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Article

Electrochemical Homogenous Catalysis of the Isoflurane Reduction in Presence of Iron(III) Tetraphenylporphyrin Chloride

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A redução eletroquímica do agente anestésico inalatório isoflurano foi estudada em eletrodo de carbono vítreo na presença de cloreto de tetrafenil porfirinaferro(III) (Fe(TPP)Cl) em solução de dimetil sulfóxido (DMSO). A capacidade da Fe(TPP)Cl como potencial catalisador homogêneo para a redução de isoflurano foi testada por voltametria cíclica e cronomperometria. Revelou-se a excelente capacidade eletrocatalítica para a redução de isoflurano com sobrepotential de aproximadamente 1150 mV mais positivo do que o potencial observado para redução de isoflurano em solução de DMSO. Uma faixa linear entre $3{,}0 \times 10^{-5}$ e $2{,}1 \times 10^{-4}$ mol L^{-1} para a determinação de isoflurano em solução de DMSO contendo Fe(TPP)Cl foi obtida de medições de voltametria cíclica. Estimou-se o limite de detecção em $1{,}8 \times 10^{-5}$ mol L^{-1}. Um possível mecanismo catalítico é proposto.

The electrochemical reduction of the inhalational anesthetic agent isoflurane was studied at glassy carbon electrode in presence of iron(III) tetraphenylporphyrin chloride (Fe(TPP)Cl) in dimethyl sulfoxide (DMSO) solution. The ability of Fe(TPP)Cl as potential homogenous catalyst for the reduction of isoflurane was tested by cyclic voltammetry and chronomperometry. It showed excellent electrocatalytic ability for the reduction of isoflurane with overpotential of about 1150 mV more positive than the potential for observed reduction of isoflurane in DMSO solution. A linear range between 3.0×10^{-5} and 2.1×10^{-4} mol L^{-1} for the determination of isoflurane in DMSO solution containing 0.04 mmol L^{-1} Fe(TPP)Cl was obtained from cyclic voltammetry measurements. The limit of detection was estimated at 1.8×10^{-5} mol L^{-1}. A possible catalytic mechanism is proposed.

Keywords: isoflurane, anesthetic, electrocatalytic reduction, iron porphyrin

Introduction

Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, trade name Forane®) is a methyl ethyl ether having many physical properties similar to those of its isomer, enflurane (Figure 1). It is a colorless, volatile, nonflammable liquid used in general inhalational anesthesia. Isoflurane is a member of the fluorinated family of anesthetics that induces and maintains general anesthesia through depression of the central nervous system with resultant loss of consciousness.[1] It was first synthesized for its anesthetic properties in 1965[2] and clinically employed since 1971. Isoflurane is resistant to degradation by the absorber breathing circuit and can therefore be used during low flow or closed system anesthesia. Monitoring the concentration of exhaled inhalation anesthetic agents, in the operating room's environment, where operating room personnel may be exposed, is essential. In addition, the concentration of these agents in a patient blood must be monitored to ensure the patient safety. The monitoring has been undertaken by measuring the concentration of these agents by different methods in the last two decades.[3-9] However, these methods require complicated and expensive instrumentation, professional operators, a time-consuming detection process and complex pre-treatment steps. Thus, a simple and inexpensive electrochemical detection of these agents in blood and inhaled air is very important. Despite the extensive use of fluorinated family of anesthetics as an inhalation anesthetic agents, there are a few reports on electrochemical investigation of these compounds in literature.

Most attempts on electrochemical studies of fluorinated ethers have been performed by some researchers.[1,10-16] In 1988, Compton *et al.*[10] reported

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the indirect electroreduction of isoflurane mediated by a polymer coated (polyvinylfluoranthene) platinum electrode. This work showed promise for the future development of amperometric sensors for anesthetic agents.[10-12] Recently, the electroreduction of stereoisomers, enflurane,[12,13] isoflurane[1] and sevoflurane,[14] were reported at Au, Ag and Cu microelectrodes in dimethyl sulfoxide (DMSO). Floate and Hahn[13] at a variety of microelectrode substrates (Au, Ag and Cu) in DMSO investigated the electrochemical reduction of isoflurane individually and as a component of a simple gas mixture with oxygen or nitrous oxide.

