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PAPER

Photochromic properties of a water-soluble methyl carboxylic acid indolylfulgimide

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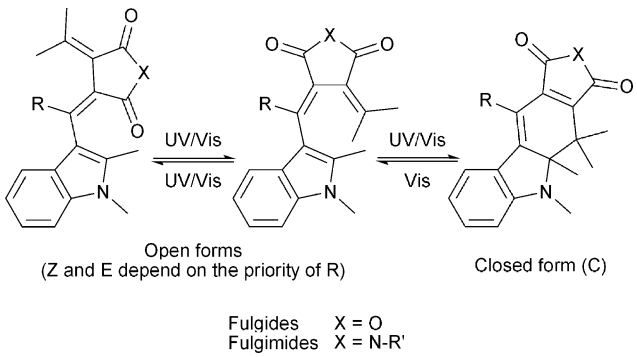
Photochromic fulgides and fulgimides have been identified as promising materials for applications in optical memory media, optical switches, and sensors. For applications in humid environments or biological systems, hydrolytic stability is crucial. A new photochromic methyl carboxylic acid indolylfulgimide was synthesized to improve hydrolytic stability in aqueous solution. The UV-vis spectra, extinction coefficient, thermal stability, and photochemical stability of the fulgimide were characterized in 50 mM sodium phosphate buffer (pH 7.4). The open and closed forms were both stable in buffer. At 37 °C after 500 h, the open forms of the fulgimide showed no degradation within experimental error (1–2%) by ^{1}H NMR and 2.3% decomposition by UV-vis spectroscopy. The closed form degraded 22% and 11% after 500 h at 37 °C in buffer by UV-vis and ^{1}H NMR data, respectively. In addition, the fulgimide cycled back and forth between the open and closed forms 80 times before degrading by 20% in buffer. The methyl group at the bridging position of the fulgimide significantly increased the thermal stability by overcoming the rapid hydrolysis of the trifluoromethyl group.

Introduction

The ability of organic photochromic compounds to interconvert between two forms by irradiation with different wavelengths of light has made them promising materials for use in optical memory devices, optical switches, and sensors.[1,2] The photochromic fulgide/fulgimide family is an important class of organic photochromic compounds that has been extensively studied (Scheme 1).[1,3–6] Fulgides display promising photochromic properties in aprotic solvents, such as a readily distinguishable absorption spectrum for each key form, efficient photoreactions, and high thermal and photochemical stabilities.[3,7,8] For instance, the most photochemically stable fulgide undergoes 10 000 photochemical cycles (back and forth conversion between the two key forms) before degrading by 13% in toluene.[9]

Hydrolytic stability is crucial for applications in biological systems and humid environments. However, the fulgide structure contains a succinic anhydride ring which causes rapid solvolytic degradation in protic solvents or aqueous media.[10,11] Fulgimides, the most important and practical derivatives of fulgides, improve the hydrolytic stability of fulgides by replacing the succinic anhydride ring with a succinimide ring (Scheme 1), thus allowing for applications in protic solvents.[1,3] In addition, fulgimides also allow another substituent to be attached onto the succinimide ring *via* the nitrogen atom while retaining the promising photochromic properties.[12]



Scheme 1 Photochromism of indolylfulgides and indolylfulgimides.

Recently, research on fulgimides has extended to their potential applications as molecular switches and sensors in biological systems.[3,12–16] Initially, fulgimides were characterized in protic solvents.[11,12] One study reported that a benzoic acid furylfulgimide in 50/50 ethanol–water underwent 10 photochromic cycles before degrading by 15%, and that the closed form degraded approximately 1% per day at room temperature.[11] In 70/30 ethanol–water at 50 °C, the open and closed forms of an ethyl ester fulgimide lost 22% and 10% of its absorbance at the absorbance maxima after 21 days, respectively.[15] Furthermore, the ethyl ester fulgimide underwent 360 photochemical cycles in 70/30 ethanol–water before degrading by 20%.[15] The photochemical stability of fulgides has not been reported in an ethanol–water system because of their rapid decomposition.

