



## **Voltammetric Determination of LSD with a Schiff Base – Chemically Modified Electrode in Aqueous Solution**

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**Abstract.** In recent years, practical, inexpensive, and highly specific electroanalytical methods based on modified electrodes have been increasingly developed for forensic science. Simple modification of the carbon paste electrode with Schiff base complexes has become a promising strategy to detect and quantify narcotics. In this context, we aimed to develop voltammetric methods to quantify lysergic acid diethylamide (LSD) by using a carbon paste electrode modified with the complex  $[UO_2(\text{Ac-ophen})] \cdot H_2O$ . The use of an aqueous solution of KCl as supporting electrolyte makes the methodology less polluting, which contrasts with methods that still employ toxic solvents. The developed method for Differential Pulse Voltammetry provides a linear response at various concentrations of LSD and affords analytical curves with standard deviation, detection, and quantification limits around 2.45, 0.625, and  $2.08 \mu\text{mol L}^{-1}$ , respectively. The recovery values of 103 and 108% prove that the developed method is suitable for application in forensic science.

**Keywords:** Forensic electroanalysis; LSD; Schiff bases; Carbon paste; Chemically modified electrodes.

### **1. Introduction**

The lysergic acid diethylamide (LSD) is a semisynthetic drug derived from lysergic acid, a natural alkaloid of the fungus *Claviceps purpurea*.<sup>1,2</sup> It is a hallucinogen with

high potential for abuse<sup>1-4</sup>, and is usually administered orally in the form of blotters, but it can also be found as microdots, gelatin, in sugar cubes or candy and even in liquid form, where each drop represents a dose<sup>1,5,6</sup>. The blotters are the most common, and they attract attention due to their variety of colors and stamps of characters, being sold containing an average between 10-100 µg of LSD<sup>7,8</sup>.

After consumption, the action of LSD starts within an hour, reaches its peak within two to four hours, and lasts six to twelve hours, depending on the concentration of your dose<sup>2,4,9</sup>. Acting on the serotonergic and dopaminergic systems, LSD psychoactive effects include repeated psychedelic experience and distortion of the senses (colors, sound, touch)<sup>1-9</sup>.

Despite the worldwide consumption of hallucinogens in the 60s, today the trafficking of such substances are mainly concentrated in the Americas and is represented by 88% of global seizures between the years 2015 and 2017, according to the World Drug Report of 2019<sup>10</sup>. In Brazil, a significant increase in the number of LSD blotters seized between 2008 and 2013 was reported by the federal police, reaching 108,856 blotters in 2011. Despite the decline in seizures in the following years, until May 2019 the police have seized 57% of total blotters recorded in the previous year, indicating a possible increase in its consumption among Brazilians<sup>11</sup>.

In addition to LSD, other drugs with halucinogenic effects, such as N-benzyl-substituted phenethylamines (NBOMes), are also available in blotters and are widely consumed in recent years, being commonly confused with LSD<sup>10,12</sup>. Due to this similarity, the correct identification of the seized drug is extremely important. The scientific police currently employ instrumental techniques based on the recommendations of groups like Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) and United Nations Office on Drug and Crime (UNODC), such as High Performance Liquid Chromatography (HPLC), Gas Chromatography (GC), and Mass Spectrometry (MS), to identify illicit drugs<sup>13-15</sup>.

Although chromatographic methods are the most often applied, they are expensive and time consuming, usually due to the sample treatment step that must be performed for this equipment<sup>7,16-18</sup>. As an alternative, voltammetric techniques have simpler, easy handling and low cost equipment, and can still be highly specific and provides limit of detection (LOD) as low as the LOD obtained in chromatographic techniques<sup>19,20</sup>.

Many studies have focused on voltammetric analysis applied in the field of forensic science, mainly in the determination of illicit drugs like cocaine<sup>21,22</sup>, LSD<sup>3,23</sup>, 25H-NBOMe<sup>24,25</sup>, MDMA (3,4-methylenedioxyamphetamine)<sup>26,27</sup>, and natural cannabis in biological and seized samples<sup>28,29</sup>. Voltammetric analysis enables the development of sensors that provide specific response to low levels of illicit drugs, especially when these sensors are obtained by chemical modification of the surface of the electrode.

Couto *et al.*<sup>3</sup> used a molecularly imprinted polymers at the surface of a screen-printed carbon electrode and analyzed MDMA in human blood and urine sample using the Square Wave Voltammetry with a LOD 0.79  $\mu\text{mol L}^{-1}$ . For the quantification of cocaine in seized samples, Garrido *et al.*<sup>22</sup> used the linear sweep voltammetry with a glassy carbon electrode modified by a combination of multi-walled carbon nanotubes with  $\beta$ -cyclodextrin, reaching a LOD of 1.02  $\mu\text{mol L}^{-1}$ .

The development of chemically modified carbon paste electrodes has attracted researchers' interest in recent years<sup>30</sup>. These sensors are low-priced and easy to manufacture, by mixing the conductive material, such as graphite powder or carbon nanotube, with an agglutinate, such as mineral oil or paraffin, and various types of modifiers such as transition metal complexes containing Schiff bases can be used<sup>30-33</sup>. Salen-type ligands (Salen = N,N-ethylene-bis(salicylideneiminato)) have been applied in many electrochemical sensors because they display versatile stereo and electronic properties<sup>30</sup>. These modifiers can improve the selectivity/sensitivity of the devices, increase the electroanalytical response, or decrease the over-potential of the analytes<sup>31-33</sup>.

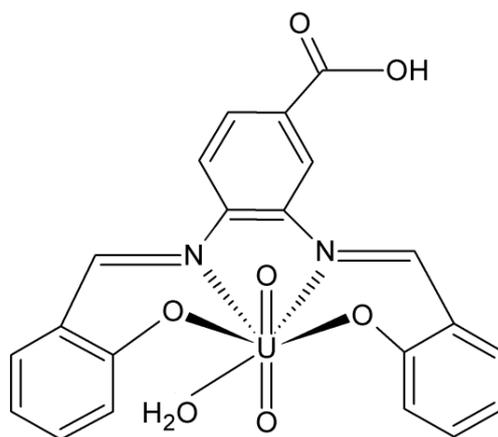
Recent works by our research group have demonstrated that uranyl ( $\text{UO}_2$ ) complexes with Schiff bases of the Salen type can efficiently detect cocaine and have potential application in the forensic context<sup>34-36</sup>. However, there are no studies on the determination of LSD at the surface of electrodes chemically modified with such complexes.

