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Fused-Fluoran Leuco Dyes with Large Color-Change Derived from Two-Step Equilibrium: *iso*-Aminobenzopyranoxanthenes

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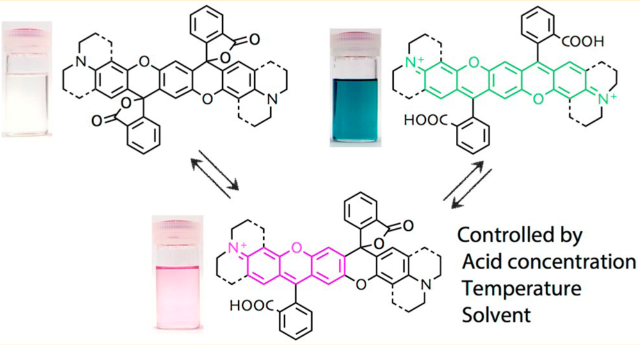
Supporting Information

ABSTRACT: Fluorans are popular leuco dyes that are used in various applications, such as carbonless-copy papers and thermal papers. Here, we describe unique leuco dyes in which two fluoran units are fused into a C_{2h} structure (*iso*-aminobenzopyranoxanthenes; *iso*-ABPXs). *iso*-ABPXs exhibited a large two-step color change (colorless/pink and pink/blue-green) due to opening−closing of two spirolactone rings. The two-step equilibrium among the colorless, pink, and blue-green forms could be well controlled by adjusting acid concentration, solvent, and/or temperature.



Fluoran leuco dyes, which consist of a xanthene chromophore and a spirolactone ring as a stimulus-responsive site, are organic dyes that can switch between colorless and colored forms in response to external stimuli (Figure 1a).[1] Color appears when acids or metal ions bind to the lactone ring. These dyes not only have been used in traditional applications such as carbonless-copy and thermal papers[2] but also have new applications such as erasable pens, electronic papers, and multifunctional films.[3] Although a variety of peripherally functionalized fluoran leuco dyes have been developed so far to obtain various colored dyes, little attention has been focused toward expanding the xanthene π-electron system. We previously reported the design of aminobenzopyranoxanthenes (ABPXs) containing two fluorans fused with C_{2v} symmetry (Figure 1a).[4] ABPXs have two spirolactone rings and therefore form three chemical species in response to external stimuli such as changes of proton and metal ion concentration: the neutral form is colorless, and the monocation (pink, $ABPX^+$) and the dication (purple, $ABPX^{2+}$) are colored. This unique two-step equilibrium can be employed for colorimetric sensing of Cu^{2+}[4c] or Hg^{2+},[5] although the difference of the longest absorption wavelengths between the monocation and the dication ($\Delta\lambda_{abs}$ = 60−70 nm) is rather small.[4b,d]

Herein, we report experimental and theoretical studies of fluoran leuco dyes of a new type, *iso*-ABPXs, in which two fluoran units are fused into a C_{2h} structure (Figure 1b). *iso*-ABPXs exhibited a large two-step color change (colorless, pink, and blue-green), with $\Delta\lambda_{abs} \approx 110$ nm. We also uncovered the reason why the monocationic form of *iso*-ABPXs is selectively formed under certain conditions, despite the symmetrical structure with identical spirolactone moieties.

Density functional theory (DFT) calculations were first conducted to evaluate *iso*-ABPXs. The dicationic form of **1** ($\mathbf{1}^{2+}$) was estimated to have a narrower HOMO−LUMO gap (2.37 eV) as compared with the corresponding ABPX (Figure 1a, R = C_2H_5) (2.59 eV). The LUMO energy of $\mathbf{1}^{2+}$ (−8.19 eV) was considerably lower than that of ABPX (−7.96 eV), whereas the HOMO energies were almost the same as each other. The difference mainly arises from the fact that the LUMO coefficients on the central benzene ring of $\mathbf{1}^{2+}$ were quite

