

Synthesis of a Flavone-Titanium (IV) Complex and Its Electrocatalytic Activity

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This work reported the synthesis and measurements of a novel complex of primuletin (a flavone of natural origin) and titanium. Through changes in the electron density, the 3HF ligand was found to have the ability to bind to the metal salt through electrochemical experiments. The Ti(IV)-primuletin-multi-walled carbon nanotube (MWCNT)-PE showed an enhanced current response and high reversibility. Additionally, it exhibited desirable electrocatalytic activity in hydroxylamine oxidation. A linear relationship was found between the catalytic current response (measured through amperometry) and the hydroxylamine concentration over a range of 2.5 μ M to 0.4 mM.

Keywords: Primuletin; Flavone-titanium (IV) complex; Flavone; Electrochemical oxidation

1. INTRODUCTION

Primuletin, a naturally occurring flavone, is widely found in plants belonging to the *Dionisya* and *Primula* species [1, 2]. Other flavonoid compounds affect the cell lines, enzymes, or receptors along with their antioxidant features and thus have gained substantial attention for their potential association with biological functions. Three properties of flavonoids explain their antioxidant activity, including the presence of a 4-oxo functional group in the C-ring, an ortho-dihydroxy structure in the B-ring, and/or the presence of a 2,3 double bond in the C-ring [3]. In addition, the antioxidant features are also associated with an OH group in the 3 position of the C-ring [4]. Only two of the above necessary conditions are satisfied in 5-hydroxyflavone; therefore, no significant antioxidant activity is observed [5, 6]. The monohydroxylated primuletin shows a low cytotoxicity against B 16 melanoma cells due to the low or absent scavenging effect and causes almost no or even no apoptosis in human leukaemia cells [7-10].

In addition, 5-hydroxyflavone could act as an activator of calcium-activated and ATP-sensitive potassium channels. The interaction with calcium-activated potassium channels must meet a structural requirement, i.e., a hydroxyl group in the 5 position [11, 12]. Therefore, 5-hydroxyflavone exhibited full vasorelaxation effects in a comparative study in the presence of 17 different flavones. Among the 25 tested flavones, 5-hydroxyflavone showed the maximum androgen receptor (AR) antagonistic activity, with an activity threefold higher than that of flutamide, a reputed AR antagonist for prostate cancer treatment [13-15].

The catalytic activity of flavone complexes has been reported by many different studies, together with varying the complex types for olefin polymerization, such as the post-metallocene complexes. Compared with traditional metallocenes, post-metallocenes are more desirable because of the more scalable and simpler chemical synthesis of these complexes. Previous studies have reported the synthesis of bidentate alkoxide ligand-based post-metallocene catalysts. Sobota reported the synthesis of the titanium complexes of guaiacol and methylmaltol and characterization of their crystal structures along with the study of their catalytic activities in the polymerization of propylene and ethylene [16-18]. The facile formation of complexes with transition metals can be realized with these highly flexible ligands. The synthesis of various analogues complexes of Ti and Zr based on methylmaltol and ethylmaltol ligands has been proposed by our research group. Through experiments on the polymerization of ethylene, the obtained complexes were found to be active under heterogeneous and homogeneous conditions [19-21].

In the present study, a Ti(IV)-primuletin-MWCNT-PE was fabricated through the electrodeposition of the Ti(IV)-primuletin complex onto a multi-walled carbon nanotube paste electrode (MWCNT-PE) surface. Additionally, the electrochemical performance and electrocatalytic activity of our developed electrode towards hydroxylamine oxidization were studied using chronoamperometry and cyclic voltammetry (CV).

2. EXPERIMENTS

2.1. Reagents and materials

Primuletin (5-hydroxyflavone) was purchased from Sigma-Aldrich. TiCl_4 was purchased from Merck. All measurements were carried out with Schlenk line techniques in an argon atmosphere. Ligand primuletin, dichloromethane, diethyl ether and hexane were purchased from Sinopharm Chemical Reagent Co., Ltd.