Isoflurane as other fluorinated stereoisomers showed a large overpotential associated with the electroreduction (–2.5 V *vs.* Ag) in DMSO solution. It is a major challenge, which calls for the development of a high-performance catalyst for facilitating the reduction process.

Porphyrins and metalloporphyrins are unique classes of compounds widely present in nature. Porphyrins were named "purple" (porphyra) for the Greek root. The name porphyria commonly w credited to Schultz, who was a German medical student in 1874.[17] Due to their distinct chemical and photophysical properties, they have a variety of applications. The most important ones include industrial (catalysts, sensors, pigments and military), analytical (high performance liquid chromatography (HPLC) and spectrophotometric regent) and medical (cancer therapy and photodiagnosis) application.

Metalloporphyrins have attracted a great deal of interest owing to the diversity of their structures and interaction between the central metal and the analyte. Metalloporphyrins are used effectively in many electrochemical studies owing to their good catalytic properties. Iron porphyrins have been used for the electrocatalytic reduction of molecular oxygen and hydrogen peroxide,[18,19] carbon dioxide,[20] some anions as nitrite, sulfite and chlorite,[21-23] nitric oxide,[24] olefination of aldehydes[25] and so on. In recent works carried out in our laboratory, the catalytic reduction of sevoflurane by cobalt(III) Schiff base complex[26] and Fe(TPP)Cl[27] (Figure 1) in DMSO containing tetrabutylammonium perchlorate was investigated. It was found that the metal complexes have a potent electrocatalytic activity toward the reduction of sevoflurane. To our best knowledge, there is no report about application of any electrocatalyst for reduction of isoflurane. Continuing our investigation, here we report application of Fe(TPP)Cl as homogeneous electrocatalyst for reduction of isoflurane in DMSO solution. The focus of these studies has been directed towards the possible development of accurate and simple electrochemical sensors for determination of fluorinated ethers as inhalation anesthetic agent.

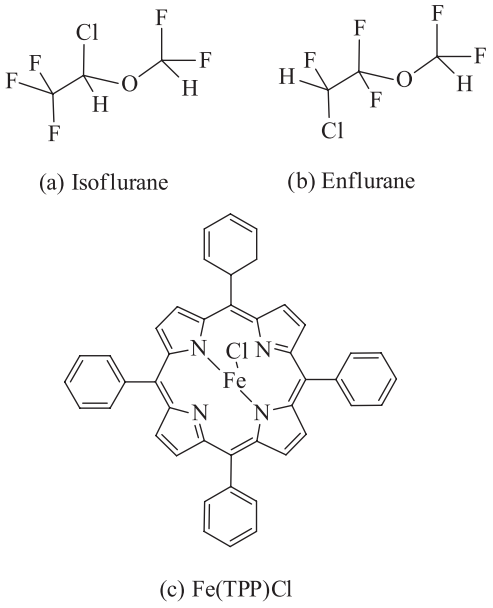

Figure 1. Structures of (a) isoflurane, (b) enflurane and (c) iron(III) tetraphenylporphyrin chloride (Fe(TPP)Cl).

Experimental

Reagents

Chemical reagents used throughout the experiments were obtained at the highest grade commercially available and utilized without further purification. Tetra-*n*-butylammonium perchlorate (TBAP) for use as electrolyte in electrochemical studies was obtained from Fluka. The anesthetic agent isoflurane was supplied by Abbott Laboratories Ltd. Fe(TPP)Cl was synthesized and characterized by reported procedure.[28] The solvent used for the electrochemical experiments was DMSO (HPLC grade, Merck). All solutions were thoroughly degassed with nitrogen (99.999% purity, Sabalan, Tehran, Iran) prior to use. Isoflurane was introduced into the electrolyte solution in liquid form by gravimetric aliquots before each voltammetric measurement. After N_2 gas purge and injection of isoflurane, the electrochemical cell was sealed to avoid loss of analyte and any interference of oxygen during measurements.

