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SYNTHESES AND ACID-STIMULUS RESPONSIVENESS OF AMINOBENZOPYRANOXANTHENE SPIROETHERS

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Dedicated to Professor Dr. Tohru Fukuyama on the occasion of his 70th birthday

Abstract – Novel aminobenzopyranoxanthene spiroethers (ABPX-SEs) based on the spirocyclization of the hydroxymethyl group were synthesized from ABPX spirolactones (ABPX-SLs). The addition of an acid induces a ring-opening reaction to yield two colored monocationic and dicationic spiro-ring species of ABPX. The acid-stimulus responsiveness of the ABPX-SEs is lower than that of ABPX-SLs in polar organic solvents. In addition, the ABPX-SEs exhibit stepwise structural changes of the three equilibrium species at acidic pH, although rapid conversion from the spirolactone to dicationic species occurs in the case of ABPX-SLs.

Xanthenes belong to a traditional class of organic dyes and have received substantial attention for more than a century owing to their high absorptivity, excellent fluorescence properties, and good photostability.[1] Conventional xanthene dyes, containing one spiro-ring as a stimulus-responsive moiety, can be reversibly interconverted between two states by the application of a chemical stimulus, e.g., in the presence of acid and/or base. The color of these dyes originates from a ring-opening reaction when the acid interacts with the spiro-ring. By virtue of their color development mechanism, xanthene dyes are used in a variety of applications, including carbonless and thermal papers,[2] erasable inks,[3] acid sensors,[4] and pH indicators.[5]

Aminobenzopyranoxanthenes (ABPX), a novel class of xanthene dye, that have attracted increasing interest because of their outstanding photophysical properties. Compared with traditional xanthene dyes, ABPX spirolactones (ABPX-SLs) (**1**), the prototypical ABPX contains two spirolactone rings and shows two-step structural changes of the three equilibrium species in response to acidification.[6] The closed spiro-ring species is colorless, while the mono- and dicationic species are colored (Figure 1). Although this unique two-step equilibrium can be exploited for application to colored materials,[7] colorimetric sensors,[8] etc., little is known about the structural features and conditions that regulate the ring-opening/closing reaction. Therefore, further studies are required to understand the effect of spiro-ring substituents on the chemical equilibrium of ABPX. Herein, we prepared ABPX spiroethers (ABPX-SEs), by reduction of the spirolactone carbonyl moiety of ABPX-SLs, and investigated their acid-stimulus responsiveness in organic solvents. Additionally, we investigated the pH-dependent properties of the prepared ABPX derivatives.

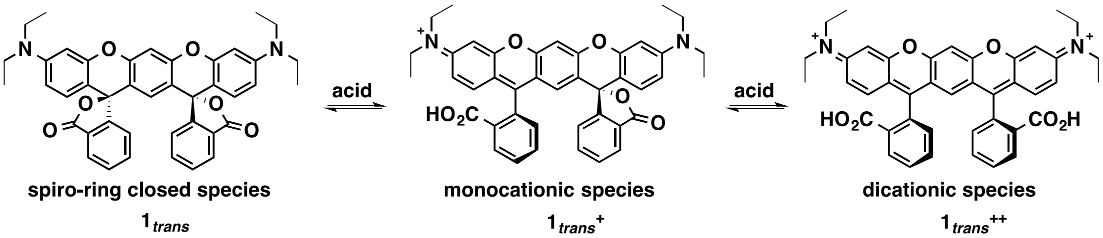
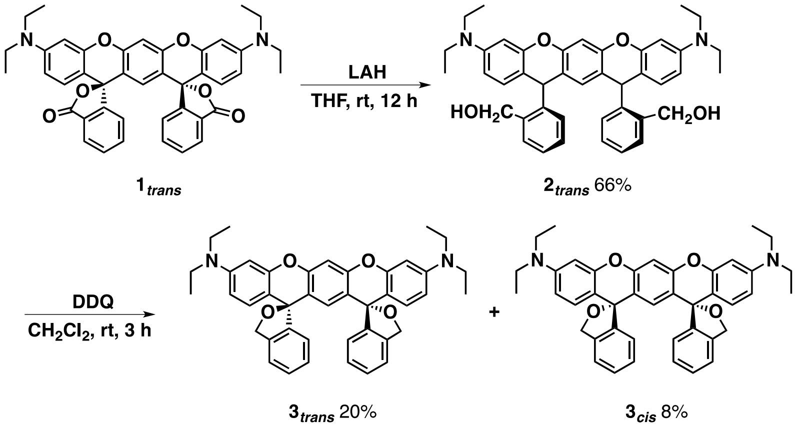