2.2. Synthesis of the complexes

The primuletin ligand (100 mg, 0.42 mM) was dissolved in dichloromethane in a Schlenk flask. The solution was then added dropwise to 0.21 mM TiCl_4 in dichloromethane. The mixture was stirred for 90 min at room temperature. After washing with diethyl ether, the solid product was dissolved in

dichloromethane and recrystallized in hexane. The resulting complex was left under vacuum until further use.

2.3. Measurements of complexes

^1H NMR spectra of the complexes was obtained by a Varian Inova 300 spectrometer. UV-Vis absorption spectra of the complexes were obtained using a Varian Cary 100 spectrophotometer. Elemental analysis was conducted using a 240 Perkin-Elmer analyser.

2.4. Theoretical calculations

Density functional theory (DFT) was used for all possible isomeric species optimizations using the B3LYP hybrid function by the three-parameter fit of the exchange-correlation potential suggested by Becke [22] and the gradient-corrected correlation functional of Lee and co-workers. The polarized Dunning-Huzinaga DZ basis set [23, 24] was used for the hydrogen, carbon, chloride and oxygen atoms. For the titanium atoms, the inner shell electrons were represented by the Los Alamos effective core potential (LANL2) of Hay and Wadt, [24] and the valence electrons were explicitly included using the associated DZ basis set.

2.5 Electrode preparation

For the preparation of the MWCNT-PE, paraffin oil was mixed with MWCNTs in a mortar (2:3, w/w) [25]. Then, the mixture was firmly packed as paste into the cavity of a polytetrafluoroethylene tube with a diameter of 1.6 mm. The fabrication of the traditional carbon paste electrode (CPE) followed a comparable procedure but used graphite instead of the MWCNTs. A copper wire was used for electron conduction. Weighing paper was used to smooth the electrode surface, which was then rinsed with water. The MWCNT-PE showed an *ca.* 1.94 times larger efficient area than that of the CPE, which was calculated based on the Randles-Sevcik equation in the presence of a probe, i.e., $\text{K}_3\text{Fe}(\text{CN})_6$. The Ti(IV)-primuletin-MWCNT-PE was fabricated by first placing the MWCNT-PE into a 0.10 M NaOH solution containing Ti(IV)-primuletin followed by consecutive scanning for 30 cycles (scan rate: 0.1 V/s; potential: 0.2 to 0.7 V). A MWCNT-PE, primuletin-MWCNT-PE, Ti(IV)-MWCNT-PE and Ti(IV)-primuletin-CPE were prepared for comparison.

3. RESULTS AND DISCUSSION

Fig. 1 shows the preparation of the Ti(IV)-primuletin complexes from the 3-hydroxyflavone ligand.

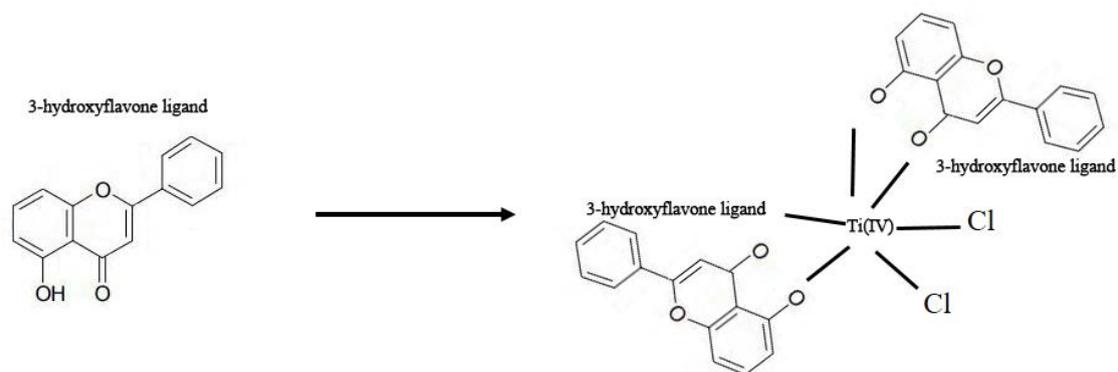


Figure 1. Preparation of the Ti(IV)-primuletin complexes.