Apparatus

Electrochemical measurements were conducted using a computer controlled μAutolab type III/FRA2 (PGSTAT, Eco-Chemie, Netherlands) and run with the General Purpose Electrochemical System (GPES) software. A three electrode system comprising a glassy carbon (GC) electrode (geometric area of 0.0314 cm^2) as working electrode, a platinum wire as auxiliary electrode and silver rod as reference electrode were used for all electrochemical

experiments. The electrochemical measurements were carried out in DMSO solution containing 0.05 mol L^{-1} TBAP. All experiments were performed at room temperature.

Results and Discussion

Electrochemical properties of Fe(TPP)Cl in DMSO

In all experiments, the iron(III) tetraphenylporphyrin (TPP) catalyst was introduced in the DMSO solution as Fe(TPP)Cl. Figure 2 demonstrates a typical cyclic voltammograms (CVs) of the Fe(TPP)Cl complex in DMSO solution at different scan rates (ν) recorded with a glassy carbon electrode. This complex exhibits three chemically reversible systems, corresponding successively to the formation of the $Fe(III)^{+}/Fe(II)$, $Fe(II)/Fe(I)^{-}$ and $Fe(I)/Fe(0)^{2-}$ couples. Such results were reported for some similar iron porphyrins.[20] The cyclic voltammogram of Fe(TPP)Cl for the three systems exhibited anodic peaks at –0.02, –1.08 and –1.56 V, corresponding to the cathodic peaks on the reverse scan –0.07, –1.13 and –1.61 V, respectively. Formal potentials (E°') taken as the average of the anodic and cathodic peak potentials ($(E_p^a + E_p^c)/2$) are at –0.043, –1.104 and –1.586 V *vs.* Ag reference electrode for each redox couple respectively. Plots of peak current *vs.* $\nu^{1/2}$ for both anodic and cathodic peaks are linear for scan rates between 25-300 mV s^{-1} (Figure 2B for the first couple). For each couple, the ratio of anodic to cathodic peak currents is approximately one and the separation between the cathodic and anodic peak potentials ($\Delta E_p = E_p^a - E_p^c$) are about 75 mV at low scan rate (25 mV s^{-1}). The electrode processes are quasi-reversible, with ΔE_p greater than the (59/n) mV (n: number of electrons) expected for a reversible system.

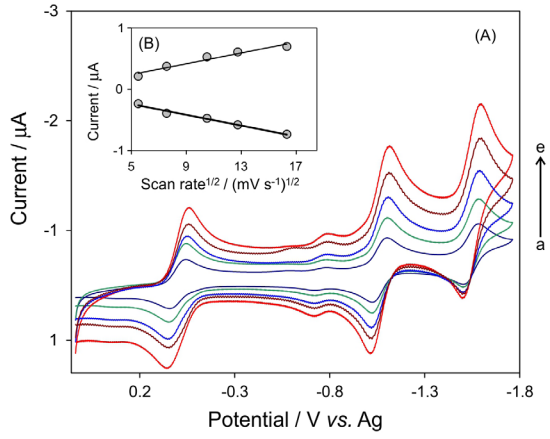

Figure 2. (A) Cyclic voltammograms for 0.04 mmol L^{-1} Fe(TPP)Cl on a glassy carbon electrode in DMSO solution containing 0.05 mol L^{-1} TBAP at scan rates: (a) 25; (b) 50 (c) 100; (d) 150; (e) 250 mV s^{-1}. (B) Plots of anodic and cathodic peak currents against (scan rate)$^{1/2}$ for both anodic and cathodic peaks for first couple.