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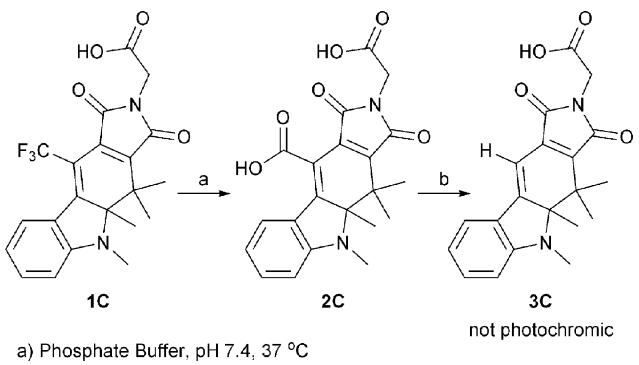
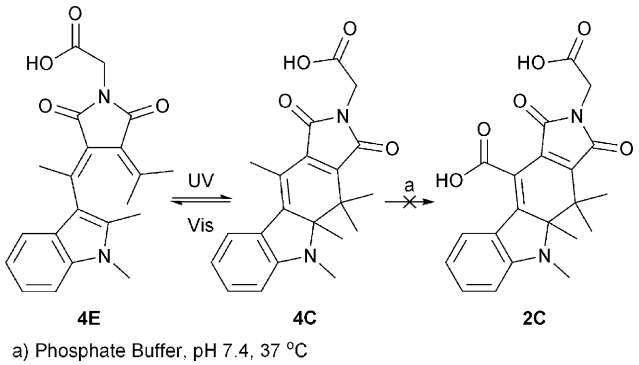
In addition, fulgimides have been applied to biological systems in aqueous solutions.[13,14] In one study, fulgimide derivatives were covalently attached to the protein concanavalin A and cycled back and forth at least twice.[14] This study also reported that the open form of the fulgimide was stable in aqueous solution for 48 h at 25 °C.[14] Another study indicated that a fulgimide can cycle back and forth seven times in cellular membranes but not very well in water.[13] These applications indicated the promising potential of fulgimides.

To rationally design fulgimides for specific applications, it is important to characterize and improve their properties in aqueous solution. In our previous report, two water-soluble fulgimides **1** and **2** were prepared, and their thermal and photochemical degradation rates in aqueous buffer were determined (Scheme 2).[17] A trifluoromethyl carboxylic acid indolylfulgimide **1** was characterized in sodium phosphate buffer (pH 7.4). The *C*-form of fulgimide **1** decomposed in buffer at 37 °C within a few hours. The thermal decomposition product was isolated and indicated that the trifluoromethyl group of the *C*-form was hydrolyzed to a carboxylic acid group. The resulting dicarboxylic acid indolylfulgimide **2** showed good thermal and photochemical stabilities in sodium phosphate buffer (pH 7.4).[17] However, the carboxylic acid group on the bridging position of fulgimide **2** can further decarboxylate under acidic conditions to produce H-carboxylic acid indolylfulgimide **3** (Scheme 2), but fulgimide **3** did not display photochromic properties. Therefore, hydrolysis of the trifluoromethyl group and the subsequent decarboxylation limited the stabilities and potential applications of fulgimides **1** and **2** in aqueous solutions due to the generation of the non-photochromic fulgimide **3**.



Scheme 2 Hydrolysis of fulgimide **1C** and subsequent decarboxylation.

Herein, a new indolylfulgimide **4** with a methyl group at the bridging position instead of the hydrolytically labile trifluoromethyl group was prepared. The methyl analog **4** is not expected to undergo hydrolysis in phosphate buffer at pH 7.4 (Scheme 3), and therefore should have improved properties in aqueous solutions. The properties of fulgimide **4**, including UV-vis spectra, extinction coefficient, thermal stability, and photochemical stability, were characterized in 50 mM sodium phosphate buffer (pH 7.4).



Scheme 3 Thermal stability of fulgimide **4** in phosphate buffer at pH 7.4.

Experimental

General procedures and materials

All commercially available materials were used without further purification. NMR spectra were recorded on a Brüker 400 MHz NMR spectrometer. ^{1}H and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm) or solvent (7.26 and 77.00 ppm, respectively for chloroform). The HRMS data was obtained at the University of Florida. UV-vis spectra were recorded with a Cary 300 Spectrophotometer. Flash chromatography was performed with 230–400 mesh silica gel. Illumination was provided by a 1000 W Hg (Xe) arc lamp with a water filter followed by a UV hot mirror followed by either a 365 nm bandpass filter or a 515 nm cutoff filter.

Synthesis of 3-acetyl-1,2-dimethylindole 6[18]

1,2-Dimethylindole **5** (5.00 g, 34.5 mmol) was dissolved in 98 mL of acetic anhydride (106 g, 1.04 mol) at room temperature and refluxed for 12 h under argon gas. The reaction mixture was concentrated *in vacuo* to yield a brown oil. The brown residue was further purified *via* silica gel chromatography (3 : 1 hexanes/EtOAc). Recrystallization from isopropanol provided 4.1 g (64%) of 3-acetyl-1,2-dimethylindole **6**.

