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Article

Selective Recognition of Synthetic Stimulants via a Thiophene-Derived Polymeric Layer on Graphite Electrodes

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Abstract: Modification of electrode surface with a selective layer gives the possibility to detect target analytes of forensic interest. 3-(4-trifluoromethyl)-phenyl)-thiophene (ThPhCF₃) was deposited on a graphite (G) electrode by electrochemical oxidation and characterized as a receptor for the recognition of synthetic stimulants (2-aminoindane, buphedrone, naphyrone). First, the structural characterization of the polymeric layer were obtained from Raman spectroscopy. Second, the electrochemical profiles of selected synthetic stimulants and their affinity to ThPhCF₃/G-modified electrodes were studied using square wave voltammetry and electrochemical impedance spectroscopy. The values of the adsorption constant show the importance of –PhCF₃ groups in the interaction with synthetic stimulants, namely recognition by the formation of hydrogen bonds (K_{ads} (buphedrone) < K_{ads} (2-AI)) and interaction with aromatic H atoms (K_{ads} (buphedrone) < K_{ads} (naphyrone)). It was demonstrated that the polymeric layer derived from thiophene with –PhCF₃ group is capable to increase the intensity of the electrochemical signal.

Keywords: thiophene-derivative; electrochemical polymerization; synthetic stimulants

1. Introduction

Application of electroanalysis allows 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. Improvement of the voltammetric signal includes 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 electrode surfaces modification, because their surface can be used 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 allows 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 is important for realizing enhanced molecular recognition. Thus, the incorporation of specific binding sites into the side chain of a conjugated polymer opens a new perspective in the field of 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 make them fascinating materials

in various areas of application [9]. Electrochemical polymerizations are alternative ways to synthesize CPs and to modify electrode surface.

Polythiophene and its derivatives electrochemically deposited on various substrates have been increased the selectivity and sensitivity of a number of electrochemical sensors [10]. Electrodes modified by the electropolymerization of thiophene and its derivatives were used for 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 a great attention in the modification of electrodes [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 a large scale applied in the electroanalysis morphine [13–15], diphenylamine [16] and ephedrine [17, 18]. N. Atta et al. have been found that morphine could be effectively adsorbed and accumulated on PEDOT/Pt electrode in the presence of anionic surfactant sodium dodecyl sulfate and 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 been 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 well-deserved recognition 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 to replace drugs of natural origin (such as cocaine) by 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 voltammetric analysis of cocaine was evident from the investigations cited in references [21–23]. M.F.M. Ribeiro et al. [21] designed a screen-printed electrode modified with uranyl Schiff base to determine cocaine with limits of detection (LOD) and quantification (LOQ) of 110 and 390 $\mu\text{mol L}^{-1}$, respectively. T.Y. Sengel et al. modified a glassy carbon electrode with antibody and poly-L-phenylalanine bearing electroactive EDOT for detection of cocaine between 0.5–25 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 of levamisole [25].

Synthetic 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 controlled drug stimulants and can be synthesized into a variety of formulations. The new type of electrode materials, nanomaterials, 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 to bind the analyte of interest through a combination of electrostatic, hydrogen and π – π interactions might be a selective modifier of the electrode surface [31]. Deposition of thiophene derivatives with $-\text{PhCF}_3$ group by means of 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 and amines that can lead to the formation of various molecular complexes, such as charge-transfer or hydrogen bonding complexes [32, 33]. Different kinds of associations 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].

Herein, we report the electrochemical deposition of fluoro derivative thiophene on surface of graphite electrode and discuss its interaction with 2-aminoindane (2-AI) and two representatives from category synthetic cathinones, namely buphedrone and naphyrone.

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), potassium hexacyanoferrate and potassium ferricyanide ($K_4[Fe(CN)_6]$ / $K_3[Fe(CN)_6]$) (Lachema, Brno, Czech Republic). 3-(4-trifluoromethyl)-phenyl)-thiophene (ThPhCF₃) used as a monomer for electrochemical polymerization, was synthesized at the Department of Organic Chemistry, UCT Prague (Czech Republic). Analytes in hydrochloride form were: 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, Netherlands) in a three-electrode system. A graphite electrode (G, 1 mm², 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 mm²) served as reference and counter electrodes, respectively. The polymeric film was electrochemically deposited on the G-electrode surface from 0.01 mol L⁻¹ ThPhCF₃, dissolved in the supporting electrolyte ACN with 0.05 mol L⁻¹ TBATFB, the potential window was from 0.0 V to +2.0 V with a scan rate of 100 mV s⁻¹, 10 cycles.

