



## Synthesis and Evaluation of Potentiometric Properties of Pyridylthiazole Derivatives

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### Abstract

Synthesis of 2-pyridylthiazole ethers (**2**, **3**), 4-nonyl-2-pyridylthiazole (**4**), 2-nonyl-4-pyridylthiazole (**5**) and 2-pyridylthiazole imine (**6**), potentially useful as effective cation-binding ligands, is described. The potentiometric properties of ion-selective membranes prepared with 30–32 wt% PVC, 66 wt% 2-nitrophenyloctyl ether and 2–4 wt% pyridylthiazole derivatives have been examined. While the membranes containing 2-pyridylthiazole ethers (**1–4**) exhibited high selectivity toward silver(I) ion, that prepared with 2-pyridylthiazole imine (**6**) resulted in negligible potentiometric response to most mono- and divalent cations.

### Introduction

For about three decades, numerous open-chained podand-type compounds have been synthesized to obtain selective ligands for alkali, alkaline earth and transition metal cations, and many of them are now available as an important class of commercial ionophores, particularly for preparing solvent polymeric ion-selective membranes [1]. Studies on podands still attract considerable interests because they may provide peculiar ionophoric ability if their flexible polyether chains are properly modified with various end groups that can help organize the ligand system. Examples include the synthesis of podands containing heterocyclic end groups such as pyridine, bipyridine, pyrazole, and thiophene [2].

Recently syntheses of another interesting class of podands that contain thiazole end groups were reported [3, 4]. It was expected that the two pyridylthiazole units substituted at each end of polyether chain would enhance overall organization of the ligand system through  $\pi$ - $\pi$  stacking. In addition, the heteroatoms in pyridine and thiazole units could act as electron donors to metal cations and stabilize the ion-ligand complex system. In continuation of our study on thiazole derivatives [4, 5] as metal cation-selective ligand system, we report herein the synthesis and potentiometric properties of various pyridylthiazole-containing polyethers and alkyl chains. Employing ion-selective solvent polymeric membranes as a tool for probing molecular structure-ionophoric property relations, we attempted to correlate the results of potentiometric measurements with the molecular structures of pyridylthiazole derivative-based podands [6].

### Experimental

**General:** Melting points were measured by using a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Galaxy FT-IR 7000 spectrophotometer. <sup>1</sup>H and <sup>13</sup>C-NMR spectra were recorded on a Varian Unity Plus 300 spectrometer; unless otherwise stated, all NMR were performed in CDCl<sub>3</sub> solution. The chemical shifts of <sup>1</sup>H-NMR spectra (300.13 MHz) are given in ppm downfield from tetramethylsilane and <sup>13</sup>C-NMR spectra were referred to CDCl<sub>3</sub> at 77.0 ppm. Coupling constant *J* values are given in Hz. Low-resolution mass spectra (MS) were recorded on a Shimadzu QP-1000 spectrometer. High-resolution MS were measured on a JEOL KMS-DX 303 spectrometer. Microanalyses were performed by CSI at Kyungpook National University. TLC analyses were carried out on precoated 0.2 mm Merck Kieselgel 60F<sub>254</sub> plates, visualizing with a 254-nm UV lamp. For routine column chromatography, E. Merck silica gel (70–230 mesh) was used as an adsorbent. Solvents were distilled before use and were dried, as necessary. Solutions were dried over anhydrous sodium sulfate. All reactions were carried out under an atmosphere of argon. 2-(2-Pyridyl)-4-hydroxymethylthiazole and 1,13-bis[2-(2-pyridyl)-4-methylthiazole] tetraethylene glycol (**1**) were prepared previously [4a]. 2-Pyridinecarboxthioamide [10], decyl thioamide [10], 2-bromoacetylpyridine [11] and 1-diazo-2-undecanone [12] were prepared following a reported procedure. Preparation of 2-(2-pyridyl)-4-formylthiazole will be described elsewhere [13]. Reagents used to prepare the ion-selective membranes, e.g., high molecular weight poly(vinyl chloride) (PVC) and 2-nitrophenyloctyl ether (NPOE), were purchased from Fluka.

