

# Solvent effects on the tautomerization, autoxidation and bond-exchange reactions of 2-mercaptopyridine derivatives

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## Abstract

Tautomerization, autoxidation and bond-exchange reactions of 2-mercaptopyridine derivatives were investigated in solution, by using several kinds of solvents. A 2-mercaptopyridine derivative having an *N*-benzylamide group was dissolved not only in water but also in cyclohexane, although the solubility toward such solvents was lower than that toward methanol or chloroform. From the UV-Vis spectra, it was confirmed that thione-type isomer was major in these solvents except for cyclohexane. Autoxidation reactions were monitored in methanol or methanol-*d*<sub>4</sub>, and *ca.* 36% of 2-mercaptopyridyl groups were oxidized into disulfide bonds within a month in <sup>1</sup>H-NMR spectral measurements. Bond-exchange reactions between 2,2'-dipyridyl disulfide and a thiol compound were observed more clearly in methanol than in chloroform, suggesting a solvent effect to dissolution of corresponding disulfide compounds.

**Keywords** : solvent effect, tautomerization reaction, autoxidation reaction, bond-exchange reaction, 2-mercaptopyridine derivative

Received May 31, 2022; accepted July 19, 2022

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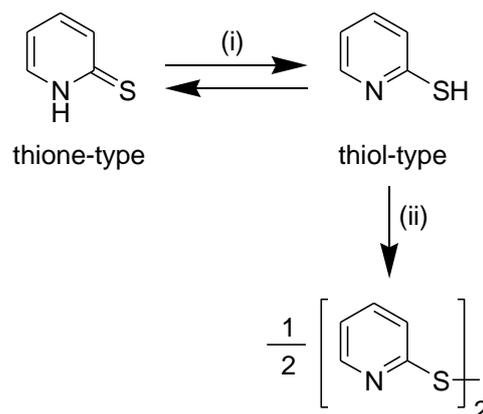
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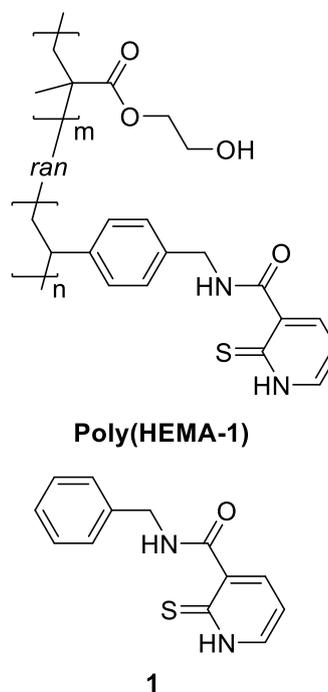
## 1. Introduction

2-Mercaptopyridine and its derivatives are known as one of chemical compounds which tautomerize their molecular structures.<sup>1,2)</sup> These compounds have a mercapto group at the *ortho* position on a pyridine ring, and the tautomerization reaction occurs between its thione-type and thiol-type isomers (Scheme 1(i)). This reaction is reversible, and the equilibrium state is changed by surrounding conditions of the molecules, such as polarity,<sup>3,4)</sup> temperature,<sup>5)</sup> and concentration.<sup>6)</sup> For example, it is known that 2-mercaptopyridines are tautomerized to the thione-type isomer in the crystal<sup>7)</sup> and polar solvents.<sup>4)</sup> 2-Mercaptopyridines would minimize their potential energy toward micro-environments *via* their tautomerization reaction, and they would maximize the interaction according to their environments, which would be called as “environmental adaptation”.

