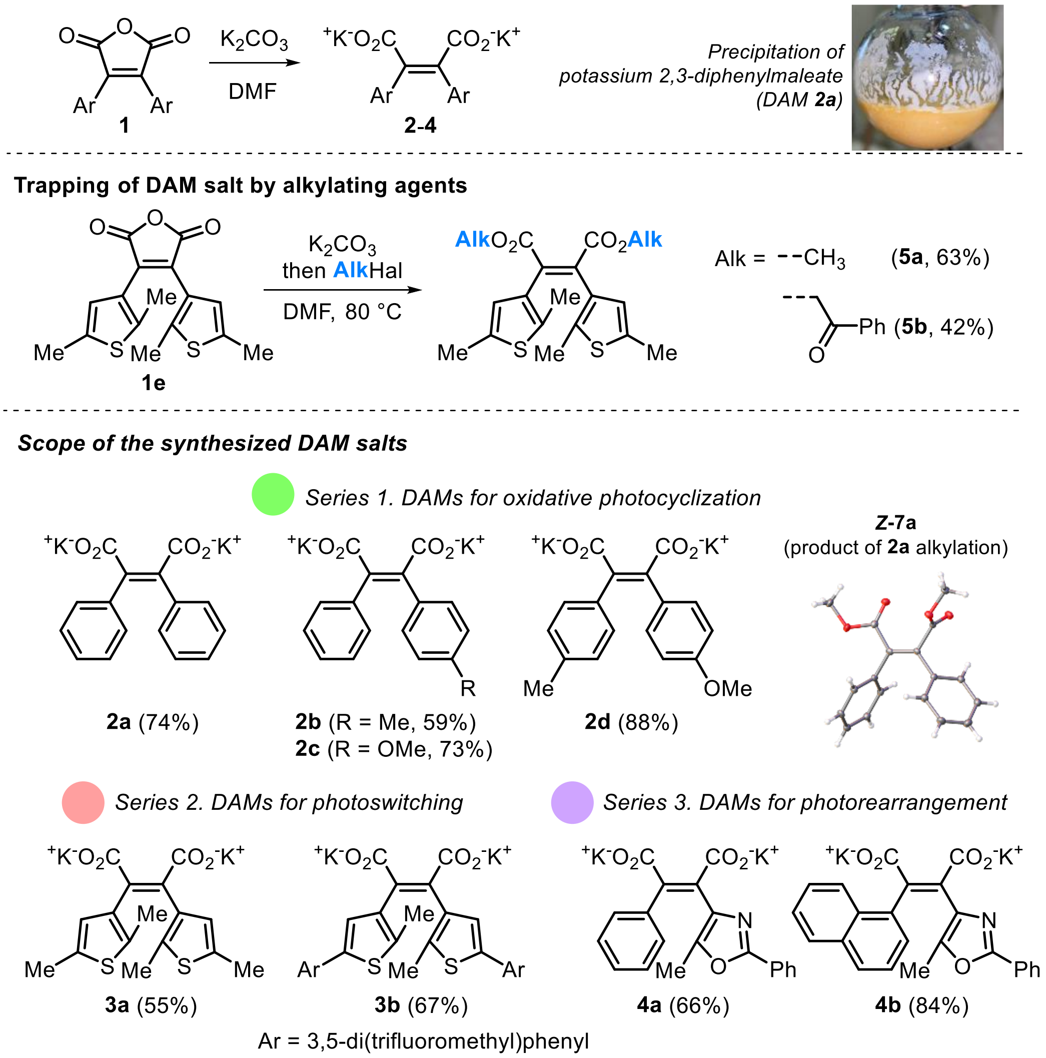
Scheme 1. Water-soluble DAEs for various photopharmacological and biomedical applications.