As shown in the spectrum of complex 1, the resonance of the hydroxyl group in the 3HF ligand at 7.08 ppm disappeared, which indicated that the 3HF ligand was deprotonated after the insertion of titanium metal. Most proton signals were found to shift to higher frequencies in the complex spectrum compared with those in the ligand spectrum, which suggested that the aromatic protons exhibited a deshielding effect ascribed to the contribution of electronic density to the metal. The present study examined the ^{13}C chemical shifts of the 3HF ligand, which were consistent with the study results reported in previous works [26, 27]. The Ti macrocyclic complexes exhibited good catalytic activity due to the presence of -OH groups [28, 29]. Based on comparison of the ^{13}C NMR spectra of complex 1 and the free ligand in the 180–110 ppm region, the complex spectrum showed the displacement of some carbon signals due to the coordination of the ligand to the metal.

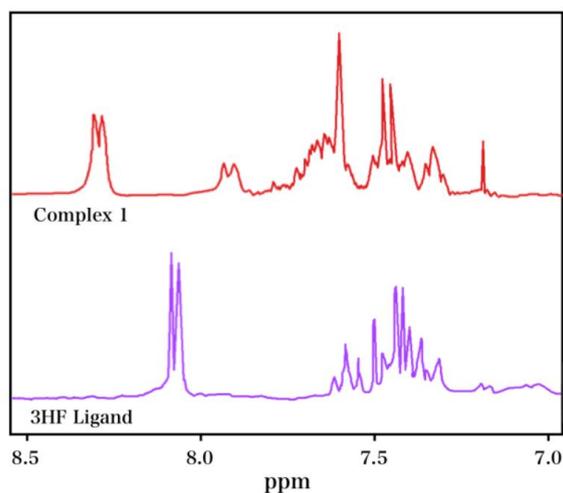


Figure 2. ^1H NMR spectra recorded for the 3HF ligand and the Ti(IV)-primuletin complex in CDCl_3 .

Fig. 3 shows the voltammetric characterization of the Ti(IV)-primuletin-MWCNT-PE, MWCNT-PE, primuletin-MWCNT-PE, Ti(IV)-MWCNT-PE and Ti(IV)-primuletin-CPE before and after the addition of 0.1 M hydroxylamine. As shown in Fig. 3A, a pair of redox peaks was found using the Ti(IV)-primuletin-MWCNT-PE before adding hydroxylamine. A significant increase in the anodic

peak current was observed after adding 0.2 M hydroxylamine; meanwhile, the cathodic peak current decreased. It can be seen that no electrochemical response was observed due to the passivation of the electrode surface by the irreversibly adsorbed oxidation product [30]. These results suggested that the Ti(IV)-primuletin-MWCNT-PE was catalytically active in hydroxylamine oxidation. As shown in Fig. 3B, C, under the same parameters, the background currents of hydroxylamine oxidation using the MWCNT-PE and primuletin-MWCNT-PE were higher, whilst no defined anodic peaks were found. These results suggested that the redox reaction was coupled with the electrode surface. On the other hand, at the Ti(IV)-MWCNT-PE and Ti(IV)-MR-CPE (Fig. 3D and 3E), peak currents of 8.77 μA and 58.1 μA , respectively, were obtained for electrocatalytic hydroxylamine oxidation. These two currents were much lower than that of the Ti(IV)-primuletin-MWCNT-PE (157 μA), as shown in Fig. 4F.

