Article

Interaction of the Polymeric Layer Derived from 3-(4-Trifluoromethyl)-phenyl)-thiophene with Synthetic Stimulants on the Phase Boundary

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Abstract: Modification of an electrode surface with a selective layer leads to amplification of the electrochemical signal. A film derived from electrochemically oxidized 3-(4-trifluoromethyl)-phenyl)-thiophene deposited on a graphite electrode ($ThPhCF_3/G$) was used to estimate the affinity for synthetic stimulants (2-aminoindane, buphedrone, naphyrone) using a combination of square wave voltammetry and electrochemical impedance spectroscopy. The modified surface was characterized using Raman spectroscopy, which confirmed that the presence of the $-PhCF_3$ group is important for the recognition of synthetic stimulants. The determined values of the adsorption constants (K_{ads}) showed the significance of charge–transfer and/or hydrogen bond interactions between—$PhCF_3$ groups in the polymeric film and the analyte of interest: buphedrone (9.79×10^5) < naphyrone (1.57×10^6) < 2-AI (1.87×10^6). Compared to electrodes modified with nanomaterial, $PThPhCF_3/G$-electrodes showed the highest sensitivity in concentration range of 1–11 μmol L^{-1} at neutral pH and a possibility of detection of 0.43–0.56 μg mL^{-1} (s_r = 0.05–0.12). The analytical performance of $ThPhCF_3/G$ promises good perspectives for the detection of synthetic stimulants in forensic samples without prior pretreatment.

Keywords: thiophene derivative; electrochemical polymerization; synthetic stimulants

1. Introduction

The application of electroanalysis allows for analytical information to be obtained as a result of an electrochemical or ion-exchange reaction occurring at the electrode surface/solution interface. In voltammetric analysis, quantitative and qualitative information is obtained from the peak height and specific voltammetric potential. Improvements in the voltammetric signal include both the introduction of new electrode materials [1–5] and the modification of the electrode surface [6–8]. The concept of electrode surface modification can bring two main advantages for electroanalysis: (i) facilitating ion/electron exchange between electrode and analyte; (ii) increasing the selectivity through the binding of the signal molecule by the modified materials. Conjugated polymers have emerged as promising candidates for the modification of electrode surfaces, because they can act as an electrochemical transducer for the molecular recognition process. Therefore, selective surfaces based on conjugated polymers and their derivatives attract a great deal of attention. The rational molecular design of polymers with certain structures enhance binding affinity and specificity of the electrode towards the analytes of interest. An advantage of the conjugated polymer-modified surface is that the relatively rigid conjugated polymer backbone can act as a scaffold capable of arraying a number of recognizing sites along the backbone, which promotes the so-called transducer function of the layer, i.e., the response from single

receptors is "integrated" and collected. Thus, the incorporation of specific binding sites into the side chain of a conjugated polymer opens a new perspective in the field of the development a new selective surface. A number of conjugated polymers derived from polyaniline (PANI), polythiophene (PTh), and polypyrrole (PPy) have been designed and synthesized for the development of sensors, making them fascinating materials in various areas of application [9]. Electrochemical polymerizations are alternative ways to synthesize conducting polymers (CPs) and to modify an electrode surface.

Polythiophene and its derivatives electrochemically deposited on various substrates improve both the selectivity and sensitivity of a number of electrochemical sensors—as reported in mini-review [10]. Electrodes modified via the electropolymerization of thiophene and its derivatives were used for the voltammetric detection of some organic and biological molecules of industrial and medicinal interest [11]. Wang and Lin described the poly(3-methylthiophene (P3MT)-modified glassy carbon electrodes that have received great attention [12]. The electroactive conducting polymer P3MT reduced the response to ascorbic acid and enhanced the selectivity towards acetaminophen. As a PTh derivative, poly(3,4-ethylenedioxythiophene) (PEDOT) in the form of polymeric and molecular-imprinted films has been routinely applied in the electroanalysis morphine [13–15], diphenylamine [16], and ephedrine [17,18]. N. Atta et al. have found that morphine could be effectively adsorbed and accumulated on the PEDOT/Pt electrode in the presence of an anionic surfactant (sodium dodecyl sulfate), and subsequently, they successfully determined its content in commercial tablets using a voltammetric approach [15]. In contrast to previously developed potentiometric sensors for the detection of diphenylamine [19], the voltammetric sensor based on PEDOT/MIP membranes has displayed significantly lower detection limits (5.4 µM vs. 290–350 µM) and consequently a wider working range [16].