Electrochemical behavior of isoflurane in the presence of Fe(TPP)Cl

A cyclic voltammogram of isoflurane in DMSO solution at a scan rate of 100 mV s^{-1} is shown in Figure 3A. An irreversible reduction peak for isoflurane is observed with a peak potential of –2.81V *vs.* Ag electrode. This behavior is in accordance with a previous result.[1] Figure 3B shows typical cyclic voltammograms of DMSO solution containing 0.04 mmol L^{-1} Fe(TPP)Cl in the absence and presence of isoflurane. As can be seen in Figure 3B, scan a, the glassy carbon electrode in solution without isoflurane exhibits a well-behaved redox reaction, but in presence of isoflurane, there is a dramatic enhancement of the cathodic peak current, and the anodic peak current disappeared. As shown in Figure 3, the cathodic peak potentials for reduction of isoflurane on the surface of glassy carbon

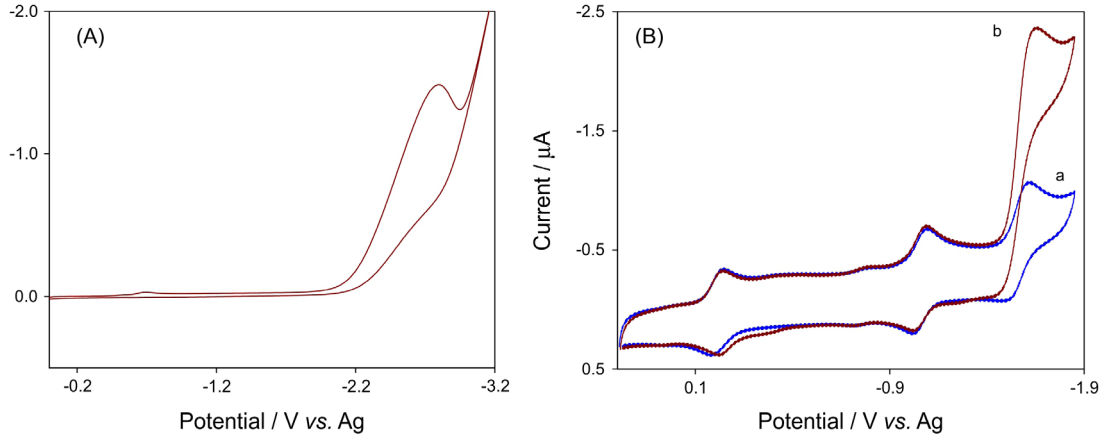

Figure 3. (A) Cyclic voltammogram of the DMSO solution containing 2.1 × 10^{-4} mol L^{-1} isoflurane and 0.05 M TBAP. (B) Representative cyclic voltammograms of 0.04 mmol L^{-1} Fe(TPP)Cl complex (a) in the absence and (b) in the presence of 2.1 × 10^{-4} mol L^{-1} isoflurane in DMSO solution containing 0.05 M TBAP. Scan rates were 100 mV s^{-1}.

electrode in the absence and presence of Fe(TPP)Cl are about −2.81 and −1.66 V, respectively. So, a decrease in overpotential of ca. 1.15 V and an enhancement of peak current indicate an electrocatalytic process in which Fe(TPP)Cl works as a homogeneous catalyst.

The cyclic voltammograms of 3×10^{-5} mol L^{-1} isoflurane in DMSO solution containing 0.04 mmol L^{-1} Fe(TPP)Cl at various scan rates on the surface of glassy carbon electrode were recorded (Figure 4A). As can be seen in Figure 4B, the plot of peak currents for the reduction of isoflurane linearly increases with $\nu^{1/2}$. It appears that the electrochemical reduction of isoflurane is a diffusion-controlled reaction.