Here, we aimed to develop voltammetric methods to detect and quantify LSD in seized samples by using a carbon paste electrode modified with a metal complex consisting of Schiff base and  $[\text{UO}_2(\text{Ac-o-phen})]\cdot\text{H}_2\text{O}$  (aquo N,N'-4-carboxyl-1,2-phenylenebis(salicylideneiminato))dioxouranium(VI)<sup>37</sup>.

## 2. Materials and methods

A potentiostat/galvanostat Autolab PGSTAT128N with NOVA 1.11 software was used for the voltammetric measurements with platinum wire as the counter electrode, Ag/AgCl (saturated with KCl (Cinética Reagentes & Soluções)) as the reference electrode, and a carbon paste electrode modified with a Schiff base complex as the working electrode. For the voltammetric measurements a 5.0 mL electrochemical cell was used with aqueous solution of KCl 0.1 mol L<sup>-1</sup> as supporting electrolyte. The parameters for analysis of LSD by Square Wave Voltammetry, Differential Pulse Voltammetry, and Cyclic Voltammetry were optimized.

The Schiff base, aquo (N,N'-4-carboxyl-1,2-phenylene-bis(salicylidenediminato)) dioxouranium(VI), [UO<sub>2</sub>(Ac-ophen)]·H<sub>2</sub>O was prepared according to the literature<sup>38</sup>, and its structure can be seen in Figure 1.



**Figure 1.** Chemical structure of [UO<sub>2</sub>(Ac-ophen)]·H<sub>2</sub>O.

To prepare the carbon paste, carbon powder (Fisher Scientific) and the Schiff base were mixed in a crucible. Paraffin (Isogama) was chosen as the binder because it is more insoluble in organic solvents (such as acetonitrile present in the LSD standard) than mineral oil, avoiding the detachment of the carbon paste during voltammetric measurement. After adding paraffin to the mixture the crucible was heated until all the paraffin had melted. Then, the three elements were mixed until a homogenous paste was obtained. A hollow cylindrical glass tube was filled with the carbon paste, and a copper electric contact was used to compress the paste. The modified electrode was then polished with circular movements on sulfite paper,

resulting in a homogeneous surface with area of 0.071 cm<sup>2</sup> and an electroactive area of 0.044 cm<sup>2</sup> (this difference is due to the insulating property of paraffin).

The standard LSD solution (Cerilliant, 1.0 mg in 1.0 mL of acetonitrile) was diluted to 10.0 mL with acetonitrile (Merck), which gave a concentration of 3.07 10<sup>-4</sup> mol L<sup>-1</sup>. This solution was stored in a dark flask placed inside the refrigerator until use. For all voltammetric analysis 3.0 mL of solution were used. In the optimization of the square wave and differential pulse voltammetry parameters, 10.0 µL of the standard LSD solution in 3.0 mL KCl 0.1 mol L<sup>-1</sup> were used. For the analytical curve, five separate solutions were prepared to maintain the constant amount of acetonitrile, that is, in 2.95 mL of KCl 0.1 mol L<sup>-1</sup> was added 10.0 to 50.0 µL of the standard LSD solution and the volume was completed to 3.0 mL with acetonitrile.

All the voltammetric measurements were performed in triplicates in a room under incandescent light, at a fixed temperature of 24 °C. These conditions were adopted because LSD is sensitive to light and degrades above 30 °C<sup>7</sup>.

### 3. Results and discussion

#### 3.1 Composition of the carbon paste

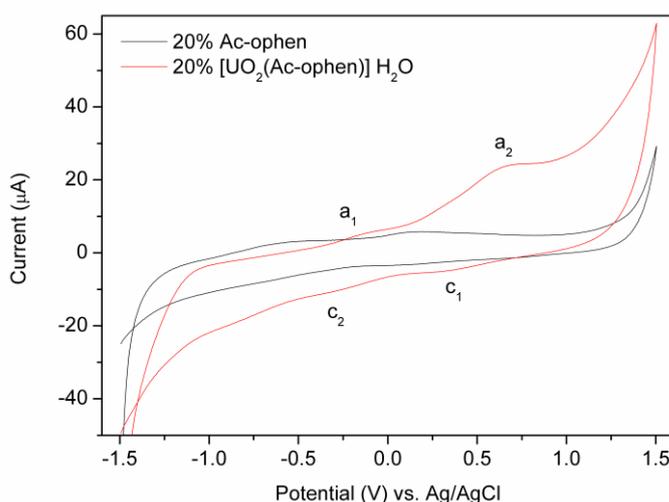
We determined the amount of paraffin in the carbon paste on the basis of the stability of paraffin in solution, predominantly when an organic solvent was added to the electrochemical cell. For this, the percentage of paraffin in the carbon paste was varied between 10 and 35 %. Then, each electrode was evaluated by cyclic voltammetry, applying 20 cycles with potential range of -1.5 and 1.5 V in the presence of 50 µL of acetonitrile. Thus, it was possible to evaluate the detachment of the carbon paste by observing the presence of particles in the electrolyte solution. The tests indicated that at least 35% (w/w) paraffin was necessary to prepare a stable carbon paste electrode.

After fixing the quantity of paraffin, we tested the performance of the electrode at different proportions of Schiff base complex and graphite powder as well as in the presence and absence of about 20% of the modifier because we aimed to achieve the best voltammogram. We found that the optimum paste should consist of graphite powder, Schiff base complex, and paraffin at 45:20:35 (w/w/w) ratio, respectively. The resulting carbon paste electrode was stable even after 100 successive Cyclic Voltammetry scans without the need to renew the surface of the

electrode. The electrode was stable even in the presence of acetonitrile, which was the solvent present in the standard solution of LSD.

### 3.2 Voltammetric profile of the Schiff base

We evaluated the electrochemical behavior of the Schiff base by Cyclic Voltammetry in two steps. First, we only analyzed the structure of Ac-ophen in the composition of the carbon paste. Then, we analyzed the complete structure  $[\text{UO}_2(\text{Ac-ophen})]\cdot\text{H}_2\text{O}$ . Figure 2 reveals that both the cathodic ( $E_{c1} = 0.36 \text{ V}$ ;  $E_{c2} = -0.28 \text{ V}$ ) and the anodic ( $E_{a1} = -0.13 \text{ V}$ ;  $E_{a2} = 0.62 \text{ V}$ ) responses originated from the metallic center inside the complex.