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**1,12-Bis[2-(2-pyridyl)-4-thiazolylmethoxy]dodecane (2):** To a stirred solution of KH (40 mg, 1 mmol) and 2-(2-pyridyl)-4-hydroxymethylthiazole (192 mg, 1 mmol) in THF (5 ml) was added a solution of 1,12-dibromododecane (197 mg, 0.6 mmol) in THF (10 ml) at 80 °C. The mixture was then refluxed for 5 h and cooled to room temperature and the solvent was evaporated under vacuum. The resulting residue was extracted with ethyl acetate and washed with brine and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane 1:9) to give a white solid **2** in 27% yield. m.p. 99–100 °C (CH<sub>2</sub>Cl<sub>2</sub>-hexane); TLC *R<sub>f</sub>* 0.43 (EtOAc/hexane, 1:2); IR (KBr): 2920, 2847, 1588, 1431, 1086, 1011 cm<sup>-1</sup>; <sup>1</sup>H-NMR: δ 8.61 (*d*, *J* = 4.5 Hz, 2H), 8.19 (*d*, *J* = 7.8, 2H), 7.78 (*td*, *J* = 7.7, 1.8, 2H), 7.33 (*s*, 2H, H-5), 7.29 (*m*, 2H), 4.69 (*s*, 4H, thiazole-CH<sub>2</sub>), 3.59 (*t*, *J* = 6.8, 4H), 1.64 (*m*, 4H), 1.32 (*m*, 14H); <sup>13</sup>C-NMR: δ 169.1 (C-2), 155.7, 151.3 (C-4), 149.4, 136.9, 124.4 (C-5), 119.7, 118.0, 71.2 (thiazole-CH<sub>2</sub>), 68.9, 29.7, 29.6, 29.5, 26.1; MS: *m/z* 550 (M<sup>+</sup>, 3), 191 (100); Anal. Calcd for C<sub>30</sub>H<sub>38</sub>N<sub>4</sub>O<sub>2</sub>S<sub>2</sub>: C 65.42, H 6.95, N 10.17; found: C 65.66, H 6.93, N 9.95.

**4-[(Decyloxy)methyl]-2-(2-pyridyl)thiazole (3):** The procedure to prepare **3** was the same as for the preparation of **2** starting with 192 mg of 2-(2-pyridyl)-4-hydroxymethylthiazole (1 mmol), 322 mg of 1-iodododecane (1.2 mmol) and 40 mg of KH (1 mmol) in THF (20 ml). Compound **3** was obtained as a white solid in 43% yield. m.p. 33–34 °C (CH<sub>2</sub>Cl<sub>2</sub>-hexane); TLC *R<sub>f</sub>* 0.50 (EtOAc/hexane 1:2); IR (KBr): 2922, 2860, 1592, 1438, 1098, 1005, 928 cm<sup>-1</sup>; <sup>1</sup>H-NMR: δ 8.60 (*m*, 1H), 8.19 (*m*, 1H), 7.77 (*td*, *J* = 7.7, 1.7, 1H), 7.33 (*s*, 1H, H-5), 7.30 (*m*, 1H), 4.69 (*s*, 2H, thiazole-CH<sub>2</sub>), 3.59 (*t*, *J* = 6.8, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.66 (*m*, 2H, OCH<sub>2</sub>CH<sub>2</sub>), 1.40–1.26 (*m*, 14H), 0.87 (*t*, *J* = 6.8, 3H); <sup>13</sup>C-NMR: δ 169.0 (C-2), 155.7, 151.3 (C-4), 149.4, 136.8, 124.3 (C-5), 119.7, 117.9, 71.1 (thiazole-CH<sub>2</sub>), 68.8, 31.8, 29.6, 29.5, 29.4, 29.2, 26.1, 22.6, 14.0; MS: *m/z* 332 (M<sup>+</sup>, 3), 176 (100); Anal. Calcd for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>OS: C 68.63, H 8.49, N 8.43; found: C 68.91, H 8.67, N 7.99.