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 by 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 (ThPhCF₃) thiophene and target analytes were measured by 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 (2.2. Modification of electrode surface). The EIS spectra were collected at a 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). A Randles circuit including resistance to charge transfer (R_{ct}) and double-layer capacitance (C_{DL}) in parallel, the solution resistance was used for curve fitting of the impedance spectra in the PSTrace 5.4 software package.

2.5. Square Wave Voltammetry

Calibration dependencies for the monitored analytes were measured in the range from 1.0–1170 μmol.L⁻¹ using square wave voltammetry (SWV). The supporting electrolyte was 5 mmol L⁻¹ $K_4[Fe(CN)_6]$ / $K_3[Fe(CN)_6]$. The SWV technique was performed in the potential range of –0.1 V do +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 the square wave voltammograms (SWVs) presented here were baseline-corrected using the moving average filter included in the PSTrace 5.4 software without affecting the results.

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 ThPhCF₃. 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 -PhCF₃ substituent of the polymer [39]. The reason of the observed shift of 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 decrease of monomer species to be oxidized around the working electrode.

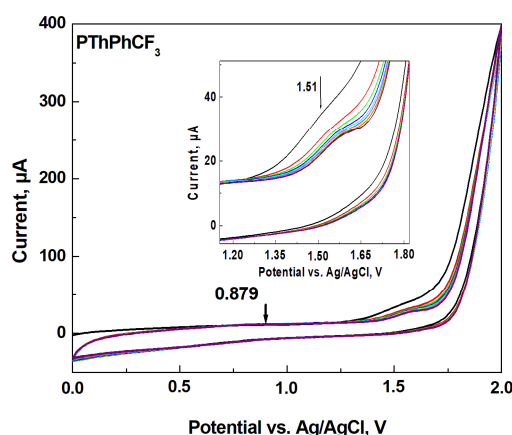


Figure 1. Cyclic voltammograms obtained at electrochemical oxidation of 3-(4-trifluoromethyl)-phenyl)-thiophene on G-electrode.

3.2. Raman Spectroscopy

In field of development of selective surface it is significance their characterization using spectroscopic methods. The application of Raman spectroscopy made possible to confirm the electrochemical modification of graphite electrode surface with a thiophene-derived polymeric layer bearing group -PhCF₃ for recognition of synthetic stimulants. Figure 2 presents the Raman spectra of the monomeric and polymeric form ThPhCF₃. The characteristic vibrations of polythiophene skeleton from Raman spectra were described by 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 PTh ring, their whole widths being dependent on the film thickness [46]. R.R. Subbulakshmi et al. have been carried out theoretical studies on molecular structure benzene derivatives with C-F group [47]. It has been found that the C-F stretching vibration can be observed over a wide frequency range of 1360-1000 cm⁻¹ because there is 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 –PhCF₃ mode [48]. Raman bands 1209, 1261, 1288, 1349 cm⁻¹ of different intensity observed in the spectrum of monomer and polymer confirm the presence of –PhCF₃ substituent in the prepared polymer layer.

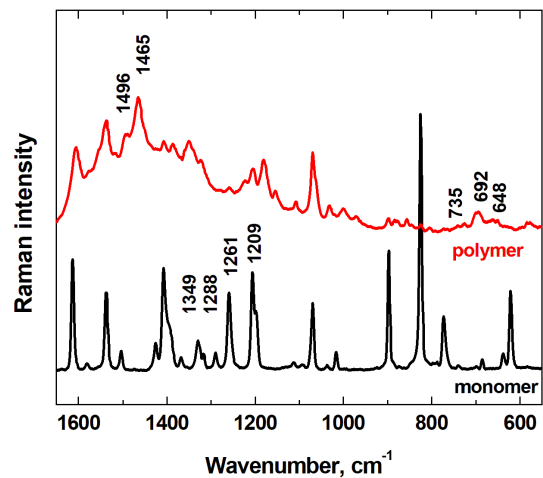


Figure 2. Raman spectra obtained for monomeric and polymeric forms of 3-(4-trifluoromethyl)-phenyl)-thiophene.

3.3. Affinity Properties of the Modified Electrodes

Evaluation of the affinity properties of the modified surface can provide an insight into the selectivity of the deposited layer to the tested analytes. The interaction of the analyte with the modified electrode surface is dependent on the surface coverage and, consequently, on the occupancy of both PThPhCF₃ binding sites (specific interactions) and uncoated segments of the electrode surface (non-specific interactions). Therefore, the adsorption constants for PTh/G and PThPhCF₃/G electrodes were estimated (Table 1). The highest affinity and the best discrimination between the tested analytes were confirmed for PThPhCF₃ modified electrodes. Importantly, the adsorption constant for 2-AI (1,87 × 10⁶) as the primary amine, which is able to form the largest number of hydrogen bonds with –CF₃ groups, is higher compared to buphedrone (MABP) (9,79 × 10⁵) and naphyrone (O-2482) (1,57 × 10⁶). In the case of PTh/G electrodes, these are of course non-specific interactions that can be the result of not only lipophilicity of the analyte (log P). The comparable adsorption constant for primary and tertiary amine can be explained by the findings reported in reference [34] which indicate the ability of the F atom in the –PhCF₃ group to interact with the aromatic H atoms.