Based on this concept, a vinyl monomer having a 2-mercaptopyridyl (2MP) moiety has been designed and copolymerized with 2-hydroxyethyl methacrylate (HEMA) by using a radical photo-initiator, for photo-adhesion between substrates of dissimilar materials **Poly(HEMA-1)**, Fig 1).<sup>8)</sup> Molecular states of 2MP moieties at the interface between the photo-adhesive layer and a substrate surface were investigated by X-ray photo-electron spectroscopic (XPS) measurements, finding that 2MP groups were tautomerized from thione-type to thiol (thiolate)-type isomers at a copper surface due to sulfur-copper interaction.<sup>9)</sup> However, systematic investigation on the influence of environmental polarity has not been performed. Furthermore, the photo-adhesive samples enforced their adhesive strength week by week, suggesting formation of cross-linking points through autoxidation of 2MP moieties to 2,2'-dipyridyl disulfide bonds.<sup>8,10)</sup> Autoxidation to disulfides is another unique reaction of 2-mercaptopyridines (Scheme 1(ii)), which is known to be underwent in water, methanol or dioxane (concentration: 0.02-1 mM).<sup>4)</sup> However, it is unknown how similar oxidation reactions proceed at



**Scheme 1.** (i) Tautomerization reaction between thione-type and thiol-type isomers of 2-mercaptopyridine, and (ii) autoxidation reaction from its thiol-type isomer to the corresponding disulfide.



**Fig 1.** Chemical structures of a photo-adhesive polymer material containing 2-mercaptopyridyl moieties (**Poly(HEMA-1)**), and of the model compound **1** using in this study.

a higher concentration. In this article, compound **1** having a 2MP moiety was designed and synthesized as a model compound of the side chain of **Poly(HEMA-1)**, and **1** was subjected to polar and nonpolar environments by using water and organic solvents, to examine the dominant molecular state among thione-type isomer, thiol-type isomer, and disulfide for each solvent.

On the other hand, as shown in Scheme 2, it is also

known that disulfide bonds are exchanged by addition of a thiol compound through a disulfide-thiol exchange reaction.<sup>11)</sup> Polymer materials containing disulfide bonds are reported to be decomposed by immersion into solution of low-molecular-weight thiols.<sup>12-14)</sup> In this article, effect of solvent polarity to the bond-exchange reactions was also examined by using 2,2'-dipyridyl disulfide **2** and a thiol, for applying polymer materials containing dipyridyl disulfide cross-linking moieties<sup>15,16)</sup> as chemo-degradable materials in future.

## 2. Experimental

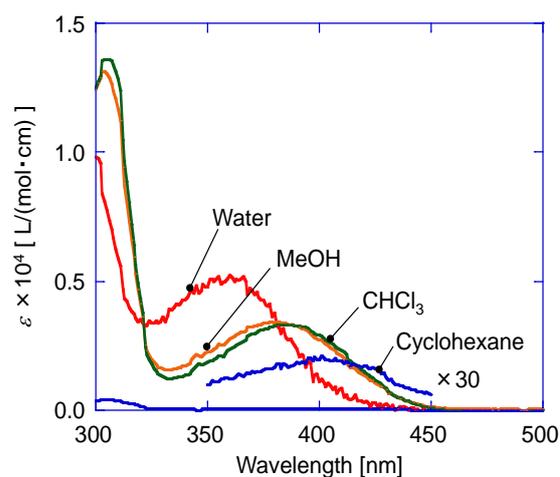
**2.1 Materials and Equipment.** 2-Mercaptopyridinic acid, benzylamine, 2,2'-dipyridyl disulfide **2**, [4-(*tert*-butyl)phenyl]methanethiol (*t*BPMT), DL-dithiothreitol (DTT), and cyclohexane were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Water soluble carbodiimide hydrochloride (WSCl HCl) was purchased from WATANABE CHEMICAL INDUSTRIES, Ltd. (Hiroshima, Japan). 4-Dimethylaminopyridine, methanol (MeOH), chloroform (CHCl<sub>3</sub>), ethyl acetate, and magnesium sulfate were purchased from NACALAI TESQUE, Inc. (Kyoto, Japan). Tetrahydrofuran (THF), dichloromethane (DCM), and chloroform-*d* (CDCl<sub>3</sub>) were purchased from FUJIFILM Wako Pure Chemical Corporation (Osaka, Japan). Methanol-*d*<sub>4</sub> (CD<sub>3</sub>OD) was purchased from Sigma-Aldrich Japan (Tokyo, Japan). All chemicals were used without further purification.

<sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded using a Bruker AVANCE III. APCI-MS spectra were recorded using an AB Sciex API2000. UV-Vis spectral measurements were performed using a U-0080D (Hitachi High-Tech Science Corporation).

**2.2 Synthesis.** Compound **1** having a 2-mercaptopyridyl moiety was synthesized as follows.

2-Mercaptopyridinic acid (0.51 g, 3.3 mmol) was added to a flask that was dried and purged with

nitrogen gas, and then dissolved in DCM/THF (7/8, v/v). WSCI HCl (0.78g, 5.0 mmol) was added and stirred at room temperature for 1 h. Benzylamine (0.51 g, 4.8 mmol) and 4-dimethylaminopyridine (0.49 g, 4.0 mmol) were then added at 0°C, and stirred over-night. After evaporating, the residue was triturated with ethyl acetate twice, followed by condensing the extract. Purification was performed with a silica gel chromatography (eluent: CHCl<sub>3</sub> to CHCl<sub>3</sub>/MeOH (100/1, v/v)) to obtain **1** in a 5.4% yield as a yellow solid. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 4.70 (2H, m, -CH<sub>2</sub>-), 6.91 (1H, m, Py-H), 7.2-7.5 (5H, m, Ar-H), 7.66 (1H, m, Py-H), 8.79 (1H, m, Py-H), 11.1 (1H, br, -CONH-), 12.6 (0.6H, br, -NHCS-). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 44, 114, 128, 128, 129, 129, 133, 137, 139, 143, 164. APCI-MS ([M+H]<sup>+</sup>): 245.1 (found), 244.34 (calcd for C<sub>13</sub>H<sub>12</sub>O<sub>1</sub>N<sub>2</sub>S<sub>1</sub>).



**Fig 2.** UV-Vis spectra of **1** in water (0.006 mM), MeOH (0.05 mM), CHCl<sub>3</sub> (0.05 mM) and cyclohexane (0.024 mM).

**2.3 Tautomerization reactions.** Using compound **1**, 0.05 mM (with MeOH or CHCl<sub>3</sub>), 0.024 mM (with cyclohexane), and 0.006 mM (with water) of solution samples were prepared, to record each UV-Vis spectrum at room temperature.

**2.4 Autoxidation reactions.** Using compound **1**, 0.05 mM of solution sample was prepared with MeOH. These samples were allowed to stand in dark at room temperature, subjected to interval UV-Vis

spectral measurements. Another condensed solution of **1** (50 mM) was also prepared with CD<sub>3</sub>OD. This solution was subjected to interval <sup>1</sup>H-NMR spectral measurements under the same standing conditions. After 79 days, an equivalent of DTT was added and allowed to stand in dark at room temperature for more 38 h, followed by a <sup>1</sup>H-NMR spectral measurement.

### 2.5 Bond-exchange reactions with a thiol.

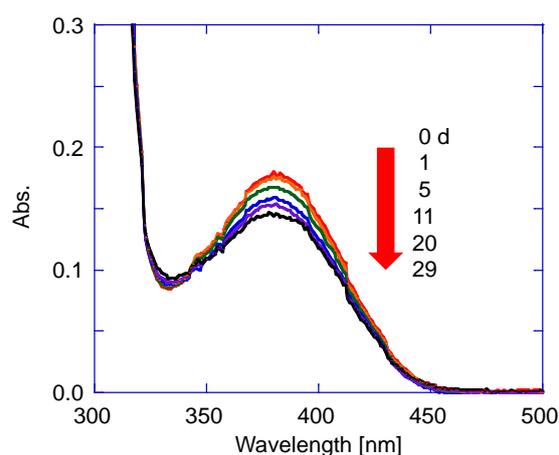
Using **2**, 0.05 mM of solution samples were prepared with MeOH or CHCl<sub>3</sub>. tBPMT (10 equiv.) was then added to each solution, which was kept at room temperature or 50°C for interval UV-Vis spectral measurements.