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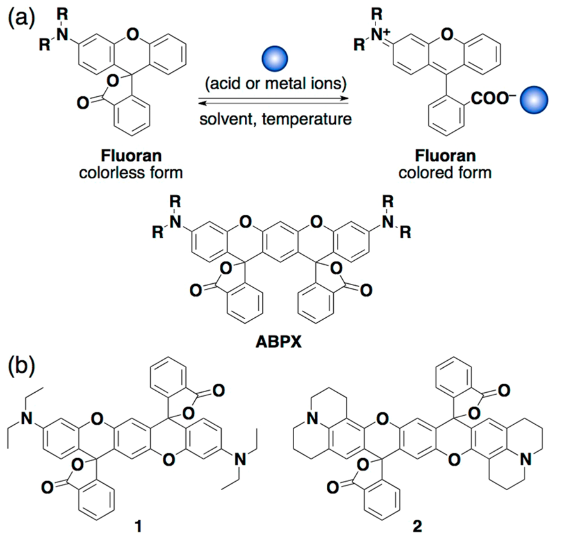


Figure 1. (a) Top: Equilibrium of two forms of fluoran. Bottom: Chemical structure of ABPX. (b) Chemical structures of *iso*-ABPXs.

different from those of ABPX (Figure S1), whereas the HOMO coefficients were almost identical with those of ABPX.

We then synthesized two types of *iso*-ABPXs ($\mathbf{1}$ and $\mathbf{2}$) by reacting 1 equiv of hydroquinone with 2 equiv of a benzophenone precursor in a strong Brønsted acid (methanesulfonic acid or sulfuric acid) in order to investigate the effect of functional groups on the nitrogen atoms (Scheme 1).[6] The reaction yield of $\mathbf{2}$ was lower than $\mathbf{1}$, although we tried several reaction conditions.[7] *iso*-ABPXs, like ABPXs, have isomers arising from the configuration of two spirolactone units. In the *trans*-forms ($\mathbf{1}_{trans}$ and $\mathbf{2}_{trans}$), the two lactone carbonyl groups are on the opposite side of the xanthene ring, whereas these groups are on the same side in the *cis*-forms ($\mathbf{1}_{cis}$ and $\mathbf{2}_{cis}$). The two isomers could be separated by normal silica-gel chromatography. In the case of $\mathbf{1}$, the configuration was confirmed by X-ray crystallography. The bond lengths between spiro-carbon and lactone oxygen atoms ($\mathbf{1}_{trans}$: 1.505(2) Å, $\mathbf{1}_{cis}$: 1.505(2) and 1.506(2) Å) were longer than the typical C(sp^3)−O bond length (1.43 Å). Such elongation, which has also been seen in the X-ray structures of other fluoran leuco dyes, gives easy cleavage of the C−O bonds to open the lactone ring.[8]

UV−vis spectra of $\mathbf{1}_{trans}$ were measured in chloroform upon addition of trifluoroacetic acid (TFA) in order to test the dependence of color change on acid concentration (Figure 2a).