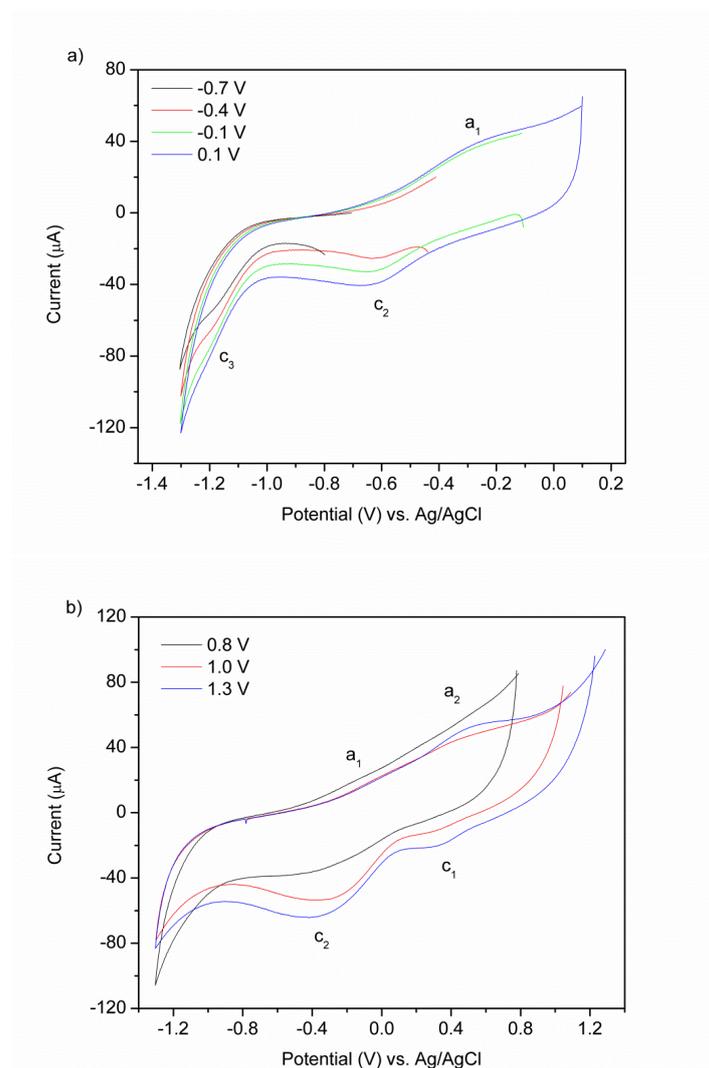
**Figure 2.** Cyclic voltammograms recorded for the carbon paste modified with  $[\text{UO}_2(\text{Ac-ophen})]\cdot\text{H}_2\text{O}$  in  $\text{KCl } 0.1 \text{ mol L}^{-1}$  as supporting electrolyte, at a scan rate of  $100 \text{ mV s}^{-1}$ .

The uranyl complex is insoluble in aqueous medium, and the supporting electrolyte was prepared with water: then, the voltammetric response was due to the electrochemical behavior of the ion  $\text{UO}_2^{2+}$ , as shown in Figure 2. The oxidative processes are observed with the uranyl complex, as a free base this behavior does not occur.

The electrochemical behavior of  $\text{UO}_2^+$  might be described as follows, Figure 3: firstly, there is a reduction of one electron and the product is unstable in aqueous solution<sup>39,40</sup>.

Then, this pentavalent uranium results in U(IV) and U(VI) by its disproportionation step. It was verified the pH value in solution may influence in the

electrochemical reactions of uranium, once at low pH is possible to observe the signal corresponded to  $U(III)^{41}$ .



**Figure 3.** a) Cyclic voltammograms in different lower potential ranges; b) Cyclic voltammograms in different higher potential ranges.

There is no electrochemical data of this uranyl complex in the literature, so because we performed all the measurements in aqueous medium, and on the basis of the literature for the uranium ion<sup>41,42</sup> we assumed that the following redox processes were involved in the electrochemical reaction of the  $UO_2^{2+}$  ion: the first cathodic peak,  $c_1$ , was due to reduction of  $U(VI)$  to  $U(V)$ , whereas the second cathodic peak,  $c_2$ , referred to reduction of  $U(V)$  to  $U(IV)$ . As for the oxidation peaks,  $a_1$  corresponded to oxidation of  $U(V)$  to  $U(VI)$ , and  $a_2$  was due to oxidation of  $U(IV)$  to  $U(VI)$ .

According to literature<sup>42</sup>, when an aqueous solution containing uranium was electrochemically characterized, it was verified a high disproportionation rate of this U(V). In this reaction, U(V) is formed on the electrode surface and as a consequence, we observed the peak  $a_2$  due to the oxidation reaction from U(IV) to U(VI).

A broader study about the potential range and the redox processes in uranium was performed (Figure 3a and 3b) to a better analysis of the electrochemical behavior exposed above: when various potential intervals are analyzed, it is possible to conclude that even when the scan is reverted to potentials lower than -0.1 V, the peak  $c_3$  – from the reaction of U(IV) to U(III)- is still present in voltammogram. Besides, when the potential interval is reverted to values higher than -0.4 V, the peak  $c_2$  is observed; when potentials higher than -0.4 V are applied, the peak  $a_1$  is verified. There is a co dependence between the peaks  $a_1$  and  $c_2$ , and this fact indicates the oxidation to form U(V).

When the potential is reverted to higher values, peak  $a_1$  disappeared, whilst peaks  $c_1$  and  $a_2$  arise. This behavior may be explained by the reduction reaction from U(VI) to U(V) and the oxidation reaction from U(IV) to U(VI). The disappearance of the signal  $a_2$  proves the disproportionation process in U(V) stated<sup>41,42</sup>.

The scan rate determined the presence of the anodic peak  $a_1$ . At high scan rates, this peak became unstable or even disappeared from the cyclic voltammogram. According to the literature<sup>41</sup>, a third cathodic peak may arise in more acidic solution and is related to reduction of U(IV) to U(III).

### 3.3 Voltammetric profile of LSD

We conducted three different types of voltammetric measurements to explore the interaction between the Schiff base complex and LSD: Cyclic Voltammetry, Square Wave Voltammetry, and Differential Pulse Voltammetry.

In presence of LSD, the carbon paste electrode without modification (65:35 (w/w) graphite:paraffin) didn't show any oxidative process for the drug, as well as the carbon paste modified with the Schiff base. Because of this absence, and the previous works of the group using the uranyl complexes whit Schiff base for cocaine detection<sup>34-36</sup>, the modification of the electrode with  $[\text{UO}_2(\text{Ac-ophen})]\cdot\text{H}_2\text{O}$  was applied.