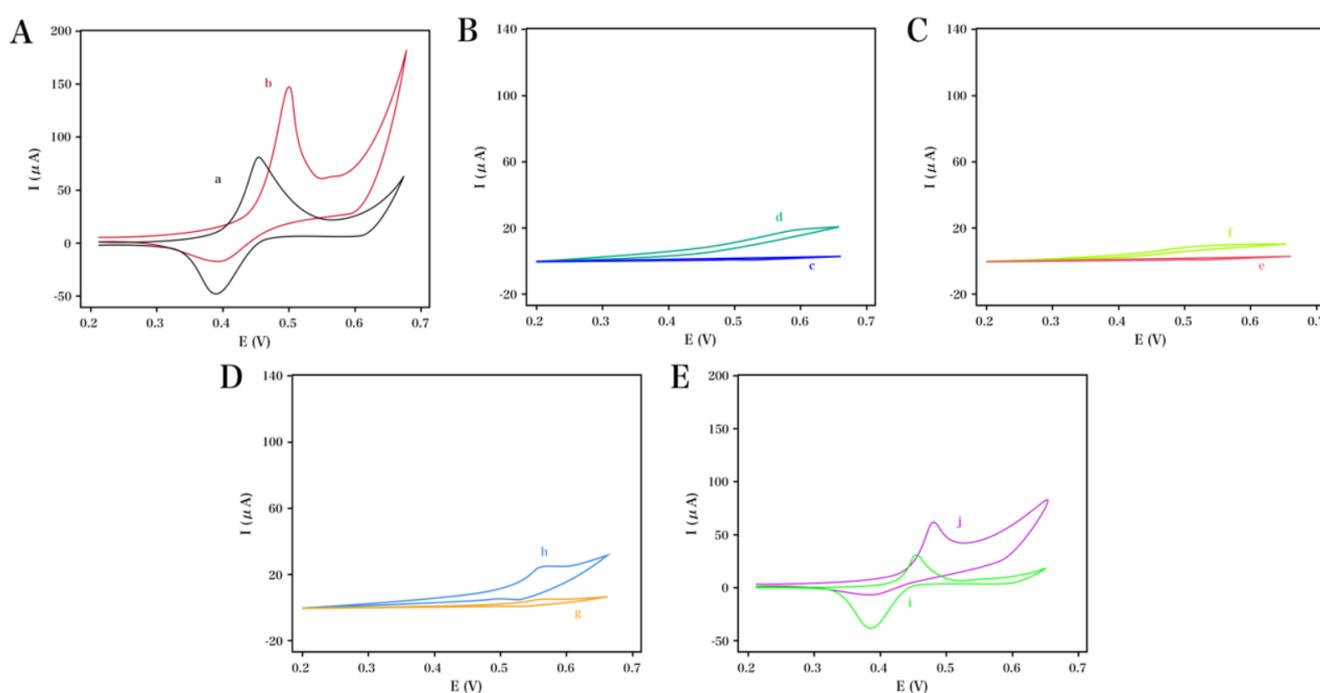


Figure 3. CVs recorded for (A) the Ti(IV)-primuletin-MWCNT-PE, (B) MWCNT-PE, (C) primuletin-MWCNT-PE, (D) Ti(IV)-MWCNT-PE and (E) Ti(IV)-primuletin-CPE before (*a, c, e, g, i*) and after (*b, d, f, h, j*) the addition of 0.2 mM hydroxylamine to a 0.1 M NaOH solution.

The effect of pH on the catalytic current of hydroxylamine oxidation was also studied. In brief, as the pH increased over the range of 0.00 to 12.50, a corresponding increase in the current also occurred. Over the pH range of 12.50 to 13.40, the maximum current was obtained. At a pH lower than 10.0, no significant catalytic current was observed. Therefore, we selected a NaOH solution with a pH of 13.0 (0.1 M) as the supporting electrolyte. Moreover, the results also indicated that the oxidation was a slow OH⁻ diffusion process rather than a charge-transfer process [31].