Water-soluble DAEs bearing solubilizing charged groups are in demand for various photopharmacological and biomedical applications (Scheme 1B). The only example of the Mallory reaction in aqueous solutions was reported for light-induced generation of a DNA/RNA intercalator by **wDAE-1** with a protonated amidine substituent.[33] Reversible switching was successfully performed for DAEs that comprised, among others,[7] phosphate and phosphonate (**wDAE-2**[34]), pyridinium (**wDAE-3**,[35,36] **wDAE-4**[37]), ammonium (**wDAE-5**[38]) and carboxylate groups (**wDAE-6**[39]). The corresponding dyes were successfully applied as photocontrollable enzyme inhibitors, DNA ligands, dyes for bioimaging, and agents for the control of physiological functions of living organisms. It should be noted that all examples of water-soluble DAEs contain charged groups in the pendant aromatic rings. This approach is not universal and requires a significant change in the synthesis strategy depending on the desired structure. Incorporation of a solubilizing group on the central part of the molecule is an alternative way that has never been tested for the synthesis of water-soluble DAEs. It can be expected that this method should allow the incorporation of any type of aromatic moieties "by choice" and pave a way towards the modular construction of water-soluble molecules with desired properties and functions. Herein, we introduce a first general class of water-soluble photoactive molecules - 2,3-DiArylMaleate (DAM) salts (Scheme 1B). In the structure of DAMs, two solubilizing carboxylate groups are directly attached to the central double bond and could be combined with various aromatic moieties while retaining the entire spectrum of DAE photoactivity in water.

To date, DAM salts have never been considered as an individual class of organic molecules, although these entities were often involved as intermediates in the synthesis/cleavage of 3,4-di(het)arylfuran-2,5-diones **1** or related maleimides (Scheme 2).[40,41] Straightforward hydrolysis of **1** in aqueous alkali is not suitable for DAM isolation due to extreme solubility of the latter. We assumed that this problem could be overcome by cleavage of 3,4-di(het)arylfuran-2,5-diones **1** in dry DMF with potassium carbonate (K_2CO_3). We attempted trapping DAMs by *in situ* alkylation in the reaction starting from **1e** (Scheme 2). Indeed, the corresponding dithienylmaleic acid esters **5a** and **5b** were isolated in 42-63% yields. To synthesize a range of multipurpose DAMs, we used a series of 3,4-di(het)arylfuran-2,5-diones **1** bearing two benzene rings (towards Mallory substrates), two thienyl rings (for photoswitchable products) and both phenyl/naphthyl and oxazolyl rings (towards photorearrangement substrates). As expected, treatment of these compounds with K_2CO_3 in dry DMF with heating results in the disappearance of the starting material. To ensure complete consumption of K_2CO_3, a slight excess of **1** was exploited (for details see Section III.1 in SI). In all cases, the reaction was accompanied by abundant precipitation of DAM salts, which were isolated by filtration. The desired salts **2-4** were isolated in 55-88% yields as stable solids and were fully characterized by ^{1}H and ^{13}C NMR spectroscopy in deuterated water. DAM **3b** bearing two lipophilic 3,5-di(trifluoromethyl)phenyl moieties was an exception. This compound was readily soluble in 1:1 water/acetonitrile mixture. The *Z*-configuration of the DAM salts was predetermined by the structure of the substrates **1** and were additionally confirmed by NOESY NMR for **4a** (Figure S13) and by X-ray crystallography data for stilbene ***Z*-7a** obtained by direct alkylation of DAM **2a**. The thermodynamic stability of *Z*-stilbenes is determined by the high activation energy barrier of *Z*- to *E*-isomerization.[42,43]

Scheme 2. Synthesis of the DAMs.



It was expected that the series of DAMs **2a-d** as close analogues of stilbene should undergo oxidative cyclization to phenanthrene derivatives (Scheme 1Aa).[15,44] Irradiation of **2a** in D_2O by UV (λ = 365 nm) led to new products according to NMR spectroscopy (Figure 1c). Complete disappearance of the substrate **2a** was reached after 240 h of the reaction. The major product in the reaction mixture was identified as phenanthrene derivative **6a** with characteristic doublets of $H^{1(8)}$ and $H^{4(5)}$ at 8.05 and 8.85 ppm (Figure 1a). Two minor photoproducts with NMR signals in the 7.20-7.40 ppm range were also detected in the reaction mixture. The preparative photoreaction of **2a** in water led to a mixture with the same composition. To isolate and characterize the products, we "transferred" the products from the aqueous phase to the organic one by trapping potassium salts with methyl iodide and separation by column chromatography (Figure

1a). Two products where obtained: the expected phenanthrene **8a** (57% yield) and methyl diphenylmaleate **7a** in the *E*-configuration. The similar reaction outcome was obtained for DAM salts **2b-d** (yields 55-66% for phenanthrenes **8b-d**; Figures S4-S6). The structures of DAM **4b** photoproducts ***E*-7b** and **8b** were supported by X-ray crystallography.