Cyclic Voltammetry gives an overview of the behavior of the molecule and provides valuable information about the kinetic mechanism. In the presence of LSD,

only peaks  $c_1$  and  $a_2$  arose in the cyclic voltammogram, which indicated interaction between the Schiff base complex in the modified electrode and the drug. This could be a catalytic response of the LSD to the oxidation of U(V). Similar voltammetric response was also observed in the analyses of cocaine using another uranyl Schiff base complex as modifier of the working electrode, whereas the presence of the drug increases the current signal for the oxidative processes of the uranyl group.<sup>35</sup> The exact mechanism of the reaction between the complex and the drugs, LSD and cocaine, has not been elucidated yet, but both drugs have a tertiary amine in their structure, which could explain the similarity in the voltammetric behavior.

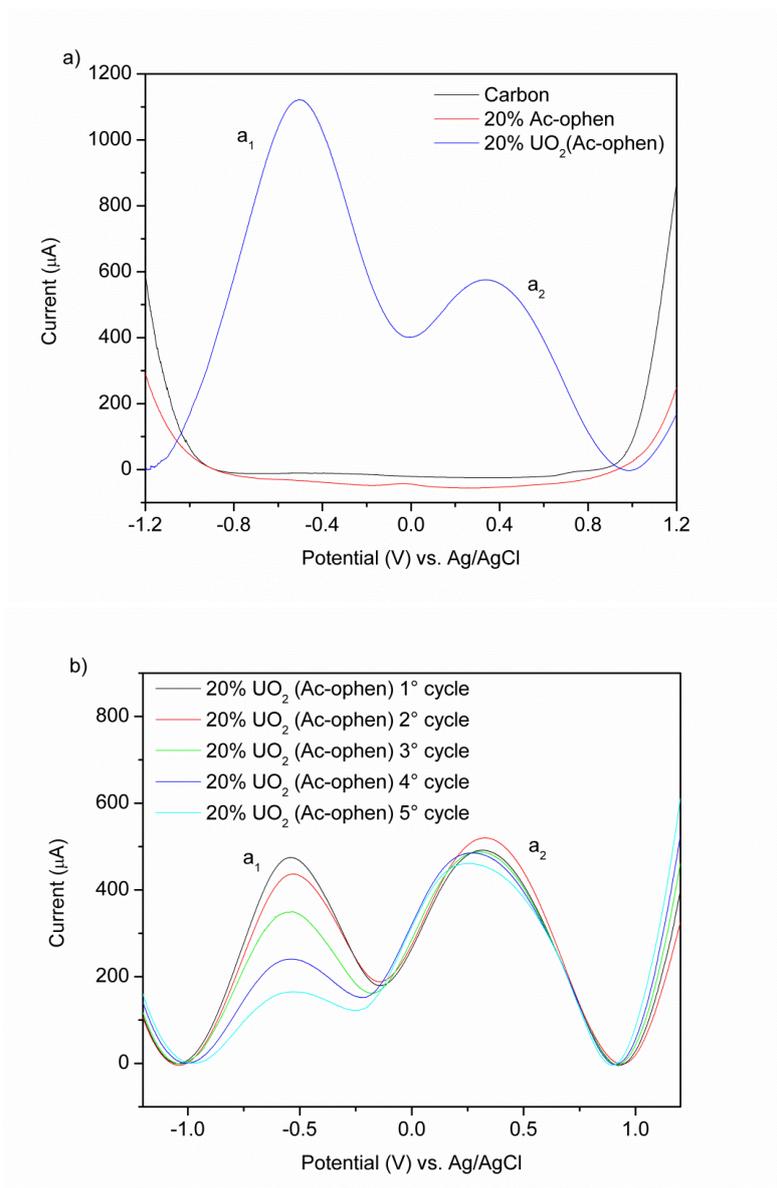
The uranyl ion can be easily coordinated by more than 6 ligands (as in the pentagonal bipyramidal geometry)<sup>43</sup>. Also, Schiff base uranium complexes present great variety of oxidation states of the metal center, which are dependent of the coordination sphere. When spatial configuration of the molecule is considered, LSD can be coordinated to the uranyl on the electrode surface as the eighth donor atom, coordinated to the metal center, or either substitute the water ligand in the coordination sphere. This observation proves the feasibility of uranium as a chemical modifier for other drugs, such as cocaine as it was mentioned before<sup>34-36</sup>.

The linear relationship between the square root of the scan rate and the peak current for both peaks  $c_1$  and  $a_2$  pointed to a controlled diffusion system, and an irreversible electrochemical behavior was evident.

### 3.4 Square wave voltammetry

The two oxidative processes observed in the oxidative direction of Square Wave Voltammetry resembled the processes we had verified during Cyclic Voltammetry (Figure 4). The instability of U(V), because of its disproportionation in solution, became clear when five consecutive cycles were applied without the renovation of the surface of the electrode<sup>40,42</sup>.

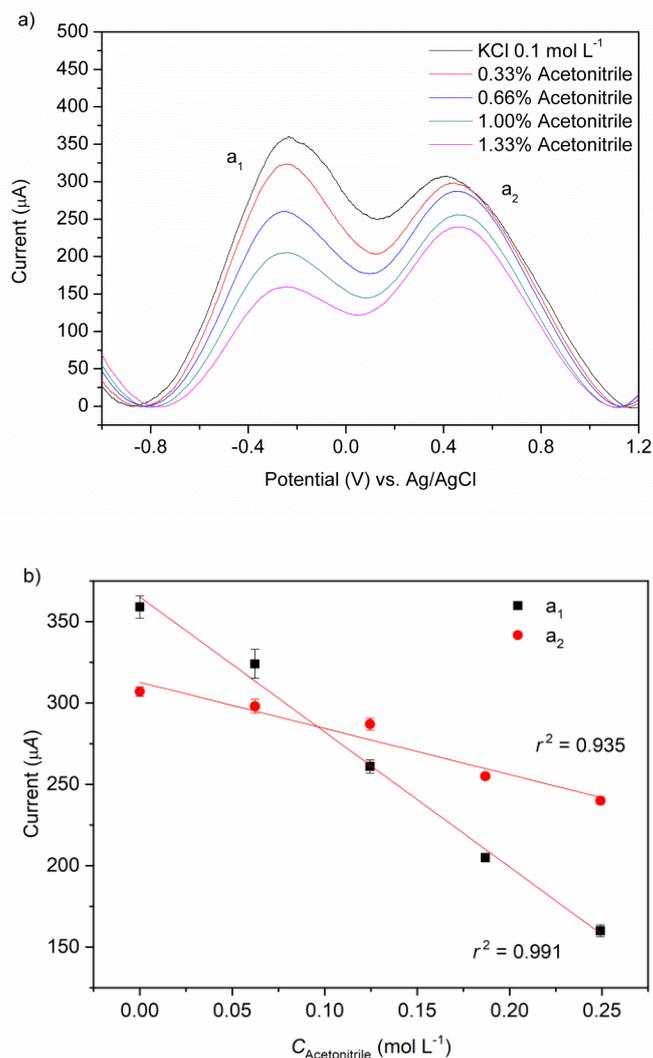
We optimized the parameters of Square Wave Voltammetry based on the intensity and definition of the two peaks in the presence of LSD. We varied the frequency, amplitude, and scan rate (step potential), and the best results were 10 Hz, 0.8 V, and 0.001 V, respectively.