In addition, the catalytic rate constant, k_{cat} , was measured using chronoamperometry. At an intermediate time at which the electrocatalytic reaction rate of hydroxylamine determined the oxidation current, the catalytic current, I_{cat} , was described by the following equation:

$$I_{cat} / I_L = \pi^{1/2} (\kappa_{cat} c_0 t)^{1/2}$$

where I_L and I_{cat} refer to the oxidation currents recorded before and after the addition of hydroxylamine, respectively. In this equation, k_{cat} , t and c_0 represent the catalytic rate constant, the time elapsed, and the bulk hydroxylamine concentration, respectively. In the presence of 0.1 M hydroxylamine, a k_{cat} of $9.14 \times 10^3 \text{ L/mol s}^{-1}$ was obtained, as shown by the slope of the I_{cat}/I_L versus $t^{1/2}$ plot in Fig. 4.

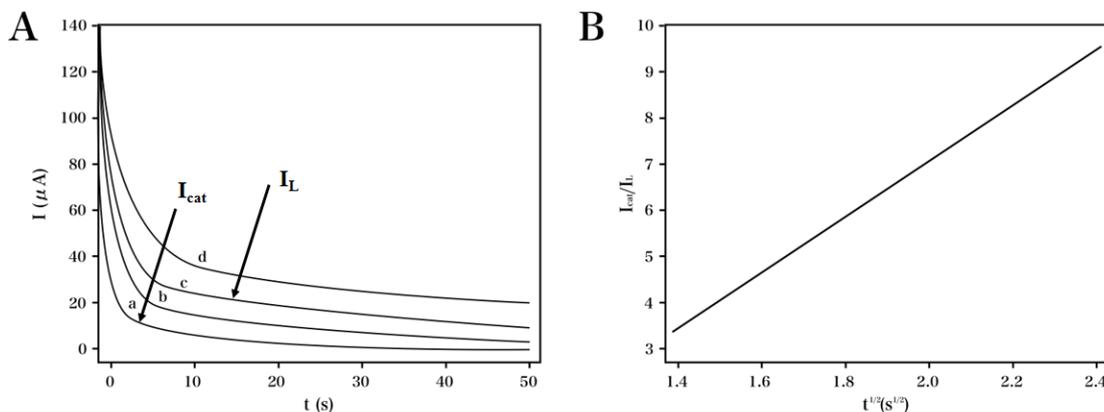


Figure 4. (A) Chronoamperograms recorded for the Ti(IV)-primuletin-MWCNT-PE in a 0.1 M NaOH solution containing (a) 0, (b) 0.5, (c) 1.0 and (d) 0.15 M hydroxylamine. (B) Plot of I_{cat}/I_L versus $t^{1/2}$ for 0.1 M hydroxylamine.

