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Toward Feedback-Controlled Anesthesia: Voltammetric Measurement of Propofol (2,6-Diisopropylphenol) in Serum-Like Electrolyte Solutions

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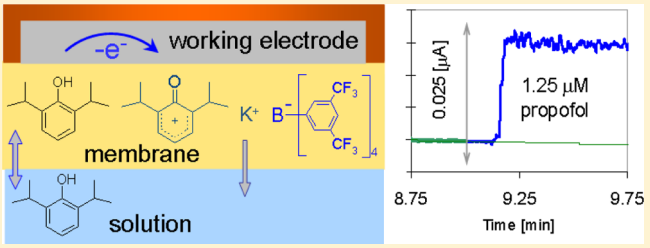
Supporting Information

ABSTRACT: Propofol is a widely used, potent intravenous anesthetic for ambulatory anesthesia and long-term sedation. The target steady state concentration of propofol in blood is 0.25−10 μg/mL (1−60 μM). Although propofol can be oxidized electrochemically, monitoring its concentration in biological matrixes is very challenging due to (i) low therapeutic concentration, (ii) high concentrations of easily oxidizable interfering compounds in the sample, and (iii) fouling of the working electrode. In this work we report the performance characteristics of an organic film coated glassy carbon (GC) electrode for continuous monitoring of propofol. The organic film (a plasticized PVC membrane) improved the detection limit and the selectivity of the voltammetric sensor due to the large difference in hydrophobicity between the analyte (propofol) and interfering compounds of the sample, e.g., ascorbic acid (AA) or *p*-acetamidophenol (APAP). Furthermore, the membrane coating prevented electrode fouling and served as a protective barrier against electrode passivation by proteins. Studies revealed that sensitivity and selectivity of the voltammetric method is greatly influenced by the composition of the PVC membrane. The detection limit of the membrane-coated sensor for propofol in PBS is reported as 0.03 ± 0.01 μM. In serum-like electrolyte solutions containing physiologically relevant levels of albumin (5%) and 3 mM AA and 1 mM APAP as interfering agents, the detection limit was 0.5 ± 0.4 μM. Both values are below the target concentrations used clinically during anesthesia or sedation.



The drug 2,6-diisopropylphenol (propofol) is an intravenous general anesthetic which is widely used in surgical and critical care settings for the purpose of general anesthesia or conscious sedation.[1] The broad appeal and popularity of propofol is related to the rapid induction and rapid elapse of anesthesia. The target steady-state concentration range of propofol in blood is 0.25−10 μg/L (1−60 μM).

Target-controlled infusion (TCI) anesthesia aims to provide stable, user-defined, blood concentrations of anesthetic drugs using small-platform delivery systems. TCI of propofol has not been approved by the FDA (U.S. Food and Drug Administration). Measuring propofol levels in real-time during anesthesia and correlating blood levels with efficacy data would greatly enhance the safety of propofol delivery and potentially permit the approval of "closed-loop TCI". To date, real-time measurements of propofol concentration in blood and other biological fluids have been elusive. Instead, most of the efforts are focused on monitoring propofol in the exhaled breath[2−5] using gas chromatography/mass spectrometry and finding the correlation between the exhaled breath and plasma values.[4]

In a recently published paper, we discussed the difficulties of the electrochemical quantification of propofol in aqueous solutions.[6] We showed that similar to other phenolic compounds,[7−12] propofol can be oxidized electrochemically. However, product(s) from the electrochemical oxidation and coupled reactions may deposit to the electrode surface causing immediate passivation or gradual electrode fouling. Although the detrimental effect of electrode fouling could be minimized, the detection limit (3.2 μM) and selectivity of the method remained inadequate for monitoring propofol in biological samples. Because of the limited selectivity of voltammetric methods, electrochemical propofol sensors are mainly used as detectors in chromatographic separation.[13−15]

Propofol is a highly lipophilic compound with reported log *P* values between 3.83[16] and 4.15[1] (where *P* is the octanol/water partition coefficient). The high lipophilicity of propofol offers an opportunity to enhance the voltammetric signal by using an organic-film modified working electrode. Because of its high lipophilicity, the concentration of propofol was expected to be orders of magnitude higher in the film than in the aqueous

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sample. On the other hand, the concentrations of the most common interfering compounds AA and APAP were expected to be lower in the film than in the aqueous solution since they are more hydrophilic. The log *P* values for ascorbic acid and 4-acetamidophenol are log $P_{AA} = -1.84$[17] and log $P_{APAP} = 0.31$,[17] respectively. Consequently, both the detection limit and the selectivity of the organic-film modified propofol sensor were expected to be significantly better than with an unmodified sensor. The influence of the organic film parameters and the experimental conditions on the responses of polymeric film coated voltammetric sensors were simulated and tested by Leddy and co-workers.[18−20]