The term "Forensic Electrochemistry" explains that voltammetric methods have received a well-deserved status in the field of forensic analysis. There are a number of works devoted to the voltammetric determination of gunshot residues or new psychoactive substances (NPS). In recent years, a trend has been observed of replacing drugs of natural origin (such as cocaine) with NPS [20]. Several electrochemical strategies have been reported in the literature for the modification of the electrode surfaces for the detection of cocaine, which is one of the most widely used drugs worldwide. The potential use of Schiff base complexes that form stable films on the electrode surface in the voltammetric analysis of cocaine was evident from the investigations reported in references [21–23]. M.F.M. Ribeiro et al. [21] designed a screen-printed electrode modified with a uranyl Schiff base to determine cocaine with limits of detection (LOD) and quantification (LOQ) of 110 and 390 µmol L^{-1}, respectively. T.Y. Sengel et al. modified a glassy carbon electrode with an antibody and poly-l-phenylalanine-bearing electroactive EDOT for the detection of cocaine between 0.5 and 25 µM [24]. Affinity polymers, such *o*-phenylenediamine (OPD) and *p*-aminobenzoic acid (PABA), were successfully integrated onto the surface of graphene-modified screen-printed electrodes to improve the selectivity of cocaine detection in street-level seized samples and to suppress interference from levamisole [25].

Cathinones and aminoindane are synthetic stimulants that represent NPS and are monitored by the United Nations Office on Drugs and Crime (UNODC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [26]. They are designed to replicate the effects of traditional drug stimulants and can be synthesized into a variety of formulations. The new type of electrode materials, nanomaterials, with molecularly imprinted polymers [27–29], improve the specificity and sensitivity of the voltammetric detection of NPS [30]. Recently, it has been confirmed that polymer-based materials that are capable of binding the analyte of interest through a combination of electrostatic, hydrogen, and $\pi-\pi$ interactions might become a selective modifier of the electrode surface [31]. The deposition of thiophene derivatives with a –PhCF$_3$ group by means of in situ electrochemical oxidation on the electrode surface is a promising alternative for molecularly imprinted polymers. Previous investigations by L. Forlani have shown some specific interactions of nitro-halogenobenzenes with amines that can lead to the formation of various molecular

complexes, such as charge-transfer or hydrogen bonding complexes [32,33]. Different kinds of association interactions were observed depending on the nature of the amine. Moreover, the F atom in the CF_3 group is prone to interact with aromatic H atoms [34].

A review of modification approaches of electrode surfaces confirms that polymer-based materials bearing recognizing sites should help in solving and preventing crimes. Moreover, forensic electrochemistry uses necessary simple, time-saving, mass-produced, and cost-effective tools. We are confident that an investigation of thiophene derivatives with a –$PhCF_3$ group as a modifier of the electrode surface should promise multiple interactions with analytes of interest (Scheme 1) and so extend the series of selective polymers for detection of the synthetic stimulants. Therefore, we report the electrochemical deposition of fluoro-derivative thiophene on the surface of a graphite electrode, study its interaction with chosen representatives from a category synthetic stimulants (2-aminoindane, buphedrone, and naphyrone), and compare their analytical performance to reported modified electrodes.
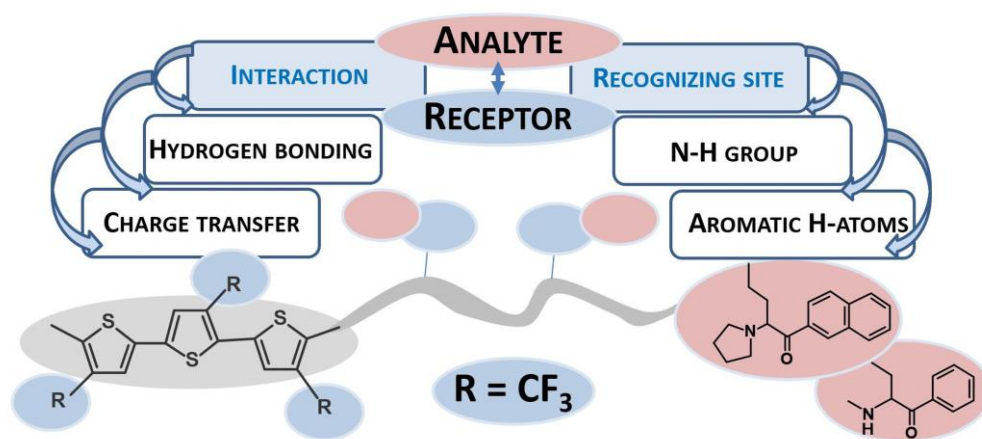
Scheme 1. Proposed interactions between the polymeric layer derived from 3-(4-trifluoromethyl)-phenyl)-thiophene and the tested synthetic stimulants.