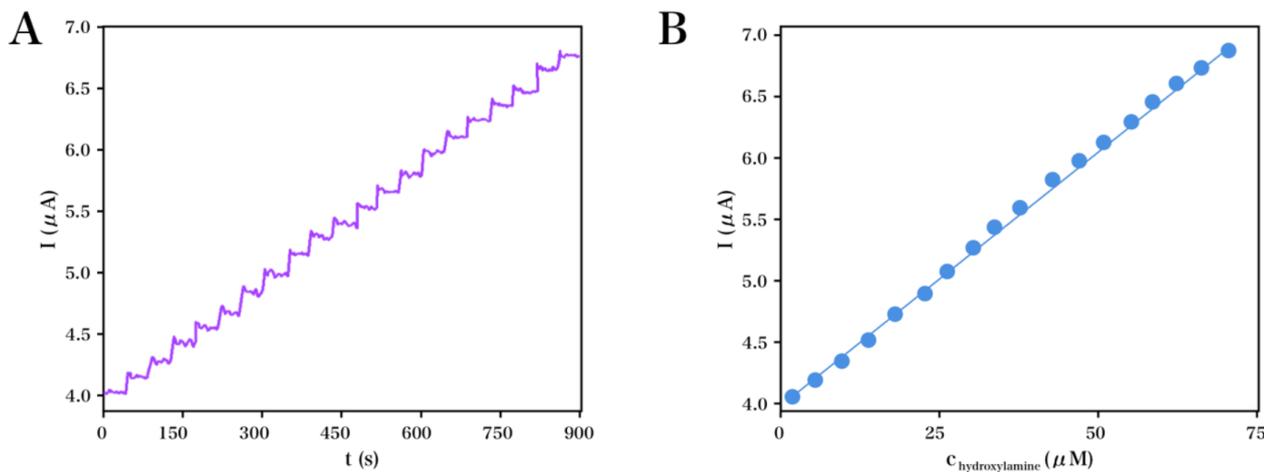


Figure 5. (A) Amperometric response recorded for the Ti(IV)-primuletin-MWCNT-PE in a 0.1 M NaOH solution after successively adding 2.5 μM hydroxylamine. (B) Plot of I against the hydroxylamine concentration.

To assess the calibration curve and the limit of detection (LOD) towards the analysis of hydroxylamine using our proposed electrode, the plot of the amperometric current and response time was recorded according to the aforementioned voltammetric results. Fig. 5 shows the conventional

amperogram after successively adding hydroxylamine into the NaOH solution (5.0 mL, 0.1 M) under continuous stirring. Within a response time of 4 s, a well-defined amperometric response was found, which indicated the high efficiency and stability of the developed electrode. On the other hand, a linear relationship was found between the current response and the concentration of hydroxylamine over a range of 2.5 to 40 μM , which had a linear correlation coefficient of 0.997 and an LOD of 0.77 μM . The comparison of other modified sensors in the detection of caffeine is displayed in Table 1.

Table 1. Comparison of the main properties of various analytical techniques in the determination of hydroxylamine.

Method	Linear range (μM)	Detection limit (μM)	Reference
Flow-injection biamperometry	0.6-40	0.1	[32]
TAA-AuNPs on MPTS modified Au electrode	0.0175-22000	—	[33]
quinizarine/ TiO_2 /CPE	10-400	0.173	[34]
HTP-MWCNT-CPE	2-10	0.16	[35]
CNT/2,7-bis(ferrocenyl ethyl)fluoren-9-one/cpE	0.5-20	0.47	[36]
Ti(IV)-primuletin-MWCNT-PE	2.5-40	0.77	This work

Using the same electrode, the RSD was determined to be 4.31% after six consecutive experiments using hydroxylamine (2.5 μM). On the other hand, six Ti(IV)-primuletin-MWCNT-PEs fabricated following the same procedure were employed to detect hydroxylamine (2.5 μM) under the optimum parameters. For these six electrodes, an RSD of 2.76% was obtained. The above results confirmed that our proposed electrode was highly stable and reproducible in the analysis of hydroxylamine.

The selectivity of our developed technique was studied by investigating the effects of different interferents on the analysis of hydroxylamine under the optimal parameters. For the analysis of 5 μM hydroxylamine, the interferent concentration that caused an error $< \pm 5.0\%$ was referred to as the tolerable limit. It was found that a 10-fold excess of NO_2^- , Zn^{2+} , Co^{2+} , and Pb^{2+} ; a 50-fold excess of PO_4^{3-} , SO_4^{2-} , F^- , Ca^{2+} , and K^+ ; and a 10-fold excess of SCN^- , Ba^{2+} , and Mg^{2+} caused no interference effects during the analysis of hydroxylamine, showing that our developed strategy was desirably selective.

4. CONCLUSIONS

In the present study, we reported the synthesis and measurements of a novel complex of primuletin (a bidentate alkoxide ligand of natural origin) and titanium, i.e., a Ti(IV)-primuletin complex. The Ti(IV)-primuletin-MWCNT-PE prepared based on the Ti(IV)-primuletin complex and

MWCNTs had an enhanced current response and high reversibility since the electrochemical responses were significantly augmented by the synergistic effects of these two materials. Additionally, our proposed electrode was highly electrocatalytically active in hydroxylamine oxidation. Furthermore, the analysis of hydroxylamine was carried out using a rapid, highly sensitive and reproducible amperometric strategy.

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