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# A photochromic prototype based on difurylperhydrocyclopentene with remarkable photoswitching behaviors and in vivo application

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**A new strategy has been developed to synthesize difurylperhydrocyclopentene derivatives. The compound displays reversible photochromism in solution and thin-film. Results show that furan is superior to thiophene in terms of the strong fluorescence, higher photocyclization conversion and cyclization quantum yield as well as better fatigue resistance. Owing to the molecule derived absolutely from C, H, and O atoms, the compound exhibits no cytotoxicity, which enables it to potentially serve as the biodegradable and biorenewable materials in vivo application.**

As the reversible switchings, photochromic materials have and continue to receive widespread interest in variety of fields such as information storage, probes, logic gates, self-assemblies as well as biological materials due to their reversible photoisomerizations between pairs of bistable isomers.[1] Among various types of photochromic materials, diarylethene derivatives (DAEs), in particular, substituted bis(hetaryl) cycloalkenes, are considered as one of the most promising families due to their remarkable thermal stability, excellent structural extensibility, and rapid light response, etc.[2] These outstanding characteristics enable the fluorescent photoswitching based on DAEs that are important for biological imaging applications, because fluorescent DAEs afford an alternative signal output between bright and dark states.[3] To date, many rational strategies for the design of DAEs have been employed. However, the aryl cores which are necessary for the versatility of the DAE architectures have been mostly limited to the thiophene unit or its heterocyclic analogues, including benzothiophene, thiazole, pyrrole, etc.[4]

As an analogue of thiophene, furan and its derivatives are silent in DAEs for years without attracting much attention. To our knowledge, only a few of furan-based DAEs, of which the central ethene bridges were chemically tailored by butene, quinone, cyclobutene and perfluorocyclopentene, have been presented, suggesting very similar switching properties between bisfurylethenes and dithienylethenes.[5] Recent studies have shown that the furan building blocks are excellent candidates for replacing thiophene in optoelectronic materials.[6] Replacing the thiophene unit with furan moiety, in which oxygen substitutes the sulfur heteroatom, can improve the fluorescence, solubility in organic solvents, and rigidity of the materials.[7] More importantly, furan-based materials can be prepared from biorenewable sources, and are regarded as biodegradable material.[7a,8]

These results encouraged us to go ahead with the facile synthesis of a superior photochromic compound based on the furan unit. In this contribution, a new type of furan-based DAEs (namely **DFC** as shown in Scheme 1) that absolutely consisted of C, H and O atoms, was developed, more conducive to biodegradation and biological applications. We commercially synthesized difurylperhydrocyclopentene derivative **DFC** by virtue of classic reactions in mild conditions, and compared its photochromic and fluorescent performances with that of diarylethene derivative having thiophene rings (**DTC**) in solution and thin-film, respectively. In addition, the photochromic and fluorescent properties of **DFC** were compared with some representative 1,2-bis(furan-3-yl) hexafluorocyclopentene derivatives (namely **5**, **6** and **7** as shown in Scheme S1 in the ESI) reported in literatures.[5c,e] Furthermore, we assessed the cell imaging and the cytotoxic effect of **DFC** for the future use as the biodegradable and biorenewable materials.

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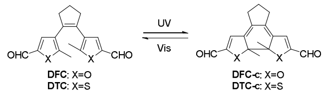

**Scheme 1.** Switching process of diheteroarylethene derivatives controlled by ultraviolet and visible light.

As known that the synthetic difficulty of furan-based DAEs is a big obstacle for their development, especially the metal-mediated cross coupling in the synthesis of furan derivatives. Therefore, we devised a new protocol to exploit the synthesis of **DFC**, which was obtained in three steps starting from commercially available 5-methylfurfural. As shown in Scheme S2, bromination at the 4-position, subsequent Miyaura boration, and coupling with 1,2-dibromocyclopentene afforded the target compound **DFC** in the total yield of 33%. This procedure has good functional group tolerance and provides the mild reaction conditions like avoiding halogen-lithium exchange with *n*-BuLi and protection-deprotection of the aldehyde. Furthermore, inspired by synthetic protocol for diarylethenes,[5e,9] a conventional workup procedure of the Suzuki coupling reaction turned to prepare **DFC** on a gram scale. The chemical structures of **DFC** and other key intermediate products were well confirmed by $^{1}$H NMR, $^{13}$C NMR, and HRMS (see the ESI for details). The diverse transformation of aldehyde groups of **DFC** provides various pathways of modification of the switching moiety and allows tuning of the photoswitching properties for different application systems.