Synthesis of *cis*/*trans* indole lactones 8[18]

Dimethyl isopropylidenesuccinate **7** (41.0 g, 0.19 mol)[18] was dissolved in 200 mL of dry THF and cooled to – 78 °C under argon gas. Lithium diisopropylamide (LDA) (76 mL of a 2 M solution in THF, 0.15 mol) was added dropwise *via* an addition funnel to the solution and allowed to react for 30 min at –78 °C under argon gas. To a solution of 3-acetyl-1,2-dimethylindole **6** (7.0 g, 38 mmol) in 200 mL of THF at 0 °C, the lithium diisopropylamide/dimethyl isopropylidenesuccinate/THF solution was added dropwise *via* cannula under argon gas. The mixture was warmed to room temperature and allowed to stir for 2 d. The solvent was then concentrated *in vacuo*. The residue was quenched with 500 mL of water, acidified with 5% H_2SO_4 solution to pH 1, and extracted with diethyl ether (3 × 200 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification was performed *via* silica gel chromatography (1 : 2 hexanes/ether) and provided 4.63 g (42%) of a *cis*/*trans* mixture of indolelactones **8** in a 1 : 2 ratio. The *cis*/*trans* mixture was further separated *via* silica gel

chromatography (4 : 1 hexanes/EtOAc) and recrystallized from ethanol for characterization purposes. *trans*-Indolelactone: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (s, 1H), 7.27–7.29 (m, 1H), 7.20 (td, J = 7.0, 1.1 Hz, 1H), 7.15 (td, J = 7.4, 1.5 Hz, 1H), 4.47 (s, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 2.56 (s, 3H), 2.25 (s, 3H), 1.80 (s, 3H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 168.8, 154.0, 136.8, 132.9, 124.8, 121.1, 120.7, 119.7, 118.9, 114.7, 109.0, 82.8, 56.7, 52.2, 29.2, 25.3, 24.3, 20.3, 11.5. $C_{20}H_{23}NO_4$ MS (APCI) m/z: 342.1713 [obtained M + H]$^+$, 342.1700 [calculated M + H]$^+$. *cis*-Indolelactone as a mixture of atropisomers, approximately 2 : 1 ratio: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (d, J = 7.8 Hz, 0.3H), 7.52 (d, J = 7.8 Hz, 0.7H), 7.17–7.23 (m, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.06 (t, J = 7.1 Hz, 1H), 4.27 (s, 0.7H), 4.11 (s, 0.3H), 3.63 (s, 3H), 3.01 (s, 2H), 2.87 (s, 1H), 2.58 (s, 2H), 2.43 (s, 1H), 2.37 (s, 3H), 1.96 (s, 3H), 1.88 (s, 2H), 1.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 170.4, 168.3, 168.0, 154.0, 153.2, 136.8, 136.2, 134.0, 131.2, 125.9, 124.5, 122.3, 120.9, 120.7, 120.6, 120.5, 119.7, 119.4, 118.9, 111.5, 109.8, 108.8, 108.1, 84.2, 83.4, 58.6, 57.7, 51.4, 51.2, 30.1, 30.0, 29.4, 29.3, 24.3, 20.4, 20.3, 12.7, 11.8. $C_{20}H_{23}NO_4$ MS (APCI) m/z: 342.1714 [obtained M + H]$^+$, 342.1700 [calculated M + H]$^+$.

Synthesis of methyl indolylfulgide 9[18,19]

Sodium hydride (60% dispersion in oil, 0.28 g, 7.00 mmol) was added to a mixture of *cis*/*trans* indolelactones **8** (1.0 g, 2.90 mmol) in 100 mL of DMF at 0 °C. The mixture was warmed to room temperature and left to react for 1 h. The reaction mixture was cooled back again to 0 °C, and H_2O (1.05 mL, 58 mmol) was added. Hydrogen gas evolved, and the reaction was left to react overnight. The mixture was concentrated *in vacuo* and yielded a white solid. The white solid was then dissolved in 100 mL of water and extracted with ethyl acetate (3 × 100 mL). The aqueous layer was acidified with concentrated HCl to pH 2 and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude diacid was suspended in 15 mL of toluene. Acetic anhydride (15 mL, 0.16 mol) was added, and the reaction mixture was refluxed for 2 h under argon gas. The solution was then concentrated *in vacuo*. The residue was partitioned between 100 mL of water and 30 mL CH_2Cl_2, and then the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification was performed *via* silica gel chromatography with CH_2Cl_2. Recrystallization from CH_2Cl_2/isopropanol provided 0.31 g (34%) of methyl indolylfulgide **9**. *E*-form: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.24–7.26 (m, 1H), 7.15 (td, J = 7.3, 1.1 Hz, 1H), 3.69 (s, 3H), 2.81 (s, 3H), 2.20 (s, 6H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.1, 163.8, 153.1, 149.5, 137.1, 135.2, 125.0, 122.1, 121.6, 120.8, 119.6, 119.1, 116.7, 109.2, 29.9, 26.2, 24.7, 23.7, 12.2. $C_{19}H_{19}NO_3$ MS (APCI) m/z: 310.1451 [obtained M + H]$^+$, 310.1438 [calculated M + H]$^+$.