## 3. Results and Discussion

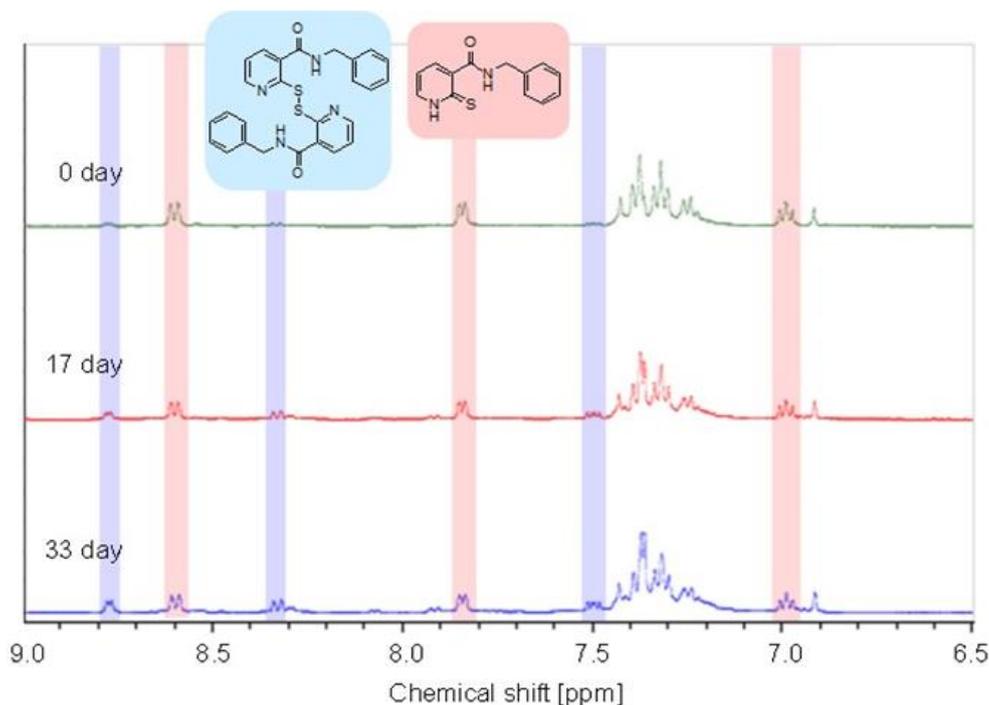
**3.1 Tautomerization reactions.** Surprisingly, compound **1** was dissolved into nonpolar solvents as well as polar solvents. In UV-Vis spectra, the thione-type isomer of 2-mercaptopyridines has a broad peak around 350–400 nm that is assigned to n-π\* transition. For compound **1**, such peak was observed clearly in the cases using water, MeOH or CHCl<sub>3</sub> as solvent, except for the case of cyclohexane (Fig 2). The values of permittivity are 2.02 (cyclohexane), 4.81 (CHCl<sub>3</sub>), 33.0 (MeOH), and 80.1 (water),<sup>17)</sup> and the peak was blue-shifted by increasing permittivity, or solvent polarity. The molar extinction coefficient  $\epsilon$  was high in cases of polar solvents, indicating that thione-type isomer was superior to thiol-type isomer in a polar environment. Comparing the results between CHCl<sub>3</sub> and MeOH, it was found that both wavelength of the peak top and the value of  $\epsilon$  were almost the same, and that there is a nonlinear relationship between permittivity and the thione/thiol ratio.