The photochromic behaviors of **DFC** and its reference compound **DTC** were evaluated in a series of solvents with varying polarity index, including hexane, toluene, dichloromethane, acetonitrile, and dimethyl formamide. As expected, **DFC** exhibits a typical photochromic response of diarylethene derivatives under alternative illumination with ultraviolet and visible light in these trial solutions. Fig. 1A shows the absorption spectral changes of **DFC** in acetonitrile. Upon irradiation with 365 nm light, a new absorption band centered at 522 nm appeared and gradually increased, which is characteristic for the formation of the closed-ring isomer **DFC-c**, accompanied by the colorless solution turned to pink (Fig. 1A inset). Upon irradiation with visible light (≥ 520 nm), the pink solution was bleached back to colorless solution and the original absorption spectrum was recovered. **DTC** also showed reversible photoisomerization along with the color interchange between colorless and blue, as shown in Fig. 1B.

The absorption spectra of **DFC** and **DTC** in various solvents are shown in Fig. S1 and S2 (ESI), and their absorption data are summarized and listed in Table S1 and S2 (ESI), respectively, showing that the absorption maxima of **DFC-c** were shorter than that of **DTC-c** in the range of 56 nm to 66 nm varying from the solvents. As shown in Fig. S1 and S2 (ESI), remarkable solvent dependence was observed for the photochromic reaction of **DFC** and **DTC**, respectively. It is found that relatively high polar solvents (dichloromethane, acetonitrile, and dimethyl formamide) are more beneficial to the photoisomerization with the enhancement of absorption coefficient of the corresponding closed-ring isomer. These findings indicate that molecule **DFC** as well as **DTC** has relatively large dipole moment and the molecule at the π–π* excited state is more stable in polar solvents.[10] Additionally, the enhancement of absorption coefficient was observed for the closed-ring form **DFC-c** with respect to **DTC-c** in the same solvent. Under irradiation with 313 nm light, the photocyclization conversion of **DFC** was determined to be as high as 39.8% by the $^{1}$H NMR analysis (Fig. S3-S6, ESI), compared with that of 27.5% for **DTC** in acetonitrile. Quantum yields of cyclization ($\Phi_{o\rightarrow c}$) and cycloreversion ($\Phi_{c\rightarrow o}$) in acetonitrile were also calculated to be the order of 22.3% and 15.1% for **DFC**, whereas **DTC** showed value on the order of 16.6% and 20.3%, respectively (the detailed calculation method as shown in the ESI). It is found that **DFC** possesses higher photocyclization conversion and quantum yield of cyclization than that of **DTC**. In comparison with the representative 1,2-bis(furan-3-yl) hexafluorocyclopentene derivatives, we found that the absorption maximum of **DFC** is close to that of **5** (525 nm) in hexane and **7** (533 nm) in methanol. The $\Phi_{o\rightarrow c}$ value of **DFC** in acetonitrile is lower than that of the reported compounds **5**, **6** and **7**; whereas, the $\Phi_{c\rightarrow o}$ value of **DFC** is higher than that of **5** and **7**.

Addition to the primary color change, the fluorescent modulation associated with isomerization of DAEs is regarded as a promising way to achieve non-destructive readouts and security recordings as well as nanoscopic visualization.[11] It is noteworthy that **DFC** without decorating a fluorophore showed a strong cyan fluorescence (Fig. 2 inset), whereas no fluorescence was observed for **DTC** in trial solvents. Fig. 2 and Fig. S7 (ESI) display the emission spectral changes of **DFC** upon photo-irradiation with 365 nm light when excited at 326 nm. The emission peak of **DFC** was observed at 465 nm, and the intensity decreased by ca. 55% till the photostationary state (PSS) was reached under irradiation with 365 nm light. The

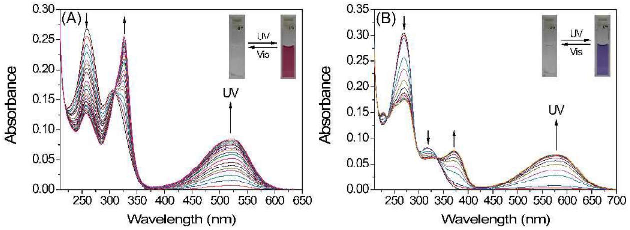

**Fig. 1** UV–vis absorption changes of (A) **DFC** (10 μM) and (B) **DTC** (10 μM) in acetonitrile upon irradiation with 365 nm light at 298 K. Inset: the corresponding photographic images upon irradiation with UV and visible light.