**Figure 4.** a) Square Wave voltammograms for the carbon paste electrode without modification, and modified with  $[\text{UO}_2(\text{Ac-ophen})]\cdot\text{H}_2\text{O}$  (20% of the composition) and Schiff base (20% of the composition) in the presence of  $1.0 \mu\text{mol L}^{-1}$  of LSD. b) Square Wave voltammograms for the carbon paste electrode modified with  $[\text{UO}_2(\text{Ac-ophen})]\cdot\text{H}_2\text{O}$  (20% of the composition). Frequency = 10 Hz, Amplitude = 0.8 V, Step potential = 0.001 V.

### 3.5 Study about the interference of acetonitrile

Before studying the response to LSD in more detail, we analyzed how acetonitrile interfered in the electrochemical system because this solvent was present in the standard solution of the drug. Figure 5 illustrates how presence of acetonitrile affects the analysis of LSD.



**Figure 5.** a) Square Wave voltammograms recorded after successive additions of acetonitrile. Frequency = 10 Hz, Amplitude = 0.8 V, Step potential = 0.001 V. b) Relation between the intensity of the current intensity and the presence of acetonitrile for each anodic peak.

Acetonitrile affects both anodic peaks  $a_1$  and  $a_2$ , the first being most affected, as shown by the greater slope in graph of Figure 5, indicating a competition between the solvent and the LSD. Possibly the acetonitrile hinders these processes. For this reason, we kept the percentage of acetonitrile constant in the electrochemical cell during the LSD analyses.

It is important to emphasize the presence of a carboxyl group in the aromatic diimine existent in the structure of this Schiff base is responsible for its insolubility in acetonitrile, then it is impossible for these oxidative processes to be of the solubilized complex. If another organic solvent was present, such as ethanol or methanol, a

yellowish color would be observed in the solution of the supporting electrolyte due to the solubility of this complex in these solvents.

Successive additions of LSD increased the amperometric intensity of peak  $a_1$  and slightly decreased peak  $a_2$ , until the percentage of acetonitrile exceeded 2% of the total volume, after that the voltammetric response became unstable, losing its linearity. A linear relation between the concentration of LSD and the amperometric response is described by the equation:  $i \text{ (A)} = (0.25 \pm 0.02) \text{ A L mol}^{-1} [\text{LSD}] + (7.93 \pm 0.57) 10^{-7} \text{ A}$ .

### 3.6 Differential pulse voltammetry

Square Wave Voltammetry and Differential Pulse Voltammetry provided similar responses in the presence of LSD. Two oxidation peaks due to the uranyl group of the Schiff base complex emerged in the voltammogram, and no oxidative processes were observed using an electrode composed with carbon, and paraffin, and modified with the Schiff base. Again, the first peak referred to the oxidation of U(V), whereas the second peak corresponded to conversion of U(IV) into U(VI). The first peak was unstable.

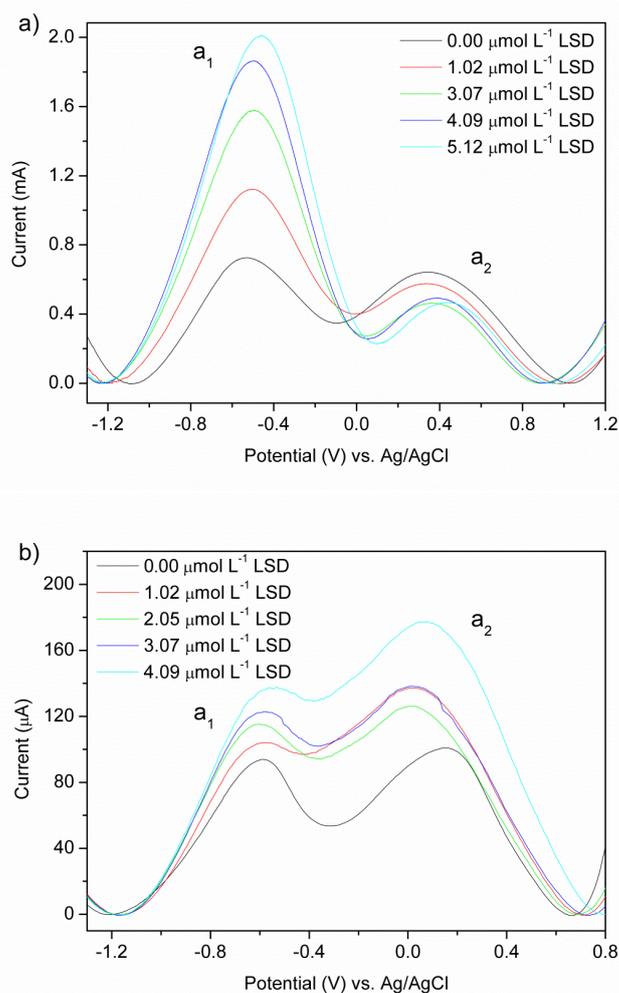
To optimize the signal, we varied the values of modulation amplitude, modulation time, interval time, and step potential. The best results were obtained with 0.8 V for modulation amplitude, 0.04 s for modulation time, 1 s for interval time, and 0.01 V for step potential. At higher step potential rates, peak  $a_1$  disappeared. At 0.10 V, just peak  $a_2$  arose.

As discussed before, acetonitrile continued to interfere in the analyses. The presence of acetonitrile affected the oxidation of U(V) to U(VI) to a larger extent as compared to the effect of acetonitrile on the oxidation of U(IV) to U(VI), probably as a result of instability. Because the acetonitrile present in the standard solution of LSD influenced the oxidation process, we obtained the calibration curve by keeping the concentration of acetonitrile constant, and under 2% v/v, in the electrochemical cell.