2. Materials and Methods

2.1. Chemicals

The following chemicals were used in this work: 99% tetrabutylammonium tetrafluoroborate (TBATFB; Sigma-Aldrich, St. Louis, MO, USA), 98% thiophene (Th; Sigma-Aldrich, St. Louis, MO, USA), 99.5% acetonitrile (ACN; Penta, Prague, Czech Republic). 3-(4-Trifluoromethyl)-phenyl)-thiophene ($ThPhCF_3$), used as a monomer for electrochemical polymerization, was synthesized at the Department of Organic Chemistry, UCT Prague (Prague, Czech Republic). All analytes were in hydrochloride form: 2-aminoindane (2-AI; Sigma-Aldrich, St. Louis, MO, USA) and synthetic cathinones (buphedrone and naphyrone). Synthetic cathinones were supplied by the Laboratory of Forensic Analysis of Biologically Active Substances (BAFA) (University of Chemistry and Technology, Prague, Czech Republic).

2.2. Modification of Electrode Surface

Electrode surface modification was carried out using cyclic voltammetry (CV) with Palmsens 3 (PalSmSens BV, Houten, The Netherlands) in a three-electrode system. A graphite electrode (Elektrochemické detektory s.r.o., Turnov, Czech Republic) was used as the working electrodes for electrochemical measurements. Ag/AgCl (3 mol L^{-1} KCl) and a Pt plate (81 mm^2) served as reference and counter electrodes, respectively. The polymeric film was electrochemically deposited on the G-electrode surface from the polymerization mixture involving 0.01 mol L^{-1} $ThPhCF_3$ (monomer), ACN (solvent), and 0.05 mol L^{-1} TBATFB (salt), and the potential window was from 0.0 V to +2.0 V, with a scan rate of 100 mV s^{-1}, 10 cycles (Scheme S1).

2.3. Raman Spectroscopy

Raman spectra were collected on a Thermo Scientific DXR Raman microscope using 633 nm laser excitation (power 0.1 mW). The scattered light was analyzed using a spectrograph with holographic gratings (600 lines per mm) with an aperture of 50 μm and an EMCCD detector. The spot size of the laser focused by the 50× objective was ~1 μm in diameter. The acquisition time was 10 s with 10 repetitions.

2.4. Electrochemical Impedance Spectroscopy

The adsorption constants between the G-electrode coated with un- (Th) /substituted (ThPhCF$_3$) thiophene and target analytes were measured using the EIS technique in the supporting electrolyte with/without the target analytes using a Palmsens 3. Phosphate buffer with the addition of 140 mmol L^{-1} NaCl (PBS) was used as a supporting electrolyte in the same three-electrode system (Section 2.2). The EIS spectra were collected at a bias potential of 0.0 V in the frequency range of 10 kHz to 10 mHz (62 points), with an applied sinusoidal potential (10 mV amplitude). To fit the EIS spectra, the Randles circuit was used. It consists of ionic resistance of the solution (R_s) in series with a parallel combination of double-layer capacitance (C_{DL}) with two "resistances" connected in series—they include charge-transfer resistance (R_{ct}) and diffusional resistance being expressed as Warburg impedance (Z_w). The curve fitting of the impedance spectra was carried out using the PSTrace 5.4 software package. The adsorption constants were calculated using the Langmuir adsorption model for double-layer capacitance (C_{DL}) values. The data used for calculation and their processing are present in "Supplementary Materials" (Tables S1 and S2, Figure S1).

2.5. Square Wave Voltammetry

Calibration dependencies for the monitored analytes were measured in the range from 1.0 to 1170 μmol L^{-1} using square wave voltammetry (SWV). The supporting electrolyte was 0.1 mol L^{-1} KCl. The SWV technique was performed in the potential range of −0.1 V to +1.6 V, at a frequency of 10 Hz, with a pulse amplitude of 25 mV and a potential step of 5 mV. For better visualization, all of the square wave voltammograms (SWVs) presented here were baseline-corrected using the moving average filter included in the PSTrace 5.4 software.