Voltammetry with an organic film modified working electrode has some resemblance to electrochemistry at the interface between two immiscible electrolyte solutions (ITIES).[21−25] However in contrast to liquid−liquid electrochemistry, in the case of our voltammetric experiments with the organic film coated sensor, the measured current is provided by the electrochemical oxidation of propofol at the working electrode in the film and not by charge-transfer processes at the ITIES. The partitioning of propofol into the organic film is based on its hydrophobic properties and is not influenced by the applied potential.

Our objective was to identify conditions that would permit electrochemical monitoring of propofol in blood, serum, or plasma to achieve the desired goal of closed-loop, feedback controlled infusion of propofol during anesthesia. To obtain a mechanically robust working electrode in this work, the organic film has been immobilized to the electrode surface in the form of a highly plasticized PVC membrane.[26−28] Coating the surface of a glassy carbon working electrode with a highly plasticized PVC membrane prevented electrode fouling and allowed for chronoamperometric detection of submicromolar levels of propofol in serum-like electrolytes containing 5% bovine serum albumin (BSA), 3 mM ascorbic acid (AA), and 1 mM *p*-acetamido phenol (APAP).

EXPERIMENTAL SECTION

Materials. 2,6-Diisopropylphenol (propofol) was purchased from Sigma Aldrich (St. Louis, MO) and prepared first as a 10 mM stock solution in 0.1 M NaOH, before diluting to a 1 mM secondary stock solution in phosphate buffer (PBS) for use in the experiments. The PBS buffer (pH ∼7.2) was prepared as a mixture of 0.1 M KH_2PO_4, 0.1 M K_2HPO_4, 0.1 M KCl, and 0.045 M NaOH. All other reagents used in this study were purchased commercially from Sigma Aldrich and were of ACS grade, unless stated otherwise. The aqueous solutions were prepared with water purified by a Milli-Q Gradient A10 System (Millipore Corp., Billerica, MA).

Membrane Solutions. PVC membrane solutions were generally prepared as 250 mg quantities, consisting of ∼25 wt % PVC, ∼50 wt % plasticizer, ∼22 wt % organic electrolyte, and ∼3 wt % ion-exchange salt. This mixture was then dissolved in 2.5 mL of tetrahydrofuran (THF). The PVC (high molecular weight) and its plasticizers, 2-nitrophenyl octyl ether (*o*-NPOE), bis(2-ethylhexyl) sebacate (DOS) and 1-octanol, were selectophore grade. The organic electrolyte, tetradodecylammonium tetrakis(pentafluorophenyl) borate (TDDATPFPhB), was prepared by a metathesis reaction between tetradodecylammonium chloride (TDDACl) and potassium tetrakis-(pentafluorophenyl) borate (KTPFPhB) (Boulder Scientific Company, CO) in dichloromethane, followed by a liquid phase extraction of the product using deionized (DI) water. The organic electrolyte, bis(triphenylphosphoranilidine) ammonium tetrakis [3,5,bis (trifluoromethyl) phenyl] borate (BTPPATFPhB), was prepared the same way from bis-(triphenylphosphoranylidene) ammonium chloride (BTPPACl) (Sigma Aldrich) and sodium tetrakis[3,5bis-(trifluoromethyl) phenyl] borate dihydrate (NaTFPhB) (Dojindo Laboratories Gaithersburg, MD). KTPFPhB also served as the ion-exchange salt, or NaTFPhB was used. The specific compositions of each PVC membrane solution mixture used during the course of this work are described in Table 1. The membrane solutions differ from each other primarily in terms of the plasticizer, the organic electrolyte, or the ion-exchange salt content.

Table 1. Composition of PVC Membrane Solutions (wt %) for Spin Coating the GC Electrode Surface[a]

PVC membrane solutions for spin coating		I	II	III	IV	V
polymer	PVC	25.5	25.1	25.5	25.0	25.5
plasticizer	*o*-NPOE	50.9				
	DOS		49.9	49.6	49.8	
	1-octanol					49.5
electrolyte	TDDATPFPhB	21.2	22.6	21.9		21.8
	BTPPATFPhB				21.8	
ion-exchange salt	NaTFPhB	2.4		3	3.4	3.2
	KTPFPhB		2.4			
solvent[b]	THF	(a)	(b)	(c)	(c)	(c)

[a]∼250 mg quantities were dissolved in 2.5 mL of THF. [b]ACS grade THF generally contains butylated hydroxytoluene (BHT) as an antioxidant/inhibitor. BHT is an electrochemically active compound with a very similar structure to propofol. To avoid possible interference from BHT, the THF used to dissolve the membrane solution ingredients was either cleaned by column chromatography (a) or distilled before use (b), or an inhibitor-free (c) THF was used.