Addition of the standard LSD solution caused the oxidative peak to increase linearly at negative potentials, as it was observed for the Square Wave Voltammetry, according to the equation  $i \text{ (A)} = (11.80 \pm 0.98) \text{ A L mol}^{-1} [\text{LSD}] + (9.02 \pm 0.24) 10^{-5} \text{ A}$ .

### 3.7 Validation and comparison of techniques

After establishing the conditions for the quantification of LSD, we verified whether the results were reliable by validating Square Wave Voltammetry and Differential Pulse Voltammetry. We fixed the concentration of acetonitrile at the same value, and we analyzed the analytical curve by correlating the concentration of LSD to the anodic peak  $a_1$  for Square Wave Voltammetry and Differential Pulse Voltammetry (Figure 6).



**Figure 6.** a) Square Wave Voltammograms for successive additions of LSD; Frequency 10 = Hz, Amplitude = 0.8 V, Step potential = 0.001 V. b) Differential Pulse voltammograms for successive addition of LSD; Modulation Amplitude = 0.8 V, Modulation Time = 0.04 s; Interval Time = 1s; Step potential = 0.01 V.

Due to the similar behavior of the linear increase in the  $a_1$  peak current, the limits of detection (LOD) and quantification (LOQ) were also similar for both techniques. Table 1 summarizes all the figures of merit calculated for Square Wave Voltammetry and Differential Pulse Voltammetry. The LOD and LOQ values were

calculated as  $3 \cdot \sigma / m$  and  $10 \cdot \sigma / m$ , respectively, where  $\sigma$  is the standard deviation observed for the linear coefficient ( $r^2$ ) in the equation for current vs concentration of LSD and  $m$  is the voltammetric sensitivity, indicated by the slope in the same equation.

**Table 1.** Comparative results obtained for the quantification of LSD by Square Wave Voltammetry and Differential Pulse Voltammetry.

	Square Wave	Differential Pulse
Equation	$i \text{ (A)} = (0.25 \pm 0.02) \text{ A L mol}^{-1} [\text{LSD}] + (7.93 \pm 0.57) \cdot 10^{-7} \text{ A}$	$i \text{ (A)} = (11.80 \pm 0.98) \text{ A L mol}^{-1} [\text{LSD}] + (9.02 \pm 0.24) \cdot 10^{-5} \text{ A}$
SD ( $\mu\text{mol L}^{-1}$ )	0.057	2.45
LOD ( $\mu\text{mol L}^{-1}$ )	0.687 ( $\pm 0.10$ )	0.625 ( $\pm 0.09$ )
LOQ ( $\mu\text{mol L}^{-1}$ )	2.28 ( $\pm 0.32$ )	2.08 ( $\pm 0.29$ )
$r^2$	0.980 ( $\pm 0.006$ )	0.973 ( $\pm 0.004$ )

The lowest concentration of LSD found in blotters (containing 10  $\mu\text{g}$  of LSD) after extraction of the analyte with an organic solvent<sup>3</sup> would correspond to a concentration of  $5.18 \cdot 10^{-6} \text{ mol L}^{-1}$ . This value was higher than the LOQ of both Square Wave Voltammetry and Differential Pulse Voltammetry, proving that these techniques are suitable strategies to determine even low concentrations of LSD within the scope of forensic routine.

Due to the unavailability of real samples of LSD, the recovery assay was performed considering two different concentrations of LSD (obtained by adding the LSD standard solution in supporting electrolyte) in the middle of the determined linear range, one for the square wave voltammetry and other for the differential pulse voltammetry. Table 2 lists these results.

**Table 2.** Results obtained for solutions of LSD by Differential Pulse Voltammetry and Square Wave Voltammetry.

	Differential Pulse Voltammetry	Square Wave Voltammetry
$I_p \text{ (A)}$	$1.23 \cdot 10^{-4} (\pm 0.02)$	$1.34 \cdot 10^{-4} (\pm 0.03)$
Concentration ( $\mu\text{mol L}^{-1}$ )	2.78 ( $\pm 0.22$ )	3.68 ( $\pm 0.25$ )
Recovery (%)	108.17 ( $\pm 1.52$ )	103.08 ( $\pm 1.44$ )
SD (%)	2.62 ( $\pm 0.36$ )	6.82 ( $\pm 0.95$ )

#### 4. Conclusions

The present work presents an overview of the electrochemical behavior of the hallucinogenic drug LSD by different techniques, namely Square Wave Voltammetry and Differential Pulse Voltammetry, on the basis of the interaction of LSD with the chemical modifier  $[\text{UO}_2(\text{Ac-ophen})] \cdot \text{H}_2\text{O}$ . Although the mechanism reaction is not completely elucidated, an innovative and pioneering way of using the Schiff base complex in the forensic context was presented.

The use of carbon paste as a working electrode also stands out due to its ease manufacture and low cost. Besides, the methods developed herein require aqueous medium instead of organic medium, like the work of Merli *et al.*<sup>3</sup>, which uses dimethylformamide/tetrabutylammonium perchlorate as supporting electrolyte, making this work more eco-friendly and sustainable.

These advantages make the tested voltammetric techniques suitable sensors for use in the forensic area. The figures of merit of the methodologies developed in this study attest that they can be used to detect and quantify even the smallest concentration of LSD reported on blotters.

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#### References

1. Drug Enforcement Administration - Drugs of abuse: A DEA Resource Guide, 2017. Retrieved from [https://www.dea.gov/sites/default/files/2018-06/drug\\_of\\_abuse.pdf](https://www.dea.gov/sites/default/files/2018-06/drug_of_abuse.pdf).
2. Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A. The pharmacology of lysergic acid diethylamide: a review. *CNS Neurosci Ther.* 2008;14(4):295–314. <https://doi.org/10.1111/j.1755-5949.2008.00059.x>
3. Merli D, Zamboni D, Protti S, Pesavento M, Profumo A. Electrochemistry and analytical determination of lysergic acid diethylamide (LSD) via adsorptive stripping voltammetry. *Talanta.* 2014;130:456–461. <https://doi.org/10.1016/j.talanta.2014.07.037>