**4-Nonyl-2-(2-pyridyl)thiazole (4):** To a stirred solution of 2-pyridinecarboxthioamide (138 mg, 1 mmol) and BF<sub>3</sub>·Et<sub>2</sub>O (0.25 mL, 2 mmol) in dry DME (5 mL) was added a solution of 1-diazo-2-undecanone (196 mg, 1 mmol) in dry DME (3 mL) for 2 h at room temperature. The mixture was then refluxed for 3 h, poured into water and extracted with ethyl acetate. The organic layer was washed with water, saturated solution of sodium bicarbonate and brine and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane 1:9) to give a yellowish oil **4** in 24% yield. TLC *R<sub>f</sub>* 0.88 (EtOAc/hexane 1:2), 0.26 (EtOAc/hexane 1:9); IR (CHCl<sub>3</sub>): 2937, 1577, 1469, 1283, 1020 cm<sup>-1</sup>; <sup>1</sup>H-NMR: δ 8.59 (*d*, *J* = 4.5, 1H), 8.18 (*d*, *J* = 7.5, 1H), 7.75 (*td*, *J* = 7.7, 1.8, 1H), 7.27 (*m*, 1H), 6.98 (*s*, 1H, H-5), 2.82 (*t*, *J* = 7.7, 2H), 1.76 (*m*, 2H), 1.35–1.27 (*m*, 12H), 0.88 (*t*, *J* = 6.8, 3H); <sup>13</sup>C-NMR: δ 168.1, 159.2 (C-2), 151.5 (C-4), 149.3, 136.8, 124.1, 119.6, 115.2 (C-5), 31.8, 31.7, 29.5, 29.4, 29.2, 29.2, 22.6, 14.0; MS: *m/z* 288 (M<sup>+</sup>, 24), 176 (100); HR-MS: 288.1664 (C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>S, calc. 288.1661).

**2-Nonyl-4-(2-pyridyl)thiazole (5):** A mixture of 2-bromoacetylpyridine (139 mg, 0.7 mmol) and decyl thioamide (187 mg, 1 mmol) in dry ethanol (10 mL) was refluxed for 2 h. The mixture was then concentrated under vacuum. The resulting residue was extracted with ethyl acetate. The organic layer was washed with water, saturated solution of sodium bicarbonate and brine and evaporated. The residue was purified by flash chromatography (ethyl acetate-hexane 1:4) to give a yellowish oil **5** in 67% yield. TLC *R<sub>f</sub>* 0.80 (EtOAc/hexane 1:2), 0.20 (EtOAc/hexane 1:9); IR (CHCl<sub>3</sub>): 2937, 1595, 1484, 757 cm<sup>-1</sup>; <sup>1</sup>H-NMR: δ 8.62 (*m*, 1H), 8.09 (*d*, *J* = 7.2, 1H), 7.91 (*s*, 1H, H-5), 7.75 (*td*, *J* = 7.5, 1.8, 1H), 7.21 (*m*, 1H), 3.06 (*t*, *J* = 7.8, 2H), 1.84 (*m*, 2H), 1.46–1.27 (*m*, 12H), 0.88 (*t*, *J* = 6.6, 3H); <sup>13</sup>C-NMR: δ 171.8 (C-2), 154.7, 152.7, 149.5 (C-4), 136.9, 122.6, 121.1, 116.1 (C-5), 33.7, 31.8, 30.1, 29.4, 29.3, 29.1, 22.7, 14.1; MS: *m/z* 288 (M<sup>+</sup>, 16), 176 (100); HR-MS: 288.1666 (C<sub>17</sub>H<sub>24</sub>N<sub>2</sub>S, calc. 288.1661).