Electrodes and Methods. Cyclic voltammetry (CV) and chronoamperometry (CA) experiments were performed in a three-electrode cell, using a CH Instruments model 900 potentiostat (CH Instruments Inc., TX). In these measurements Ag|AgCl|3.0 M KCl (CH Instruments) and a platinum wire served as the reference and counter electrodes, respectively. The potential of the reference electrode was regularly checked versus a saturated calomel reference electrode. Readings for our Ag/AgCl reference electrode were generally recorded as −35.3/mV in 3.0 M KCl. For details on the theory and application of CV and CA methods, the book of Bard and Falkner is recommended.[29]

For the working electrode, a PVC membrane coated glassy carbon (GC) (i.d. = 3 mm) was used (BASi, IN). The working electrode was first polished (0.3 and 0.05 μm alumina slurry), then rinsed and sonicated in DI water, and dried. The electrode was spin-coated with a PVC membrane using a drill press (Supporting Information, Figure S1). The electrode was dipped into a PVC membrane solution and rotated for 20 s at 1100 rpm and left in an up-right position until the complete evaporation of THF (∼1 h). This protocol resulted in a few micrometer thick PVC membrane-coating on the electrode surface. Prior to electrochemical experiments, the PVC membrane-coated electrodes were soaked in PBS for 15 min.

Electrochemically oxidizable impurities in the membrane may interfere with the voltammetric determination of the analyte. In this work, impurities in KTPFPhB resulted in an

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oxidation peak at ~1.6 V in the cyclic voltammograms recorded in the background electrolyte. This interference was minimized by implementing an electrochemical pretreatment protocol in which the potential of the membrane coated electrode was cycled between 0.8 and 1.8 V for 100 scans at 0.1 V s^{-1} in the background electrolyte prior to exposing the membrane coated sensor to any solution containing propofol, the target analyte. An example of CV scans recorded during the electrochemical cleaning/pretreatment is shown in the Supporting Information (Figure S2). The electrochemical pretreatment step was no longer required once we used high-purity KTPFPhB.

RESULTS AND DISCUSSION

Cyclic Voltammetry with the PVC Membrane Coated GC Electrode. In this work, a plasticized PVC membrane coated GC electrode was used for the measurement of propofol in the presence of interfering compounds at physiologically relevant pH values. As plasticizers, *o*-NPOE and DOS were used with dielectric constants of 23.9[30] and 3.9,[30] respectively. On the basis of previous CV experiments with propofol in acetonitrile, we expected no or minimal electrode fouling when the electrochemical oxidation of propofol is performed in an organic phase. An example of CVs recorded in acetonitrile is shown in the Supporting Information (Figure S3).

To perform voltammetric measurements with the plasticized PVC membrane coated electrode, the membranes were prepared with an organic electrolyte (TDDATPFPhB) in combination with an ion-exchange salt (e.g., KTPFPhB), which served as the background electrolyte. On the basis of the early works of Nieman[31] and Ammann,[32] these and similar additives are commonly used to reduce the resistance of liquid membrane ion-selective electrodes. The organic electrolyte has been used in combination with an ion-exchange salt because it provided the lowest resistance.[32] In general, the primary role of the ion-exchange salt in ion-selective membranes is to improve the permselectivity of the membrane. The permselectivity of the PVC membrane coating during the voltammetric determination of propofol improves the selectivity of the sensor against negatively charged interfering compounds like ascorbate anion. However, in this work the ion exchange salt was incorporated into the membrane with an additional consideration. We assumed that the oxidation of propofol generates positively charged cationic species, e.g., phenoxonium ions[33] in the membrane and the excess positive charge is compensated by the release of hydrophilic cations from the ion exchange salt into the solution.

CVs recorded with the PVC membrane coated electrode in PBS containing 111.1 μM propofol (Supporting Information, Figure S4) were very similar to the CVs recorded in acetonitrile (Supporting Information, Figure S3). No electrode passivation or decrease in the peak current was detected for a series of continuous scans (six in total). The peak current increased linearly with propofol concentration. The traces of the forward scans recorded at 0.1 V s^{-1} and the calibration curve constructed from the peak current values at 1.25 V are shown in Figure 1.

