

Investigation of a green oligomer of an indolizine

Haruyasu Asahara,^{a,b} Ayaka Awane,^a Kengo Muragishi,^a Ryuichi Sugimoto,^{a,b}
Kazuhiko Saigo,^{a,b} and Nagatoshi Nishiwaki^{*a,b}

^a School of Environmental Science and Engineering, and ^b Research Center for Material Science and Engineering, Kochi University of Technology, Kami, Kochi 782-8502, Japan
E-mail: nishiwaki.nagatoshi@kochi-tech.ac.jp

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Abstract

An indolizine-based oligomer was synthesized by stirring a solution of 1-(α -alkoxybenzyl)-indolizine derivative in chloroform at room temperature. The oligomer was characterized as an octamer; it was the main component in the obtained mixture of oligomers. The oligomerization was accelerated by both acid and light. The green color of the oligomer under acidic conditions turned yellowish brown under basic conditions; this color change could be repeated by changing the acidic/basic conditions.

Keywords: Indolizine; pH sensitive behavior; ethynylpyridine; color change; oligomer

Introduction

An indolizine framework consists of an electron-deficient pyridine ring and an [*a*]-fused electron-rich pyrrole ring, which provides a biased electron density. Because of such an electronic structure, indolizine derivatives exhibit potential biological activities^{1,2} and optical properties.³⁻⁵ Therefore, numerous indolizines have been synthesized by several methods.⁶⁻⁸

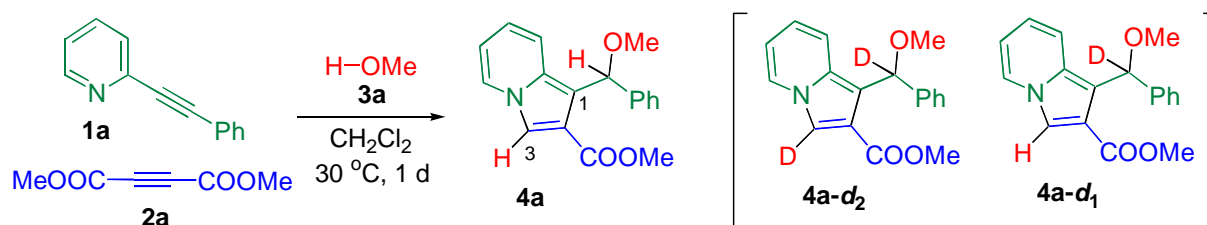
Previously, we demonstrated a synthetic method for functionalized indolizines from 2-ethynylpyridines using functionalities; a nucleophilic ring nitrogen and reactive ethynyl group.⁹ When a solution of indolizine in chloroform-*d* was stood at room temperature for 1 day, the color of the solution changed from yellowish brown to bluish green. This experimental result prompted us to study this phenomenon; we clarified that an indolizine-based oligomer was formed.¹⁰

However, detailed information was not obtained because of poor experimental environment. After our preliminary finding, any report dealing with indolizine-based oligomer has not been found to our best of knowledge during the last quarter century, which prompted us to focus and reinvestigate this phenomenon.

Results and Discussion

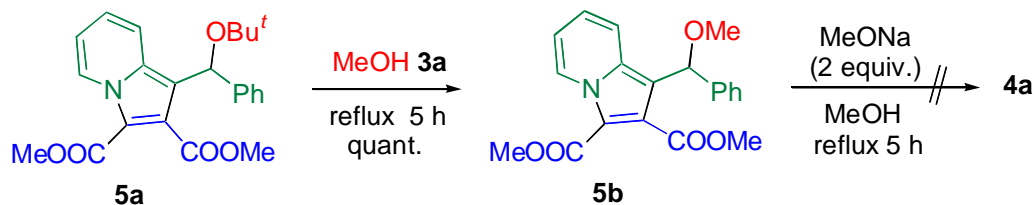
Synthesis of indolizines **4** and **5**

Indolizine **4a** can be efficiently prepared by the three-component cycloaddition of 2-phenylethynylpyridine **1a** and dimethyl acetylenedicarboxylate **2a** in the presence of a proton source such as methanol **3a** which accompanies demethoxycarboxylation of **2a** (Scheme 1). The two proton at the 3-position and on the substituent at the 1-position are derived from methanol, which was confirmed by conducting the same reaction using methanol-*d*₁, which afforded **4a-d**₂. The deuterium at the 3-position was exchanged to proton leading to **4a-d**₁ upon treatment with column chromatography on silica gel. Indolizines **4b**, **4c**, and **4d** were prepared in a similar manner using a combination of 2-(4-methylphenyl)ethynylpyridine (**1b**) and 2-(4-butylphenyl)ethynylpyridine (**1c**), diethyl acetylenedicarboxylate **2b**, and ethanol **3b**. Compared with other established methods using ethynylpyridines,^{11–23} this method is environmentally benign because it is not necessary to use any transition metal catalyst or strong base.



Scheme 1. Three component synthesis of indolizine **4a**.

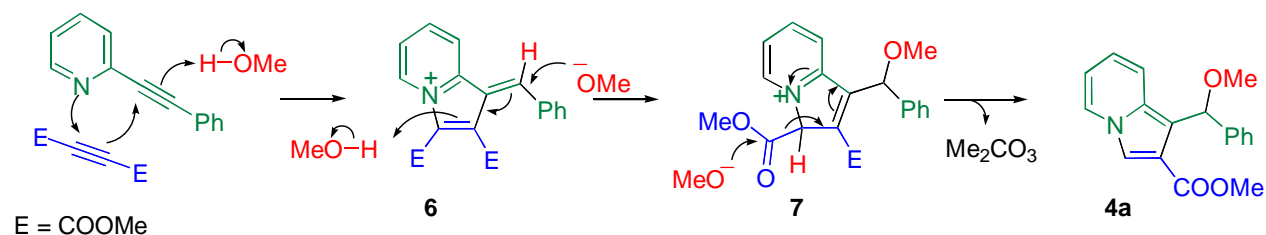
When *tert*-butyl alcohol **3c** was used as a proton source, demethoxycarboxylation did not proceed to afford indolizine **5a**. The isolated **5a** was quantitatively transformed to **5b** upon heating in methanol **3a**; however, further change such as demethoxycarboxylation did not occur even though **5b** was treated with sodium methoxide in methanol under reflux (Scheme 2).



Scheme 2. Study on the alkoxy exchange of 2,3-bis(methoxycarbonyl)indolizines **5**.

On the basis of the abovementioned results, a plausible mechanism for the formation of **4a** is illustrated in Scheme 3. This reaction is initiated by [3+2] cycloaddition followed by protonation, affording 1-benzylideneindolizine intermediate **6**. Then a counter anion is introduced on the

substituent at the 1-position, and the 3-position of the indolizine is easily protonated to furnish **7**. When the formed methoxide anion attacks the carbonyl group, demethoxycarboxylation; subsequent rearomatization of the indolizine framework affords the final product proceeds leading to **4a**, which is consistent with the detection of dimethyl carbonate. On the other hand, the bulky *tert*-butoxide cannot attack the ester function because of steric hindrance, thus only deprotonation at the 3-position occurs to give **5a**. Although there is another possibility that bis(methoxycarbonyl)indolizine **5b** serves as the intermediate for this reaction, it is excluded by the experimental fact shown in Scheme 2.