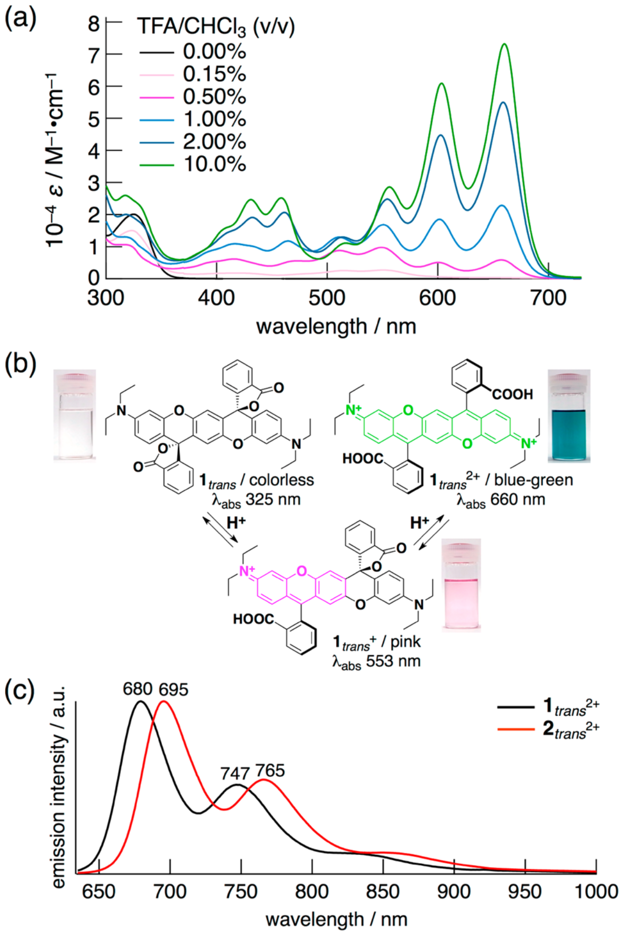
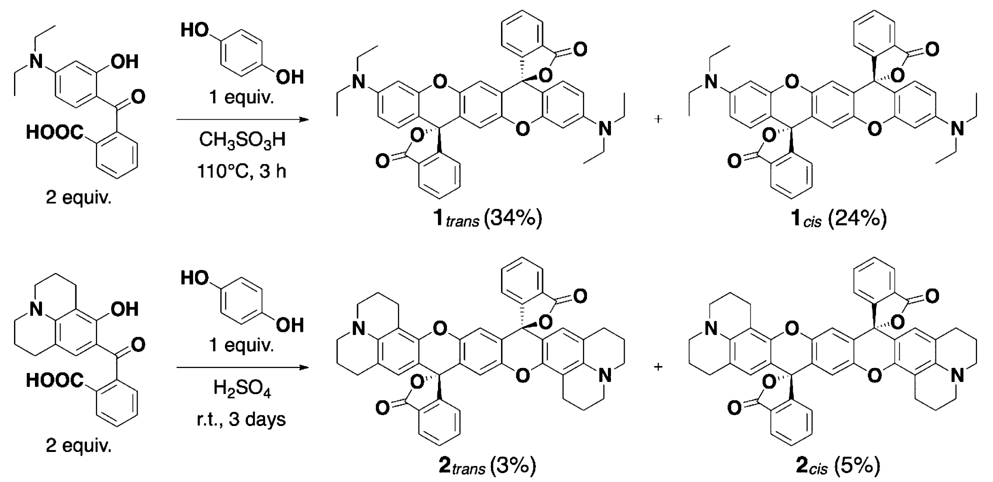


Figure 2. (a) Absorption spectra of $\mathbf{1}_{trans}$ in CHCl$_3$ with various amounts of TFA. (b) Two-step equilibrium of $\mathbf{1}_{trans}$ in solution. (c) Fluorescence emission spectra of $\mathbf{1}_{trans}{}^{2+}$ and $\mathbf{2}_{trans}{}^{2+}$ in 10% (v/v) TFA/CHCl$_3$. Excitation wavelength is 620 nm.

The chloroform solution of $\mathbf{1}_{trans}$ was colorless, and an absorbance peak at 325 nm was observed. When a small