Chronoamperometry with the PVC Membrane Coated GC Electrode. For continuous monitoring, chronoamperometry (CA) is a better alternative than CV. In CA experiments, the charging current is smaller and the detection limit (DL) is lower. The CA response of three freshly prepared PVC membrane coated sensors for propofol in PBS is shown in Figure 2 (Table 1, solution I). An applied potential of 1.2 V was

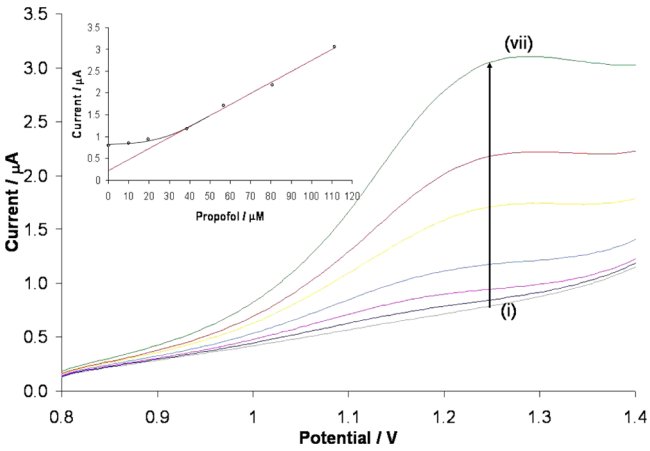

Figure 1. Forward CV scans recorded with a PVC-membrane coated GC electrode (solution I) for (i) 0 μM, (ii) 9.9 μM, (iii) 19.6 μM, (iv) 38.5 μM, (v) 56.6 μM, (vi) 80.5 μM, and (vii) 111.1 μM propofol in PBS. Inset: Calibration curve for propofol based on peak current measurements at 1.25 V.

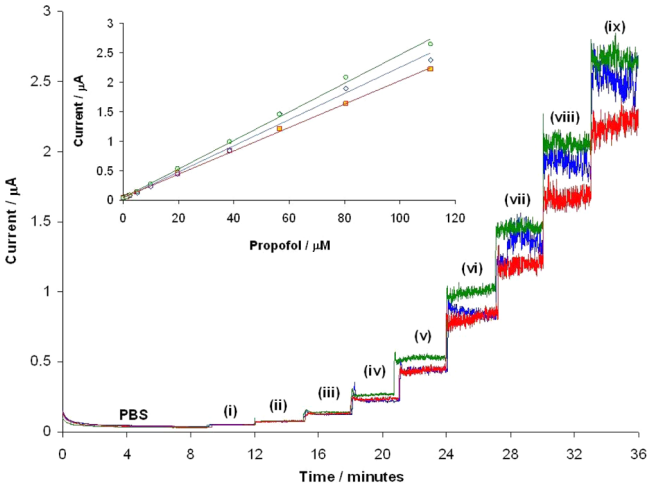

Figure 2. CA response of PVC-membrane coated GC electrode (solution I) for (i) 1.25 μM, (ii) 2.5 μM, (iii) 4.98 μM, (iv) 9.9 μM, (v) 19.6 μM, (vi) 38.4 μM, (vii) 56.6 μM, (viii) 80.5 μM, and (ix) 111.1 μM propofol in PBS buffer. Inset: Calibration curves for propofol based on current measurements after 2 min of each addition.

used in all CA experiments vs a Ag|AgCl|3.0 M KCl reference electrode. Propofol concentration of the solution was increased by injecting aliquots of propofol standards at 3 min intervals into a continuously stirred PBS background solution. As can be seen from Figure 2, the response of the PVC membrane coated electrode is fast, and the sensor-to-sensor reproducibility is very good. The differences in the slopes of the calibration curves are related to the differences in the thickness of the organic membrane coatings on the GC electrode. Propofol sensors with thicker membrane coatings have reduced sensitivity and slower response compared to sensors with thinner membranes. (The comment is based on results collected in an automated flow analytical system using the membrane coated voltammetric sensor for propofol monitoring. These results will be shown in an upcoming paper.)

Because of concerns about performing voltammetric measurements in a resistive organic film, *o*-NPOE, which has a relatively large dielectric constant (ε_r = 23.9),[30] was initially used as the plasticizer in the PVC membrane coatings (Figure

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2). However, once we realized that the resistance of the membrane, due to its small thickness and large organic salt content was not critical, we also tested other plasticizers. The different membrane coatings resulted in CVs with significantly different peak potentials and peak currents (Supporting Information, Figure S5). CA experiments with the DOS plasticized membrane coated GC electrodes were performed with the same protocol as before but with a different applied potential value.