Figure 1. Interaction of ABPX spirolactones ($\mathbf{1}_{trans}$) with acid to form the ring-opened, colored monocationic ($\mathbf{1}_{trans}{}^{+}$) and dicationic ($\mathbf{1}_{trans}{}^{++}$) species

Compound **1** has two stereoisomers, the *trans*- and *cis*-forms, which result from different orientations of the spirolactone pair. Compound $\mathbf{1}_{trans}$ was used as the starting material for simple purification. As shown in Scheme 1, lithium aluminum hydride (LAH) in tetrahydrofuran at room temperature reduced $\mathbf{1}_{trans}$ to ABPX-SEs ($\mathbf{2}_{trans}$) in 66% yield without *trans*–*cis* isomerization. Oxidation of compound $\mathbf{2}_{trans}$ by 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) proceeded readily in CH_2Cl_2 and generated compound **3**. Unfortunately, under the oxidative conditions used in this study, both *trans*- and *cis*-isomers ($\mathbf{3}_{trans}$ and $\mathbf{3}_{cis}$) were obtained.



Scheme 1. Syntheses of ABPX-SEs (**3**)

Thus, these stereoisomers were separated by silica gel column chromatography, and their structures were subsequently characterized.[9] For the acid-stimulus responsiveness, there was no significant difference between two stereoisomers of compounds **1** and **3**. Therefore, detailed investigations were performed with *trans*-form.

Initially, the acid-stimulus responsiveness of $\mathbf{1}_{trans}$ and $\mathbf{3}_{trans}$ was investigated in polar solvents such as MeOH, acetone, MeCN, and DMSO containing 1.0% trifluoroacetic acid (TFA), as shown in Figure 2. For $\mathbf{1}_{trans}$, an absorption band at 550–590 nm, attributed to the dicationic species, was preferentially observed in MeOH, acetone, and MeCN. In contrast, the absorption maxima of compound $\mathbf{3}_{trans}$ appeared at a shorter wavelength in MeOH, acetone, and MeCN. The absorption bands at approximately 540 and 490 nm were attributed to the electronic 0-0 transition and the vibronic 0-1 transition of the monocationic species, respectively, suggesting that the closed spiro-ring and monocationic species coexisted in DMSO for both compounds.

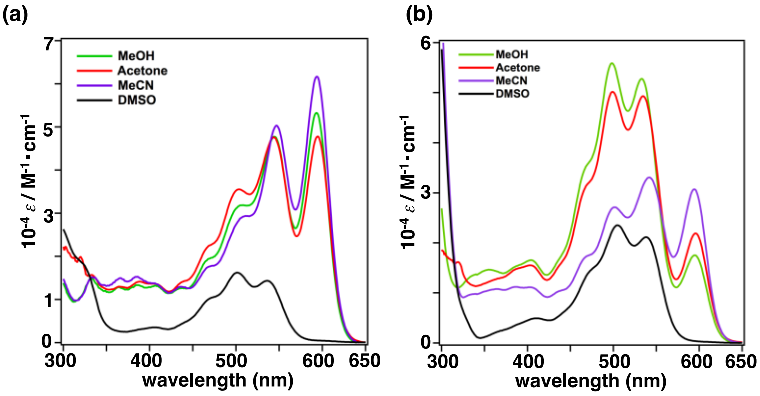


Figure 2. Absorption spectra of (a) ABPX-SLs ($\mathbf{1}_{trans}$) and (b) ABPX-SEs ($\mathbf{3}_{trans}$) in MeOH, acetone, MeCN, and DMSO containing 1.0% TFA