Table 1. Adsorption constant values¹ of polymeric films derived from thiophene and its derivative with the tested analytes.

Analyte	Log P	PTh/G	PThPhCF ₃ /G
2-AI	0.97	8.04 × 10 ⁵	1.87 × 10 ⁶
Buphedrone (MABP)	2.11	6.01 × 10 ⁵	9.79 × 10 ⁵
Naphyrone (O-2482)	4.50	3.49 × 10 ⁵	1.57 × 10 ⁶

¹ error < 25 %, Adsorption constant values were obtained accordingly [49].

3.4. Square Wave Voltammetry

All analytes differ according to the type of amine group. 2-Aminoindane is a cyclic analogue of amphetamine, its primary group cannot be directly oxidized in the potential region of 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 more electroactive group, a secondary amine group.

The electrochemical profile of buphedrone and naphyrone at PTh- and PThPhCF₃- modified G-electrodes by SWV is revealed at an anodic region potential between 0.8 and 1.1 V (Figure 3). Voltammetric studies of synthetic cathinones as one representative group in the NPS category have received the most attention. Therefore, we decided to comment/discuss our results in comparison with results published in the literature (Table 2). 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) [50]. Nanomaterials are particularly attractive for electrochemical sensing due to their unique electrocatalytic properties, conductivity, and strong adsorption capacity, possibility of oxidation or reduction of the analyte on the electrode [51]. It should be noted that the effect of nanomaterials on the electrochemical signal was observable in a remarkably increasing anodic current intensity for the secondary amine NEH: G/SPE (3.07 μ A) < MWCNT/SPE (10.24 μ A) < GPH/SPE (3.07 μ A).

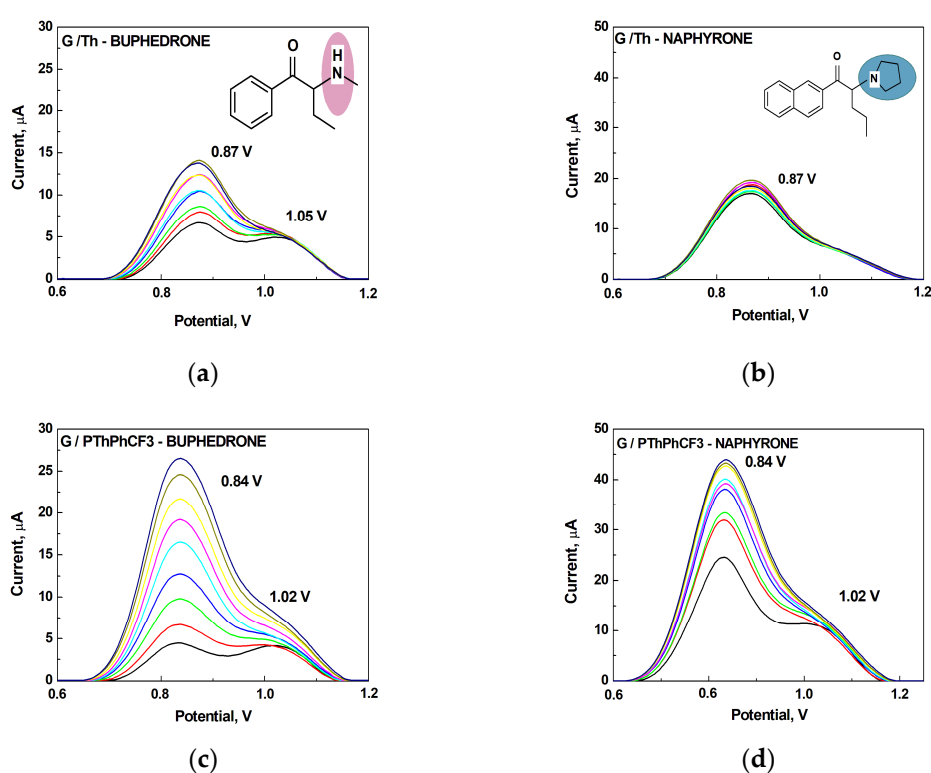
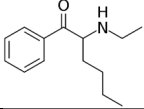
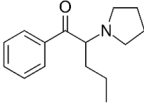
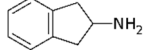
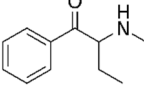
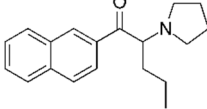


Figure 3. Comparing electrochemical profiles of buphedrone and naphyrone on square wave voltammograms obtained with graphite electrodes modified polymeric film derived from unsubstituted (a, b) and substituted (c, d) thiophene derivative.