To study the response of the membrane coated propofol sensor in the presence of easily oxidizable compounds that may interfere with the determination of propofol in whole blood, serum, or plasma, similar triplicate measurements were performed in the presence of 3 mM ascorbic acid (AA) and 1 mM 4-acetamidophenol (APAP). The selected concentrations of AA and APAP are at the high end of physiologically relevant concentrations. In these experiments, the samples contained also physiologically relevant concentrations of albumin (5% bovine serum albumin, BSA). The influence of albumin on the response of the propofol sensor was tested because albumin is the most abundant plasma protein which may influence the response of an electrochemical sensor when adsorbed to the surface. In addition, it is known that up to 96% of propofol is bound to albumin,[34,35] i.e., in the presence of albumin the free propofol concentration in the solution is significantly reduced compared to its nominal value.

Propofol detection in the presence of these particular interfering agents was first evaluated individually and then in a mixture of all three (in order to model measurements recorded in the patient's serum or whole blood).

Limit of Detection for Propofol with the Membrane-Coated Sensor. IUPAC defines the limit of detection as the smallest concentration (or quantity) that can be detected in an analytical procedure with a given certainty.[36] This concentration is derived from the mean of the measured signal in the blank ($\bar{x}_{bi}$), the standard deviations of the blank measurement (S_{bi}), and the slope of the analytical calibration curve (S) as $c^1_{DL} = (x_L - \bar{x}_{bi})/S$, where $x_L = \bar{x}_{bi} + 3S_{bi}$.

The detection limit for propofol determination with the membrane coated sensor in cyclic voltammetric experiments (Figure 1) by considering the standard deviation of the background current recorded in repeated CV scans ($n = 3$) was calculated as $c^1_{DL} = 2.2$ μM. In monitoring experiments, in addition to the smallest concentration that can be determined, the resolution of the concentration measurements is also very important. The resolution of the measurement is defined as the minimum difference between two concentrations that can be distinguished with a given probability. The resolution of the concentration measurements (c^2_{DL}) in this work has been calculated as $c^2_{DL} = 3 \times \text{rmsd}/S$, where rmsd is the residual mean standard deviation of the data points of the calibration curve around the best line fit and S is the slope of the fitted line. By considering the peak current values recorded in the CV experiments between 40 and 111.1 μM (Figure 1 inset), $c^2_{DL} = 8.8$ μM was calculated. c^2_{DL} is greater than c^1_{DL} because the scatter of the data points around the best fit line is much larger at high concentrations than at low concentrations.

In Figure 3 we show a close-up of the CA response for 1.25 μM propofol in PBS (top) and in PBS containing 3 mM AA, 1 mM APAP, and 5% BSA (bottom) in combination with details on the evaluation of c^1_{DL} based on the background current noise. First a line was fitted to a 1 min segment of the background current (just before the first addition of propofol) and the rmsd