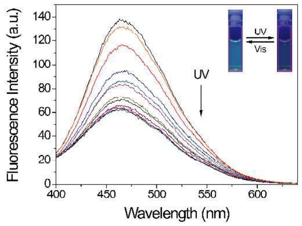

**Fig. 2** Fluorescence changes of **DFC** (10 μM) in acetonitrile upon irradiation with 365 nm light at 298 K, $\lambda_{ex}$ = 326 nm. Slits: 5 nm/ 5 nm. Inset: the corresponding photographic images upon irradiation with UV and visible light.

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fluorescence quantum yield and the fluorescence life time in toluene are 19% and 4.74 ns for **DFC**, and 0.36% and 7.09 ns for **DTC**, respectively. Impressively, the fluorescence quantum yield of **DFC** is 53-fold larger than that of **DTC**. This may be due to the π-electron in **DFC** has larger chance to be excited into higher energy levels, and probably easier to undergo a radiative decay in case the other competitive factors are fair, focusing on the aspect of transition oscillator strengths (Fig. S8 and Table S3-S4). Compared with hexafluorocyclopentene analogues, the fluorescence maximum of **DFC** is 44 nm longer than that of **6**, and the fluorescence quantum yield of **DFC** is much larger than that of **5** and **6** (both of 3%) in hexane.[5c] The fluorescence intensity reversibly changed under alternative illumination with 365 nm and visible light (≥ 520 nm).

Fatigue resistance is an indispensable property for the practical use of photochromic materials in various applications, including bioimaging and biodegradable materials. The fatigue resistance of **DFC** in acetonitrile was tested by coloration-decoloration experiments. As shown in Fig. S9A (ESI), by monitoring UV–vis absorption (detection absorbance at $\lambda_{\mathrm{max}}$ = 522 nm), at least 5 switching cycles can be performed with ca. 15% of decomposition under air atmosphere, suggesting nice fatigue resistance of **DFC** in acetonitrile. The thiophene analogue **DTC** is photochemically less stable as decreased to ca. 38% relative to the initial intensity of the band at 578 nm of the closed form after 5 switching cycles (Fig. S9B, ESI). In addition, the photoswitching cycles of **DFC** monitored by the fluorescence intensity at 465 nm showed ca. 17% of decomposition under the same condition (Fig. S10, ESI). The better fatigue resistance of **DFC** than **DTC** maybe rationally attributed to the higher bond energy of C-O than C-S regarding photochemical cleavage[12] as illustrated in Scheme S3 (ESI).

The thermal irreversibility of the photochemical cyclization is another integrant property for the application of the diarylethene derivatives, and especially the closed-ring forms of the switches are stable up to temperatures well above 373 K.[13] The thermal stabilities of the closed-ring forms of **DFC** and **DTC** were investigated under argon atmosphere. For **DFC**, it was found that the closed-ring form showed good thermal stability up to 383 K in toluene with a prolonged period of 2 h. The closed-ring form of **DTC** appeared to be much stable at the same temperature, and bleached within 2.5 h. Accordingly, the thermal fading kinetics is shown in Fig. S11-S12 (ESI) in details.

To gauge the photophysical properities of **DFC** in solid state, the absorption and fluorescence changes in thin-films were studied under illumination with 365 nm light. Excitingly, the distinct color and fluorescent changes of **DFC** under solid state were observed when it was exposed to UV light (Fig. S13 inset, ESI). As shown in Fig. S13 (ESI), the absorption maximum at 355 nm, and the emission maximum at 467 nm, originated from **DFC**. Likewise in solutions, prolonged irradiation to the thin-films resulted in the appearance of a new band centered at 543 nm in absorption spectra and the fluorencence quenching, which is indicative that the photocyclization of **DFC** proeceeds appreciably in thin-film. Upon irradiation with visible light (≥ 540 nm), both the absorption and luminescence spectra recovered, suggesting that the closed-ring isomer converted to the open-ring isomer. Analogue **DTC** did not show any fluorescent emission in thin-film.