3. Results and Discussion

3.1. Cyclic Voltammetry

The 3′-substituted thiophenes are generally more suitable for electrochemical oxidation and surface modification due to their high stability and ease of preparation [35]. The effect of the substituent on the polymerization process has been noted in the electrochemical polymerization of the terthiophene derivative, 3′-(2-aminopyrimidyl)-2,2′:5′,2″-terthiophene (oxidized peak at +1.25 V) [36] and 15-crown-5 substituted thiophene that was in direct n-conjugation with the macrocycle (oxidized peak at + 1.4 V) [37]. Figure 1 shows the cyclic voltammograms obtained during the electropolymerization of ThPhCF$_3$. Two irreversible anodic peaks, E_{a1} = 0.879 V and E_{a2} = 1.51 V, were observable. The current intensity for E_{a1} increased up to 3 scan, while the current intensity for E_{a2} decreased. An oxidation peak of 1.56 V was recently reported in the electrochemical synthesis of a copolymer based on EDOT and 1-(3,5-bis(trifluoromethyl) phenyl)-2,5-di(thiophen-2-yl)-1H-pyrrole [38]. There are no significant changes in the cyclic voltammogram depending on the number of cycles, but the anodic peak E_{a2} has slightly shifted towards more positive potentials. J. C. Ahumada et al. attributed this phenomenon to the electron-withdrawing nature of the –PhCF$_3$ substituent of the polymer [39]. The reason of the observed shift in the anodic peak can be attributed to different conformational states of the polymer chains formed by growing through thiophene units. As noted by Tanaka et al., the increase in thickness of the polymer film also increases the electrical resistance and leads to a peak shift [40]. The drop in current at 1.56 V is due to the decreased concentration of monomer species to be oxidized around

the working electrode. The reproducibility of process modification (s_r = 1.8%) carried out with the same procedure for three electrodes was confirmed (Figure S2).
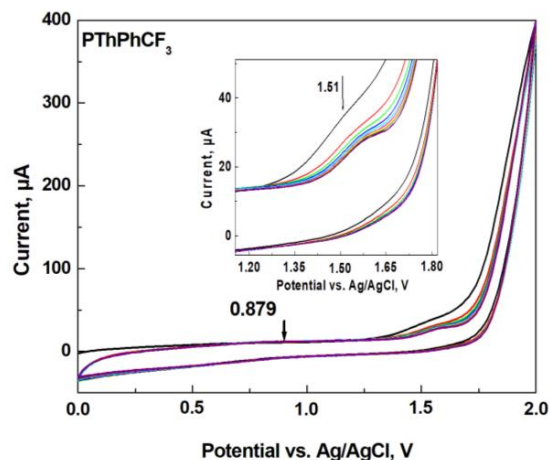

Figure 1. Cyclic voltammograms obtained at electrochemical oxidation of 3-(4-trifluoromethyl)-phenyl)-thiophene on the G-electrode.

3.2. Raman Spectroscopy

In the field of the development of selective surfaces, their characterization using spectroscopic methods has great significance. The application of Raman spectroscopy made possible the confirmation of the electrochemical modification of a graphite electrode surface with a thiophene-derived polymeric layer bearing group –PhCF$_3$ for the recognition of synthetic stimulants. Figure 2 presents the Raman spectra of the monomeric and polymeric form of ThPhCF$_3$. The characteristic vibrations of the polythiophene skeleton from the Raman spectra were described by a number of authors [41–45]. The shoulder band at 1496 cm^{-1} and the intensive band at 1465 cm^{-1} are attributed to the C=C stretching of the PTh ring, with their whole widths being dependent on the film thickness [46]. R.R. Subbulakshmi et al. carried out theoretical studies on the molecular structure of benzene derivatives with a C–F group [47]. It was found that the C–F stretching vibration could be observed over a wide frequency range of 1360–1000 cm^{-1} because there was significant influence of neighboring atoms or groups. In our case, in the region of 735 to 648 cm^{-1}, less intense bands of C–S–C ring deformation and kinks attributed to PTh are observed. The regions 1205 to 1420 cm^{-1} are assigned to the –PhCF$_3$ mode [48]. Raman bands 1209, 1261, 1288, and 1349 cm^{-1} of different intensities observed in the spectrum of the monomer and polymer confirm the presence of the –PhCF$_3$ substituent in the prepared polymer layer.