**N-Dodecyl-2-(2-pyridyl)-4-methylidene thiazole (6):** To a stirred suspension of 2-(2-pyridyl)-4-formylthiazole (38 mg, 0.2 mmol) and MgSO<sub>4</sub> (25 mg) in dry diethyl ether (5 mL) was added dodecylamine (38.9 mg, 0.21 mmol). After the reaction mixture was stirred at room temperature for 36 h, the MgSO<sub>4</sub> was filtered off and washed with ether (20 mL) and concentrated. The residue was crystallized from dichloromethane and hexane to give a white solid **6** in 77% yield. m.p. 46–47 °C; TLC *R<sub>f</sub>* 0.41 (EtOAc/hexane 1:2); IR (KBr): 2919, 2857, 1645, 1583, 1497, 1436, 1274, 1012, 795 cm<sup>-1</sup>; <sup>1</sup>H-NMR: δ 8.61 (*d*, *J* = 5.1), 8.45 (*s*, 1H, C=NH), 8.28 (*d*, *J* = 8.1, 1H), 7.86 (*s*, 1H, H-5), 7.80 (*td*, *J* = 7.8, 1.8, 1H), 7.33 (*m*, 1H), 3.66 (*t*, *J* = 7.1, 2H), 1.74 (*tt*, *J* = 7.1, 7.1, 2H), 1.34–1.26 (*m*, 18H), 0.88 (*t*, *J* = 6.6, 3H); <sup>13</sup>C-NMR: δ 169.5 (C-2), 154.8, 154.7 (N=CH), 150.9 (C-4), 149.4, 137.0, 124.7), 122.2, 120.0 (C-5), 61.9, 31.9, 30.7, 29.6, 29.6, 29.6, 29.4, 29.3, 27.4, 22.6, 14.1. MS: *m/z* 357 (M<sup>+</sup>, 39), 216 (100); HR-MS: 357.2245 (C<sub>21</sub>H<sub>31</sub>N<sub>3</sub>S, calc. 357.2239).

**Evaluation of potentiometric property.** The PVC-based membranes were normally prepared with 2–4 wt% ionophores (compounds **1–6** in Scheme 1), 30–32 wt% PVC and 66 wt% plasticizer NPOE. These membrane components dissolved in 1 mL of THF were then poured into a glass ring (i.d. 18 mm) placed on a slide glass, and dried overnight at room temperature. Small disks were punched out from the cast films and mounted in Philips electrode bodies (IS-561; Glasblaserei Möller, Zurich, Switzerland). For all electrodes, 0.1 M KCl was used as the internal reference electrolyte. The external reference electrode was an Orion sleeve-type double junction Ag/AgCl reference electrode (Model 90-02). Potential difference between the ISEs and the reference electrode was measured using an IBM computer equipped with a home made high-impedance input 16-channel analog-to-digital converter. The dynamic response curves were obtained by adding the standard solutions to the magnetically stirred background electrolyte (200 mL, 0.01 M magnesium acetate buffer, pH 4.5) every 100 seconds to vary the concentrations of primary ions (alkali, alkaline earth metal and various transition metal ions).

stepwise from  $10^{-8}$  to  $10^{-3}$  M, and the measurements of *emf* values were taken every second at room temperature. Selectivity coefficients ( $k_{Ag^+,M}^{MPPM}$ ) were estimated according to the separate solution-matched potential method at the  $10^{-3}$  M ion concentration [9]. This method appropriately describes the selectivity of ISEs if they do not provide Nernstian response.