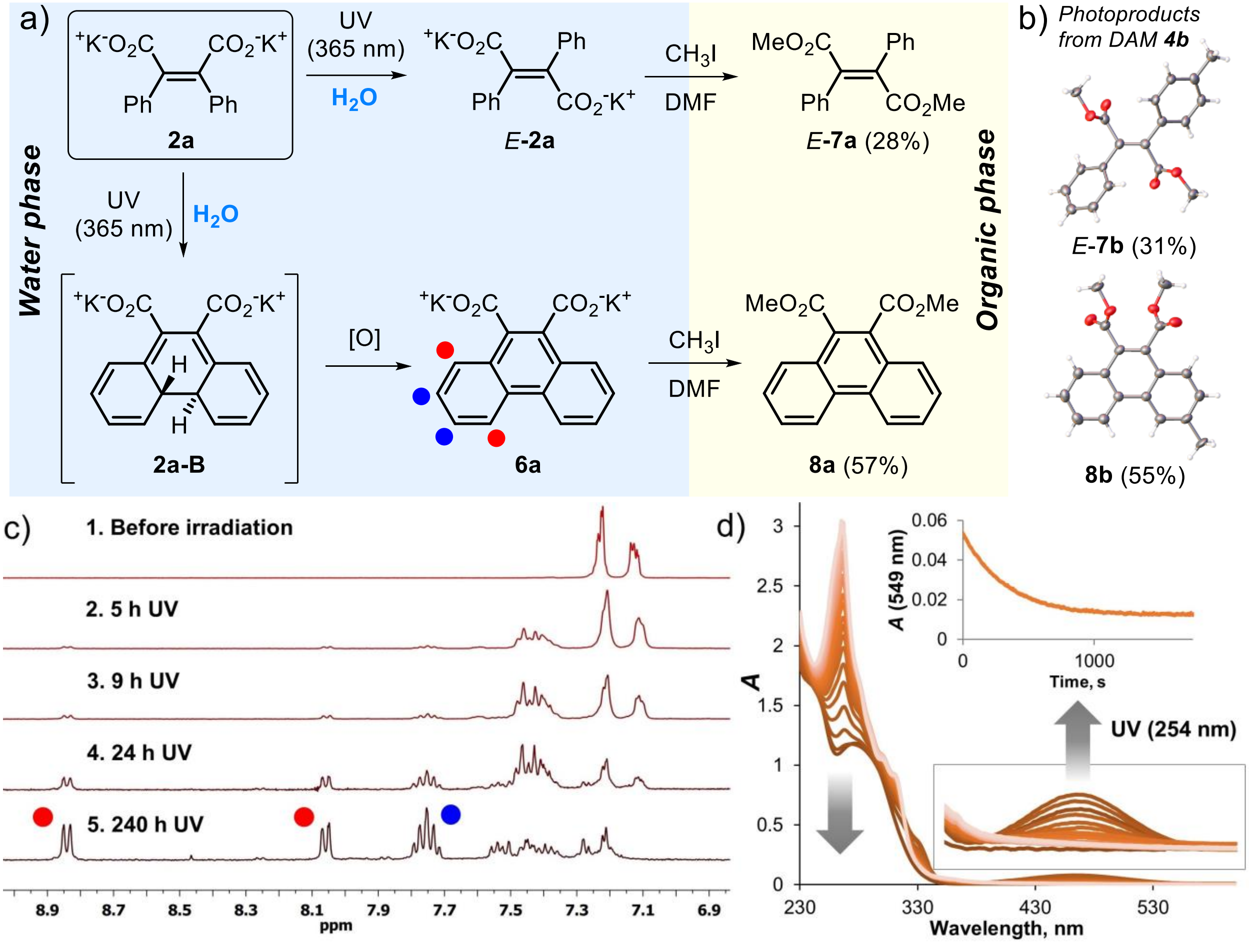


Figure 1. Photochemical reactions of DAM **2a** in water (a). Molecular structures of trapped photoproducts of DAM **2b** obtained by X-ray crystallography (b). ^{1}H NMR spectra under irradiation of **2a** with UV (365 nm) in D_2O (c). UV-Vis spectra under irradiation with UV (254 nm) in H_2O (buffer pH = 7.00) (d) and thermal decay of colored intermediate **2a-B** (inset).

The main products of DAM salts photolysis were found to be typical Mallory products, phenanthrenes **6**, formed by 6π-photocyclization followed by oxidation by oxygen species.[45] The side process is *quasi*-irreversible *Z*-/*E*-isomerization, probably due to a low quantum yield. Photolysis of **2a** in the buffer solution (pH = 7.00) allowed us to detect the elusive 4*a*,4*b*-dihydrophenanthrene intermediate of the Mallory reaction,[45,46] a closed-ring isomer **2a-B**. These species are usually highly unstable and could be isolated in specific cases only.[46,47] This entity has absorbance maxima at 459 nm due to a conjugated system of π-bonds (Figure 1d). Simulation of the spectrum by DFT calculations gave the value of 490 nm for this species (Table S2). The intermediate **2a-B** was thermally unstable and underwent fast bleaching in the dark. Apparently, the slight electron donating effect of carboxylate anions contributes to the stabilization of dearomatized 4*a*,4*b*-dihydrophenanthrene core.

The next probed photochemical reaction was the reversible switching of thiophene-derived DAMs **3a,b** between initial and closed-ring isomers (Scheme 1Ab).[14] Irradiation of **3a** with UV (254 nm) for 4.5 h resulted in the formation of the closed-ring isomer **3a-B** (Figure 2a) with an absorbance maximum at 450 nm (Figure S20) with conversion ≈ 40%, that was clearly observed by the shift of thiophene protons in the NMR spectra (Figure 2b). Subsequent irradiation with blue light resulted in the restoration of the initial spectrum. However, prolonged irradiation with UV to reach higher conversion results in two new products (Figure 2b, Figure S7). Their structures were proved to be as follows: a product of formal 1,2-dyotropic rearrangement **9**[48] and the *E*-isomer of **3a** (see Section III.4). Their structures were proved again by transferring the preparative reaction mixture to the organic phase followed by isolation of products **10** and ***E*-5a**. After 23 h of preparative photolysis the yields were 58% and 24%, respectively.

