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Synthesis of *N*,*N'*-Bis(thioacetoxyalkoxy)piperazine and Its Self-assembled Monolayer (SAM) Formation on Gold Electrode

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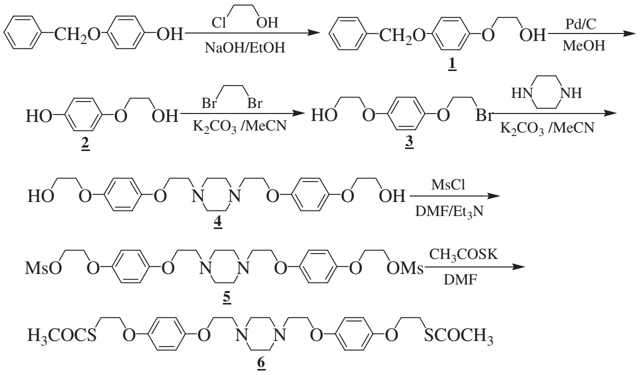
A novel terminal thioacetate-substitued alkoxy piperazine was successfully synthesized from 4-(benzyloxy)phenol after six-step reaction and employed as the surface-active material in fabrication of self-assembled monolayers (SAMs). Cyclic voltammetric (CV) results showed that the SAM-modified gold electrode had special capacity in recognition for Fe^{3+}.

In recent years, self-assembled monolayer (SAM)-modified electrodes have been in focus of research in the field of electrochemistry.[1] Much more effort has been taken to understand the fundamental and applied research of SAMs of thiols on Au(III) surfaces.[2] Highly stable and ordered SAMs can be formed because sulfur atoms have srong bond interactions with gold electrodes. However, functional end groups of thiol compounds commonly used are just limited to carboxyl, amino, and hydroxy,[3] which greatly limit the scope of the application of such electrodes. This disadvantage can be circumvented with the invention of new thiol compounds having specific function. On the one hand, the introduction of groups of N–SH could greatly increase orders of the self-assembled monolayers, reduce the defects of the SAMs, and enhance intermolecular ($\pi \cdots \pi$) interactions between the benzene rings in order to further stabilize the SAMs. On the other hand, owing to the conjunction between lone pair electrons of piperazine and empty d orbitals of metal atoms, N-functionalized piperazine has strong ability to complex metal ions, such as transition-metal ions, heavy metal ions, lanthanide ions, actinide ions, and even for organic or inorganic anions.[4]

Usually, thioacetate-terminated conjuncted molecules have been used for SAM fabrication because aromatic thiols can easily undergo oxidation to form disulfide or other oxidized products in the presence of a small amount of oxygen. Furthermore, the oxides formed above could easily deposit on surfaces of the gold electrodes, and they are so difficult to be removed that self-assembly fails. Tour et al. have noted that thioacetate groups could be used directly to assemble on the gold surface without deprotecting the acetyl group although higher concentration and longer adsorption time were required to achieve similar surface coverage relative to those of thiol group.[5]

However, so far attention has mainly been paid to aliphatic thiols. Terminal thioacetate-functionalized alkoxy piperazines have not yet been explored.

Herein, we wish to report a novel terminal thioacetate-substitued alkoxy piperazine which has been synthesized recently in this laboratory. In this study, we mainly report the synthesis of new functional surface-active material, 1,4-bis{2-[4-(2-thioacetoxyethoxy)phenoxy]ethyl}piperazine. In addition, application, preliminarily studied by cyclic voltammetric (CV) technique, are briefly introduced.



Scheme 1. Synthesis procedure of 1,4-bis{2-[4-(2-thioacetoxyethoxy)phenoxy]ethyl}piperazine.

N,*N'*-bis(thioacetoxyalkoxy)piperazine (BTP) was prepared according to the synthetic procedure as illustrated in Scheme 1. First, 2-[4-(benzyloxy)phenoxy]ethanol (**1**) was prepared from 4-(benzyloxy)phenol and chlorohydrin heated to reflux in mixed solution of ethanol and sodium hydroxide. Then it was converted to 4-(2-hydroxyethoxy)phenol (**2**) by catalytic hydrogenation with Pd/C in methanol solution at room temperature. A key intermediate, an asymmetric hydroquinone alkoxy compound of 2-[4-(2-bromoethoxy)phenoxy]ethanol (**3**), was obtained by the reaction between compound **2** and 1,2-dibromoethane. The nucleophilic substitution reaction of compound **3** and piperazine led to another crucial intermediate of 1,4-bis{2-[4-(2-hydroxyethoxy)phenoxy]ethyl}piperazine (4).