By increasing scan rate, the cathodic peak potential for reduction of isoflurane shifted slightly toward the negative direction due to the irreversibility of charge transfer step in the electrode process. The current function ($Ip/\nu^{1/2}$) significantly decreased with increasing scan rates (Figure 4C). It is speculated that the irreversible electron-transfer process is affected by a following chemical step within the range of the scan rate used in this study. A Tafel plot is a useful device for evaluating kinetic parameters. Figure 4D shows the Tafel plot drawn using the data derived from the rising part of the current-voltage curve at a scan rate of 5 mV s^{-1}. The number of electron (n) involved in the rate-determining step nα (α is transfer coefficient), can be estimated from the slope of Tafel.[29] A Tafel slope of 149 mV was obtained, indicating that one electron is involved in the rate-determining step, assuming a transfer coefficient (α) of 0.4.

Based on our results, it seems that the following reaction probably occurs in the system under study here.

$Fe(I)^- + e^- \rightarrow Fe(0)^{2-}$, reduction of iron(I) (1)

$Fe(0)^{2-} + R - Cl \rightarrow [RFe(II)Cl]^{2-}$ +or $RFe(II)^- + Cl^-$, oxidative addition (2)

$RFe(II)^- + e^- \rightarrow RFe(I)^{2-}$, reduction of organoiron(II) (3)

$RFe(I)^{2-} \rightarrow Fe(I)^- + R^-$ (4)

or

$RFe(I)^{2-} + R - Cl \rightarrow [R^2Fe(III)Cl]^{2-}$, second oxidative addition (4)

$[R_2Fe(III)Cl]^{2-} \rightarrow + R - R + Fe(I)^- + Cl^-$, reductive elimination (5)