Inspired by the excellent fluorescent performance of **DFC** in solution and solid state, we subsequently applied it in cellular imaging. The cellular imaging was accessed by confocal laser scanning experiments using HeLa cells as the example cell line. **DFC** and its photostationary state (**DFC-c**) were selected as the imaging agents, respectively, to avert the harmful effect of UV irradiation to living cells. Fig. 3A and 3C show the fluorescence images of HeLa cell after treatment with **DFC** (20 μM) in RPMI-1640/DMSO (99:1, v/v) solution for 30 min at 37 °C, which reveals a bright blue fluorescence. Under the same conditions, HeLa cells incubated with 20 μM of **DFC-c** were imaged, as shown in Fig. 3D and 3F, weak fluorescence was observed, which is consistent with the results demonstrated in Fig. 2. The fluorescence of the HeLa cells treated with **DFC** is significantly stronger than that of **DFC-c**. Notably, the bright field images of cells with the treatment of **DFC** and **DFC-c** did not show any gross morphological changes, suggesting that cells were viable throughout the imaging experiments. Fluorescence signals localized in cells suggested that the imaging agents could be endocytosed by cells for bioimaging. As expected, the cells treated with **DTC** and its photostationary state (**DTC-c**) exhibited nearly no fluorescence, as shown in Fig. S14 (ESI). Though **DFC** shows a blue fluorescence in cell imaging, we believe that as a photochromic prototype, **DFC** with appropriate structural modifications can work as excellent fluorescent switches for biological applications, like other fluorescent diarylethenes did.[3]

To evaluate the efficacy of **DFC** as the potential biodegradable and biorenewable materials, the cytotoxicity of **DFC** was further evaluated quantitatively via CCK-8 assay and the results were displayed in Fig. 4. MC3T3-E1 cells were treated with **DFC** and **DTC** solutions at various concentrations ranging from 0.1 to 100 μM. The above results suggested that no cytotoxicity was detected for **DFC**. Even at the highest concentration of **DFC** (100 μM), the cell viability was still as high as 99%. Different from **DFC**, reference compound **DTC** exhibited an increasing cytotoxicity with increased concentration itself in cells. In particular, at the concentration of 100 μM, its cell viability was only 70% of that of **DFC**. Therefore, these results can further support the underlying application of **DFC** as the biodegradable and biorenewable materials.

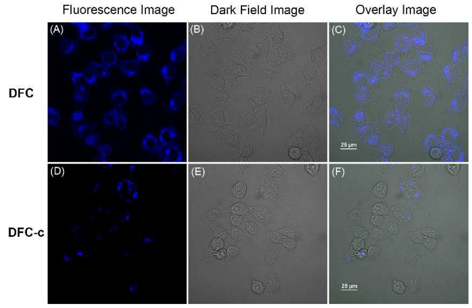

**Fig. 3** Confocal fluorescence and bright field images of HeLa cells by **DFC** (A–C) and **DFC-c** (D–E), respectively. $\lambda_{\mathrm{ex}}$ = 404 nm. Collecting region: 450–525 nm. Scale Bar, 25 μm.

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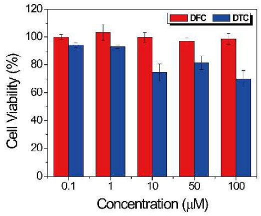

**Fig. 4** In vitro cytotoxicity of **DFC** and **DTC** against MC3T3-E1 cells as a function of compounds concentration using a CCK-8 assay. Each point represents the mean ± SD; n = 5.

In summary, a systematic synthetic access to photoswitchable difurylperhydrocyclopentenes is opened up by starting from commercial 5-methylfurfural. The photochromic and fluorescent performances of diarylethene derivative bearing with furan units (**DFC**) were investigated in solution as well as in thin-film. **DFC** exhibited higher photocyclization conversion and cyclization quantum yield than that of thiophene-based analogue **DTC** in acetonitrile. **DFC** showed strong fluorescence whereas **DTC** did not exhibit any fluorescence. In thin-film, **DFC** also showed the typical switching characteristics under alternative illumination with ultraviolet and visible light. Based on the fluorescence signal switch, **DFC** has been successfully used as an active component in high-resolution biological imaging systems. Moreover, **DFC** was noncytotoxic even in the high concentration. As a novel photochromic prototype, this ready-to-use and biocompatible molecule combined with structural extendibility, not only indicates an efficient strategy for constructing furan-cored photochromic materials with advanced optoelectronic properties but also makes the photochromic materials more biodegradable and biorenewable in vivo application. Currently, we are developing the photoswitches with better water solubility and the red-shifted fluorescence for further practical applications by diverse structural modifications based on **DFC**.

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