The most important step was the introduction of the thioacetate group. After exploratory research, we decided to protect the two hydroxy groups of compound **4** as mesyl groups by use of methanesulfonyl chloride. Finally, target product **6** (BTP) was successfully obtained through the transesterification of compound **5** treated with potassium thioacetate.[6] The structure of key intermediates and target compound BTP were identified by ^{1}H NMR, ^{13}C NMR, MS, IR sprectra and elemental analysis.[7]

Then a SAM modified gold electrode (BTP/Au) was obtained by modifing with BTP, based on the strong interaction of –S– with gold surface. Cyclic voltammetry (CV) was employed to assess the quality of monolayer films and investigate the ionic selection of the SAM-modified gold electrode. Electrochemical measurements were performed in a conventional three-electrode electrochemical cell using a CHI-411A electrochemical analyzer (CHI, Shanghai Chenghua Co.). A Pt sheet auxiliary electrode and a saturated calomel reference electrode (SCE) were used. The bare Au electrode and the BTP/Au electrodes were used as the working electrodes. All the

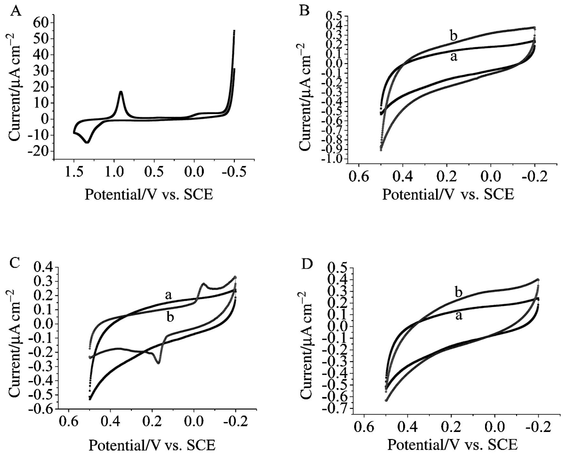


Figure 1. Cyclic voltammograms of (A) bare gold electrode in 0.5 M H_2SO_4 and (B) SAM of BTP on Au surface (a) and Cu^{2+} at the SAM of BTP on Au surface (b). (C) SAM of BTP on Au surface (a) and Fe^{3+} at the SAM of BTP on Au surface (b). (D) SAM of BTP on Au surface (a) and Ag^{+} at the SAM of BTP on Au surface (b) in 0.1 M potassium chloride at a potential scan rate of 50 mV s^{-1}.

electrochemical measurements were made at ambient temperature (25 ± 1 °C).

Immediately before use, the gold disk electrode (CHI, 2 mm in diameter) was pretreated by polishing with alumina powder (0.3 μm) on a microcloth. Then the electrode was ultrasonicated in Millipore water to remove alumina particles. Meanwhile, it was cleaned in "piranha" solution, which is a mixture of 30% H_2O_2 and concentrated H_2SO_4 in 1:3 ratio (Caution! Piranha solution is very corrosive and direct contact with skin and eye should be avoided.). Finally, the polished gold disc electrode was thoroughly cleaned, rinsed in Millipore water, and subjected to electrochemical pretreatment by consecutive potential cycling in a 0.5 M H_2SO_4 solution within a potential window between −0.50 and +1.60 V(vs. SCE) at 50 mV s^{-1} before the SAM formation. The cycling was continued until a reproducible voltammogram (Figure 1A) showing the presence of gold oxide formation and reduction was obtained.[8]

The pretreated Au electrode was immersed in a 10 mM BTP chloroform solution in the dark for 24 h at room temperature of 25 °C. After the electrode was rinsed carefully with ethanol for 1 min and Millipore water for another 1 min consecutively, the BTP-modified gold electrode (BTP/Au) was obtained.

Fe^{3+}, Cu^{2+}, and Ag^{+}, carrying different charges, were used to investigate the electrochemical properties of the BTP/Au electrode. Immediately prior to use, the BTP/Au electrodes were modified by immersion in a freshly prepared 5 mM aqueous solution of iron trichloride, copper sulfate, and silver nitrate for 2 h followed by rinsing with Millipore water. CVs were recorded in 0.1 M KCl at a scan rate of 50 mV s^{-1} and presented in Figure 1B, Figure 1C, and Figure 1D. It could be observed from these figures that after modification by different metallic ions, only the Fe^{3+} at the BTP/Au electrode (Figure 1C-b) showed a reversible voltammogram especially at 0.17 and 0.084 V implying a electron-transfer reaction, which illustrated that Fe^{3+} had been adsorbed in the BTP/Au SAM. However, the voltammetric peaks for Cu^{2+} (Figure 1B-b) and Ag^{+} (Figure 1D-b) were not detected for BTP/Au electrode implying that they cannot be adsorbed. It suggested that the SAM-modified gold electrode formed above had selective recognition for Fe^{3+} ions.