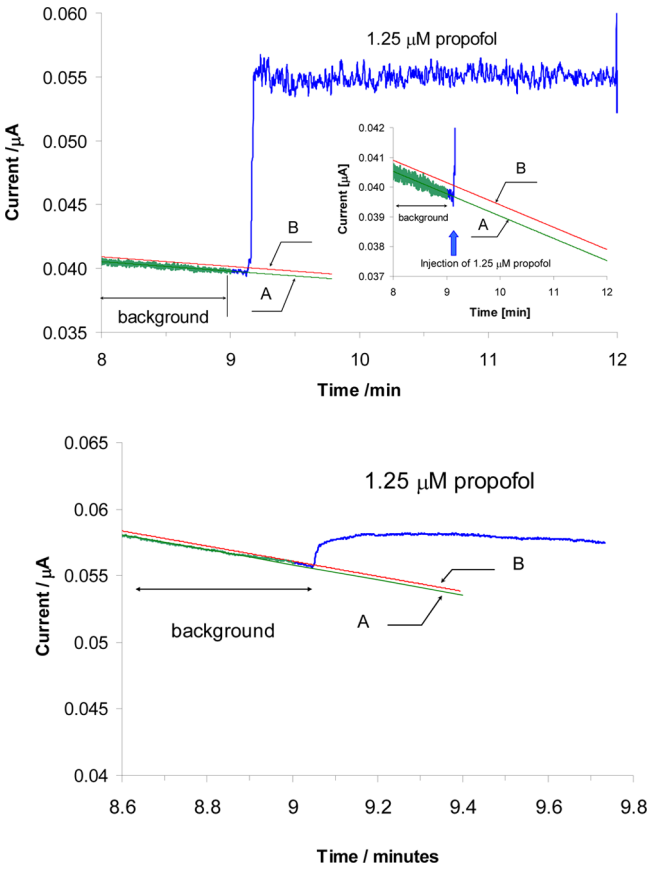

Figure 3. CA response of a PVC-membrane coated GC electrode in PBS (top) and in PBS containing 3 mM AA, 1 mM APAP, and 5% BSA (bottom). In both experiments, the stirred background solution was spiked with 1.25 μM of propofol at ~9 min. (A) A regression line fitted to data points measured in the background 1 min before spiking the background with a propofol standard, (B) line with the same slope as line A but shifted parallel to line A by a value of 3 times of the rmsd of the points around line A. It represents a hypothetical average current following a concentration change corresponding to the theoretical detection limit. The inset in the top figure shows a section of the background current on an expanded current scale with lines A and B.

of the data points around the line was determined (rmsd_{bgc}) (line A in the figure). Next, a second line was plotted parallel to line A at a distance of $3 \times \text{rmsd}_{bgc}$ (line B in the figure). This second line represents a theoretical current response in a solution with a concentration equal to the detection limit of the method. A comparison of the current change recorded upon the addition of 1.25 μM propofol and the current change equal to $3 \times \text{rmsd}_{bgc}$ (the shift between lines A and B in the inset of Figure 3) suggests impressive DL values. The detection limits and resolutions for propofol in chronoamperometric measurements using a GC working electrode with different membrane coatings in PBS and in PBS containing a variety of potential interferences are summarized in Table 2. The resolutions of the CA measurements (c^2_{DL}) were calculated as above, using the slope and the rmsd data of the calibration curve ($c^2_{DL} = 3 \times \text{rmsd}/S$). As shown in Figure 3 (bottom) the interfering compounds increased the background current and decreased the slope of the calibration curves.

In summary, the results in Table 2 show that propofol can be determined in PBS with the plasticized PVC membrane coated GC electrode down to nanomolar concentrations. Submicro-

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Table 2. Detection Limits (c^1_{DL}) and Resolutions (c^2_{DL}) for Propofol Measurements in PBS and in PBS Containing Ascorbic Acid (AA) or 4-Acetamidophenol (APAP) or Bovine Serum Albumin (BSA) or AA, APAP, and BSA Together (MIXED) As Interfering Agents, Using *o*-NPOE and DOS Plasticized PVC Membrane Coated GC Electrodes[a]

plasticizer	membrane solution	background	linear range [μM]	average c^1_{DL} [b] [μM]	average c^2_{DL} [b] [μM]
o-NPOE	I	PBS	0–56.6	0.03 ± 0.01	1.1 ± 0.2
	I	3 mM AA	0–56.6	0.04 ± 0.05	2.0 ± 1.0
	I	1 mM APAP	0–56.6	0.08 ± 0.02	4.6 ± 0.9
	I	5% BSA	5.0–56.6	2.2 ± 3.1	14.5 ± 1.8
	I	MIXED[c]	2.5–109.8	0.5 ± 0.4	28.2 ± 5.2
DOS	II	PBS	0–111.1	0.12 ± 0.05	4.3 ± 0.4
	II	MIXED[c]	0–111.1	3.0 ± 0.3	4.5 ± 2.3
	III	PBS	0–56.6	0.013 ± 0.004	5.5 ± 1.4
	III	MIXED[c]	0–56.6	0.6 ± 0.4	4.3 ± 1.2
	IV	PBS	0–56.6	0.022 ± 0.006	2.2 ± 0.6
	IV	MIXED[c]	9.9–111	2.1 ± 1.7	12.6 ± 0.2

[a]The membrane compositions are provided in Table 1. The DL values are provided with their standard deviations (n = 3). [b] $c^1_{DL} = 3 \times rmsd_{bgc}/S$; $c^2_{DL} = 3 \times rmsd/S$. where $rmsd_{bgc}$ and rmsd were calculated by fitting a line to a section of the background current or the points of the calibration curve, respectively. The slope values (S) were calculated by least-squares regression in the concentration range quoted as a linear range. [c]MIXED = 3.0 mM AA + 1.0 mM APAP + 5% w/v BSA, in PBS

molar detection limits could be achieved even in the presence of a large excess of easily oxidizable compounds, like AA and APAP. However, in the presence of physiologically relevant levels of albumin, the detection limit is shifted toward somewhat larger concentrations. This shift in the DLs toward larger concentrations is a consequence of the decrease in the sensitivity of the measurements in the presence of albumin. The slope of the calibration curves were 6–18 times larger in PBS than in the MIXED background electrolyte (PBS with 3 mM AA, 1 mM APAP, and 5% BSA) using the DOS or *o*-NPOE plasticized PVC membranes on the surface of the GC working electrode. Parallel to the decrease in the slope values in the MIXED background, the rmsd values of the calibration points around the regression lines increased, which made the calculated resolution of the measurements worse.