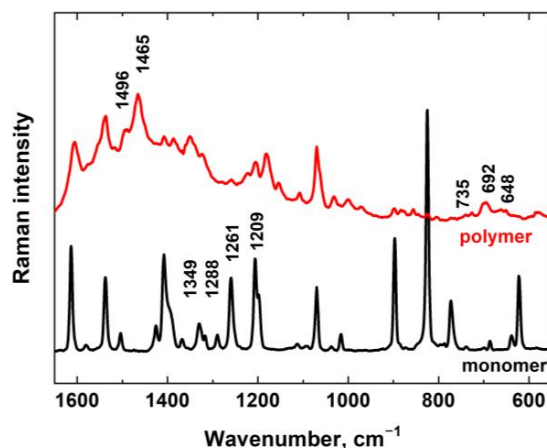**Figure 2.** Raman spectra obtained for monomeric and polymeric forms of 3-(4-trifluoromethyl)-phenyl)-thiophene.

3.3. Affinity Properties of the Modified Electrodes

A comparison of the adsorption constant values for polymeric films derived from unsubstituted (ThPh) and substituted (ThPhCF$_3$) thiophene should confirm the significance of the –PhCF$_3$ group in the interaction with the tested synthetic stimulants. The adsorption constant (K_{ads}) values were measured using the EIS method and calculated using the Langmuir adsorption model for double-layer capacitance (C_{DL}) values (Tables S1 and S2, Figure S1). The adsorption constant (K_{ads}) values were varied in the following order:

naphyrone (3.49×10^5) < buphedrone (6.01×10^5) < 2-AI (8.04×10^5) for PTh/G electrode

and

buphedrone (9.79×10^5) < naphyrone (1.57×10^6) < 2-AI (1.87×10^6) for PThPhCF$_3$/G electrode

In the case of the PTh/G electrode, an insignificant effect of the type of amino group on the K_{ads} values is evident. In the case of the PThPhCF$_3$/G electrode, the higher affinity for 2-AI and naphyrone can be the result of interactions between the –PhCF$_3$ group and the tested analytes. It is considered that fluorine-containing hydrogen bonds are not typical and do not behave as conventional ones (e.g., O···H–O and N···H–N), as demonstrated by the more angular nature and preference for less electronegative donors [49]. Pietruś et al. have found that F···H–N$^+$ is determined by the donor–acceptor distance and strongly influenced by the distance between F···N [50]. It can be suggested that the affinity between the PThPhCF$_3$/G electrode and synthetic stimulants is determined by a combination of various interactions, including hydrogen bonds, π-π stacking, aromatic atoms, and others.

3.4. Square Wave Voltammetry

All the analytes differ according to the type of amine group. 2-Aminoindane is a cyclic analogue of amphetamine, and its primary group cannot be directly oxidized in the potential region of the graphite electrode. Buphedrone (MABP) and naphyrone (O-2482) differ in the type of amine group and the substitution on the aromatic ring. Among the selected analytes, buphedrone has a secondary amine group that is easy to oxidize.