where

$R = F_3C{-}CHCl{-}O{-}CF_2H$, isoflurane

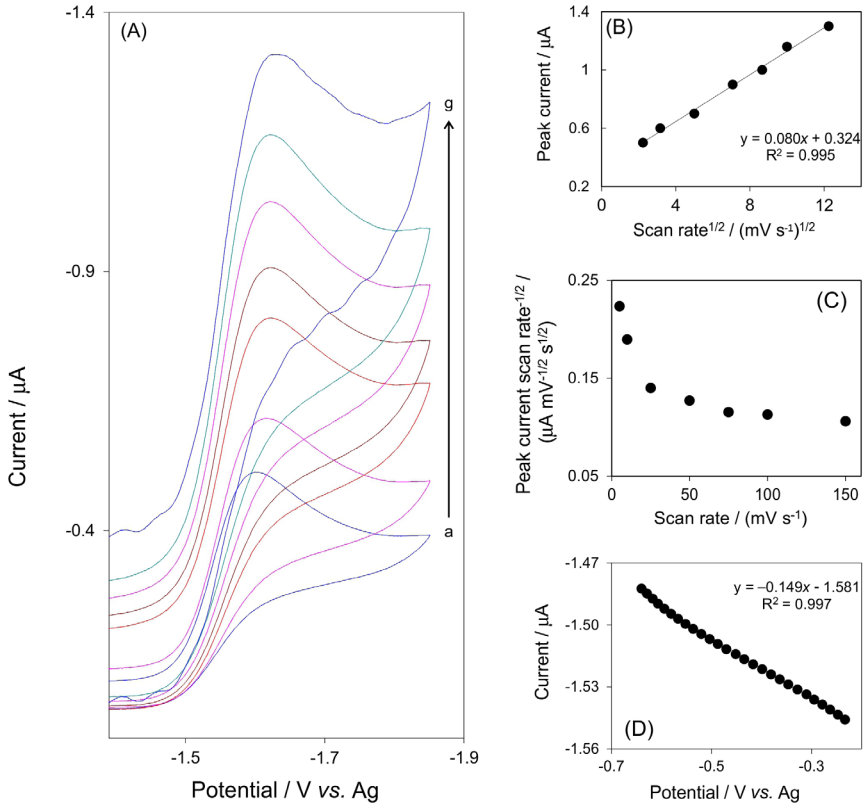

Figure 4. (A) Cyclic voltammograms for DMSO solution containing 0.05 mol L^{-1} TBAP in the presence of 3×10^{-4} mol L^{-1} isoflurane, 0.04 mmol L^{-1} Fe(TPP)Cl at various scan rates: (a) 5, (b) 10, (c) 25, (d) 50, (e) 75, (f)100 and (g) 150 mV s^{-1}. (B) Plot of the electrocatalytic currents *vs.* square root of scan rates. (C) Plot of the current function $I_p/\nu^{1/2}$ *vs.* scan rate for reduction of isoflurane. (D) Tafel plot derived from the voltammogram recorded at scan rate of 5 mV s^{-1}.

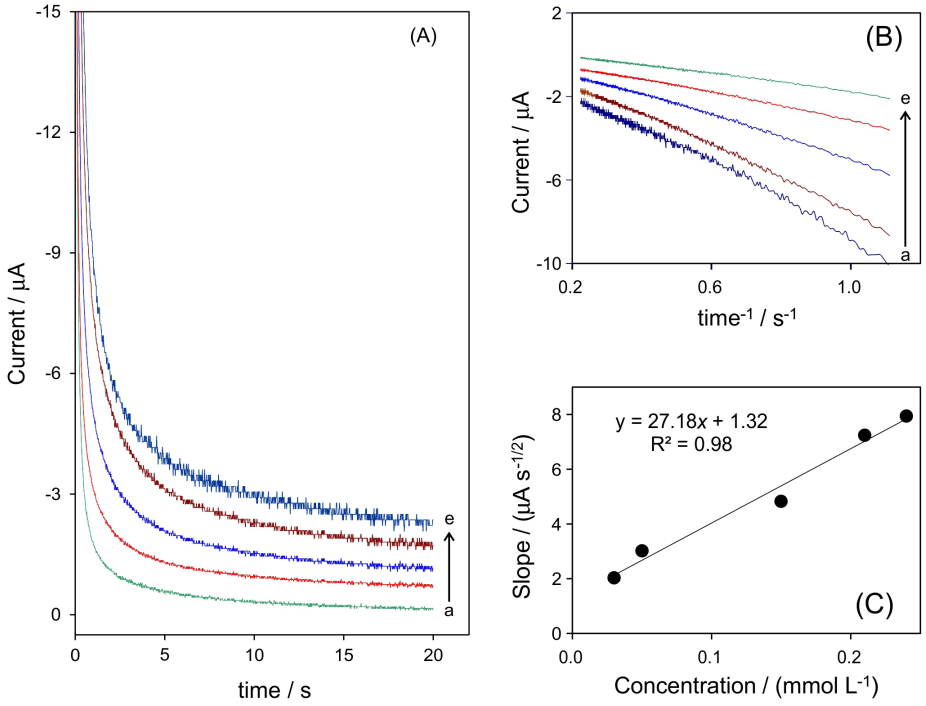

Figure 5. (A) Chronoamperometric response for DMSO containing 0.05 mmol L^{-1} TBAP in the presence of 0.04 mmol L^{-1} Fe(TPP)Cl, at a potential step of –2 V for different concentrations of isoflurane: (a) 3×10^{-5}, (b) 4.5×10^{-5}, (c) 1.5×10^{-4}, (d) 2.1×10^{-4} and (e) 2.4×10^{-4} mol L^{-1}. (B) Plot of current *vs.* $t^{-1/2}$ obtained from chronoamperograms (A) for the same concentrations of isoflurane. (C) Plot of the slope of straight lines against the isoflurane concentration.