Synthesis of amide acid ester 10

N,*N*-Diisopropylethylamine (0.64 g, 4.97 mmol) was added dropwise to a mixture of the HCl salt of glycine methyl ester (0.23 g, 2.58 mmol) and methyl indolylfulgide **9** (0.22 g, 0.71 mmol) in 50 mL of acetonitrile at room temperature. The reaction mixture was allowed to stir overnight and then concentrated *in vacuo*. The residue was quenched with 50 mL of water and extracted with EtOAc (3 × 35 mL). The aqueous layer was acidified with 0.5 M HCl to pH 1 and extracted with EtOAc (3 × 35 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Trituration with $CHCl_3$ provided 0.11 g (39%) of the amide acid ester **10**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.34 (d, J = 7.9 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.06 (td, J = 7.5, 1.0 Hz, 1H), 6.95 (td, J = 7.5, 0.7 Hz, 1H), 4.09 (d, J = 17.5 Hz, 1H), 4.01 (d, J = 17.6 Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 2.33 (s, 3H), 2.16 (s, 3H), 1.87 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.9, 171.9, 171.1, 149.1, 143.1, 138.5, 135.4, 133.8, 128.4, 127.5, 121.7, 120.1, 120.1, 114.9, 109.8, 52.6, 42.2, 29.7, 24.3, 22.5, 22.3, 11.4. $C_{22}H_{26}N_2O_5$ MS (APCI) m/z: 399.1927 [obtained M + H]$^+$, 399.1914 [calculated M + H]$^+$.

Synthesis of amide diacid 11

NaOH (0.1 g, 2.50 mmol) was added to the amide acid ester **10** (0.11 g, 0.28 mmol) in 100 mL of methanol and stirred at room temperature overnight. The solution was concentrated *in vacuo*. The resulting white precipitate was dissolved in 25 mL of Na_2CO_3 (0.19 M) and extracted with EtOAc (2 × 25 mL). The aqueous layer was carefully acidified with concentrated HCl to pH 1 and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A trituration was performed using chloroform to yield 0.09 g (85%) of amide diacid **11**. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.34 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.06 (td, J = 7.6, 1.0 Hz, 1H), 6.95 (td, J = 7.4, 1.0 Hz, 1H), 4.06 (d, J = 17.6 Hz, 1H), 4.00 (d, J = 17.8 Hz, 1H), 3.62 (s, 3H), 2.33 (s, 3H), 2.15 (s, 3H), 1.86 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 173.0, 172.8, 171.1, 149.0, 142.9, 138.5, 135.3, 133.9, 128.4, 127.5, 121.7, 120.1, 120.0, 114.8, 109.8, 42.2, 29.7, 24.2, 22.5, 22.3, 11.4. $C_{21}H_{24}N_2O_5$ MS (ESI) m/z: 407.1585 [obtained M + Na]$^+$, 407.1577 [calculated M + Na]$^+$.

Synthesis of methyl carboxylic acid indolylfulgimide 4

Acetic anhydride (15 mL) was added to the amide diacid **11** (0.07 g, 0.18 mmol) in 15 mL of toluene at 0 °C. The reaction mixture was allowed to stir at 0 °C for 2 h and then warmed to room temperature. The reaction mixture was dissolved in 25 mL of EtOAc and extracted with saturated $NaHCO_3$ (3 × 20 mL) and H_2O (2 × 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (70 : 30 : 1 EtOAc/hexanes/AcOH) and provided an *E*/*Z* mixture (95 : 5) of methyl carboxylic acid indolylfulgimide **4**, which was difficult to separate. The *E*/*Z* mixture was illuminated with 365 nm light in toluene until photostationary state was reached, and then the *C*-form was purified by silica gel chromatography (70 : 30 : 0.5 EtOAc/hexanes/AcOH). Recrystallization from CH_2Cl_2–hexanes provided 21 mg (31%) of *C*-form methyl carboxylic acid indolylfulgimide **4**. The *E*-form was prepared by illuminating the *C*-form in $CDCl_3$ with visible light >515 nm. *C*-form: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, J = 7.6 Hz, 1H), 7.22 (td, J = 7.6, 1.0 Hz, 1H), 6.73 (td, J = 7.4, 1.1 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 4.28 (s, 2H), 2.89 (s, 3H), 2.41 (s, 3H), 1.76 (s, 3H), 1.28 (s, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 171.5, 169.3, 168.7, 157.3, 150.7, 138.6, 136.3, 131.7, 126.0, 124.5, 118.0, 115.0, 108.1, 72.5, 40.0, 38.1, 31.8, 19.9, 19.0, 15.5, 13.7. $C_{21}H_{22}N_2O_4$ MS (ESI) *m/z*: 365.1517 [obtained M-H]$^-$, 365.1507 [calculated M-H]$^-$. *E*-form: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 5.1 Hz, 1H), 7.21 (td, J = 7.0, 1.0 Hz, 1H), 7.13 (td, J = 7.4, 1.0 Hz, 1H), 4.48 (d, J = 17.2 Hz, 1H), 4.43 (d, J = 17.3 Hz, 1H), 3.67 (s, 3H), 2.80 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2, 167.9, 149.0, 145.2, 137.1, 134.4, 125.5, 123.6, 122.5, 121.6, 120.4, 119.7, 117.1, 109.0, 38.3, 29.8, 26.3, 22.9, 22.2, 12.0.