The electrochemical profile of buphedrone and naphyrone at PTh- and PThPhCF$_3$-modified G-electrodes by SWV is revealed by an anodic region potential between 0.8 and 1.1 V (Figure 3). In the case of buphedrone (MABP) and naphyrone (O-2482), the intensities of electrochemical signals were similar for both G- and PTh/G electrodes. Voltammetric studies of synthetic cathiones as one representative group in the NPS category have received the most attention. Therefore, we decided to comment on/discuss our results in comparison with results published in the literature (Table 1). For this purpose, the analogues of buphedrone and naphyrone were selected, namely N-ethylhexedrone (NEH) and alpha-pyrrolidinovalerophenone (PVP), respectively (Table 2). Selected cathinones (NEH and PVP) were characterized using the SWV technique on the surfaces of graphite SPE electrodes modified with such nanomaterials as graphene (GPH/SPE) and multiwalled carbon nanotubes (MWCNT/SPEs) [51]. Nanomaterials are particularly attractive for electrochemical sensing due to their unique electrocatalytic properties, conductivity, strong adsorption capacity, and possibility of oxidation or reduction of the analyte on the electrode [52]. It should be noted that the effect of nanomaterials on the electrochemical signal was observable with a remarkably increasing anodic current intensity for the secondary amine NEH: G/SPE (3.07 μA) < MWCNT/SPE (10.24 μA) < GPH/SPE (3.07 μA). In contrary to unmodified electrodes, the electrooxidation potential values of the tested analytes has been shifted to negative ones after modification with different kinds of nanomaterials.
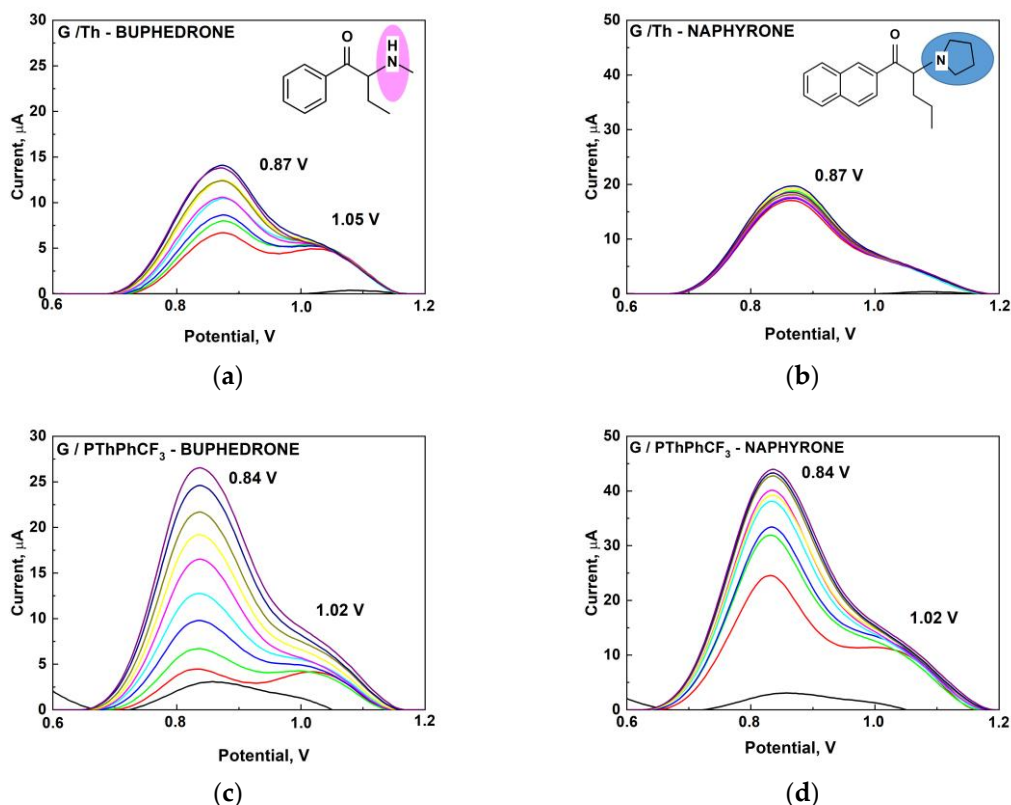
Figure 3. Comparing electrochemical profiles of buphedrone and naphyrone on square wave voltammograms obtained with graphite electrodes modified with polymeric film derived from an unsubstituted (**a**,**b**) and substituted (**c**,**d**) thiophene derivative. Concentrations: 0.0 µmol L^{-1} (black), 1.0 µmol L^{-1} (red), 3.0 µmol L^{-1} (green), 4.9 µmol L^{-1} (blue), 8.0 µmol L^{-1} (cyan), 10.9 µmol L^{-1} (magenta), 40.4 µmol L^{-1} (yellow), 70.4 µmol L^{-1} (dark yellow), 90.1 µmol L^{-1} (navy), 247.0 µmol L^{-1} (purple).

Table 1. Oxidation potentials obtained using square wave voltammetry for the new psychoactive substances tested in the literature [a] [51] and in the present study [b].