Scheme 3. A plausible mechanism for the formation of indolizine **4a**.

Oligomerization of indolizine **4**

When a solution of indolizine **4** in chloroform-*d* was allowed to stand at room temperature for one day, the color of the solution changed from yellowish brown to bluish green. The ¹H NMR spectrum of the green solution showed only the signals of methanol. This indicates that a scarcely soluble green material was formed in chloroform without any special treatment, simultaneously eliminating methanol. Similar color change was also observed when indolizine **4a** was stood in a silica gel column, or when a solution of **4a** in THF was stirred with 10mol% of hydrochloric acid at room temperature. These results indicate that oligomerization of **4a** occurs under weak acidic conditions. On the other hand, bis(methoxycarbonyl)indolizines, *e.g.* **5b**, were stable under the same conditions.

The consumption of **4a** was monitored by ¹H NMR using three types of deuterated solvents; benzene-*d*₆, chloroform-*d*, and acetic acid-*d*₄. Different rates were observed depending on both the solvent and light. Although no change was observed in benzene-*d*₆ and chloroform-*d* solutions in the dark, indolizine **4a** was consumed in the acetic acid-*d*₄ solution (Figure 1, upper). In contrast, the reaction proceeded faster in the light in acetic acid-*d*₄ and chloroform-*d* solutions. In the case of benzene-*d*₆, indolizine **4a** was slightly converted to an unidentified product, but the color of the solution did not change (Figure 1, lower). The initial consumption rate of **4a** was $4.3 \times 10^{-4} \text{ s}^{-1}$ (in acetic acid-*d*₄ in the light), $1.8 \times 10^{-4} \text{ s}^{-1}$ (in chloroform-*d* in the light), and $2.6 \times 10^{-5} \text{ s}^{-1}$ (in acetic acid-*d*₄ in the dark). Chloroform easily decomposes to hydrogen chloride in light. Hence, indolizine **4a** may have been consumed by the acid.^{24,25} Because different reaction rates were also observed in acetic acid-*d*₄ between under light and dark conditions, this reaction is accelerated by both acid and light; however, the role of light is not well understood.

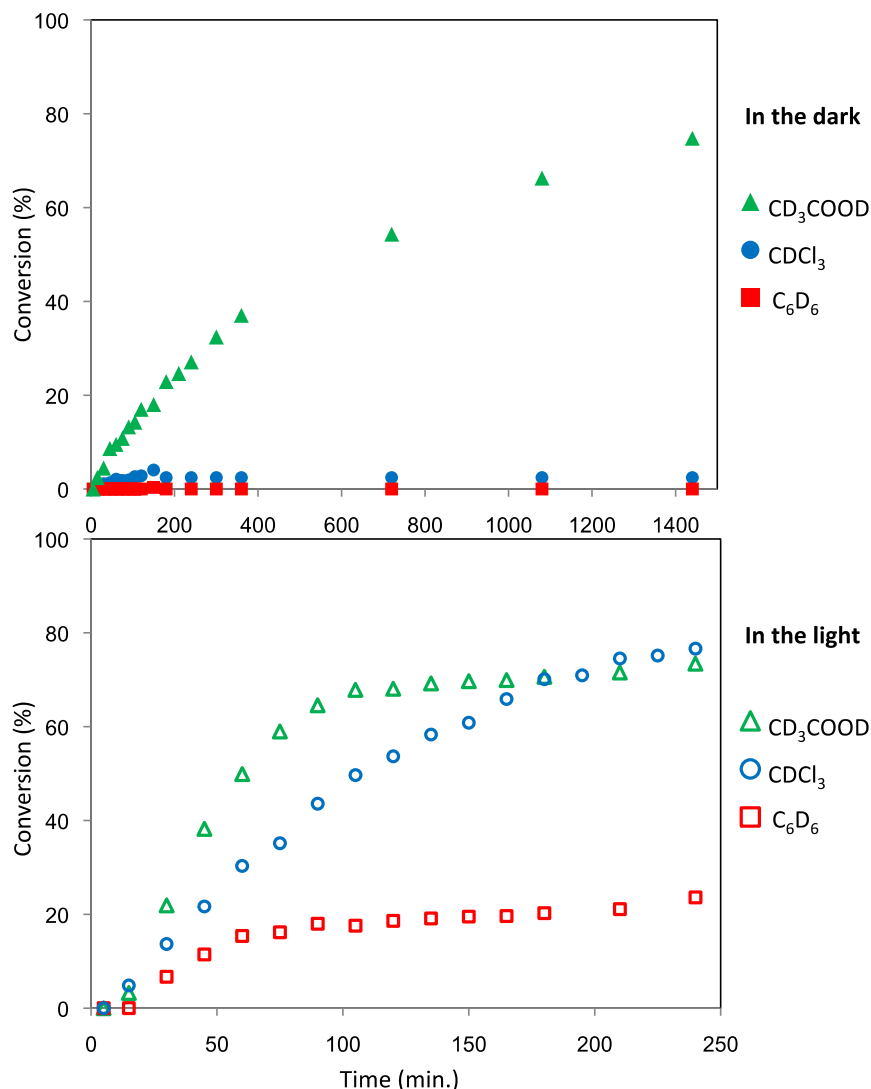


Figure 1. Consumption of indolizine **4a** in the dark (upper) and light (lower), monitored by ¹H NMR.

Generally, electron-rich heterocyclic compounds such as pyrrole undergo acid catalysed self-condensation to afford polypyrroles.^{26–31} Indolizine is also an electron-rich heterocyclic compound, hence, similar self-condensation is considered to proceed, which is catalyzed by a trace amount of hydrogen chloride generated by decomposition of chloroform,^{24,25} however, direct linkage of bulkier indolizines seems difficult. On the other hand, indolizine **4a** has an electrophilic carbon at the 1-position, which serves as a spacer to diminish the steric hindrance between indolizine frameworks and facilitate the oligomerization.