Spectral determination

A concentrated, air-saturated stock solution of **4C** in 50 mM sodium phosphate buffer (pH 7.4) was prepared from 10 mg of solid sample. From the stock solution, five samples ranging in concentration from 0.20 to 0.05 mM were then prepared by dilution with buffer. A UV-vis spectrum was then acquired for each sample. Extinction coefficient and λ_{max} were determined. According to ^{1}H NMR data, *E*- to *Z*-form isomerization occurred rapidly (<5 min) in sodium phosphate buffer at room temperature, thus the open form was characterized as an *E*/*Z* mixture. To obtain the extinction coefficient and λ_{max} of the *E*/*Z* mixture at equilibrium, five diluted **4C** solutions in buffer were quantitatively converted to *E*/*Z* mixtures by irradiation with visible light >515 nm light. The UV-vis spectrum of each *E*/*Z* mixture was measured, and the extinction coefficient was obtained using the previously determined extinction coefficient of **4C**.

Photostationary state (PSS) measurements

To measure the $PSS_{365\,nm}$ of **4**, solutions of **4C** in D_2O with 50 mM sodium phosphate buffer (pD 7.4) or toluene-d_8 were converted to **4E/Z** using visible light >515 nm. PSS was then achieved by irradiation of **4E/Z** with 365 nm light until no change in composition was observed. The *C*/*E*/*Z*- ratio was monitored by ^{1}H NMR spectroscopy.

Thermal/Hydrolytic stability

The thermal/hydrolytic stability of the *E*/*Z*- and *C*-form of fulgimide **4** was measured using both UV-vis and ^{1}H NMR spectroscopy. For the UV-vis experiment, a solution of **4C** was prepared in 50 mM sodium phosphate buffer (pH 7.4) and transferred into several ampoules. An NMR sample of **4C** was prepared in D_2O with 50 mM sodium phosphate buffer (pD 7.4). UV-vis and ^{1}H NMR spectra of initial samples were acquired. The ampoules and NMR tube were then sealed and incubated in a water bath maintained at 37 °C. At predetermined times, an ampoule and the NMR tube were removed, and their contents were analyzed by UV-vis and ^{1}H NMR spectroscopy, respectively. The sealed NMR tube was then returned to the water bath. UV-vis and ^{1}H NMR spectra were then compared to the initial spectra. The **4E/Z** solutions were obtained by irradiation of freshly prepared **4C** solutions with visible light >515 nm. These **4E/Z** solutions were then analyzed in the same manner as **4C**. For ^{1}H NMR spectroscopy, added DMSO was utilized as an internal standard, and signals corresponding to the individual species were integrated relative to the internal standard.

Photochemical stability

To measure the photochemical stability of **4**, a solution of **4C** in 50 mM sodium phosphate buffer (pH 7.4) was quantitatively converted to a solution of **4E/Z** by irradiating with visible light >515 nm. Initial absorbance of **4E/Z** solution in buffer was 0.9–1.2 at the absorption maximum. The sample was irradiated to $PSS_{365\,nm}$ with 365 nm light, and the absorbance at λ_{max} of the *C*-form was measured. Then, a fresh **4E/Z** solution was irradiated to 90% of $PSS_{365\,nm}$. The time taken to achieve 90% of the absorbance at $PSS_{365\,nm}$ was then recorded (coloration reaction *E*/*Z* to *C*). The 90% PSS mixture was then irradiated with visible light >515 nm. The time taken for the absorbance at λ_{max} of the *C*-form to reach <1% was recorded (decoloration reaction *C* to *E*/*Z*). Once the duration of irradiation was established for both the 90% $PSS_{365\,nm}$ coloration and <1% *C*-form decoloration reactions, the system was automated through the use of a filter switch. All solutions were capped and stirred. After a designated number of irradiation cycles (coloration followed by decoloration), the sample was fully converted to $PSS_{365\,nm}$, and its UV-vis spectrum scanned. The photochemical stability was then determined by comparison with the initial $PSS_{365\,nm}$ (PSS at zero irradiation cycles) absorption spectrum. The photochemical stability of **4** in toluene was measured in the same manner.

Results and discussion

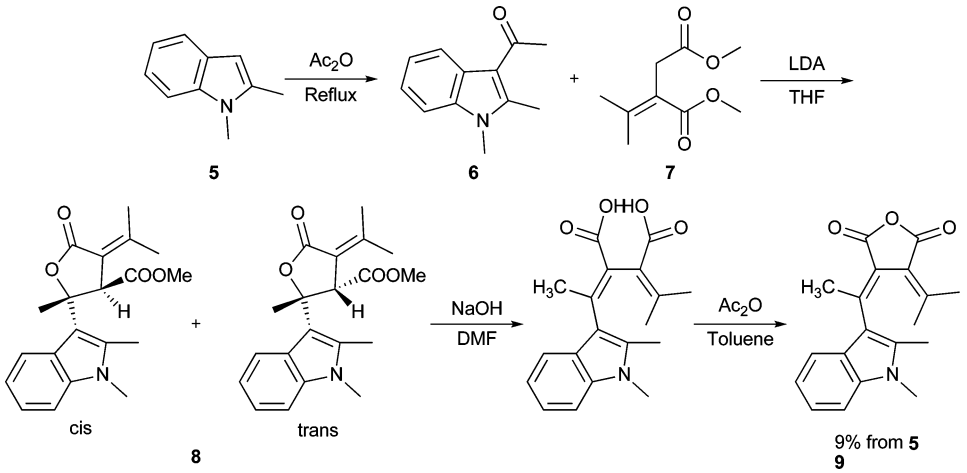
Synthesis of methyl carboxylic acid indolylfulgimide 4