## Results and discussion

### Synthesis of ionophores

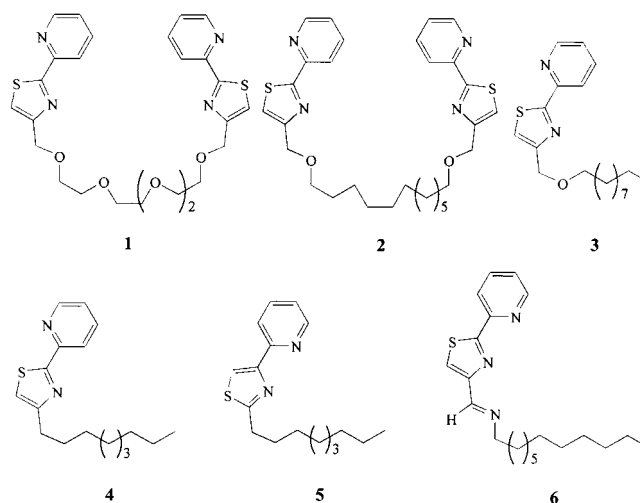
Six podands based on pyridylthiazole derivatives were synthesized as fully described in experimental section and their structures are shown in Scheme 1. Reaction of 2-(2-pyridyl)-4-hydroxymethylthiazole with tetraethylene glycol di-*p*-tosylate in the presence of potassium hydride gives 1,13-bis(2-pyridyl-4-methylthiazole)tetraethylene glycol **1** in 31% yield [4a]. In order to understand the ionophoric activity of compound **1**, we modified its ether moiety and synthesized a series of structurally similar podands: 2-(2-pyridyl)-4-hydroxymethylthiazole was reacted with 1,12-dibromododecane and 1-iodododecane in the presence of potassium hydride in THF to give **2** (27%) and **3** (43%), respectively.

4-Nonyl-2-(2-pyridyl)thiazole **4** was obtained from the reaction of 2-pyridinecarboxithioamide with 1-diazo-2-undecanone in the presence of two equivalents of boron trifluoride in DME at 80 °C in 24% yield [5a, 5b]. 2-Nonyl-4-(2-pyridyl)thiazole **5** was prepared from the reaction of 2-bromoacetylpyridine with decyl thioamide in absolute ethanol in 67% yield. Imine compound **6** was prepared by reacting of 2-(2-pyridyl)-4-formylthiazole with dodecylamine in the presence of magnesium sulfate in 77% yield. The structures of compounds **2–6** were confirmed by  $^1\text{H}$ ,  $^{13}\text{C}$ -NMR, mass, and elemental analysis data. Podands **1** and **2** have two 2-pyridylthiazole units and different ether linkage between two thiazoles and podands **3–6** has one unit containing alkyl ether, alkyl, and imine moiety with different chain length.

### Evaluation of potentiometric properties

For a series of thiazole derivatives shown in Scheme 1, we compared their potentiometric properties with plasticized PVC membranes. In general, the ion-selective electrode (ISE) membranes were prepared by adding 2–4 wt% podand in 30–32 wt% PVC and 66 wt% plasticizer (NPOE) [7]. Since our primary objective was to examine the structure-selectivity relations for the pyridylthiazole-containing podands, we tried to use the same matrix compositions for all compounds examined instead of performing extensive matrix optimization study.

The *emf* responses and selectivities of the ISEs based on compound **1** and **2** to various transition metal ions are summarized in Table 1. Both ISEs exhibit highest selectivity toward silver ion, and their calibration curves from  $10^{-8}$  to  $10^{-3}$  M are given in Figure 1. In spite of the



Scheme 1.

Table 1. Matched-potential selectivity coefficients ( $k_{Ag^+,M}^{MPPM}$ ) of pyridylthiazole-based ion-selective membranes for various cations with respect to silver ion [9]