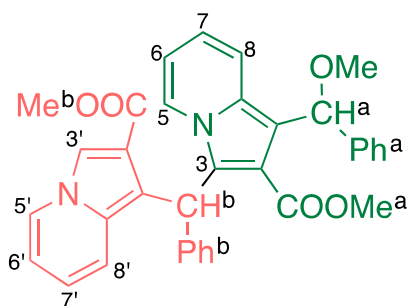
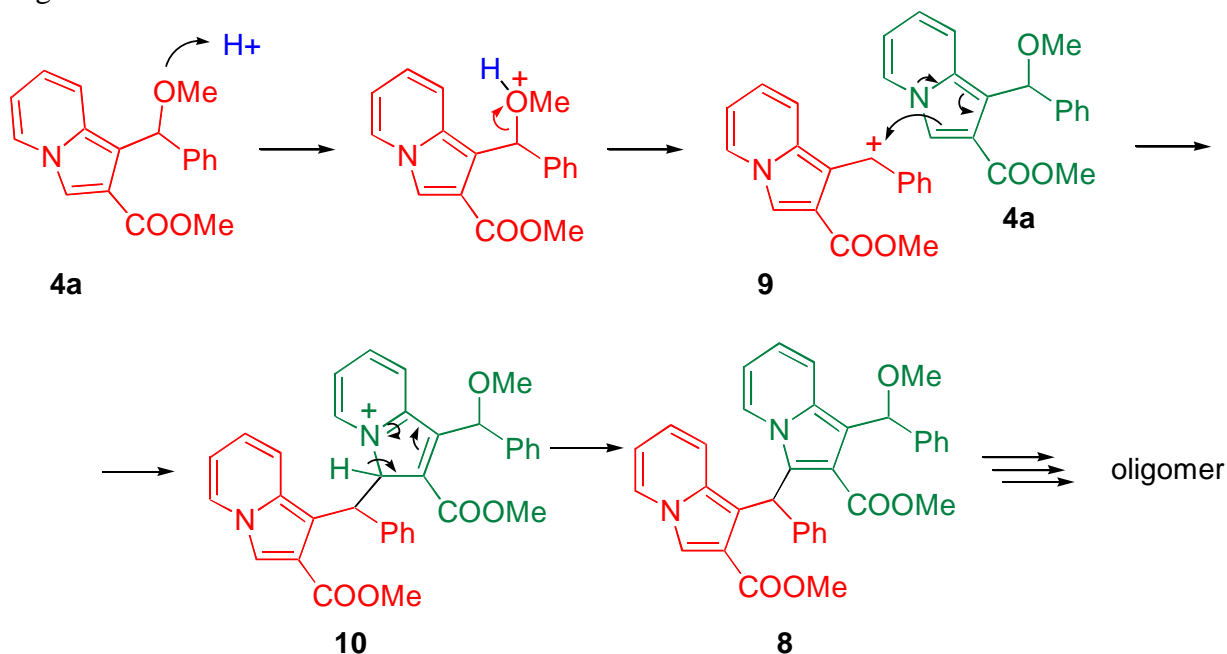


Figure 2 Dimeric product of **4a** (Compound **8**).

Since the ^1H NMR showed only the signals of eliminated methanol after the color was changed, the NMR spectrum of the product could not be measured; hardly soluble tiny green particles were homogeneously dispersed in the solvent. Considering the solubility of the monomer **4a**, dimer or trimer should be soluble in organic solvents. However, no signal was observed in the monitoring of the reaction by ^1H NMR because of their extremely small amounts in the reaction mixture. Fortunately, a trace amount of dimer **8** could be isolated by quick treatment with silica gel column chromatography of the reaction mixture stopped in a short reaction time (1 h). The spectral data of **8** indicated this was bimolecularly condensed compounds accompanied by elimination of one molecule of methanol (Figure 2). In the ^1H NMR, signals of inner protons (H-5, -6, -8', Ph^b , COOMe^b) were observed in higher fields than the signals of the outer protons or the corresponding signals of monomer **4a**. This observation could be explained by that the indolizine rings are torsionally restrained and the protons at the inside positions are located above the other indolizine ring.



Scheme 4. A plausible mechanism for the oligomerization of indolizine **4a**.

The dimer **8** was found to be a mixture of isomers (73:27) by ^1H NMR and coalesced spectrum was not obtained at 70 °C. The ^{13}C NMR was too complex to be assigned, but six methoxy carbon signals were observed.

As shown in Scheme 1, proton exchange of **4a** occurs easily under weakly acidic conditions such as in a silica gel column, which indicates the 3-position has high electron density. In addition, an alkoxy group can be easily eliminated from the α -alkoxybenzyl group at the 1-position only when **5a** is heated in methanol as shown in Scheme 2. Considering these structural features, indolizine **4a** may have undergone self-condensation in the presence of acid catalyst, forming an oligomeric structure. In particular, a methanol is easily eliminated from the 1-position as a result of protonation affording a stable benzylic cation **9**. The cation is attacked by another molecule of **4a** leading to dimer **8** via deprotonation of the adduct intermediate **10**. Oligomerization is achieved by repeating this sequence.

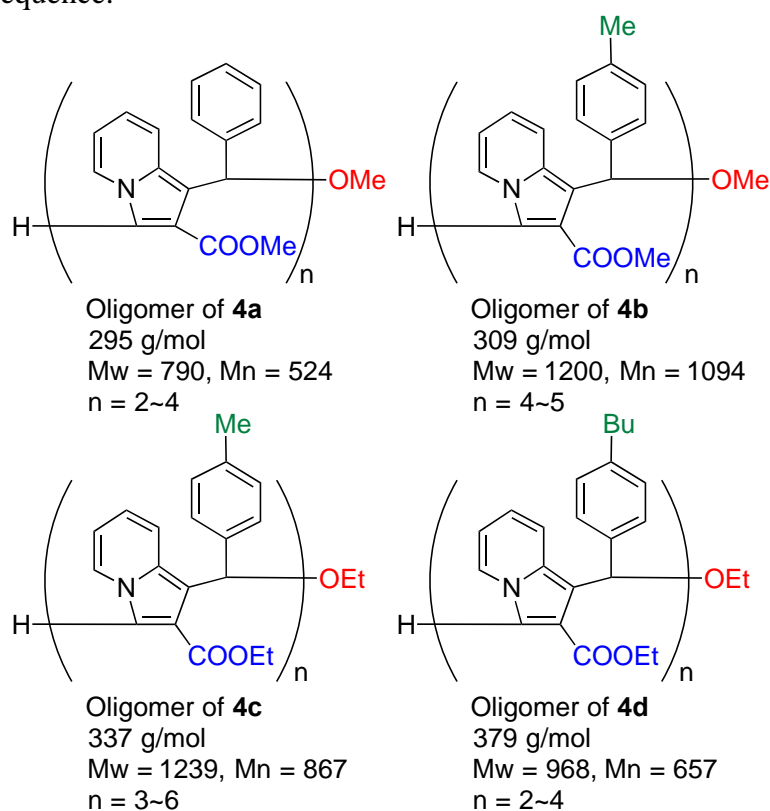


Figure 3. Structures of oligomers and gel permeation chromatography results.

Since indolizine oligomer **4a** was not sufficiently soluble to allow measurement of the ^1H NMR spectrum, a longer alkyl chain was introduced into the indolizine framework to improve the solubility. The chloroform solutions of each indolizine **4b**, **4c**, and **4d** turned green after standing at room temperature for one day; however, no signal was observed in the ^1H NMR spectra. Then, these four types of indolizines were subjected to gel permeation chromatography (GPC) measurements because the measurable concentration for GPC is lower than that for NMR; the

results are shown in Figure 3. Each oligomer had a similar molecular weight (M_w and M_n), and the degree of oligomerization was between 2 and 6, contrary to our expectation. The insoluble oligomers with a higher degree of oligomerization are removed by filtration during the pretreatment for GPC measurements.

Next, the mass spectrum of the oligomer of indolizine **4b** was measured using the MALDI ionization method (Figure 4). The spectrum showed similar peak patterns repeated at an interval of 277 Da. This indicated that a methanol molecule was removed from the indolizine. Hence, the green material was confirmed to be a mixture of oligomers of the indolizine **4b**. The mountain range was observed until 6.0 kDa, where the degree of oligomerization was 20; the octamer was the main component in the mixture.