Scheme 1. Synthesis of *iso*-ABPX Dyes 1 and 2



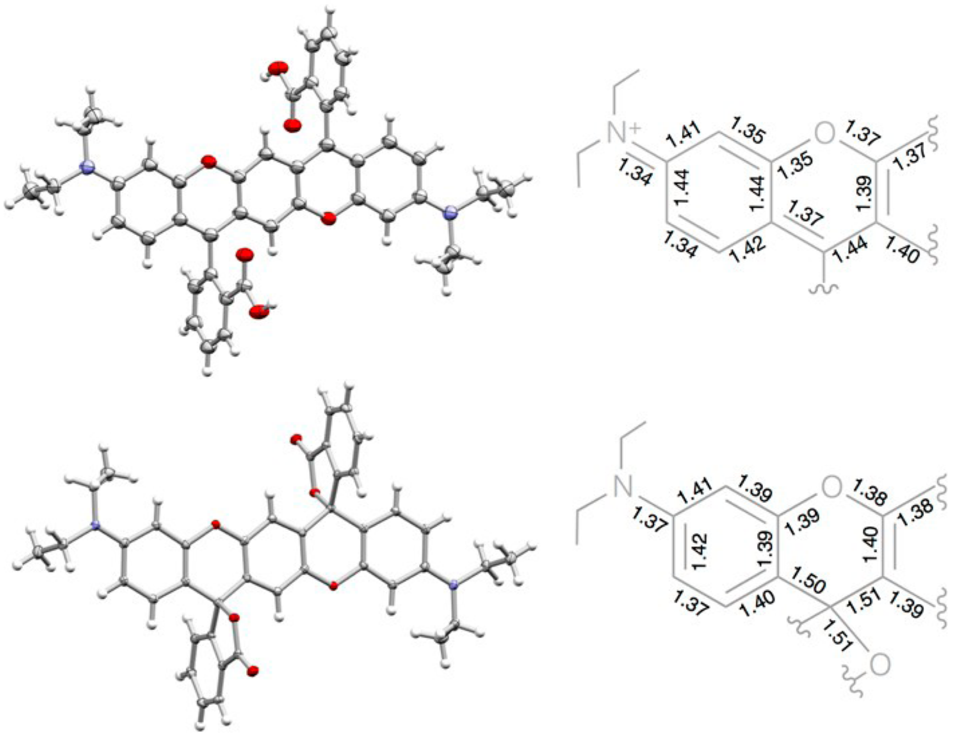


Figure 3. X-ray structures of $\mathbf{1}_{trans}{}^{2+}\cdot 2(BF_4{}^-)$ (top) and $\mathbf{1}_{trans}$ (bottom). Left: ORTEP diagrams (ellipsoids are set at 40% probability). Solvent molecules, counteranions, and disorders were omitted for clarity. Right: Bond lengths of benzopyranoxanthene rings.

amount of TFA was added to the chloroform solution of $\mathbf{1}_{trans}$, the color of the solution turned to light pink and a peak appeared at 553 nm. As the TFA concentration was increased, the solution turned blue-green, and a new peak appeared at 660 nm. The color was turned off by addition of base, in accordance with the expected characteristic of leuco dyes. Almost the same spectral changes were observed for $\mathbf{1}_{cis}$ (Figure S2). No interconversion between $\mathbf{1}_{trans}$ and $\mathbf{1}_{cis}$ was observed, at least after several hours in TFA/$CHCl_3$.

We assigned the pink species and the blue-green species to the monocationic form of $\mathbf{1}_{trans}$ ($\mathbf{1}_{trans}{}^{+}$) and the dication $\mathbf{1}_{trans}{}^{2+}$, respectively; these assignments were strongly supported by TD-DFT calculations (Figures 2b, S3). As compared to the peak positions of the corresponding ABPX, the peaks of $\mathbf{1}_{trans}{}^{+}$ and $\mathbf{1}_{trans}{}^{2+}$ were red-shifted by 25 and 62 nm, respectively. $\Delta\lambda_{abs}$ was ∼110 nm for $\mathbf{1}_{trans}$, which was 1.5−1.8 times larger than $\Delta\lambda_{abs}$ (60−70 nm) for previously reported ABPXs. A solution of $\mathbf{2}_{trans}$ changed color in the same manner as in the case of $\mathbf{1}_{trans}$. One-twentieth the amount of acid (0.5%) was sufficient to form the dication of $\mathbf{2}_{trans}$, indicating that the julolidine unit shifted the lactone ring opening−closing equilibrium to the open form (Figure S4).[9]

Fluorescence emission from the dicationic forms was detected in 10% TFA/chloroform. The peak position was 680 nm ($\mathbf{1}_{trans}{}^{2+}$) or 695 nm ($\mathbf{2}_{trans}{}^{2+}$), and the vibronic structures were observed in the near-infrared region (Figure 2c). These emission bands are comparable in wavelength to those of xanthene dyes developed for bioimaging applications.[10] The fluorescence quantum yield was 9% ($\mathbf{1}_{trans}{}^{2+}$) or 8% ($\mathbf{2}_{trans}{}^{2+}$).