Interference	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
$\text{Ni}^{2+}$	-4.5	<-6	-4.5	<-6	<-6
$\text{Zn}^{2+}$	-5.9	<-6	<-6	<-6	<-6
$\text{Mn}^{2+}$		<-6		-	
$\text{Co}^{2+}$	-5.7	<-6	<-6	<-6	-3.9
$\text{Pb}^{2+}$	-3.5	<-6	-5.5	<-6	<-6
$\text{Cd}^{2+}$	-4.8	<-6			
$\text{Cu}^{2+}$	-3.1	-2.6	-2.7	-2.7	-1.4
$\text{Fe}^{2+}$	-4.6			-	
$\text{Hg}^{2+}$	-2.8	-1.5	-1.5	-2.0	-1.1
$\text{Li}^+$	-5.4	<-6			
$\text{Na}^+$	-5.6	<-6			
$\text{K}^+$	-3.9	<-6			
$\text{Rb}^+$	-3.9	<-6			
$\text{Ca}^{2+}$	-5.4	<-6			
$\text{Ba}^{2+}$	-4.8	<-6			
$\text{NH}_4^+$	-4.0	<-6			
$\text{Cs}^+$	-4.1				
Slope <sup>a</sup> (mV/dec.)	35.4	47.7	51.1	52.9	59.3 <sup>b</sup>

<sup>a</sup>Slopes are determined in the  $10^{-5}$ – $10^{-3}$  M range.

<sup>b</sup>The compound **5**-based electrode exhibited slow (40–50 s) and super-Nernstian response in the  $10^{-5}$ – $10^{-4}$  M range.

structural similarity between compound **1** and **2**, the potentiometric response of the compound **2**-based electrode (maximum response slope,  $S_{\text{max}} = 47.7$  mV/decade) was superior to that of the compound **1**-based electrode ( $S_{\text{max}} = 35.4$  mV/decade). The electrode based on compound **1** that contain polyether chain exhibited less sensitive response to transition metal ions than that based on compound **2** that contain simple alkyl chain. This result indicates that the incoming metal cations are coordinated mainly to two pyridylthiazole groups in compound **1** and **2**.

The ionophoric ability of compound **1** and **2** was examined by measuring the potentiometric properties of ISEs based on compound **3**, **4** and **5** which has single pyridylth-

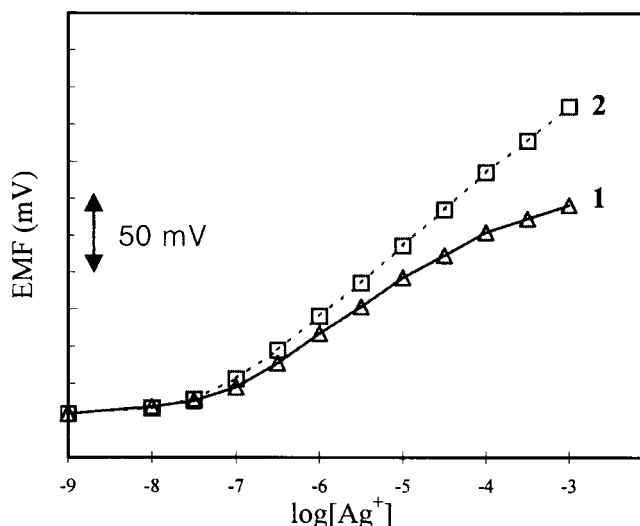


Figure 1. Calibration plots of the electrodes based on compounds 1 (triangle) and 2 (square) to silver ion. Buffer condition: 0.01 M magnesium acetate, pH 4.5.