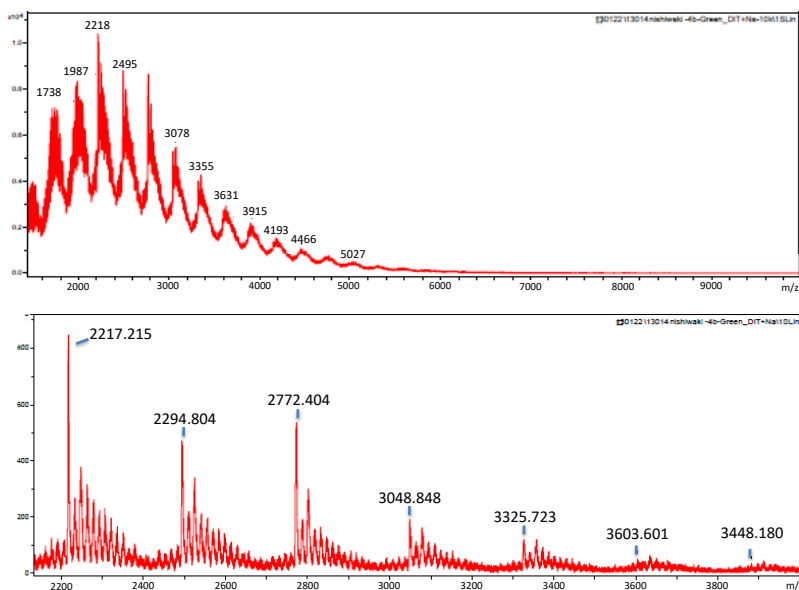


Figure 4. Mass spectrum of the oligomer of indolizine **4b**. 1.2–10.0 kDa (upper), 2.1–4.0 kDa (lower).

pH Sensitive behavior of the oligomer

Although the prepared oligomer was green, it turned yellowish brown by treating with a base such as sodium hydroxide, ammonia and DBU. This color change was reversible; it turned to green again by treating with an acid. This color change was confirmed from the UV–visible spectra of the oligomer (Figures 5). In the UV–visible spectrum, the absorption was observed at 670 nm in the green state. This absorption disappeared, and a new absorption was observed between 500 nm and 600 nm in the brown state. This change of color was reversible and its pK_{obs} was 11.1. (Figure 5, right).

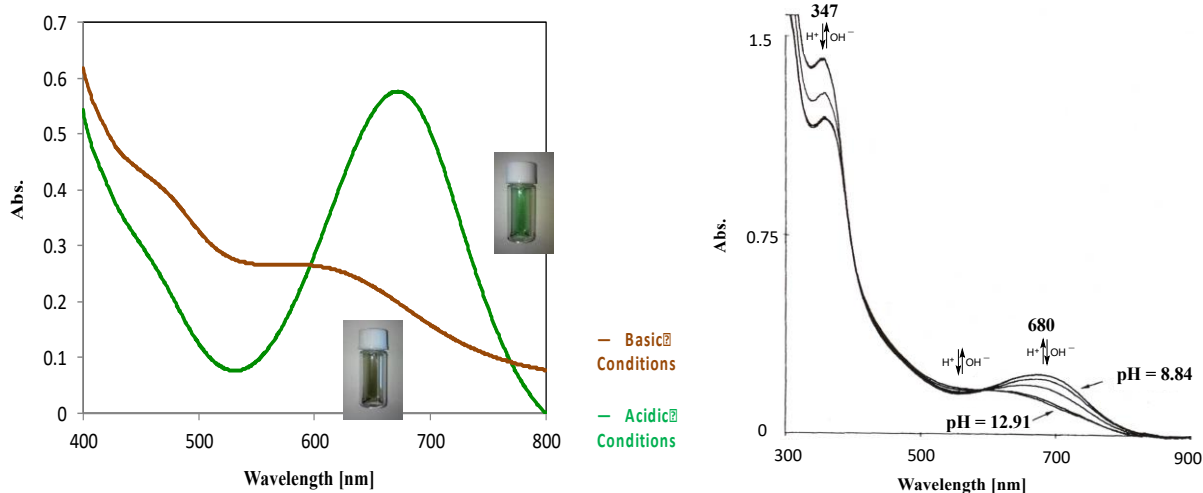


Figure 5. UV-visible spectra of the oligomer of indolizine **4b** (left) and **4a** under different pH conditions (right).

The reversibility of the color change was studied. To a solution of oligomer of **4b** (3 mg, corresponding to 10 μ mol monomer) in methanol (100 mL), either small amount of concentrated acid or base, 10 M hydrochloric acid or 10 M sodium hydroxide aqueous solution (100–300 μ L), was added until the color of the solution changed. The absorbance at 650 nm was plotted in Figure 6, in which the solution was acidified at even runs, and was basified at odd runs.

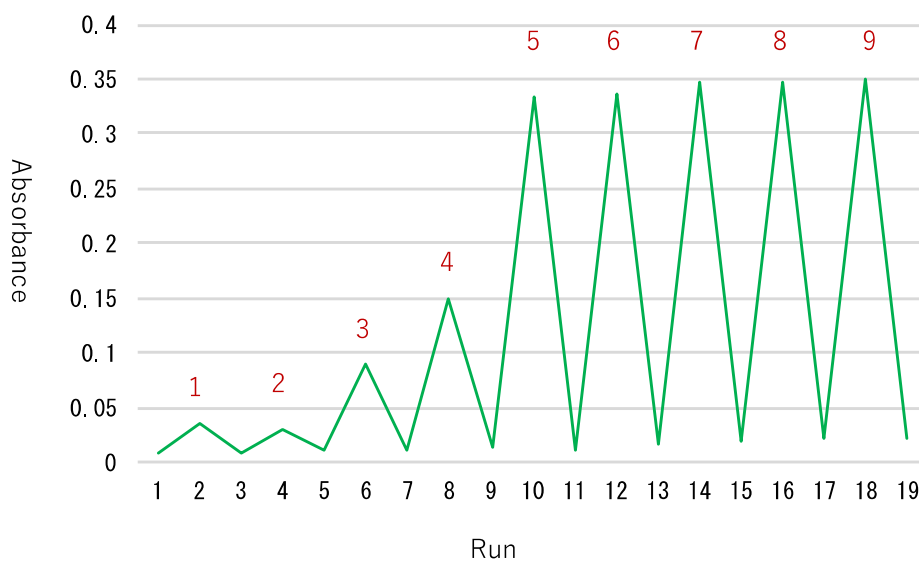


Figure 6. The change of absorbance at 650 nm. The solution was basified at odd runs, and the solution was acidified at even runs.

In the IR spectrum, although the absorption of the carbonyl group was observed at 1738 cm^{-1} in the green state, it shifted to 1668 cm^{-1} in the brown state (Figure 7). Hence, the carbonyl group probably became an enolate under the basic conditions. Based on these spectral changes, the plausible structures of the oligomer in both the states are shown in Scheme 5. As mentioned above, because an indolizine is easily protonated at the 3-position, the oligomer is present in the protonated form under acidic conditions, and in the deprotonated form under basic conditions. It is known that the pyridinium ion serves as an acceptor to form charge-transfer complexes.^{32,33}

Although the similar complex might be formed to produce a green color under acidic conditions, we have not obtained any evidence at present.