Selectivity of the Propofol Sensor: Importance of the Extraction Properties of the Membrane Coating on the Sensor Response for Propofol and Potential Interferences. To elucidate the impressive detection limit of the propofol sensor in the presence of the most common electrochemical interferences (Table 2), CV scans were recorded both with the bare GC electrode and PVC membrane-coated GC electrode in 3 mM AA and 1 mM APAP solutions. The results of these experiments are shown in Figure 4a,b. The influence of the PVC membrane coating on the CV response is remarkable in both experiments. No measurable oxidation peak is obtained with the PVC membrane-coated electrode for 3 mM AA. The peak current related to the oxidation of APAP was about 140 times smaller with the PVC membrane-coated electrode in 1 mM APAP solution compared to the bare GC electrode. This large decrease in the sensitivity for AA and APAP compared to an uncoated electrode is obtained because almost no AA or APAP is extracted into the highly hydrophobic membrane. The measured currents are also smaller because the diffusion coefficients in the membrane are much smaller compared to the diffusion coefficients in the aqueous solution. The anion exclusion properties of the membranes with KTPFPhB or NaTFPhB content is an additional benefit with respect to anionic interferences like ascorbate anion. Figure 5 shows that the chronoamperometric current in a sample with 10 μM

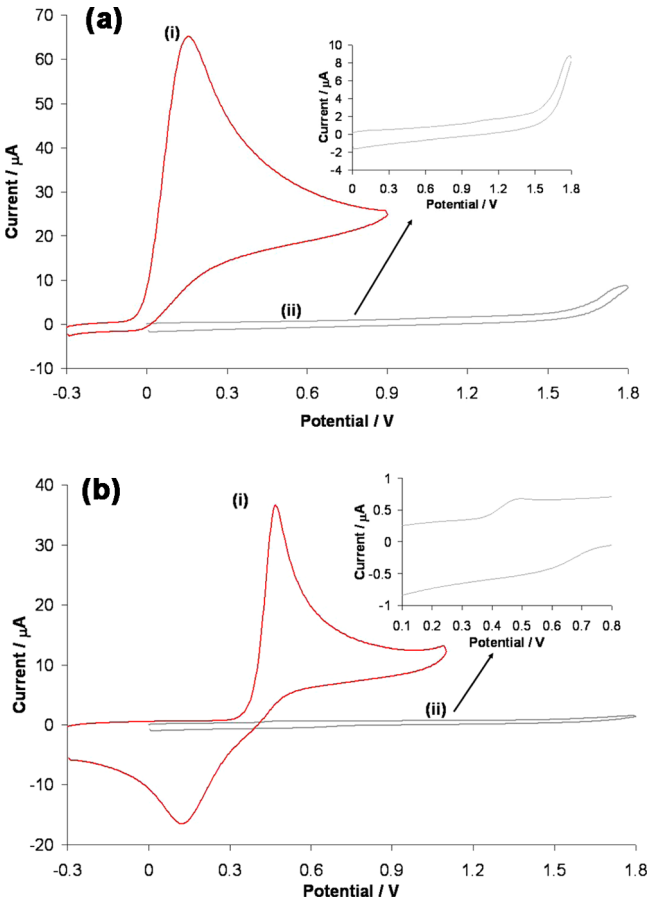

Figure 4. (a) CV scans recorded for 3.0 mM AA in PBS using a (i) bare GC electrode and (ii) PVC-membrane coated GC electrode (membrane solution I). Scan rate, v = 0.1 V s^{-1}. (b) CV scans recorded for 1.0 mM APAP in PBS using a (i) bare GC electrode and (ii) PVC-membrane coated GC electrode. Scan rate, v = 0.1 V s^{-1}.

propofol remains constant upon the stepwise change of AA concentration in that sample from 0 up to 3 mM.