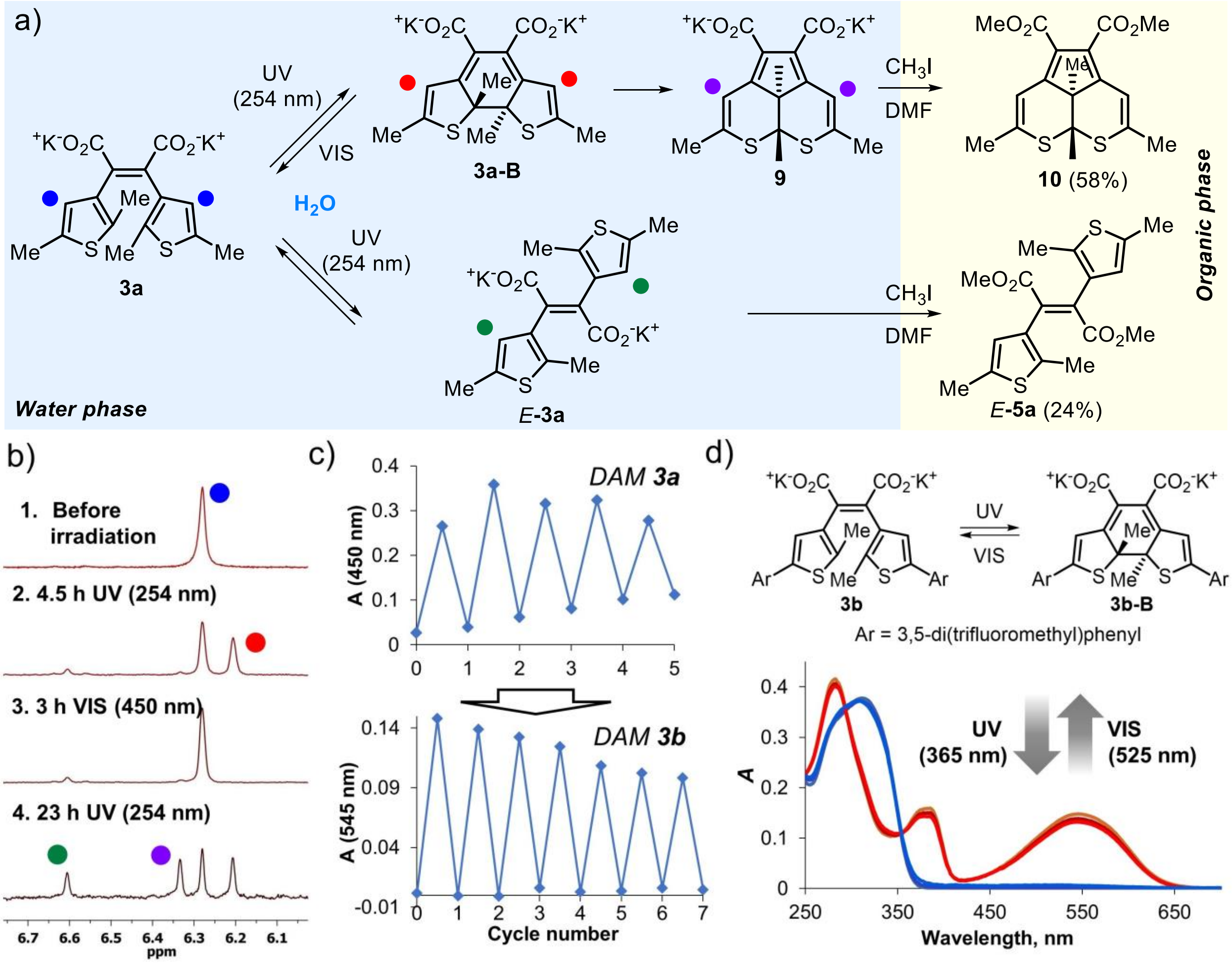


Figure 2. Photochemical reactions of DAM **3a** in water (a). ^{1}H NMR spectroscopy under irradiation with UV (254 nm) in D_2O (b). Multiple photoswitching of DAMs **3a** and **3b** in H_2O (buffer pH = 7.00) (c). Photoswitching of DAM **3b** and changes in UV-Vis spectra during three cycles of cyclization-cycloreversion in MeCN / H_2O 1:1 (d).

Similarly to the diphenyl-substituted DAMs **2a-d**, dithienylethene derivative **3a** undergoes *Z*-/*E*-isomerization as well as irreversible phototransformation. For application as a photoswitch, these side reactions are highly undesirable. To bypass the 1,2-dyotropic rearrangement, we introduced additional 3,5-di(trifluoromethyl)phenyl groups[49] to the thiophene rings in DAM **3b**. This resulted in reduced solubility in water, and the photoreactions of **3b** were performed in water/acetonitrile solutions (1:1). As expected, **3b** displayed an enhanced photoswitching, as was demonstrated by multiple cycles of cyclization/cycloreversion (Figures 1c, S23). The suppress of *Z*-/*E*-isomerization was observed by NMR spectroscopy (Figure S10). In the UV-Vis spectra, **3b** revealed the formation of a prominent band of the closed-ring isomer **3b-B** at 545 nm under UV, which completely disappeared upon green light irradiation (Figure 1d). Thus, the proper structural design allowed us to obtain the photoswitchable DAM salt with good photostability.