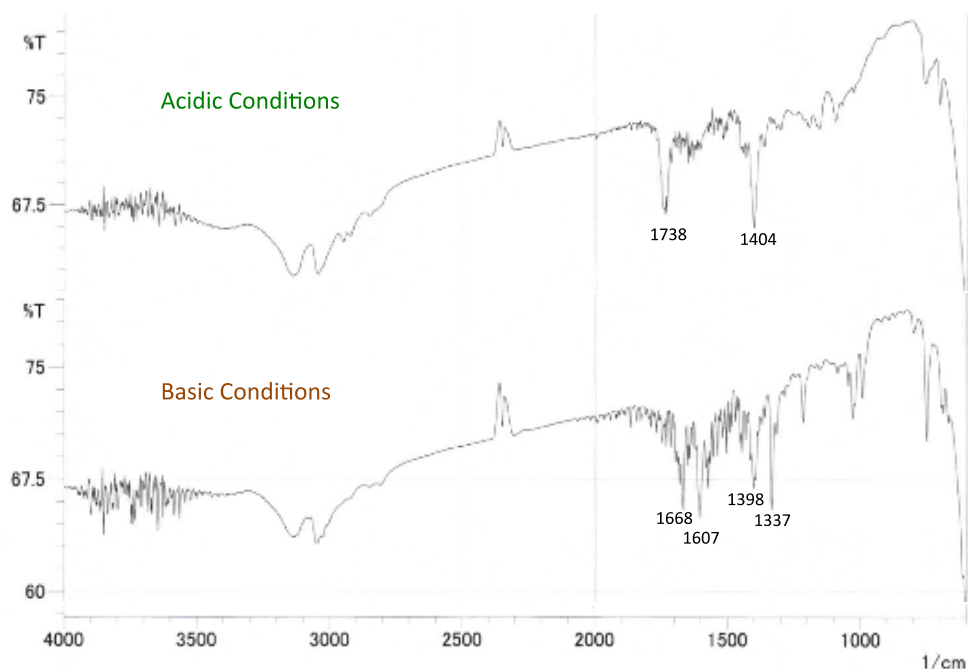
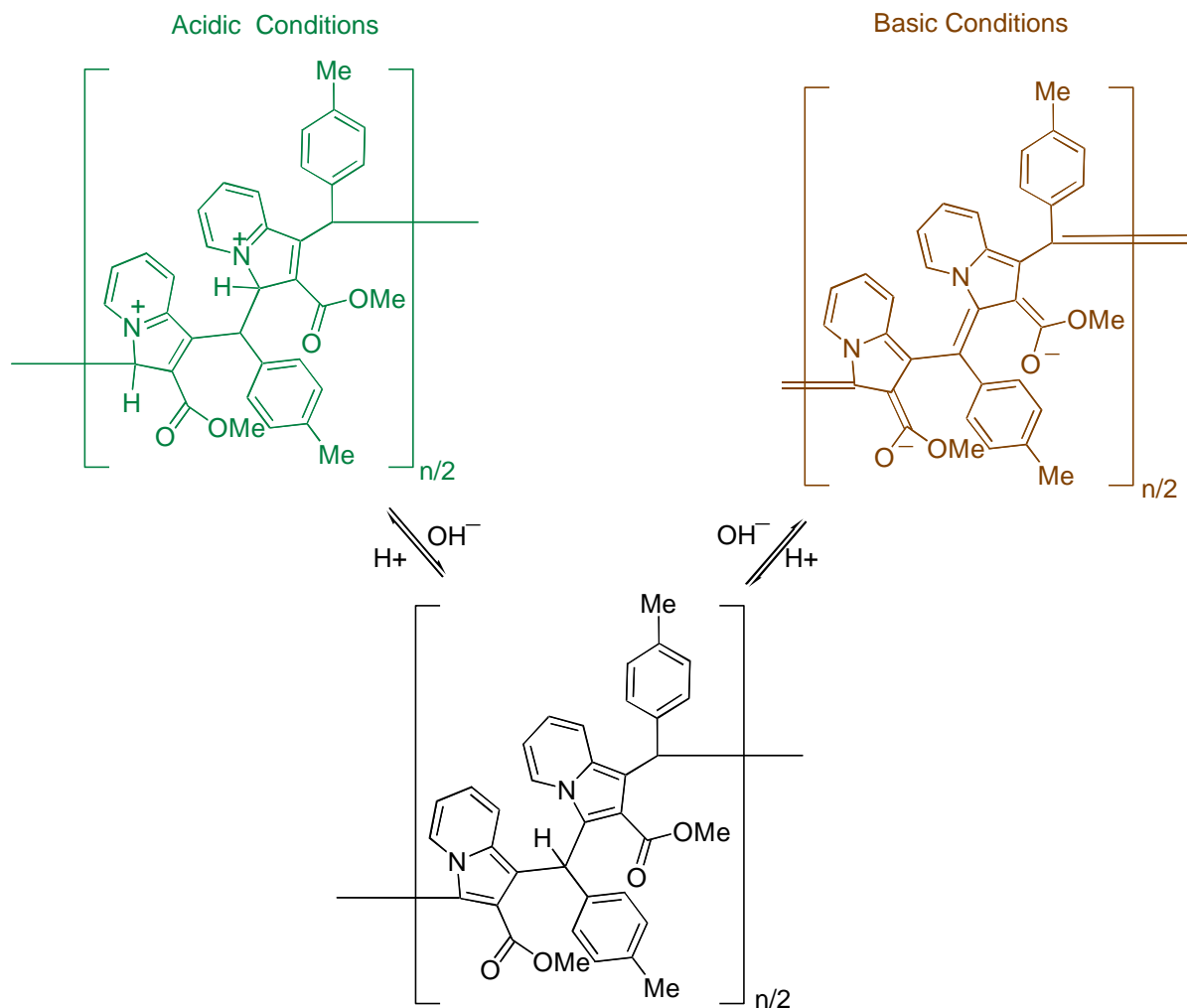


Figure 7. IR spectra of the oligomer of indolizine **4b** under acidic (upper) and basic (lower) conditions.

Conclusions

As a result of revisiting the oligomerization of indolizine **4**, both acid catalyst and light were found to be crucial for this reaction although the role of the light has not clarified. During the synthesis of indolizines **4** and the oligomer, no metallic reagent²⁶⁻³¹ was necessary. The obtained oligomer shows a green color under acidic conditions and turns to yellowish brown under basic conditions, which is reversible. The application of this oligomer is under investigation, and the results will be reported in due course.



Scheme 5. Structural changes in the oligomer of indolizine **4b** under acidic and basic conditions.

Experimental Section

General

All reagents were purchased from commercial sources and used directly without further purification. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400 spectrometer (400 MHz and 100 MHz, respectively), JEOL FT-NMR GSX spectrometer at 270 MHz and JEOL FT-NMR JMN FX90Q at 90 MHz using TMS and 1,1,2,2-tetrachloroethane as an internal standard. ^1H NMR data is reported as follows: chemical shift (δ , ppm), (chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz). ^{13}C NMR data is reported in terms of chemical shift (δ , ppm). IR spectra were recorded on Shimadzu IR Affinity-1 Spectrometer, and were reported in frequency of absorption. Mass spectra were obtained on a

Bruker Autoflex II and a JEOL JMS-Q1050GC mass spectrometer using acetonitrile as a solvent and dithranol (1,8-dihydroxyanthracen-9(10*H*)-one) as a matrix. High resolution mass spectrum was recorded with a JEOL JMS-DX303 mass spectrometer. GPC using Shodex column KF-804F and KF-806L was performed by Shimadzu LC-6A equipped with a Tosoh UV-8020 UV detector and a Jasco RI-2031 refractive index detector. The measurement of GPC was conducted using chloroform as a solvent and polystyrene standard as a molecular weight reference. UV-vis. spectra were measured on a Jasco V-550. Elemental microanalyses were performed using a Yanaco CHN coder. Melting points were recorded with a Yanaco micro-melting-points apparatus and were uncorrected.