The dicationic form of *iso*-ABPX was unambiguously identified by X-ray crystallography. There has been one report on the X-ray structure of ring-opened fluoran leuco dyes, except for rhodamines.[11] We succeeded in obtaining single crystals of $\mathbf{1}_{trans}{}^{2+}\cdot 2(BF_4{}^-)$ by using an excess of HBF_4. A quinoidal structure was observed for the outer benzene ring of a xanthene moiety of $\mathbf{1}_{trans}{}^{2+}$, compared to that of $\mathbf{1}_{trans}$ (Figure 3).

As the equilibrium between colorless and color forms of fluoran leuco dyes is sensitive to solvent and temperature,[12] the effects of the external environment on the optical properties were investigated to examine what factors would influence the two-step equilibrium. We measured the electronic absorption spectra in various alcohols with constant acid concentration (0.5% TFA) at 25 °C (Figure 4a). Interestingly, the spectral pattern was sensitively dependent on the alkyl chain length of alcohols. We found that the dielectric constant (ε_r) plays an important role in determining the ratio of the chemical species in alcohols.[13] In the case of $\mathbf{1}_{trans}$, the dicationic form ($\mathbf{1}_{trans}{}^{2+}$) was formed in alcohols with $\varepsilon_r > 20$, whereas the preferential form in alcohols with $\varepsilon_r < 15$ was the neutral form ($\mathbf{1}_{trans}$). Although the monocationic form ($\mathbf{1}_{trans}{}^{+}$) existed in these solvents, the ratio was larger in alcohols with moderate ε_r. Solvatochromism was also observed in $\mathbf{2}_{trans}$ (Figure S5).

We calculated the relative energies of $\mathbf{1}_{trans}$, $\mathbf{1}_{trans}{}^{+}$, and $\mathbf{1}_{trans}{}^{2+}$ in five alcohol solvents. It is clear from Figure 4c that all the species are stabilized in solvent with large ε_r and that the stabilization is larger in the order of $\mathbf{1}_{trans}{}^{2+}$, $\mathbf{1}_{trans}{}^{+}$, $\mathbf{1}_{trans}$. The changes of the stabilization slope likely reflect the species ratio. Thermochromic effect was investigated in 0.1% TFA/MeOH solution, since the $\mathbf{1}_{trans}{}^{+}$:$\mathbf{1}_{trans}{}^{2+}$ ratio was about 1:1 at 25 °C. The blue-green solution at −10 °C gradually changed to pink when the solution temperature was raised to 50 °C. Isosbestic points observed at 471 and 539 nm support the existence of an equilibrium between $\mathbf{1}_{trans}{}^{2+}$ and $\mathbf{1}_{trans}{}^{+}$ (Figure S7). As expected, the color change was reversed when the solution temperature was lowered. We consider that the origin of the thermochromism is temperature dependence of the dielectric constant of methanol (ε_r(50 °C) = 28.0; ε_r(−10 °C) = 40.1).[14]