Indolylfulgide **9** was synthesized as a precursor to methyl carboxylic acid indolylfulgimide **4** in four steps from 1,2-dimethylindole using a modified version of a previously reported procedure (Scheme 4).[18] 1,2-Dimethyl-3-acetylindole **6** was prepared by refluxing 1,2-dimethylindole **5** in acetic anhydride. A Stobbe condensation between the 1,2-dimethyl-3-acetylindole **6** and dimethyl isopropylidenesuccinate **7** resulted in a mixture of *cis*/*trans* indolelactones **8**. The indolelactones were treated with sodium hydroxide in DMF instead of the usual KOH in THF, to produce the diacid.[7,19] The methyl indolylfulgide **9** was afforded in 9% overall yield from 1,2-dimethylindole **5** by treating the diacid with acetic anhydride in toluene.

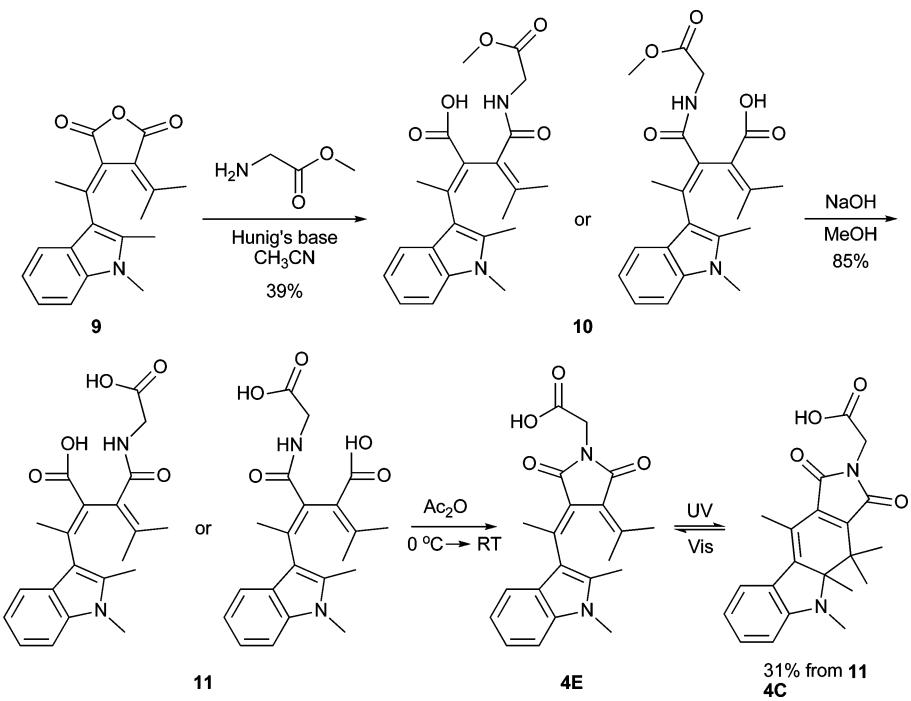
Methyl carboxylic acid indolylfulgimide **4** was synthesized from indolylfulgide **9** in three steps (Scheme 5). The anhydride ring of **9** was opened *via* addition of glycine methyl ester. The resulting methyl ester succinamic acid **10**, one of two possible regioisomers,[20] was saponified to generate the corresponding carboxylic acid succinamic acid **11**. Subsequent dehydration of the succinamic acid intermediate with acetic anhydride yielded carboxylic acid indolylfulgimide **4** as a 95 : 5 *E*/*Z* mixture, which was then converted to **4C** by irradiation with 365 nm light. Fulgimide **4C** was obtained in 31% yield from **11** after column chromatography and recrystallization.

UV-vis absorption spectra

The UV-vis absorption spectra of fulgimide **4E/Z** and **4C** were measured in 50 mM sodium phosphate buffer (pH 7.4) (Fig. 1, Table 1). The wavelengths of the absorbance maxima and the extinction coefficients are shown in Table 1. Rapid *E*/*Z* isomerization of fulgimide **4** was observed in buffer, thus the open form was



Scheme 4 Synthesis of methyl indolylfulgide **9**.



Scheme 5 Synthesis of methyl carboxylic indolylfulgimide **4**.