4. Canezin J, Cailleux A, Turcant A, LeBouil A, Harry P, Allain P. Determination of LSD and its metabolites in human biological fluids by high performance liquid chromatography with electrospray tandem mass spectrometry. *J Chromatogr B*. 2001;765(1):15–27. [https://doi.org/10.1016/S0378-4347\(01\)00386-3](https://doi.org/10.1016/S0378-4347(01)00386-3)
5. National Institute on Drug Abuse - Epidemiologic Trends in Drug Abuse, Volume 1, 2002. Retrieve from [https://archives.drugabuse.gov/sites/default/files/vol1\\_1202.pdf](https://archives.drugabuse.gov/sites/default/files/vol1_1202.pdf).
6. Cody JT. Chapter 4: Hallucinogens. In: Bogusz MJ, Handbook of analytical separations. Amsterdam: Elsevier Science BV; 2008. P.175–20. [https://doi.org/10.1016/S1567-7192\(06\)06004-9](https://doi.org/10.1016/S1567-7192(06)06004-9)
7. Reuschel SA, Eades D, Foltz RL. Recent advances in chromatographic and mass spectrometric methods for determination of LSD and its metabolites in physiological specimens. *J Chromatogr B*. 1999;733:145-159. [https://doi.org/10.1016/S0378-4347\(99\)00189-9](https://doi.org/10.1016/S0378-4347(99)00189-9)
8. McDonald PA, Martin CF, Woods DJ, Baker PB, Gough TA. An analytical study of illicit lysergide. *J Forensic Sci*. 1984;29(1):120-130. <https://doi.org/10.1520/JFS11642J>
9. Marta RFLO. Metabolism of lysergic acid diethylamide (LSD): an update. *Drug Metab Rev*. 2019;51(3):378-387. <https://doi.org/10.1080/03602532.2019.1638931>
10. United Nations Office on Drugs and Crime (UNODC). World Drug Report 2017. Retrieve from <https://wdr.unodc.org/wdr2019/>.
11. Polícia Federal. Estatística de Drogas Apreendidas. Retrieved from <http://www.pf.gov.br/imprensa/estatistica/drogas/>.
12. Zawilska JB, Kacela M, Adamowicz P. NBOMes-High Potent and Toxic Alternative of LSD. *Front Neurosci*. 2020;14(78):1-15. <https://doi.org/10.3389/fnins.2020.00078>
13. Scientific working group for the analysis of sized drugs (SWGDRUG). Recommendations. Retrieved from [http://www.swgdrug.org/Documents/SWGDRUG%20Recommendations%20Version%208\\_FINAL\\_ForPosting\\_092919.pdf](http://www.swgdrug.org/Documents/SWGDRUG%20Recommendations%20Version%208_FINAL_ForPosting_092919.pdf).
14. United Nations International Drug Control Programme (UNDCP). Rapid on-site screening of drugs of abuse - A summary of commercially available products and their applications: guidance for the selection of suitable products Part I Biological specimens. Retrieved from [https://www.unodc.org/pdf/scientific/Scitec18\\_final1.pdf](https://www.unodc.org/pdf/scientific/Scitec18_final1.pdf).
15. Bruni AT, Velho JA, de Oliveira MF. Fundamentos da química forense. 1. ed. Campinas: Editora Millennium; 2012. 358 p.
16. Johansen SS, Jensen JL. Liquid chromatography-tandem mass spectrometry determination of LSD, iso-LSD, and the main metabolite 2-oxo-3-hydroxy-LSD in forensic samples and application in forensic case. *J Chromatogr B*. 2005;825(1):21-28. <https://doi.org/10.1016/j.jchromb.2004.12.040>

17. Pietsch J, Schulz K, Korner B, Trauer H, Drebler J, Gey M. Alternative method for forensic determination of lysergic acid diethylamide and related compounds in body fluids by liquid-liquid extraction and HPLC with fluorescence detection. *Chromatographia*. 2004;60(1):89-92. <https://doi.org/10.1365/s10337-004-0344-3>
18. Musshoff F, Daldrop T. Gas chromatographic/mass spectrometric determination of lysergic acid diethylamide (LSD) in serum samples. *Forensic Sci int*. 1997;88(2):133-140. [https://doi.org/10.1016/S0379-0738\(97\)00063-7](https://doi.org/10.1016/S0379-0738(97)00063-7)
19. Stradiotto NR, Yamanaka H, Zanoni MVB. Electrochemical sensors: a powerful tool in analytical chemistry. *J Brazil Chem Soc*. 2003;14(2):159-173. <https://doi.org/10.1590/S0103-50532003000200003>
20. Shaw L, Dennany L. Applications of electrochemical sensors: forensic drug analysis. *Curr Opin Electrochem*. 2017;3:23-28. <https://doi.org/10.1016/j.coelec.2017.05.001>
21. Oiye EN, de Figueiredo NB, de Andrade JF, Tristão HM, de Oliveira MF. Voltammetric determination of cocaine in confiscated samples using a cobalt hexacyanoferrate film-modified electrode. *Forensic Sci Int*. 2009;192:94-97. <https://doi.org/10.1016/j.forsciint.2009.08.004>
22. Garrido JMPJ, Borges F, Brett CMA, Garrido EMPJ. Carbon nanotube  $\beta$ -cyclodextrin-modified electrode for quantification of cocaine in seized street samples. *Ionics*. 2016;22(12):2511–2518. <https://doi.org/10.1007/s11581-016-1765-3>
23. Ribeiro MFM, Oiye EN, Katayama JMT, Ipólito AJ, de Oliveira MF. Simple and fast analysis of lsd by cyclic voltammetry in aqueous medium. *ECS Transactions*. 2017;80(10):1259-1268. <https://doi.org/10.1149/08010.1259ecst>
24. Tadini MC, Balbino MA, Eleoterio IC, de Oliveira LS, Dias LG, Demets GJF, de Oliveira MF. Developing electrodes chemically modified with cucurbit[6]uril to detect 3,4-methylenedioxymethamphetamine (MDMA) by voltammetry. *Electrochim Acta*. 2014;121:188-193. <https://doi.org/10.1016/j.electacta.2013.12.107>
25. Couto RAS, Costa SS, Junior BM, Pacheco JG, Fernandes E, Carvalho F, Rodrigues CMP, Delerue-Matos C, Braga AAC, Gonçalves LM, Quinaz, MB. Electrochemical sensing of ecstasy with electropolymerized molecularly imprinted poly(o-phenylenediamine) polymer on the surface of disposable screen-printed carbon electrodes. *Sensor Actuat B*. 2019;290:378–386. <https://doi.org/10.1016/j.snb.2019.03.138>
26. Oiye EM, Katayama JMT, Ribeiro MFM, de Oliveira MF. Electrochemical analysis of 25H-NBOMe by square wave voltammetry. *Forensic Chemi*. 2017;5:86-90. <https://doi.org/10.1016/j.forc.2017.07.001>
27. Souza GA, Pimentel DM, Lima AB, Guedes TJ, Arantes LC, de Oliveira AC, Sousa RMF, Muñoz RAA, dos Santos WTP. Electrochemical sensing of NBOMes and other