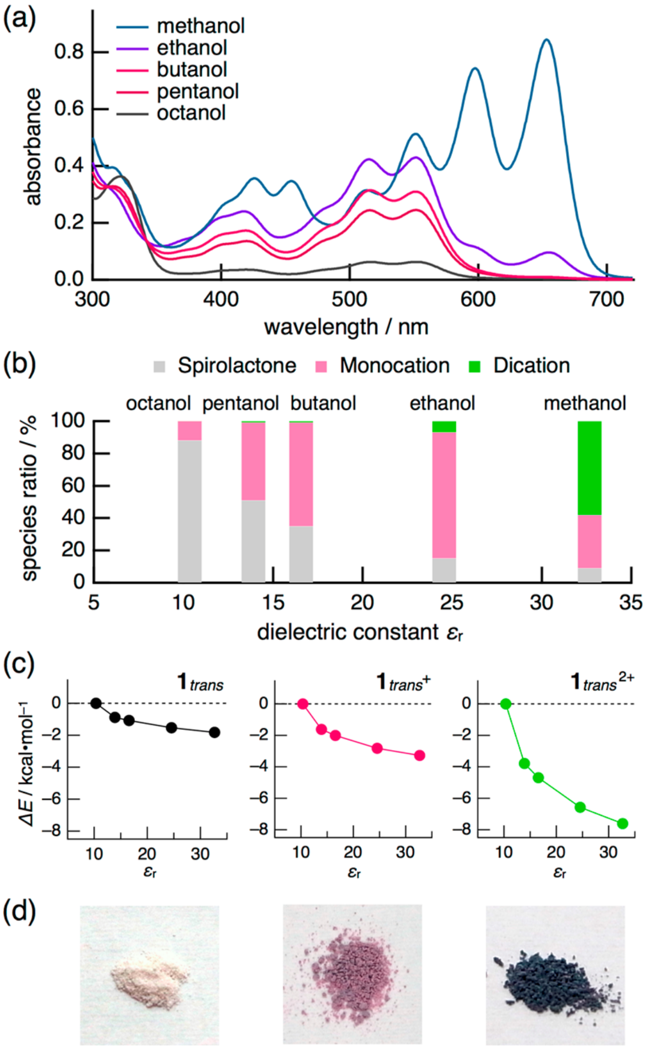


Figure 4. (a) Absorption spectra of $\mathbf{1}_{trans}$ (20 μM) in various alcohols with 0.5% TFA at 25 °C. (b) Relationship between the ratio of chemical species and solvents' dielectric constant at 25 °C (20 °C for octanol). (c) Calculated relative energies of chemical species, with consideration of solvent effect (B3LYP/6-31G**). Energies for ε_r = 10.34 were set to zero. (d) Pictures of the $\mathbf{1}_{trans}$ powder, mixed with several molar equivalents of catechol: 0.0, 0.1, and 2.0 (from left to right).

The two-step color change was also observed in the solid state. A mixture of $\mathbf{1}_{trans}$ and catechol was ground using an agate mortar. The colorless powder of $\mathbf{1}_{trans}$ turned pink with 0.1 equiv of catechol, and green powder was obtained with 2.0 equiv of catechol (Figure 4d). These colors immediately disappeared when the powders were exposed to solvent vapor. These changes are considered to arise from formation of 1:1 and 1:2 complexes of the zwitterionic form of $\mathbf{1}_{trans}$ with catechol.[15] Since the combination of fluoran leuco dyes and phenolic compounds is the most widely used system for applications in thermal and carbonless-copy papers,[16] we believe that the *iso*-ABPXs are a promising new class of leuco dye with multicolor changes.

In summary, we have designed and synthesized fluoran-fused fluoran leuco dyes, *iso*-ABPXs that exhibit large two-step color changes. The structure of the dicationic form of the *iso*-ABPX with diethylamino moieties was unequivocally established by X-ray crystallography. The molar ratio of the three chemical species (neutral form, monocation, and dication) could be well controlled by adjusting the solvent, temperature, and/or acid concentration. The dielectric constant (ε_r) of the solvent is a critical parameter determining the species ratio in TFA/alcohol solutions. The unique properties of the present leuco dyes suggest that these dyes may find various applications, including multicolor thermochromic inks, colorimetric pH/alcohol indicators, and near-infrared fluorescent bioimaging.

■ EXPERIMENTAL SECTION

General Remarks. Unless otherwise noted, materials were used after appropriate purification. ^{1}H NMR spectra were obtained on a 300, 400, or 500 MHz spectrometer. ^{13}C NMR spectra were obtained on a 75, 100, or 125 MHz spectrometer. ^{1}H and ^{13}C NMR spectra were referenced to tetramethylsilane (TMS) or $CHCl_3$ as an internal standard. Chemical shifts are expressed in δ (ppm) values. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, td = triplet doublet, and m = multiplet. High-resolution mass spectra (HRMS) were recorded by ESI-TOF mass spectrometers. Melting points are uncorrected. Electronic absorption spectra were measured with a temperature control unit and a 1 cm quartz cuvette at 25 °C unless otherwise noted. The absolute fluorescence quantum yield was measured using an integrating sphere. 9-(2-Carboxybenzoyl)-8-hydroxyjulolidine was synthesized using the procedure reported previously.[17]