Finally, we studied the DAMs **4a,b** as analogues of DAEs that undergo irreversible photorearrangement with formal cycloreversion of the oxazole ring (Scheme 1Ac).[16,28] ^{1}H NMR monitoring of **4a** disclosed an almost quantitative conversion to a new product with characteristic doublets at 7.95 and 8.05 ppm, showing the formation of the naphthalene system of **11a** (Figure 3). The side *Z*-/*E*-isomerization was negligible, unlike DAMs **2a-d** and **3a** and similarly to **3b**. UV-Vis spectroscopy also disclosed the nearly-quantitative conversion to a sole product accompanied with the isosbestic point at 260 nm (Figure 3c). Preparative photolysis of **4a** with subsequent alkylation afforded naphthalene derivative **12a** with 88% yield. The related result was obtained for DAM **4b** (Figure S12), which formed the corresponding phenanthrene in the irreversible photorearrangement with good yield (alkylated product **12b** was isolated with 69% yield).

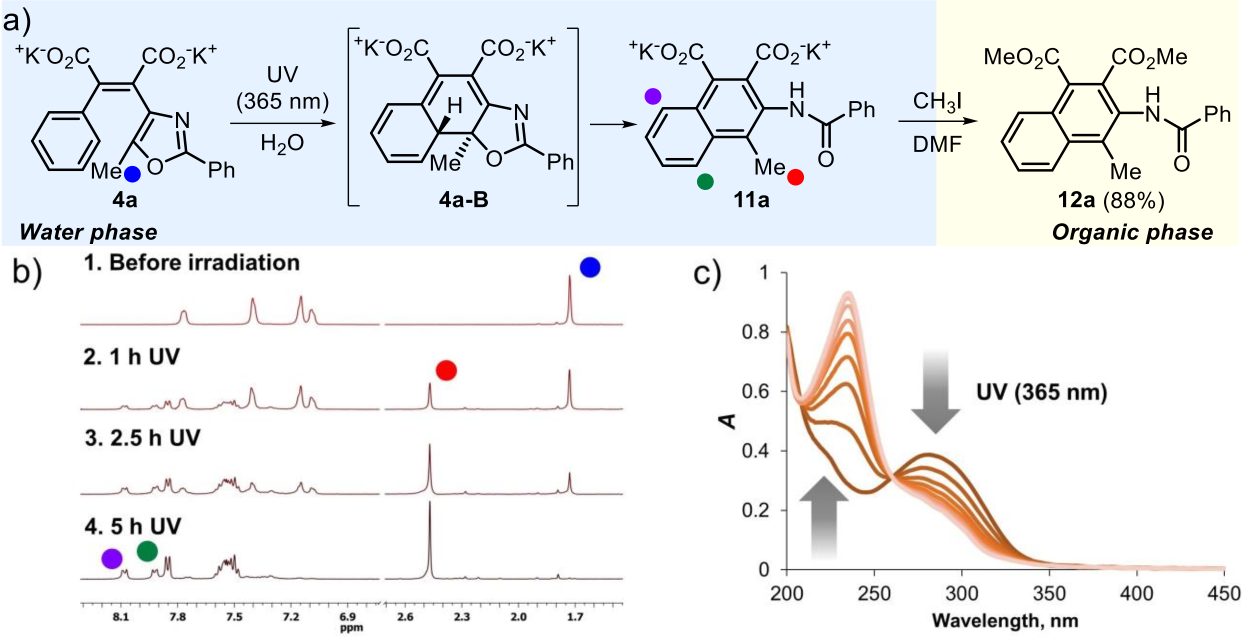


Figure 3. Photochemical rearrangement of DAM **4a** in water (a). ^{1}H NMR spectra under irradiation with UV (365 nm) in D_2O (b). UV-Vis spectra under irradiation with UV (365 nm) in H_2O (c).

In conclusion, we introduce the first versatile class of water-soluble diarylethenes, namely, potassium 2,3-diarylmaleates (DAMs). A technologically simple method for their synthesis from accessible substrates was suggested. Three types of efficient photochemical reactions of DAM salts were demonstrated: the Mallory reaction, photoswitching, and photorearrangement. Due to availability and versatility, DAMs could be considered as promising photoactive agents for the development of new bioinspired and photopharmacological applications that require solubility in water.

Acknowledgments

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