General procedure for preparation of indolizines **4**⁹

To a solution of 2-phenylethynylpyridine **1a** (179 mg, 1.0 mmol) in dichloromethane (10 mL), dimethyl acetylenedicarboxylate **2a** (213 mg, 1.5 mmol) and methanol **3a** (0.81 mL, 20 mmol) were added, and the resultant mixture was stirred at 30 °C for 1 d. After removal of the solvent, the residue was treated with column chromatography on silica gel wrapped with aluminium foil to afford indolizine **4a** (eluted with dichloromethane, 177 mg, 0.6 mmol, 60%) as a pale yellow oil. Other indolizines were also prepared in a similar manner.

1-[Methoxy(phenyl)methyl]-2-methoxycarbonylindolizine (4a). Pale yellow oil. ¹H NMR (400 MHz, C₆D₆, TMS) δ 2.93 (s, 3H), 3.11 (s, 3H), 5.46 (s, 1H), 6.22 (ddd, *J* 6.4, 7.2, 1.2 Hz, 1H), 6.40 (ddd, *J* 8.8, 6.4, 0.8 Hz, 1H), 6.53 (s, 1H), 7.09 (ddd, *J* 8.8, 1.2, 1.2 Hz, 1H), 7.20 (tt, *J* 7.2, 1.2 Hz, 1H), 7.34 (dd, *J* 8.0, 7.2 Hz, 2H), 7.75 (dd, *J* 8.0, 1.2 Hz, 2H), 8.82 (ddd, *J* 7.2, 0.8, 1.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, TMS) δ 51.5 (CH₃), 56.2 (CH₃), 75.0 (CH), 100.2 (CH), 110.6 (CH), 114.6 (C), 118.4 (CH), 118.9 (CH), 126.0 (CH), 127.1 (CH), 128.7 (CH), 130.0 (CH), 132.4 (C), 133.9 (C), 136.5 (C), 169.5 (C); IR (neat/cm⁻¹) 1745; MS (FAB) 295 (M⁺, 37), 264 (23), 236 (100), 220 (14), 204 (14). Anal. Calcd. for C₁₈H₁₇NO₃: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.87; H, 5.87; N, 4.69 %.

1-[Methoxy(4-methylphenyl)methyl]-2-methoxycarbonylindolizine (4b). Pale yellow oil (182 mg, 59%): ¹H NMR (400 MHz, C₆D₆, TMS) δ= 2.20 (s, 3H), 2.96 (s, 3H), 3.12 (s, 3H), 5.51 (s, 1H), 6.23 (ddd, *J* 6.4, 7.2, 1.2 Hz, 1H), 6.41 (ddd, *J* 9.2, 6.4, 0.8 Hz, 1H), 6.55 (s, 1H), 7.10 (ddd, *J* 9.2, 1.2, 1.2 Hz, 1H), 7.17 (d, *J* 8.0 Hz, 2H), 7.68 (d, *J* 8.0 Hz, 2H), 8.84 (ddd, *J* 7.2, 1.2, 0.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃, TMS) δ= 14.2 (CH₃), 51.5 (CH₃), 56.2 (CH₃), 75.1 (CH), 100.2 (CH), 110.5 (CH), 114.5 (C), 118.3 (CH), 118.8 (CH), 126.0 (CH), 129.5 (CH), 129.9 (CH), 132.5 (C), 133.6 (C), 133.9 (C), 136.6 (C), 169.5 (C); MS (EI) 309 (M⁺, 13), 250 (100), 234 (24), 218 (16), 204 (16), 59 (12); IR (KBr/cm⁻¹) 1748. Anal. Calcd. for C₁₉H₁₉NO₃: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.49; H, 6.34; N, 4.31 %.

1-[Ethoxy(4-methylphenyl)methyl]-2-ethoxycarbonylindolizine (4c). Pale yellow oil (169 mg, 50%): ¹H NMR (400 MHz, C₆D₆, TMS) δ 0.56 (dd, *J* 6.8, 6.8 Hz, 3H), 0.72 (dd, *J* 7.2, 7.2 Hz, 3H), 1.99 (s, 3H), 2.86 (dq, *J* 8.8, 6.8 Hz, 1H), 3.07 (dq, *J* 8.8, 6.8 Hz, 1H), 3.52 (dq, *J* 10.8, 7.2 Hz, 1H), 3.67 (dq, *J* 10.8, 7.2 Hz, 1H), 5.47 (s, 1H), 6.04 (ddd, *J* 6.4, 7.2, 1.2 Hz, 1H), 6.21 (ddd, *J* 9.2, 6.4, 0.8 Hz, 1H), 6.36 (s, 1H), 6.90 (ddd, *J* 9.2, 1.2, 1.2 Hz, 1H), 6.97 (d, *J* 8.0 Hz, 2H), 7.52

(d, J 8.0 Hz, 2H), 8.76 (ddd, J 7.2, 0.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6 , TMS) δ 13.8 (CH₃), 15.0 (CH₃), 21.0 (CH₃), 61.0 (CH₂), 64.5 (CH₂), 73.9 (CH), 100.1 (CH), 110.3 (CH), 115.1 (C), 118.2 (CH), 118.8 (CH), 126.3 (CH), 129.4 (CH), 129.9 (CH), 132.2 (C), 133.7 (C), 133.9 (C), 136.5 (C), 169.3 (C); MS (EI) 337 (M^+ , 11), 264 (100), 236 (35), 234 (29), 204 (21), 191 (17), 91 (11). Anal. Calcd. for $\text{C}_{21}\text{H}_{23}\text{NO}_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.68; H, 6.58; N, 4.47 %.

1-[Ethoxy(4-butylphenyl)methyl]-2-ethoxycarbonylindolizine (4d). Pale yellow oil (152 mg, 40%); ^1H NMR (400 MHz, C_6D_6 , TMS) δ = 0.79 (t, J 7.2 Hz, 3H), 0.87 (dd, J 7.2, 7.2 Hz, 3H), 0.93 (dd, J 7.2, 7.2 Hz, 3H), 1.30 (tq, J 7.2, 7.2 Hz, 2H), 1.57 (tt, J 7.6, 7.2 Hz, 2H), 2.56 (t, J 7.6 Hz, 2H), 3.05 (dq, J 8.8, 7.2 Hz, 1H), 3.27 (dq, J 8.8, 7.2 Hz, 1H), 3.74 (dq, J 10.8, 7.2 Hz, 1H), 3.89 (dq, J 10.8, 7.2 Hz, 1H), 5.69 (s, 1H), 6.25 (ddd, J 6.4, 7.2, 1.2 Hz, 1H), 6.42 (ddd, J 8.8, 6.4, 0.8 Hz, 1H), 6.59 (s, 1H), 7.12 (ddd, J 8.8, 1.2, 1.2 Hz, 1H), 7.25 (d, J 8.0 Hz, 2H), 7.79 (d, J 8.0 Hz, 2H), 8.97 (ddd, J 7.2, 0.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6 , TMS) δ = 13.8 (CH₃), 14.0 (CH₃), 15.0 (CH₃), 22.6 (CH₂), 33.9 (CH₂), 35.6 (CH₂), 61.1 (CH₂), 64.5 (CH₂), 73.9 (CH), 100.1 (CH), 110.3 (CH), 115.1 (C), 118.2 (CH), 118.8 (CH), 126.3 (CH), 128.9 (CH), 130.0 (CH), 132.2 (C), 133.9 (C), 141.6 (C), 151.7 (C), 169.3 (C); MS (EI) 379 (M^+ , 13), 306 (100), 278 (31), 263 (22), 234 (25), 204 (42), 192 (21), 161 (42), 107 (18), 91 (96), 77 (36), 69 (27), 57 (25).