Synthesis of $\mathbf{1}_{trans}$ and $\mathbf{1}_{cis}$. To a solution of 2-[4-(diethylamino)-2-hydroxybenzoyl]benzoic acid (620 mg, 2.0 mmol) dissolved in methanesulfonic acid (5.0 mL), hydroquinone (110 mg, 1.0 mmol) was added and heated at 110 °C for 3 h. After cooling down to room temperature, the reaction mixture was neutralized by 2 M NaOH solution and extracted by $CHCl_3$ (10 mL for 3 times). The solvent was evaporated to give a purple solid. The crude product was purified by silica-gel chromatography, eluted by $CHCl_3$/MeOH = 40:1 to 30:1, and the products $\mathbf{1}_{trans}$ and $\mathbf{1}_{cis}$ were obtained separately. The *trans*-form was found to be eluted faster than the *cis*-form.

$\mathbf{1}_{trans}$. Colorless powder, yield 34% (226 mg). R_f = 0.48 ($CHCl_3$/MeOH = 30:1). Mp >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.0 Hz, 2H), 7.72 (td, J = 7.5, 1.0 Hz, 2H), 7.65 (td, J = 7.5, 1.0 Hz, 2H), 7.25 (s, 1H), 6.69 (s, 2H), 6.56 (d, J = 8.5 Hz, 2H), 6.35 (d, J = 2.5 Hz, 2H), 6.32 (s, 2H), 3.31 (q, J = 7.0 Hz, 8H), 1.13 (t, J = 7.0 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 152.9, 152.6, 149.7, 147.4, 135.1, 129.8, 128.8, 127.0, 125.0, 124.2, 122.4, 115.6, 108.4, 104.1, 97.4, 83.5, 44.5, 12.4; HRMS (ESI) m/z calcd for $C_{42}H_{37}N_2O_6$ ([M + H]$^+$): 665.2651; found: 665.2657.

$\mathbf{1}_{cis}$. Colorless powder, yield 24% (160 mg). R_f = 0.36 ($CHCl_3$/MeOH = 30:1). Mp >300 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 7.0 Hz, 2H), 7.67 (td, J = 7.3, 1.2 Hz, 2H), 7.63 (td, J = 7.5, 1.5 Hz, 2H), 7.20 (d, J = 6.0 Hz, 2H), 6.71 (s, 2H), 6.57 (d, J = 8.5 Hz, 2H), 6.35 (d, J = 2.5 Hz, 2H), 6.34 (d, J = 3.0 Hz, 2H), 6.32 (s, 2H), 3.31 (q, J = 7.0 Hz, 8H), 1.13 (t, J = 7.0 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 153.0, 152.7, 149.7, 147.2, 134.8, 129.7, 128.7, 126.9, 125.1, 123.9, 122.5, 115.6, 108.4, 104.2, 97.4, 83.1, 44.5, 12.4; HRMS (ESI) m/z calcd for $C_{42}H_{37}N_2O_6$ ([M + H]$^+$): 665.2651; found: 665.2657.

$\mathbf{1}_{trans}^{2+}$ was generated from $\mathbf{1}_{trans}$. ^{1}H NMR (400 MHz, 10% (v/v) TFA/$CDCl_3$): δ 8.54 (m, 2H), 7.99−7.91 (m, 4H), 7.43−7.42 (m, 4H), 7.31−7.28 (m, 4H), 7.14−7.12 (m, 2H), 6.88 (broad s, 2H), 3.78 (broad s, 8H), 1.14 (broad s, 12H).