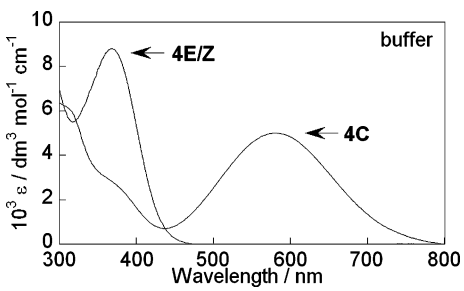


Fig. 1 UV-vis absorption spectra of fulgimide **4** in 50 mM sodium phosphate buffer (pH 7.4).

characterized as an equilibrium mixture of **4E/Z** (7 : 3 ratio). An increased isomerization rate in polar solvents was expected due to the greater contribution of the polar resonance form (Scheme 6).[13]

Table 1 Extinction coefficients at λ_{max} for fulgimide **4** in 50 mM sodium phosphate buffer (pH 7.4) and λ_{max} in toluene

	λ_{max}/nm (ε_{max}/dm^3 mol^{-1} cm^{-1})		$PSS_{365\,nm}$[a]
Medium	*E*/*Z*-form[b]	*C*-form	*C* : *E* : *Z*
Buffer	369 (8.8×10^3)	580 (5.0×10^3)	87 : 10 : 3
Toluene	363[c]	568	58 : 24 : 18

[a] PSS: Photostationary state. [b] Fast isomerization in buffer. [c] Characterized as the *E*-form in toluene.

For comparison, UV-vis spectra were also evaluated in toluene where no *E*/*Z* isomerization occurred (Table 1). Fulgimide **4C** showed a small bathochromic shift of 12 nm as the solvent was switched from toluene to buffer. A similar bathochromic shift was also observed for trifluoromethyl carboxylic acid indolylfulgimide

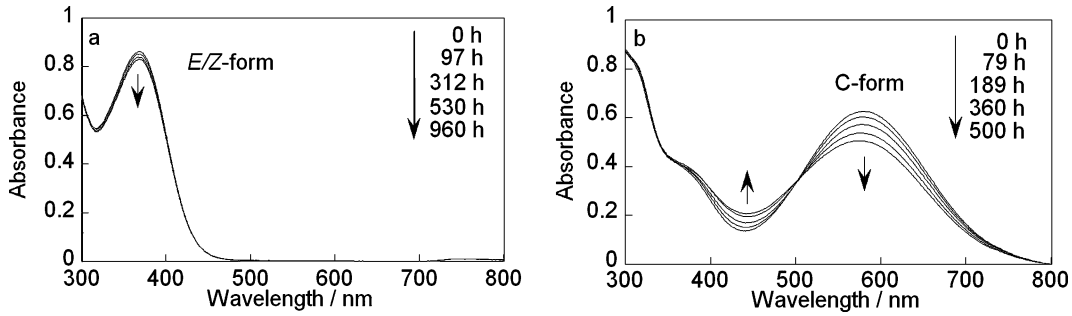
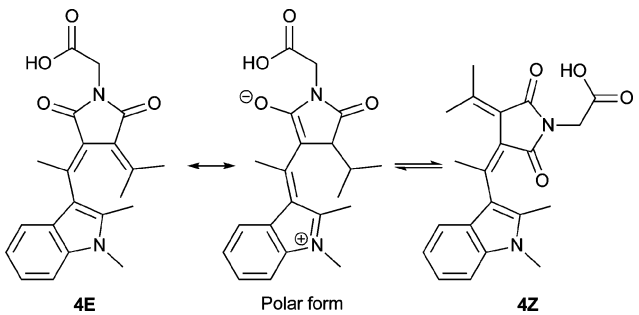


Fig. 2 Thermal decomposition of fulgimide **4** in 50 mM sodium phosphate buffer (pH 7.4) at 37 °C by UV-vis spectroscopy: (a) *E*/*Z*-form, (b) *C*-form.



Scheme 6 Isomerization of methyl carboxylic indolylfulgimide **4** in polar solvent.

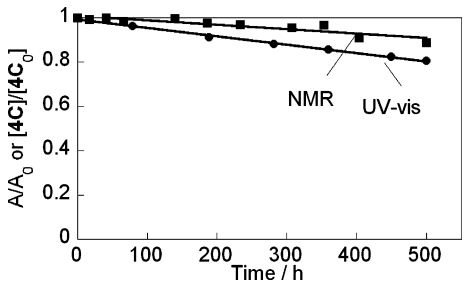


Fig. 3 Thermal decomposition of fulgimide **4C** in 50 mM sodium phosphate buffer (pD/pH 7.4) at 37 °C by ^{1}H NMR and UV-vis spectroscopy.