1-[tert-Butoxy(phenyl)methyl]-2,3-bis(methoxycarbonyl)indolizine (5a). Colorless plates (304 mg, 77%); mp 118–119 °C; ^1H NMR (90 MHz, CDCl_3 , TMS) δ = 1.22 (s, 9H), 3.87 (s, 3H), 3.95 (s, 3H), 5.94 (s, 1H), 6.80 (ddd, J 8.6, 6.7, 1.9 Hz, 1H), 6.98 (ddd, J 8.6, 8.8, 1.9 Hz, 1H), 7.1–7.6 (m, 5H), 7.73 (ddd, J 8.6, 1.9, 1.2 Hz, 1H), 9.35 (ddd, J 6.7, 1.9, 1.2 Hz, 1H); ^{13}C NMR (23 MHz, CDCl_3 , TMS) δ = 27.9 (CH₃), 51.0 (CH₃), 51.9 (CH₃), 68.9 (CH), 74.9 (C), 109.7 (C), 113.8 (CH), 117.8 (C), 119.4 (CH), 121.7 (CH), 125.3 (C), 126.1 (CH), 126.4 (CH), 126.8 (CH), 127.8 (CH), 133.8 (C), 144.0 (C), 160.5 (C), 166.9 (C); IR (neat/ cm^{-1}) 1738, 1694; MS (EI) 395 (M^+ , 44), 338 (27), 322 (100), 306 (86), 262 (25), 230 (53). Anal. Calcd. for $\text{C}_{23}\text{H}_{25}\text{NO}_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.77; H, 6.36; N, 3.54 %.

1-[Methoxy(phenyl)methyl]-2,3-bis(methoxycarbonyl)indolizine (5b). A solution of indolizine 5a (198 mg, 0.5 mmol) in methanol (10 mL) was heated under reflux for 5 hours. After evaporation, 5b (173 mg, 0.49 mmol, 98%) was obtained without any detectable by-product. Pale yellow plates; mp 107–108 °C; ^1H NMR (90 MHz, CDCl_3 , TMS) δ = 3.38 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 5.58 (s, 1H), 6.8–7.6 (m, 8H), 9.38 (br d, J 6.9 Hz, 1H); ^{13}C NMR (23 MHz, CDCl_3 , TMS) δ = 51.1 (CH₃), 52.1 (CH₃), 56.6 (CH₃), 78.1 (CH), 109.9 (C), 113.6 (C), 114.0 (CH), 118.7 (CH), 122.2 (CH), 126.2 (CH), 126.8 (CH), 127.0 (CH), 127.2 (C), 127.9 (CH), 133.8 (C), 141.2 (C), 160.4 (C), 166.6 (C); IR (neat/ cm^{-1}) 1742, 1704; MS (EI) 353 (M^+ , 35), 338 (27), 322 (100), 306 (38), 276 (26), 204 (17). Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{NO}_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.56; H, 5.32; N, 3.91 %.

Monitoring the oligomerization of indolizine 4a by ^1H NMR

To a solution of indolizine 4a (3 mg, 10 μmol) in chloroform-*d* (0.5 mL), 1,1,2,2-tetrachloroethane (8 mg) was added as an internal standard, and subjected to the measurements of ^1H NMR at several-minute intervals. The experiment was conducted in the air, and aluminium foil was used

to keep in the dark. The experiment in the light was conducted in the ambient atmosphere without irradiation of special light. The reaction rate was calculated by comparison of the integral values of indolizine **4a** and tetrachloroethane. Eliminated molecule was confirmed to be methanol by comparison of ^1H and ^{13}C NMR spectra with those of authentic sample.

Isolation of dimer 8. A solution of **4a** (50 mg, 0.17 mmol) in chloroform (15 mL) was stirred at room temperature for 1 h. The solution was concentrated and the residue was treated with column chromatography on silica gel to give dimer **8** (eluted with hexane/AcOEt = 90/10, 10 mg, 0.018 mmol) with recovery of 70% of **4a**.

Dimer 8. Brownish yellow solid, mp 41–44 °C; The dimer was found to be a mixture of isomers (73/27) by ^1H NMR. ^1H NMR (270 MHz, C_6D_6 , TMS) the major isomer δ 2.97 (s, 3H), 3.05 (s, 3H, COOMe^b), 3.11 (s, 3H, COOMe^a), 5.10 (s, 1H, H^a), 6.0–6.4 (m, 5H, H-6, -7, -6', -7', -8'), 6.33 (s, 1H, H^b), 6.60 (s, 1H, H-3'), 7.0–7.5 (m, 9H, Ph^b, H-8, -*m*, -*p*), 7.74 (dd, *J* 6.2, 1.1 Hz, 1H, H-*o*), 8.24 (dd, *J* 6.2, 1.1 Hz, 1H, H-5), 8.72 (dd, *J* 5.9, 1.1 Hz, 1H, H-5'), the minor isomer; δ 2.877 (s, 3H, OMe), 2.884 (s, 3H, COOMe^b), 3.11 (s, 3H, COOMe^a), 5.21 (s, 1H, H^a), 6.0–6.4 (m, 5H, H-6, -7, -6', -7', -8'), 6.37 (s, 1H, H^b), 6.68 (s, 1H, H-3'), 7.0–7.5 (m, 9H, Ph^b, H-8, -*m*, -*p*), 7.82 (dd, *J* 7.3, 1.6 Hz, 2H, H-*o*), 8.35 (dd, *J* 6.2, 1.1 Hz, 1H, H-5), 8.84 (dd, *J* 5.9, 1.1 Hz, 1H, H-5'); MS (EI) 558(M⁺, 11), 499 (100); IR (neat/cm⁻¹) 1740. HRMS Calcd. for $\text{C}_{35}\text{H}_{30}\text{N}_2\text{O}_5$: 558.2156. Found: 558.2158.

UV-vis spectra of oligomer of **4b**

To a suspension of oligomer of **4b** (0.3 mg, corresponding to 1 μmol monomer) in methanol (10 mL) was subjected to the measurement of UV-vis spectrum. The solution turned to yellowish brown when 1 M sodium hydroxide aqueous solution (10 μL , 10 μmol) was added. After drying up, the residue (0.4 mg) was dissolved into methanol (5 mL), and was subjected to the measurement of UV-vis. spectrum.

UV-vis spectra of oligomer of **4a** under different pH conditions

Several buffer solutions having different pH values were prepared by mixing 0.25 M aqueous solutions of boric acid and sodium hydroxide with different ratio. A solution (suspension) of oligomer **4a** (1.33 g/L) in 1,4-dioxane was also prepared. After mixing the buffer solution and dioxane solution (10/1 v/v), pH value and UV-vis. spectrum were measured.