Synthesis of $\mathbf{2}_{trans}$ and $\mathbf{2}_{cis}$. To a solution of 9-(2-carboxybenzoyl)-8-hydroxyjulolidine (1.0 g, 3.0 mmol) dissolved in sulfuric acid (3.0 mL) at 0 °C, hydroquinone (170 mg, 1.5 mmol) was added and stirred at room temperature for 3 days. The reaction mixture was neutralized by 2 M NaOH solution and was filtered through the Celite pad. The aqueous solution was extracted by $CHCl_3$ (30 mL for 4 times). The organic layer was evaporated to give a black-purple solid. The crude product was purified by silica-gel chromatography, eluted by $CHCl_3$/MeOH = 10:1 to 5:1, and the products $\mathbf{2}_{trans}$ and $\mathbf{2}_{cis}$ were obtained separately.

2$_{trans}$. Slightly brown powder, yield 3% (32 mg). R_f = 0.44 ($CHCl_3$/MeOH = 20:1). Mp >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 7.2 Hz, 2H), 7.72 (t, J = 7.2 Hz, 2H), 7.65 (t, J = 7.2 Hz, 2H), 7.24 (d, J = 7.6 Hz, 2H), 6.64 (s, 2H), 6.12 (s, 2H), 3.13 (m, 8H), 2.80 (m, 4H), 2.52 (m, 4H), 1.97 (m, 4H), 1.86 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 147.8, 147.2, 144.6, 135.1, 129.7, 126.9, 125.0, 124.3, 122.0, 117.7, 115.1, 107.1, 104.0, 84.3, 49.8, 49.4, 27.3, 21.7, 21.1, 21.0; HRMS (ESI) m/z calcd for $C_{46}H_{37}N_2O_6$ ($[M + H]^+$): 713.2646; found: 713.2655.

2$_{cis}$. Slightly brown powder, yield 5% (53 mg). R_f = 0.39 ($CHCl_3$/MeOH = 20:1). Mp >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 6.0 Hz, 2H), 7.66 (td, J = 7.4, 1.7 Hz, 2H), 7.62 (td, J = 7.5, 1.3 Hz, 2H), 7.16 (d, J = 6.8 Hz, 2H), 6.70 (s, 2H), 6.15 (s, 2H), 3.11 (m, 8H), 2.80 (m, 4H), 2.51 (m, 4H), 1.95 (m, 4H), 1.85 (m, 4H); HRMS (ESI) m/z calcd for $C_{46}H_{37}N_2O_6$ ($[M + H]^+$): 713.2646; found: 713.2674. Solubility of **2**$_{cis}$ in $CDCl_3$ was too low to measure the ^{13}C NMR spectra.

2$_{trans}^{2+}$ was generated from **2**$_{trans}$. ^{1}H NMR (400 MHz, 0.5% (v/v) TFA/$CDCl_3$): δ 8.47 (d, 2H, J = 7.2 Hz), 7.89 (t, 2H, J = 7.8 Hz), 7.85 (t, 2H, J = 8.2 Hz), 7.38 (d, 2H, J = 8.0 Hz), 7.30 (s, 2H), 6.80 (s, 2H), 3.68 (m, 8H), 2.98 (m, 4H), 2.76 (m, 4H), 2.08 (m, 8H).

Computational Details. Density functional calculations were performed using the Gaussian09 program package.[18] Geometry optimization for the ground state was performed at the B3LYP density functional and the 6-31G** basis sets. Excitation wavelengths and oscillator strengths were calculated by the TD-DFT approach at the same level as above. The solvent effect was taken into account using the self-consistent reaction field (SCRF) method. The dielectric constants we used in Figure 4 are slightly different from the constants used in the Gaussian09 program package (Table S2).

Solid-State Mixing Experiment. To the powder of **1**$_{trans}$ (24 mg) several molar equivalents (0, 0.1, 2.0 equiv) of catechol were added and ground for 30 s in an agate mortar. After grinding, the mixed powder was collected and transferred to a white plate and the colors were compared.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02403.

^{1}H and ^{13}C NMR spectra, absorption spectra, calculated absorption spectra, X-ray crystallography details and Cartesian coordinates (PDF)

Crystallographic data for **1**$_{trans}$ (CIF)

Crystallographic data for **1**$_{cis}$ (CIF)

Crystallographic data for **1**$_{trans}^{2+}\cdot 2(BF_4^-)$ (CIF)

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Notes

The authors declare no competing financial interest.

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