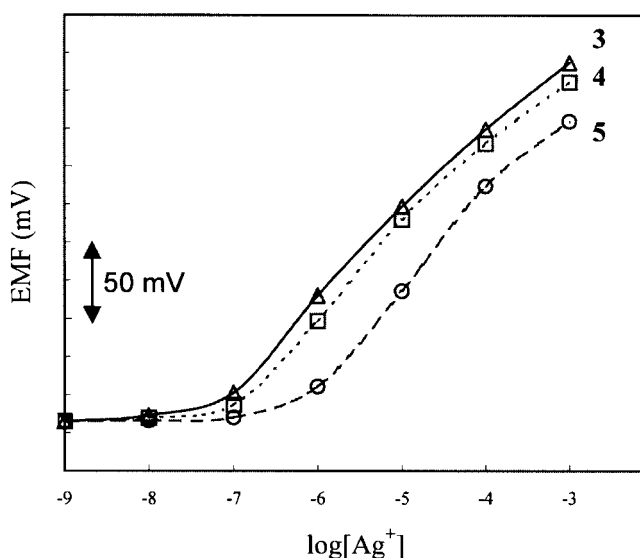


Figure 2. Calibration plots of the electrodes based on compounds 3 (triangle), 4 (square), and 5 (circle) to silver ion. Buffer condition: 0.01 M magnesium acetate, pH 4.5.

iazole unit. While the pyridylthiazole unit of compound 3 is attached to decyloxymethyl group, those of compound 4 and 5 to nonyl group. Compound 4 and 5 differ each other in their thiazole sulfur position. The *emf* responses of these three electrodes to silver ion are compared in Figure 2. It can be seen that the compound 3- and 4-based electrodes exhibited near Nernstian responses to silver ion, whose response characteristics are similar to that of the compound 2-based electrode. These results suggest that the single pyridylthiazole unit mainly dictate the binding ability of the compounds 1–4. On the other hand, the compound 5-based electrode exhibited poor potentiometric performance, particularly in terms of its slow response time (typically 40 ~ 50 s, while other electrodes within 10 s).

To correlate above experimental results with the molecular structures of compounds 3, 4 and 5, PM3 semi-empirical method was used. It was observed in the optimized structures

of compounds 3 and 4 that the two nitrogens in pyridylthiazole unit are in *anti* position due in part to the through space electrostatic interaction between the pyridine nitrogen (electrostatic potential charge,  $\delta q = -0.40$ ) and the thiazole sulfur ( $\delta q = +0.17$ ). On the other hand, when the pyridyl nitrogen and the thiazole sulfur are separated by four bonds as in compound 5, PM3 calculation predicted that the two nitrogens in pyridylthiazole be in *syn* conformation [8]. The same conclusion could be drawn with the *ab-initio* calculations performed with 3-21G\*+ basis set. Very slow response of the compound 5-based electrode implicate that the two nitrogens in *syn* conformation are not energetically advantageous for binding silver ion. The electrode based on compound 6, which also provides multi nitrogen binding sites like compound 5, exhibited very poor *emf* response to most metal ions including silver ion.

The potentiometric selectivities of the pyridylthiazole derivative-based electrodes investigated in this experiment are listed in Table 1. Selectivity coefficients were determined using the matched potential method, which is known to be practical if the electrodes exhibit non-Nernstian response to the ions of different charges [9]. As can be seen from Table 1, although mercury and copper ions are the major interferents to silver ion, the potentiometric selectivity of compound 4-based electrodes are quite comparable to that of the calix[4]arene derivative-based electrodes, but with a much lower detection limit ( $\sim 10^{-7}$  vs  $\sim 10^{-5.5}$ ) [14]. Since both  $\text{Ag}^+$  and  $\text{Hg}^{2+}$  ions tend to form linear 1:2-complex with monodentate ligands, we presume that two pyridylthiazole derivatives be involved in binding these ions. Further experimental study is on progress to elucidate the structure of silver-pyridylthiazole derivative complex.

## Conclusion

The present work shows that pyridylthiazole derivatives are good silver-selective ionophores. Comparing the potentiometric responses of the electrodes based on compounds 1–6, it was concluded that the pyridylthiazole unit is the primary binding site for the metal cations. The calculated structures of pyridylthiazole derivatives depend on the through space interactions between the pyridyl nitrogen and thiazole sulfur: two nitrogens in compound 3 and 4 tend to be in *anti* conformation, while those in compound 5 in *syn* conformation. The experimental results showed that the pyridylthiazole derivatives with *anti* conformation (compounds 1–4) exhibit better potentiometric response to silver ion than those with *syn* conformation (compounds 5).

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