To investigate the acidic pH responsiveness, titrations were performed using solutions of compounds $\mathbf{1}_{trans}$ (5 μM) and $\mathbf{3}_{trans}$ (27 μM) in acetate buffer and monitored by UV-vis spectrophotometry (Figure 3). Small aliquots of HCl or AcOH were added to adjust the solution pH. Above pH 4.2, the absorption spectra of compound $\mathbf{1}_{trans}$ showed a peak in the UV region, indicative of the colorless closed spiro-ring species. At pH ≤ 3.3, the absorption spectrum exhibited a major vibronic band peak at 550–590 nm (in the visible region), and the solution changed from colorless to purple, as could be detected by the naked eye. This drastic color change is typical for the colored dicationic species of $\mathbf{1}_{trans}$. Compound $\mathbf{3}_{trans}$ absorbed UV light under neutral and slightly acidic conditions, similar to compound $\mathbf{1}_{trans}$. Notably, upon the addition of HCl, the absorption spectrum of $\mathbf{3}_{trans}^{++}$ showed a new vibronic band at 490–540 nm in addition to the band due to the dicationic species ($\mathbf{3}_{trans}^{++}$) (Figure 4). These features in the absorption spectrum showed that the reaction is an equilibrium conversion of the closed spiro-ring species to a monocationic species

($\mathbf{3}_{trans}^{+}$) in response to the lowered pH. In addition, the absorbance corresponding to $\mathbf{3}_{trans}^{+}$ and $\mathbf{3}_{trans}^{++}$ simultaneously increased as the solution was more acidic than pH 3.3, indicating the difference of pK_a values from $\mathbf{3}_{trans}$ to $\mathbf{3}_{trans}^{+}$, and then to $\mathbf{3}_{trans}^{++}$ was very small in aqueous solution.

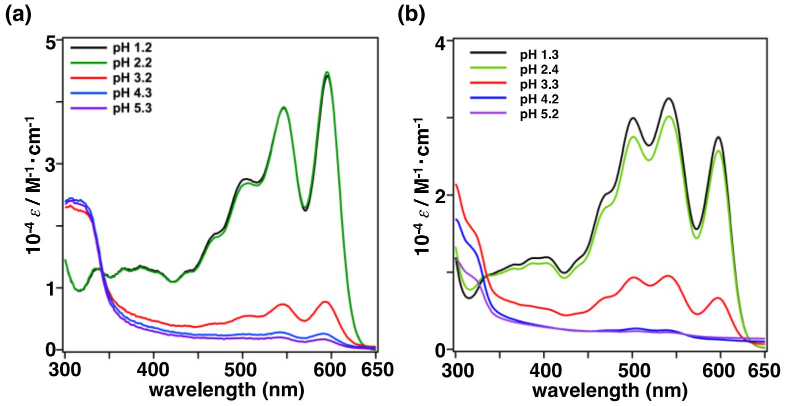


Figure 3. Absorption spectra during pH titrations of (a) ABPX-SLs ($\mathbf{1}_{trans}$) and (b) ABPX-SEs ($\mathbf{3}_{trans}$) in acetate buffer solution

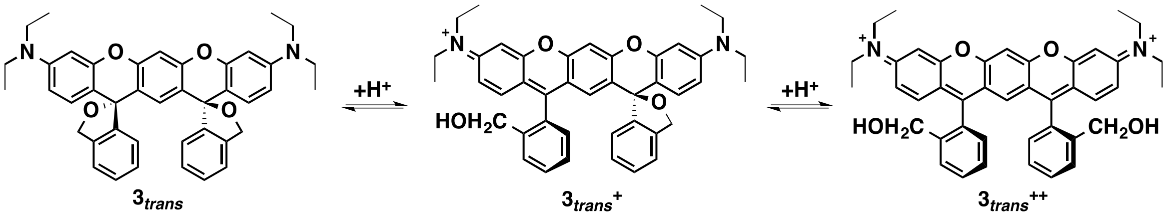


Figure 4. Protolytic reaction of ABPX spiroethers ($\mathbf{3}_{trans}$)

In conclusion, we have synthesized novel ABPX-SEs and investigated their acid-stimulus responsiveness. In the case of for ABPX-SEs, a monocationic species is preferentially formed in polar organic solvents, indicating that the oxygen of the spiroether shows acid affinity than the oxygen of the spirolactone. Interestingly, ABPX-SEs exhibit stepwise structural changes of three equilibrium species under acidic conditions. This trend is in contrast to that seen for ABPX-SLs, which show rapid conversion from the colorless spirolactone species to the colored dicationic species. We are currently investigating the structure-pH responsiveness for ABPX and will report the results in due course.

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9. For experimental details and spectral data of new compounds, see the supporting information.