Chronoamperometry study

The catalytic reduction of isoflurane by Fe(TPP)Cl as homogenous electrocatalyst was studied by chronoamperometry. Figure 5 shows the chronoamperograms that were obtained for a series of isoflurane solutions with various concentrations (3×10^{-5} to 2.1×10^{-4} mol L^{-1}). The results show that an increase in concentration of isoflurane was accompanied by an increase in cathodic current obtained for a potential step of –2 V *vs.* Ag. For an electroactive material with a diffusion coefficient of D (cm^2 s^{-1}), the current for the electrochemical reaction (at a mass transport limited rate) is described by the Cottrell equation.[29]

$$I = nFAD^{1/2}C\pi^{-1/2}t^{-1/2} \quad (1)$$

where D (cm^2 s^{-1}) and C (mol cm^{-3}) are the diffusion coefficient and the bulk concentration, respectively. Under diffusion control, a plot of I *vs.* $t^{-1/2}$ ($s^{-1/2}$) will be linear, and the value of D can be obtained from the slope. Figure 5B shows the fitted experimental plots for different concentrations of isoflurane. The slopes of the resulting straight lines were plotted *vs.* the isoflurane concentration (Figure 5C), and the mean value of D was found to be 6.31×10^{-5} cm^2 s^{-1}.

Effect of isoflurane concentration

Figure 6 displays a series of cyclic voltammograms recorded with the glassy carbon electrode in the presence of different concentrations of isoflurane ranging from 3×10^{-5} to 2.4×10^{-4} mol L^{-1} in DMSO containing 0.04 mmol L^{-1} Fe(TPP)Cl. The correlation between the reduction peak intensity and isoflurane concentration is

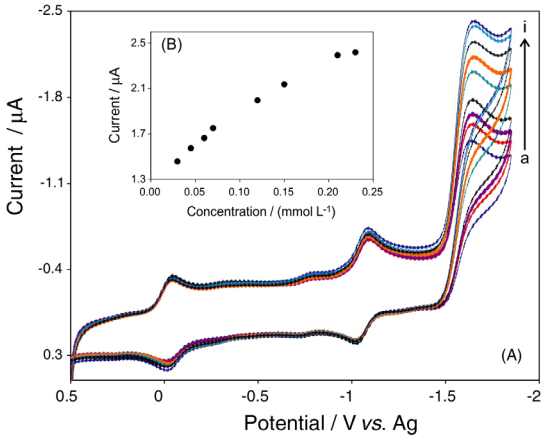

Figure 6. (A) Cyclic voltammograms for DMSO containing 0.05 mmol L^{-1} TBAP in the presence of 0.04 mmol L^{-1} Fe(TPP)Cl, and different concentrations of isoflurane: (a) 3×10^{-5}, (b) 4.5×10^{-5}, (c) 6×10^{-5}, (d) 7×10^{-5} (e) 1.2×10^{-4}, (f) 1.5×10^{-4} and (g) 2.1×10^{-4} mol L^{-1}. (B) Plot of the peak currents as function of concentrations of isoflurane.

shown in Figure 6B. The voltammetric calibration curve for the peak current *vs.* isoflurane concentration is linear (correlation coefficient = 0.997) in the range of 3×10^{-5} to 2.1×10^{-4} mol L^{-1}. The linear regression equation is expressed as: $I_{(\mu A)} = 1.53 \times 10^{-6} C_{isoflurane}$ (mol L^{-1}) – 1.578 and the limit of detection (3σ) is 1.8×10^{-5} mol L^{-1}, where σ is the standard deviation of responses for blank solution.

Conclusions

The effect of Fe(TPP)Cl toward isoflurane electroreduction in DMSO was illustrated. Resulting voltammograms obtained with a glassy carbon electrode in a solution containing isoflurane and iron porphyrin complex indicates a well-defined irreversible peak at nearly –1.66 V *vs.* Ag. Fe(TPP)Cl catalyzed the electroreduction of isoflurane in DMSO solution with an overpotential of about 1150 mV lower than that electroreduction in absence of the catalyst. It is concluded that the catalytic process is controlled by the rate of electron transfer between isoflurane and Fe(TPP)Cl complex and diffusion of isoflurane. This investigation provides area for the development of simple and sensitive electrochemical gas sensor for measuring inhalation anesthetic agent vapor under clinically related conditions.

Acknowledgement

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