- new psychoactive substances in blotting paper by square-wave voltammetry on boron-doped diamond electrode. *Anal Methods*. 2018;10:2411-2418. <https://doi.org/10.1039/C8AY00385H>
28. Balbino MA, Oiye EN, Ribeiro MFM, Júnior JWC, Eleotério IC, Ipólito AJ, de Oliveira MF. Use of screen-printed electrodes for quantification of cocaine and  $\Delta^9$ -THC: adaptations to portable systems for forensic purposes. *J Solid State Electr*. 2016;20:2435-2443. <https://doi.org/10.1007/s10008-016-3145-3>
  29. Balbino MA, de Menezes MM, Eleoterio IC, Saczk AA, Okumura LL, Tristão HM, de Oliveira MF. Voltammetric determination of  $\Delta^9$ -THC in glassy carbon electrode: An important contribution to forensic electroanalysis. *Forensic Sci Int*. 2012;221:29–32. <https://doi.org/10.1016/j.forsciint.2012.03.020>
  30. Fatibello-Filho O, Dockal ER, Marcolino-Júnior LH, Teixeira MFS. Electrochemical modified electrodes based on metal-salen complexes. *Anal Lett*. 2007;40(10):1825–1852. <https://doi.org/10.1080/00032710701487122>
  31. Oiye EN, Ribeiro MFM, Katayama JMT, Tadini MC, Balbino MA, Eleotério IC, Magalhães J, Castro AS, Silva RSM, Júnior JWC, Dockal ER, de Oliveira MF. Electrochemical sensors containing Schiff bases and their transition metal complexes to detect analytes of forensic, pharmaceutical and environmental interest: A Review. *Cr Rev Anal Chem*. 2019;49(6):488-509. <https://doi.org/10.1080/10408347.2018.1561242>
  32. Teixeira MFS, Marino G, Dockal ER, Cavalheiro ETG. Voltammetric determination of pyridoxine (Vitamin B6) at a carbon paste electrode modified with vanadyl(IV)–Salen complex. *Anal Chim Acta*. 2004;508(1):79–85. <https://doi.org/10.1016/j.aca.2003.11.046>
  33. Raymundo-Pereira PA, Teixeira MFS, Fatibello-Filho O, Dockal ER, Bonifácio VG, Marcolino-Junior LH. Electrochemical sensor for ranitidine determination based on carbon paste electrode modified with oxovanadium (IV) salen complex. *Mater Sci Eng C*. 2013;33(7):4081–4085. <https://doi.org/10.1016/j.msec.2013.05.051>
  34. de Oliveira LS, Poles APS, Balbino MA, de Menezes MMT, de Andrade JF, Dockal ER, Tristão HM, de Oliveira MF. Voltammetric determination of cocaine in confiscated sample using a carbon paste electrode modified with different  $[\text{UO}_2(\text{X-MeOsalen})(\text{H}_2\text{O})]$   $\text{H}_2\text{O}$  complexes. *Sensors*. 2013;13(6):7668-7679. <https://doi.org/10.3390/s130607668>
  35. de Oliveira LS, Poles APS, Balbino MA, de Menezes MMT, de Andrade JF, Dockal ER, Tristão HM, de Oliveira MF. Voltammetric analysis of cocaine using platinum and glassy carbon electrodes chemically modified with uranyl Schiff base films. *Microche J*. 2013;110(6):374-378. <https://doi.org/10.1016/j.microc.2013.04.017>
  36. Ribeiro MFM, Cruz-Junior JW, Dockal ER, McCord BR, de Oliveira MF. Voltammetric determination of cocaine using carbon screen printed electrodes chemically modified with uranyl Schiff base films. *Electroanalysis*. 2015;27(2):1-8.

37. Asadi Z, Asadi M, Firuzabadi FD, Yousefi R, Jamshidi M. Synthesis, characterization, anticancer activity, thermal and electrochemical studies of some novel uranyl Schiff base complexes. *J Iran Chem Soc.* 2014;11(2):423-429. <https://doi.org/10.1007/s13738-013-0314-5>
38. Signorini O, Dockal ER, Castellano G, Oliva G. Synthesis and characterization of aquo[N,N'-ethylenebis(3-ethoxysalicylideneaminato)]dioxouranium(VI). *Polyhedron.* 1996;15:245-255. [https://doi.org/10.1016/0277-5387\(95\)00243-L](https://doi.org/10.1016/0277-5387(95)00243-L)
39. Kim SY, Asakura T, Morita Y, Uchiyama G, Ikeda Y. Electrochemical redox reactions of uranium (VI) complexes with multidentate ligands in dimethyl sulfoxide. *Radiochim Acta.* 2005;93(2):75-81.
40. Mizuoka K, Kim SY, Hasegawa M, Hoshi T, Uchiyama G, Ikeda Y. Electrochemical and spectroelectrochemical studies on UO<sub>2</sub>(saloph)L (saloph = N,N'-Disalicylidene-o-phenylenediaminate, L = Dimethyl Sulfoxide or N,N-Dimethylformamide). *Inorg Chem.* 2003;42(4):1031-1038. <https://doi.org/10.1021/ic0260926>
41. Kihara S, Yoshida Z, Aoyagi H, Maeda K, Shirai O, Kitatsuji Y, Yoshida Y. A critical evaluation of the redox properties of uranium, neptunium and plutonium ions in acidic aqueous solutions. *Pure Appl Chem.* 1999;71:1771-1807. <https://doi.org/10.1351/pac199971091771>
42. Sipos L, Galus Z. Redox processes of uranium (VI), (V), (IV), and (III) in acetate buffers. *Inorg Nucl Chem Lett.* 1971;7(3):299-304. [https://doi.org/10.1016/0020-1650\(71\)80209-X](https://doi.org/10.1016/0020-1650(71)80209-X)
43. Gao S, Lan WB, Lin YW, Liao LF, Nie CM. Molecular recognition of  $\alpha,\beta$ -unsaturated carbonyl compounds and chiral guests by uranyl-salophen receptors. *Acta Phys-Chim Sin.* 2016;32(3):683-690. <https://doi.org/10.3866/PKU.WHXB201512302>