In the cyclic voltammetry experiments with the membrane coated electrode (Figure 1), the peak currents increased linearly with the square root of the scan rate between 10 and 150 mV/s

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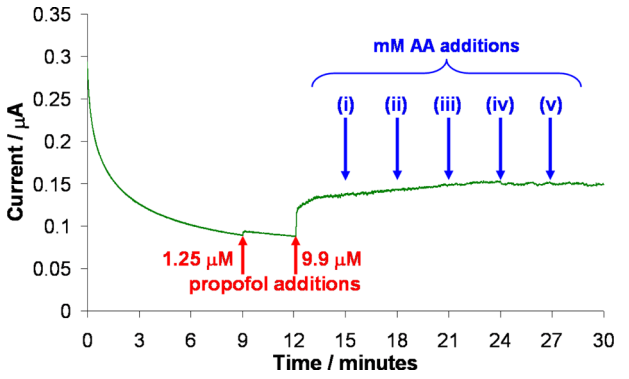

Figure 5. CA response recorded with a PVC-membrane coated GC electrode (membrane solution III) for 1.25 and 9.9 μM propofol in a PBS solution containing 5% w/v BSA, followed by additions of (i) 0.53 mM, (ii) 1.0 mM, (iii); 1.48 mM, (iv) 1.98 mM, and (v) 3.08 mM AA at 3 min intervals.

(not shown) and were barely influenced by the rotation rate between 400 and 1600 rpm indicating that the diffusion in the membrane dominates the mass transfer rate. On the basis of the scan rate dependence of the peak current for the membrane-coated sensor in propofol solutions, we assumed that the Randles-Sevcik equation (eq 6.2.19 in ref 29) can be used to describe the peak current dependence on the concentration. With this assumption, the current ratio measured with the coated and uncoated sensor (eq 1) can be used to calculate the partition coefficient ($P_{mw} = c_m/c_w$) of an electrochemically active solute between the membrane and aqueous solution.

$$\frac{i_m}{i_w} = \frac{D_m^{1/2}}{D_w^{1/2}} \frac{c_m}{c_w} \quad (1)$$

In eq 1, i_m is the peak current recorded with the membrane-coated sensor in an aqueous solution with a concentration of c_w; i_w is the peak current measured in the same solution with an uncoated sensor; D_m and D_w are diffusion coefficients of the solute in the membrane and the aqueous solution; and c_m is the concentration of the solute in the membrane. The calculation of c_m and P_{mw} (membrane/water partition coefficient) requires the knowledge of the diffusion coefficient of the solute in the membrane. By using diffusion coefficients measured in ion-selective membranes of similar composition ($D_m = 4 \times 10^{-8}$ cm^2/s)[37,38] and the experimentally measured i_w/i_m ratio of ~140 (Figure 4b) in combination with $D_w = 8 \times 10^{-6}$ cm^2/s[39] and $c_w = 1$ mM in eq 1, $P_{mw} = 0.1$ was calculated for APAP, for PVC membrane I (*o*-NPOE). This is more than an order of magnitude smaller than the octanol/water partition coefficient values for APAP, ranging between $P_{ow} = 2.9$ and $P_{ow} = 1.6$. The partition coefficients calculated for membranes III (DOS) and V (1-octanol) using the same protocol were $P_{mw} = 0.5$ and $P_{mw} = 1.6$, respectively. Weber[40] found a 1:1 correlation between the log P_{mw} and log P_{ow} values for membranes without background electrolyte and ion-exchanger. Apparently the high concentration of background electrolyte and ion-exchange salt influence the extraction properties of the membrane.

CONCLUSIONS

In this paper, we have described an organic-film modified GC working electrode for the quantitative assessment of physiologically relevant levels of propofol in serum-like electrolyte solutions. The membrane prevented fouling of the working electrode during propofol detection and improved the selectivity of the sensor due to the large difference in hydrophobicity between the analyte (propofol) and interfering compounds present in the sample, e.g., AA and APAP.

The sensitivity and selectivity of the membrane-coated working electrode for propofol is greatly influenced by the composition of the PVC membrane including the dielectric properties of the plasticizer, the composition and concentration of the background electrolyte, and the cation-exchanger incorporated into the membrane. The membrane composition also affects the peak potential at which propofol is oxidized in the membrane (Supporting Information, Figure S5).

The DL of CA measurements of propofol in PBS buffer (pH 7.2) and in PBS solutions containing 3 mM AA, 1 mM APAP, and 5% BSA were 0.03 ($\pm$0.01) μM and 0.45 ($\pm$0.4) μM, respectively. These values are well below the physiologically relevant target concentrations used during anesthesia or sedation.[2,41]

ASSOCIATED CONTENT

Supporting Information

Additional information as noted in text. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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