**3.2 Autoxidation reactions.** A MeOH solution of **1** was allowed to stand in dark at room temperature, to measure time course of UV-Vis spectral changes. The peak intensity at 379 nm was decreased gradually with an isosbestic point,

indicating autoxidation of **1** to the disulfide compound *via* tautomerization reaction from the thione-type to the thiol-type isomers (Fig 3). On the other hand, Fig 4 shows <sup>1</sup>H-NMR spectral changes of **1** in CD<sub>3</sub>OD at a higher concentration (one thousand times higher than that in UV-Vis spectral measurements). Peaks at 8.60, 7.84, and 6.99 ppm were assigned to protons of the 2MP group of the thione-type isomer, while peaks at 8.77, 8.33, and 7.50 ppm were assigned to protons of that of the corresponding disulfide compound. The latter peaks were appeared gradually day by day, and disappeared after adding DTT (a reducing reagent) to the CD<sub>3</sub>OD solution. It was estimated that *ca.* 36% of **1** was oxidized to the corresponding disulfide after 33 days. It was also observed that the disulfide compound was generated just after starting the measurement (0 day in Fig 4), indicating that **1** was oxidized easily. In the photo-adhesive polymer material **Poly(HEMA-1)**, *see* Fig 1),<sup>8)</sup> ratio of 2MP groups toward hydroxy groups from HEMA was 1.3 mol%, and the concentration of 2MP groups in the adhesive layer was calculated to *ca.* 110 mM. Although both the concentration and mobility of 2MP groups are still different, similar oxidation



**Fig 3.** UV-Vis spectral changes of **1** in MeOH (0.05 mM) where the sample was allowed to stand in dark at room temperature.

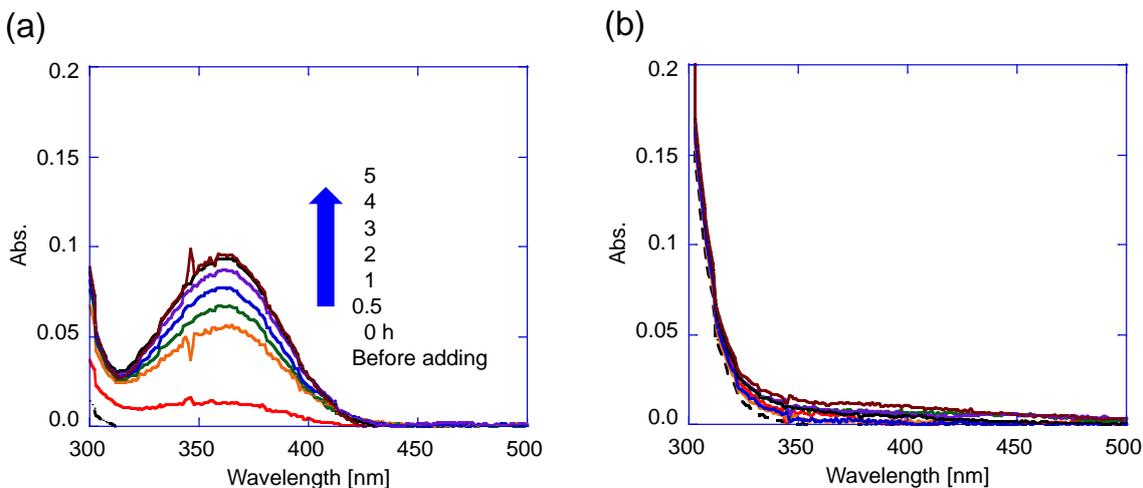


**Fig 4.**  $^1\text{H-NMR}$  spectral changes of **1** in  $\text{CD}_3\text{OD}$  (50 mM) where the sample was allowed to stand in dark at room temperature.

reactions to form disulfide bonds (*i.e.* cross-linking points in the adhesive layer) would proceed. There are small additional peaks in the region from 8.6 to 7.5 ppm after 17 and 33 days in Fig 4. Although clear assignment was not achieved, these peaks could be assigned to protons of 2MP groups of the thiol-type isomer of **1**, or supramolecular complexes where compound **1** stacks noncovalently with each other *via* hydrogen bonds of two amide bonds.