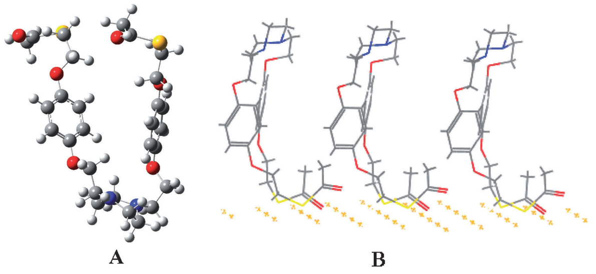


Figure 2. (A) Energy minimized steric structure of BTP and (B) idealized representation of a SAM of BTP on Au surface.

The most stable structure of BTP (Figure 2A) obtained through Materials Studio software showed us that the two thioacetate-terminated conjugated molecules were toward the same direction, which meant that both of the sulfur atoms could be bonded to the surface of the gold electrode. The idealized representative structure of a BTP/Au SAM formed above is shown in Figure 2B.

Morever, according to HSAB (Hard and Soft Acids and Bases) theory, the piperazine is a kind of hard base, while the Fe^{3+} is beyond hard acid, and then it can be adsorbed onto the surface of BTP/Au electrode. It is greatly in accordance with the above experimental result that BTP/Au electrode had special selection of Fe^{3+} in the presence of Cu^{2+} and Ag^{+}.

In summary, a novel functional end group of thioacetate was prepared, and the SAM-modified gold electrode formed had special selection of Fe^{3+}. This ability has been exploited in the design of redox responsive ligands, thus allowing the voltammetric detection of metallic cations in solutions, which will offer the experimental and theoretical bases for their applications in molecular device and biological sensors.

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6 The general procedure for synthesis of BTP is presented as

bellow: 2-[4-(benzyloxy)phenoxy]ethanol (**1**): 4-(benzyloxy)phenol (20.0 g, 0.1 mol) was dissolved in ethanol (100 mL). When this whole solution was heated to reflux, the mixed solvent which contained NaOH (11.2 g, 0.2 mol) and ethanol (100 mL) was added dropwise over 20–30 min to the above solution. The reaction mixture was then refluxed for 0.5 h, and then a solution of chlorohydrin (16.1 g, 0.2 mol) was added. Subsquently the whole solution was continually refluxed at this temperature for 15 h. After cooling to room temperature, the resulting solution was filtered. The collected filtrate was concentrated under reduced pressure, and the residue was washed with NaOH (20%). The crude product was recrystallized by ethanol to afford the white solid product **1** with good yields (97.5%); 4-(2-hydroxyethoxy)phenol (**2**): To a solution of compound **1** (24.6 g, 0.1 mol) in MeOH (300 mL) was added Pd/C (0.5 g), running under hydrogen with stirring at room temperature. After 4 h, MeOH was evaporated in vacuo, and the yellow product **2** was directly obtained in 99.6% yield; 2-[4-(2-bromoethoxy)phenoxy]ethanol (**3**): A mixture of compound **2** (10.0 g, 0.06 mol), K_2CO_3 (17.9 g, 0.13 mol), and 1,2-dibromoethane (3.5 g, 0.13 mol) in MeCN (150 mL) was heated under reflux for 10 h. After cooling to ambient temperature, the mixture was filtered. The solvent was removed under reduced pressure, and then the residue was purified by column chromatography (acetone/petroleum ether, 1:3) to yield the white compound **3** in 38.6% yield; 1,4-bis{2-[4-(2-hydroxyethoxy)phenoxy]ethyl}piperazine (**4**): To a stirred solution of piperazine (0.78 g, 0.01 mol) in hot MeCN (50 mL) was added compound **3** (5.0 g, 0.012 mol). The reaction mixture was refluxed for 10 h. After completion of reaction, K_2CO_3 and the organic phase were obtained by filtered. The crude product was purifed by water and recrystalled by methanol to yield white compound **4** with the yield of 91.0%; 1,4-bis(2-{4-[2-(methanesulfonyloxy)ethoxy]phenoxy}ethyl)piperazine (**5**): To an ice-cold solution of compound **4** (0.5 g, 1.12 mmol) in DMF (20 mL) was added a solution of triethylamine (2 mL). Mesyl chloride was added dropwise after the reaction mixture was cooled to $-5\,°\mathrm{C}$, and the solution was stirred for 2 h at $-5\,°\mathrm{C}$, overninght at room temperature. The reaction mixture was quenced with water. Precipitation was filtered and purified by column chromatography (dichloromethane/methanol, 30:1) to give yiellow solide **5** in 87.4% yield; 1,4-bis{2-[4-(2-thioacetoxyethoxy)phenoxy]ethyl}piperazine (**6**): A mixture of compound **5** (1.0 g, 1.66 mmol) treating with potassium thioacetate (1.52 g, 13.68 mmol) in DMF (20 mL), were stirred at room temperature for 2 h. Water was added in the resulting solution and a white product precipitated. Crude product was obtained by filtered and was purified through column chromatography (dichloromethane/methanol, 20:1) to give white compound **6** in 84.9% yield.