In this study, the intensity of anodic current was increased for PThPhCF₃/G-electrodes towards the tertiary amine, naphyrone. In contrary to literature data, both synthetic cathinones 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 PThPhCF₃/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 [50]. Profiling of the electrochemical oxidation products of 4-Cl- α PVP showed transformation of the pyrrolidine ring to the primary amine at 1.10 V via a ring-opening intermediate [52]. We can assume that the weak peaks at 1.02 as shoulders (Figure 3 c-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 for this assumption.

Table 2. Oxidation potentials obtained using square wave voltammetry for the new psychoactive substances tested in the present study and in literature [50].

NPS*	Structure	Working electrode	E _{anodic} , V	I _{anodic} , μA
NEH ^{a)}		G/SPE	1.04	3.07
		GPH/SPE	0.85	17.66
		MWCNT/SPE	0.92	10.24
PVP ^{a)}		G/SPE	0.76 / 0.92 (a split peak)	9.03 / 2.04
		GPH/SPE	0.69 / 0.83	3.90 / 5.04
		MWCNT/SPE	0.70 / 0.86	9.35 / 2.31
2-Aminoindane ^{b)}		PTh/G	0.88 / 1.06	8.66
		PThPhCF ₃ /G	1.095	9.81 / –
Buphedrone (MABP) ^{b)}		PTh/G	0.87 / 1.05	8.66
		PThPhCF ₃ /G	0.84 / 1.02	9.81 / –
Naphyrone (O-2482) ^{b)}		PTh/G	0.87	18.78
		PThPhCF ₃ /G	0.84 / 1.02	33.42 / –

* Abbreviation: PVP - alpha-pyrrolidinovalerophenone, NEH - N-ethylhexedrone, ^{a)} Experimental conditions: c(NPS)=0.5 mmol L⁻¹ in 20 mmol L⁻¹ PBS pH=7. ^{b)} Experimental conditions: c(NPS) = 4.99 μmol L⁻¹ in 0.01 mol L⁻¹ PBS pH=7. .

3.5. Analytical Application

Chromatographic methods are preferable by forensic laboratories for an identification of synthetic cathinones although they require expensive equipment, and/or complicated sample preparation. With the point of view of 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 ThPhCF₃/G-modified electrodes might be crucial for forensic analysis. The electrochemical oxidation of thiophene modified with -PhCF₃ substituent and its deposition on the electrode surface extends our ongoing research focused on improving the properties of electrochemical sensors for the detection of synthetic stimulants [53, 54] regarding the application of monomeric and polymeric units for electrode modification. The current results of our investigations are summarized in Table 3. Doses of synthetic cathinones ranging from 5 to 20 mg are taken, usually orally, but also intranasally, rectally, and intravenously [55].

Table 3. Comparing electroanalytical methods used for determination of synthetic stimulants (n=3).

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 ± 0.4) × 10 ⁻⁴	0.10	[53]
	EIS ^{b)}	4.0 × 10 ⁻⁵ (8.5 μg/mL)	(4.0 ± 1.7) × 10 ⁻⁵	0.27	[54]
	SWV	2.0 × 10 ⁻⁶ (0.43 μg/mL)	(2.0 ± 0.6) × 10 ⁻⁶	0.12	Present
Naphyrone (O-2482)	SWV	2.0 × 10 ⁻⁶ (0.56 μg/mL)	(2.0 ± 0.2) × 10 ⁻⁶	0.05	Present

Composition of active surface: a) Ion-selective membrane contained 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) 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 (ThPhCF₃) 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. The relationship between the adsorption constants and the structure of selected synthetic stimulants allowed to determine the role of the –PhCF₃ group for their recognition. It was found the importance of both hydrogen bonding and aromatic H atoms at interaction with PThPhCF₃/G-electrodes and their effect on the increase of the electrochemical signal. Experimental finding show the importance of finding and studying new materials for the detection of commonly abused new psychoactive substances.

Author Contributions: Conceptualization, T.V.S.; methodology, T.V.S.; investigation, N.Š.; data curation, T.V.S. and N.Š.; writing—original draft preparation and editing, T.V.S. and G.B.; Review and editing M.V. and G.B.; Project administration, M.V.; Resources, T.V.S and M.V.

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

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