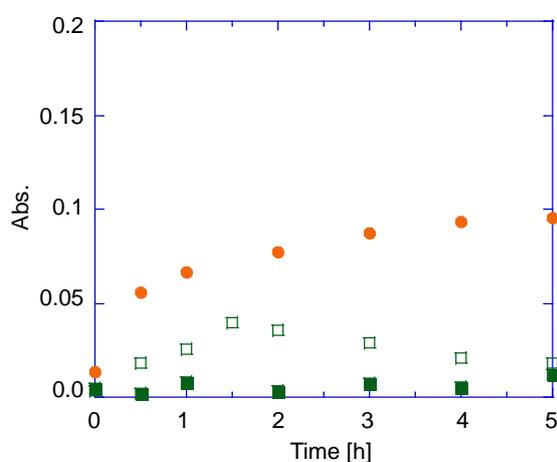
### 3.3 Bond-exchange reactions with a thiol.

As shown in Fig 5(a), UV-Vis spectral changes were observed, when ten equivalents of a thiol compound (*t*BPMT) was added to 2,2'-dipyridyl disulfide **2** in MeOH. A broad peak was appeared immediately around 360 nm, and the peak intensity was saturated within 4 h. This peak is assigned to  $n\text{-}\pi^*$  transition of the thione-type isomer of 2-mercaptopyridine,



**Fig 5.** UV-Vis spectral changes of **2** in (a) MeOH (0.05 mM) and (b)  $\text{CHCl}_3$  (0.05 mM), after adding ten equivalents of *t*BPMT where the sample was allowed to stand in dark at room temperature.

generated by the disulfide-thiol exchange reactions shown in Scheme 2. A similar experiment was performed with  $\text{CHCl}_3$  as solvent, instead of MeOH. In this case, however, the corresponding peak did not appear even after 5 h (Fig 5(b)). These results suggest that the bond-exchange reactions between **2** and *t*BPMT do not proceed in  $\text{CHCl}_3$ , because the thiol-type isomer tautomerize immediately to the thione-type isomer in  $\text{CHCl}_3$  as well as in MeOH, if 2-mercaptopyridine is generated by the bond-exchange reactions between **2** and *t*BPMT. Solubility of **2** toward  $\text{CHCl}_3$  (or solubility of the resulting asymmetric disulfide compound toward MeOH) would be superior to that toward MeOH (or  $\text{CHCl}_3$ ), which could disturb the progress of the bond-exchange reaction. Time courses of absorbance at the maximum absorption wavelength in the experiments are shown in Fig. 6. It was also found that the bond-exchange reactions proceeded a little even in  $\text{CHCl}_3$ , when the solution was heated at



**Fig 6.** Time courses of absorbance at the maximum absorption wavelength in UV-Vis spectra of **2** with *t*BPMT in MeOH (orange, solid circle),  $\text{CHCl}_3$  (green, solid square), and  $\text{CHCl}_3$  at 50°C (green, open square).

50°C.

#### 4. Conclusion

The molecular state of 2-mercaptopyridine derivatives was revealed in their tautomerization, autoxidation, and bond-exchange reactions, by spectroscopic measurements with several kinds of

solvents. Results on the MeOH (or  $\text{CD}_3\text{OD}$ ) solution of **1** would be indirect evidences for the molecular behavior of 2MP groups of **Poly(HEMA-1)** in the adhesive layer.<sup>8,10</sup> Furthermore, results on the bond-exchange reactions between **2** and a thiol compound would give us a hint to fabricate an effective chemo-degradable polymer material, because the bond-exchange reaction was almost irreversible theoretically, due to fast tautomerization reactions of 2-mercaptopyridine to the thione-type isomer.

**Acknowledgement.** MF acknowledges Prof. Eiki Matsui at National Institute of Technology, Fukui College for the use of APCI-MS instrument and UV-Vis spectrometer. This work was supported by a research grant from Advanced Research Center for Regional Cooperation, National Institute of Technology, Fukui College.

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