NPS *	Structure	Working Electrode	E_{anodic}, V	J_{anodic}, µA mm^{-2}
NEH [a]		G/SPE	1.04	0.43
		GPH/SPE	0.85	2.50
		MWCNT/SPE	0.92	1.45
PVP [a]		G/SPE	0.76/0.92 (a split peak)	1.28/0.29
		GPH/SPE	0.69/0.83	0.55/0.71
		MWCNT/SPE	0.70/0.86	1.32/0.33
2-Aminoindane [b]		PTh/G	0.88/1.06	2.76
		PThPhCF$_3$/G	1.095	3.12/−
Buphedrone (MABP) [b]		PTh/G	0.87/1.05	2.76
		PThPhCF$_3$/G	0.84/1.02	3.12/−
Naphyrone (O-2482) [b]		PTh/G	0.87	5.98
		PThPhCF$_3$/G	0.84/1.02	10.64/−

* Abbreviation: PVP—alpha-pyrrolidinovalerophenone, NEH—N-ethylhexedrone, [a] Experimental conditions from [51]: electrode diameter 3.0 mm, c(NPS) = 0.5 mmol L^{-1} in 20 mmol L^{-1} PBS pH = 7. [b] Experimental conditions from present studies: electrode diameter 2.0 mm, c(NPS) = 4.99 µmol L^{-1} in 0.01 mol L^{-1} PBS pH = 7.

Table 2. Comparing analytical performance of GPH-SPEs and PThPhCF$_3$/G-modified electrodes.

Analyte	Electrode	pH	Sensitivity, μA L μmol^{-1}	Intercept, μA	Correlation Coefficient	*LOD*, μmol L^{-1}	*LOQ*, μmol L^{-1}
2-AI			0.583	10.047	0.9833	1.8	5.4
Buphedrone (MABP)	PThPhCF$_3$/G	7.0	1.419	1.369	0.9851	1.7	5.0
Naphyrone (O-2482)			1.176	27.885	0.9806	1.9	5.5
NEH *	GPH-SPE	12.0	0.041	1.539	0.9700	16.67	–
PVP *			0.155	0.831	0.8310	1.67	–

* The data are from reference [51].

In this study, the intensity of the anodic current was increased for PThPhCF$_3$/G-electrodes towards the tertiary amine, naphyrone. Contrary to literature data, both synthetic catinones showed the split peaks: 0.84/1.02 V for buphedrone and 0.84/1.02 V for naphyrone. For 2-AI, only an anodic peak at 1.095 V was observed. We were interested in the origin of the appearance of these split peaks for synthetic cathinones and its absence for 2-AI at the PThPhCF$_3$/G-electrode. A.-M. Dragan et al. found that the electrochemical oxidation of NEH proceeds during the oxidative dealkylation of the secondary amine and the formation of the primary amine [51]. Profiling of the electrochemical oxidation products of 4-Cl- alpha PVP showed transformation of the pyrrolidine ring to the primary amine at 1.10 V via a ring-opening intermediate [53]. We can assume that the weak peaks observed at 1.02 V as shoulders (Figure 3c,d) might be the result of the formation and subsequent oxidation of the primary amine as the oxidation product of buphedrone (MABP) and naphyrone (O-2482). In fact, the anodic peak of greater intensity that was observable in the SWV-voltammogram at 1.095 V for 2-AI can be an evidence of this assumption.

3.5. Analytical Parameters and Application

The sensitivity and limits of detection (LOD) and quantification (LOQ) of PThPhCF$_3$/G-modified electrodes that are crucial for analytical application are present in Table 2 and Figure S3. Compared to GPH-SPEs electrodes [51], PThPhCF$_3$/G-modified electrodes showed the highest sensitivity and applicability at neutral pH (Table 2). The measurement at pH 7 opens a possibility of detecting synthetic stimulants without the pretreatment of forensic samples, such as real oral fluids.

In order to investigate and evaluate the stability of PThPhCF$_3$-polymeric films, the modified electrodes were stored at a laboratory temperature of 25 °C for 8 days with doubly distilled water. For PThPhCF$_3$-modified electrodes, the electrochemical signal retained 82% of initial values after 8 days. The studies of the pH effect showed that the basic medium significantly eliminates the life-time of PThPhCF$_3$-polymeric films.