References

1. Huang, W.; Zuo, T.; Jin, H.; Liu, Z.; Yang, Z.; Yu, X.; Zhang, L.; Zhang, L. *Mol. Diversity* **2013**, *17*, 221–243.
<https://doi.org/10.1007/s11030-013-9424-3>
2. Dinica, R. M.; Furdui, B.; Ghinea, I. O.; Bahrim, G.; Bonte, S.; Demeunynck, M. *Marine Drugs* **2013**, *11*, 431–439.
<https://doi.org/10.3390/md11020431>

3. Wan, J.; Zheng, C. J.; Fung, M. K.; Liu, Z. K.; Lee, C. S.; Zhang, X. H. *J. Mater. Chem.* **2012**, *22*, 4502–4510.
<https://doi.org/10.1039/c2jm14904d>
4. Dumitrascu, F.; Vasilescu, M.; Draghici, C.; Caproiu, M.; Teodor B.; Loredana, D. D. G. *Arkivoc* **2011**, (x), 338–350.
5. Becuwe, M.; Landy, D.; Delattre, F.; Cazier, F. Fountentin, S. *Sensors* **2008**, *8*, 3689–3705.
<https://doi.org/10.3390/s8063689>
6. Kumar, V. *Med. Chem. Res.* **2014**, *23*, 3593–3606.
<https://doi.org/10.1007/s00044-014-0940-1>
7. Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, *46*, 5237–5257.
<https://doi.org/10.1016/j.ejmech.2011.08.042>
8. Lazzaroni, R.; Settambolo, R.; Rocchiccioli, S., Guazzelli, G. *J. Organometal. Chem.* **2007**, *692*, 1812–1816.
9. Nishiwaki, N.; Furuta, K.; Komatsu, M.; Ohshiro, Y. *J. Chem. Soc., Chem. Commun.*, **1990**, 1151–1152.
<https://doi.org/10.1039/c39900001151>
10. Nishiwaki, N.; Furuta, K.; Komatsu, M.; Ohshiro, Y. *Polymer J.* **1991**, *23*, 789–794.
<https://doi.org/10.1295/polymj.23.789>
11. Jha, R.R.; Danodia, A.K.; Verma, A.K. *Tetrahedron Lett.* **2014**, *55*, 4724–4730.
<https://doi.org/10.1016/j.tetlet.2014.06.092>
12. Chernyak, D.; Gevorgyan, V. *Chem. Heterocycl. Compd.* **2012**, *47*, 1516–1526.
<https://doi.org/10.1007/s10593-012-0942-1>
13. Verma, A. K.; Jha, R. R.; Chaudhary, R.; Tiwari, R. K.; Reddy, K. S. K.; Danodia, A. *J. Org. Chem.*, **2012**, *77*, 8191–8205.
<https://doi.org/10.1021/jo301572p>
14. Specowius, V.; Bendrath, F.; Winterberg, M.; Ayub, K.; Langer, P.; *Adv. Synth. Catal.*, **2012**, *354*, 1163–1169.
<https://doi.org/10.1002/adsc.201100795>
15. Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440–1452.
<https://doi.org/10.1021/ja0773507>
16. Chernyak, D.; Gevorgyan, V. *Chem. Heterocycl. Compd.* **2012**, *47*, 1516–1526.
<https://doi.org/10.1007/s10593-012-0942-1>
17. Li, H.; Xia, Z.; Chen, S.; Koya, K.; Ono, M.; Sun, L. *Org. Proc. Res. Develop.* **2007**, *11*, 246–250.
<https://doi.org/10.1021/op6002852>
18. Hardin, A. R.; Sarpong, R. *Org. Lett.* **2007**, *9*, 4547–4550.
<https://doi.org/10.1021/ol701973s>
19. Schwier, T.; Sromek, A. W.; Yap, D. M. L.; Chernyak, D.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 9868–9878.

- <https://doi.org/10.1021/ja072446m>
20. Sashida, H.; Kato, M.; Tsuchiya, T. *Chem. Pharm. Bull.* **1988**, *36*, 3826–3832.
<https://doi.org/10.1248/cpb.36.3826>
21. Tsuchiya, T.; Kato, M.; Sashida, H. *Chem. Pharm. Bull.* **1984**, *32*, 4666–4669.
<https://doi.org/10.1248/cpb.32.4666>
22. Ohsawa, A.; Abe, Y.; Igeta, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 3273–3275.
<https://doi.org/10.1246/bcsj.53.3273>
23. Ohsawa, A.; Abe, Y.; Igeta, H. *Chem. Lett.* **1979**, *8*, 241–244.
<https://doi.org/10.1246/cl.1979.241>
24. Wu, Y. H.; Ling, L.; Zhang, J.; Yu, J.; Tong, S. L.; Yan, Y. *Inorg. Chem. Commun.* **2014**, *45*, 10–14.
<https://doi.org/10.1016/j.inoche.2014.03.017>
25. Dutta, T.; Che, Y.; Zhong, H.; Laity, J. H.; Dusevich, V.; Murowchick, J. B.; Zang, L.; Peng, Z. *RSC Adv.* **2013**, *3*, 6008–6015.
<https://doi.org/10.1039/c3ra23421e>
26. Yang, Y.; Zhang, Q.; Zheng, J.; Zhang, S. *Polymer* **2013**, *54*, 3254–3260.
<https://doi.org/10.1016/j.polymer.2013.04.038>
27. Wang, K.; Hoshina, Y.; Cao, Y.; Tagaya, M.; Kobayashi, T. *Ind. Eng. Chem. Res.*, **2013**, *52*, 2762–2771.
<https://doi.org/10.1021/ie302814a>
28. Markova, M. V.; Shmidt, E. Y.; Morozova, L. V.; Tatarinova, I. V.; Prozorova, G. F.; Mikhaleva, A. I.; Trofimov, B. A. *Chem. Heterocycl. Compd.* **2012**, *48*, 280–286.
<https://doi.org/10.1007/s10593-012-0987-1>
29. Can, M.; Oezaslan, H.; Isildak, O.; Pekmez, N. O.; Yildiz, A. *Polymer* **2004**, *45*, 7011–7016.
<https://doi.org/10.1016/j.polymer.2004.08.003>
30. Langsdorf, B. L.; Sultan, J.; Pickup, P. G. *Phys. Chem. B* **2003**, *107*, 8412–8415.
<https://doi.org/10.1021/jp035210n>
31. Hawkins, S. J.; Ratcliffe, N. M. *J. Mater. Chem.* **2000**, *10*, 2057–2062.
<https://doi.org/10.1039/b001912g>
32. Hizal, G.; Emiroglu, S. E.; Yagci, Y. *Polym. Int.* **1998**, *47*, 391–396.
[https://doi.org/10.1002/\(SICI\)1097-0126\(199812\)47:4<391::AID-PI114>3.0.CO;2-#](https://doi.org/10.1002/(SICI)1097-0126(199812)47:4<391::AID-PI114>3.0.CO;2-#)
33. Yoon, K. B.; Huh, T. J.; Kochi, J. K. *J. Phys. Chem.* **1995**, *99*, 7042–7053.
<https://doi.org/10.1021/j100018a042>