7 Spectra of six compounds are summarized as follows: Compound **1**: mp: 100–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.79–3.85 (2H, t, $-C\mathit{H}_2OH$), 4.04–4.18 (2H, t, $-OC\mathit{H}_2$-CH_2OH), 5.02 (2H, s, $-OC\mathit{H}_2C_6H_5$), 6.85–6.93 (4H, m, $-C_6H_4-$), 7.18–7.44 (5H, m, $-C_6H_5$); compound **2**: mp: 84–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$); δ 2.01–2.03 (1H, t, $-CH_2O\mathit{H}$), 3.93–3.96 (2H, m, $-C\mathit{H}_2OH$), 4.02–4.04 (2H, t, $-OC\mathit{H}_2CH_2OH$), 4.49 (1H, s, $-C_6H_4O\mathit{H}$), 6.76–6.83 (4H, m, $-C_6H_4-$); compound **3**: mp: 79–80 °C; ^{1}H NMR (500 MHz, $CDC1_3$): δ 1.99–2.02 (1H, t, $-CH_2O\mathit{H}$), 3.61–3.63 (2H, t, $-CH_2Br$), 3.93–3.96 (2H, m, $-C\mathit{H}_2OH$), 4.03–4.05 (2H, t, $-OC\mathit{H}_2CH_2OH$), 4.24–4.26 (2H, $-OC\mathit{H}_2CH_2Br$), 6.85–6.86 (4H, d, $-C_6H_4-$); compound **4**: mp: 134–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.08 (2H, s, –OH), 2.64 (8H, s, $-NC\mathit{H}_2C\mathit{H}_2N-$), 2.79 (4H, t, $-C\mathit{H}_2CH_2OC_6H_4-$), 3.93–3.94 (4H, s, $-C\mathit{H}_2OH$), 4.02–4.04 (4H, m, $-C\mathit{H}_2OC_6H_4-$), 4.05–4.07 (4H, m, $-C_6H_4OC\mathit{H}_2CH_2OH$), 6.84 (8H, s, $-C_6H_4-$); MS, m/z: 447 $(M + H)^+$; CHN analysis: %C (calcd 64.55, found 64.36), %H (calcd 7.67, found 7.41), %N (calcd 6.27, found 6.03); compound **5**: mp: 132–133 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.65 (8H, s, $-NC\mathit{H}_2C\mathit{H}_2N-$), 2.81 (4H, t, $-C\mathit{H}_2CH_2OC_6H_4-$), 3.06–3.11 (6H, s, $-CH_3$), 4.05–4.07 (4H, m, $-C_6H_4OCH_2C\mathit{H}_2O-$), 4.18–4.20 (4H, m, $-C\mathit{H}_2OC_6H_4-$), 4.54–4.56 (4H, m, $-C_6H_4OC\mathit{H}_2CH_2O-$), 6.84 (8H, s, $-C_6H_4-$); CHNS analysis: %C (calcd 51.81, found 51.55), %H (calcd 6.35, found 6.14), %N (calcd 4.65, found 4.46), %S (calcd 10.64, found 10.42); compound **6**: mp: 142–143 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (6H, s, $-CH_3$), 2.63 (8H, s, $-NC\mathit{H}_2C\mathit{H}_2N-$), 2.79 (4H, t, $-C\mathit{H}_2CH_2OC_6H_4-$), 3.25 (4H, t, $-CH_2C\mathit{H}_2S-$), 4.03–4.04 (4H, m, $-C\mathit{H}_2OC_6H_4-$), 4.05–4.06 (4H, m, $-C_6H_4OC\mathit{H}_2CH_2S-$), 6.83 (8H, s, $-C_6H_4-$); ^{13}C NMR (500 MHz, $CDCl_3$): δ 195.37, 153.40, 152.67, 115.77, 115.68, 67.32, 66.64, 57.34, 53.61, 30.56, 28.64; MS, m/z: 563 $(M + H)^+$; IR (KBr, ν, cm^{-1}): 1689.6; CHNS analysis: %C (calcd 59.76, found 59.53), %H (calcd 6.81, found 6.56), %N (calcd 4.98, found 4.75), %S (calcd 11.40, found 11.17).

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