Chromatographic methods are preferred by forensic laboratories for the identification of synthetic cathinones, although they require expensive equipment and/or complicated sample preparation. With the point of view of the development of screening tests, electrochemical sensors using selective surfaces could be an alternative to colorimetric tests. In this context, the recognition of synthetic stimulants using ThPhCF$_3$/G-modified electrodes might be crucial for forensic analysis. Doses of synthetic stimulants [54] are ranging from 5 to 20 mg. In this context, the detection of synthetic stimulants using ThPhCF$_3$/G-modified electrodes might extend our ongoing research focused on improving the properties of electrochemical sensors using different modification approaches [55,56]. Table 3 summarizes the results of our investigations that were focused on seeking a suitable receptor (monomeric or polymeric form) as a modifier of the electrode surface to the electrochemical detection of synthetic stimulants. Recently, it has been proposed that 4-tert-butylcalix[4]arene tetraacetate (monomer) is an active component of an ion-selective electrode for potentiometric detection and electrochemically oxidized 4′-(N-3-thiophenecarboxamido)benzo-15-crown-5 (polymer) for electrochemical impedimetric detection. It is possible to comment on the progress in particularly decreasing detection

limits. An application of the SWV-method with a ThPhCF$_3$/G-modified electrode allowed for the detection of 0.43–0.56 µg mL^{-1} of the chosen synthetic stimulants.

Table 3. Comparing electroanalytical methods used for the determination of synthetic stimulants (n = 3) with the method of standard addition.

NPS *	Method	Introduced, mol L^{-1}	Found, mol L^{-1}	S$_r$	Reference
Buphedrone (MABP)	ISE [a]	2.1×10^{-4} (44 µg/mL)	$(2.1 \pm 0.4) \times 10^{-4}$	0.10	[55]
	EIS [b]	4.0×10^{-5} (8.5 µg/mL)	$(4.0 \pm 1.7) \times 10^{-5}$	0.27	[56]
	SWV	2.0×10^{-6} (0.43 µg/mL)	$(2.0 \pm 0.6) \times 10^{-6}$	0.12	Present
Naphyrone (O-2482)	SWV	2.0×10^{-6} (0.56 µg/mL)	$(2.0 \pm 0.2) \times 10^{-6}$	0.05	Present

* Composition of active surface: [a] potentiometry with ion-selective membrane containing 5 wt % of the 4-tert-butylcalix[4]arene tetraacetate, 50 mol % of the lipophilic additive in PVC and NPOE (1:2 mass ratio); [b] electrochemical impedance spectroscopy with platinum disk electrode coated with electrochemically oxidized 4′-(N-3-thiophenecarboxamido)benzo-15-crown-5.

4. Conclusions

A polymeric film derived from 3-(4-trifluoromethyl)-phenyl)-thiophene (ThPhCF$_3$) deposited on the surface of graphite electrode was applied to study the interaction with synthetic stimulants containing primary (2-AI), secondary (buphedrone), and tertiary (naphyrone) amino groups. Such modified electrodes exhibit the sensitivity of 0.583 µA L µmol^{-1} to 2-AI, 1.369 µA L µmol^{-1} to MABP, and 1.176 µA L µmol^{-1} to O-2482. The limit of detection was, for all stimulants, in a narrow interval from 1.7 to 1.9 µmol L^{-1}, and the limit of quantification achieved 5.4 µmol L^{-1} for 2-AI, 5.0 µmol L^{-1} for MABP, and 5.5 µmol L^{-1} for O-2482. Future research on PThPhCF$_3$/G-electrodes should explore the potential of various polymer–analyte interactions (hydrogen bonding, π-π stacking, dipole–dipole interactions dependent on the protonation status of the analyte) to improve selectivity for a broader range of synthetic stimulants. The relationship between the adsorption constants and the structure of selected synthetic stimulants allowed for a determination of the role of the –PhCF$_3$ group for their recognition. The importance of both hydrogen bonding and aromatic H atoms in the interaction with PThPhCF$_3$/G-electrodes and their effect on the increase in the electrochemical signal were found. Future research of PThPhCF$_3$/G-electrodes should explore the potential of various polymer–analyte interactions (hydrogen bonding, π-π stacking, dipole–dipole interactions dependent on the protonation status of the analyte) for the improvement of selectivity for a broader range of synthetic stimulants.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/chemosensors12060099/s1, Figure S1: Linear Langmuir isotherms obtained from experimental results and used for calculations of adsorption constants; Figure S2: Confirmation of the reproducibility of process modification (sr = 1.8%) carried out with the same procedure for three electrodes; Figure S3: Calibration dependences determined for PThPhCF$_3$/G-modified electrodes in solutions of the tested analytes; Scheme S1: Experimental procedure for the modification of the electrode surface used in the present study; Table S1: Experimental data used for the calculation adsorption constants with PTh/G-electrodes; Table S2: Experimental data used for calculation adsorption constants with PTh PhCF$_3$/G-electrodes.

Conflicts of Interest: The authors declare no conflicts of interest.

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