1.[17] Furthermore, increasing solvent polarity significantly improved the photostationary state (PSS) of fulgimide **4** at 365 nm by providing higher percentage of *C*-form in buffer (Table 1). The higher percentage of *C*-form in buffer is due to changes in the quantum yields with solvent.[13,21]

Thermal stability

Thermal stability of fulgides and fulgimides is an essential characteristic for their applications in optical memory devices or as optical switches.[7,9,11] The thermal stability of fulgmide **4** was measured by both UV-vis and NMR in 50 mM sodium phosphate buffer (pH/pD 7.4) at 37 °C, as these conditions mimic physiological conditions. Both ^{1}H NMR and UV-vis spectroscopy showed that the *E*/*Z* mixture of **4** was very stable in buffer. NMR data showed no decomposition within experimental error (1–2%) after 500 h at 37 °C. UV-vis spectra showed 2.3% decomposition after 500 h and 3.1% after 960 h for the *E*/*Z* mixture in buffer at 37 °C (Fig. 2a). The closed form of **4** was less thermally stable than the open forms. UV-vis data showed that after 500 h at 37 °C the *C*-form had decomposed 22% while the ^{1}H NMR data showed only 11% loss after 500 h (Fig. 2b, 3). Previously by UV-vis spectroscopy, we have observed a solvent isotope effect of approximately 3–4 for the decomposition of *C*-form fulgimides in deuterated buffer *versus* non-deuterated buffer.[17] Therefore, the difference between the ^{1}H NMR and UV-vis results for fulgimide **4** may be due to a solvent isotope effect. By both ^{1}H NMR and UV-vis, the *C*-form is the least stable form. Ultimately, the thermal stability of the *C*-form was increased from hours to months by replacing the trifluoromethyl group with a methyl group at the bridging position.

Photochemical stability

The ability of fulgimide **4** to cycle back and forth between the open and closed forms was measure in toluene and sodium phosphate buffer (pH 7.4). In toluene, fulgimide **4** underwent 250 photochemical cycles before degrading by 20% (Fig. 4). Our previous study indicated that the trifluoromethyl carboxylic acid fulgimide **1** only underwent 21 photochromic cycles before degrading by 20% in toluene.[15] The replacement of the trifluoromethyl group with a methyl group increased the photochemical stability of carboxylic acid fulgimide by a factor of 10. The cycling times were approximately 30 s (*E*/*Z*- to *C*-form) and 35 s (*C*- to *E*/*Z*-form). The photochemical stability of **4** was also measured in sodium phosphate buffer (pH 7.4), where it degraded by 20% after being cycled back and forth 80 times (Fig. 4, 5). The lower number of photochemical cycles in buffer may be due to the longer cycling time, 80 s (*E*/*Z* - to *C*-form) and 300 s (*C*- to *E*/*Z*-form). The observation is consistent with previous studies, where most fulgimides have lower quantum yields (longer cycling times) in aqueous solution compared to toluene.[17,21]

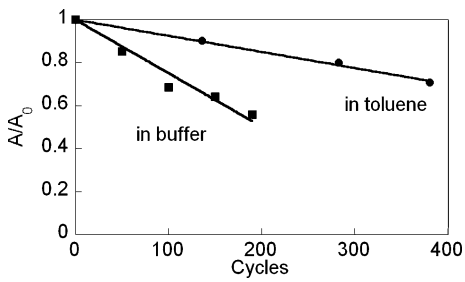


Fig. 4 Photochemical decomposition of **4** in toluene (circles) and in 50 mM sodium phosphate buffer (pH 7.4, squares).

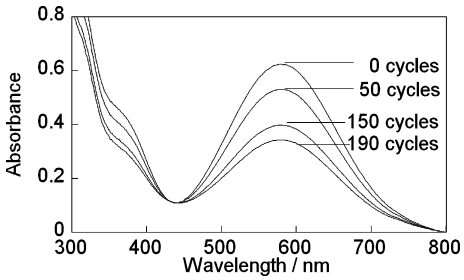


Fig. 5 PSS spectra of **4** in 50 mM sodium phosphate buffer (pH 7.4) after the indicated number of cycles.

Conclusion

Methyl carboxylic acid indolylfulgimide **4** was successfully synthesized in 10% yield from methyl indolylfulgide **9** and displayed enhanced thermal and photochemical stability in 50 mM sodium phosphate buffer (pH 7.4). Little or no degradation was observed for the open forms of **4** in buffer at 37 °C. The *C*-form was less thermally stable, it degraded 22% (UV-vis) and 11% (NMR) after 500 h at 37 °C in buffer. However, the thermal stability of fulgimide **4C** was significantly greater than **1C**, which rapidly decomposed to **2C** in buffer. Moreover, fulgimide **4** was stable during acidic extraction while fulgimide **2** converted to non-photochromic fulgimide **3**.[17] The methyl carboxylic acid indolylfulgimide **4** underwent 10 times the number of photochemical cycles as the trifluoromethyl analog **1** in toluene and comparisons in buffer could not be made due to the instability of **1**. Ultimately, the replacement of the trifluoromethyl group with a methyl group at the bridging position significantly increased the thermal stability of fulgimide **4** in aqueous solution.

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