National University of Science and Technology POLITEHNICA Bucharest
Doctoral School of Chemical Engineering and Biotechnologies

Summary of PhD THESIS

STUDIES ON ELECTROCHEMICAL AND SPECTRAL CHARACTERISTICS OF SEVERAL NITROGEN HETEROCYCLES

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ABBREVATIONS LIST

Abbreviation	Significance
MM1	1,2,3,4-tetrahydroacridine-9-carboxamide
MM4	1,2,3,4-tetrahydroacridine-9-carboxylic acid
MM11 (4a)	7,7′-(ethane-1,2-diyl)bis(2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic acid)
MM12 (4b)	7,7′-(ethane-1,2-diyl)bis(1,2,3,4-tetrahydroacridine-9-carboxylic acid)
H2**L**	salophen ligand
Ni(II)**L**	Ni(II)-salophen
CME	Chemically modified electrode
GC	Vitreous carbon electrode
WE	Working electrode
RE	Reference electrode
CH_3CN, ACN	Acetonitrile
DMF	Dimethylformamide
TBAP	Tetrabutylammonium perchlorate
CV	Cyclic voltammetry
DPV	Differential pulse voltammetry
RDE	Voltammetry with rotating disc electrode
UV-Vis	Ultraviolet and visible spectral range
DFT	Density functional theory

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CHAPTER 1. PRESENTATION OF THE DOCTORAL TOPIC, THE METHODS AND CONCEPTS USED

1.1..INVESTIGATED ORGANIC COMPOUNDS

The study conducted within the framework of this doctoral thesis refers to two nitrogen-containing heterocycles, namely tetrahydroacridines and salen derivatives.

Acridines and their homologous derivatives form an important class of nitrogen-containing heterocycles that are widely distributed in nature, being found in both plants and marine organisms.They have been intensively studied with regard to their synthesis [1-3],

their physicochemical properties [4-7] and their structural requirements [8]. On the other hand, they have also been the subject of considerable investigation regarding their possible applications [9-13]. After their discovery, acridines were initially used as pigments and dyes [14]. Subsequently, they have been extensively investigated as potential pharmaceutical agents for the treatment of a wide range of diseases, including cancer [15], Alzheimer's disease [16-18], bacterial infections [19] and protozoa [20]. Their mode of action is mainly attributed to intercalation into DNA and RNA chains by forming hydrogen bonds and stacking them between base pairs, resulting in DNA crosslinks and strand breaks [20]. These bonds have subsequent effects on biological processes related to DNA and its associated enzymes [21,22]. Tetrahydroacridines, the reduced homologues of acridines, have received increased attention due to their ability to inhibit topoisomerase enzymes and block DNA transcription [23–27]. They have been widely explored for the treatment of Alzheimer's disease [28–38], human cancer [39–41] and tuberculosis [42], as shown in Figure 1. In addition, new natural and synthetic acridine derivatives have been tested for antimalarial and antileishmanial [43–47], antifungal [48,49], antiparasitic [50], anti-inflammatory [51–60] Fand analgesic [61–63] activities, with some derivatives being approved for chemotherapy [64]. In addition, through sustained efforts, acridine derivatives with increased therapeutic potency and selectivity, such as fluorescent materials [65–67], have been developed. The presence of an aromatic ring, a π system, and a nitrogen atom with a lone pair of electrons in the chemical structure of acridines and tetrahydroacridines makes them suitable as corrosion inhibitors [68] and metal chemosensors [69–71].

Acridines, like other π-conjugated organic molecules, have also been used in several other cutting-edge fields due to their strong electron-donating ability [72] and remarkable optoelectronic properties [73–77]. These include organic electronics [78,79] as well as the field of organic light-emitting diodes [80–83]. In addition, their partially hydrogenated analogs, tetrahydroacridines are a class of organic compounds best known for their large medical potential. They are widely explored in the treatment of different diseases such as Alzheimer's disease (AD) [84], tuberculosis [85], and human cancer [86], due to their ability to inhibit topoisomerase enzymes and block DNA transcription [87, 88]. For example, 9-aminotetrahydroacridine (tacrine) was the first drug approved for the treatment of AD but was later withdrawn due to its hepatotoxicity [89]. Furthermore, the presence of an amide group (-NHCO-) and a polyalkylquinoline skeleton in the structure of tetrahydroacridines or their bioisosteres is a common scaffold found in numerous potential acetylcholinesterase inhibitors [90]. They have been known since 1882 when the first synthesis methods were developed, which involve a cyclocondensation of an o-aminocarbonyl component (isatin, ortho-aminobenzaldehyde, ortho-aminoketone) with a carbonyl component bearing a reactive methylene group [91-92].

Tetrahydroacridines are molecules containing an annelated quinoline skeleton with saturated rings. They are a subclass of acridines, which are known to be π-conjugated heteroorganic molecules. Due to their electron donation properties [93] they have found applications in cutting-edge fields such as OLED applications [94]. However, the study of their optoelectrical properties is very scarce compared to their acridine counterparts [95].ated analogues have been used as electron-donating groups for OLED applications [96,97].

The second class of compounds that have been studied in this thesis are Salophen and Its Ni(II) complex, Ni(II)-Salophen [98]. Over the past few decades, transition metal complexes containing N_2O_2 coordination sites, such as salicylidenes [99], have aroused the increased interest of researchers due to their multiple applications in topical fields such as non-linear optics [100], molecular magnetism [101], functional materials and organic electronics [102], light-emitting diodes (OLEDs) [99,103], and display magnetic properties

[104]. Among them, salen-like ligands (Figure 2a) were studied for their properties and applications in biology [105], catalysis [106], and electrocatalysis [107]. They are diimines prepared from differently substituted aldehydes and various 1,2 diamines. N,N'-Bis-(2-hydroxybenzylidene)-benzene-1,2-diamine (H2**L**) and its Ni(II) complex (Ni(II)**L** (Figure 2) were studied using many techniques and in various conditions. Connections with previous results [108] were made. Studying the relationship between the chemical structures and characteristics of Schiff bases and their complexes is very important for understanding their various forms of activity [109]. Numerous studies have focused on the electrochemical behavior of salen ligands and their metal complexes on the relation between electrochemical potential and structure [110,111]. The electrochemical behavior of Schiff bases has been investigated particularly in dipolar aprotic solvents, where hydrolysis of the iminic moiety is impeded [112,113]. This involves the hydrogenation of the >C=N bond, with the formation of saturated amines or dimeric diamines in several cases [114]. The overall two-electron process gives rise to a single reduction wave or it takes place in two separate one-electron steps, depending on the structure of the substrate and on the proton-donor ability of the medium [113,115]. On the other hand, nickel complexes are powerful catalysts in the chemical and electrochemical reduction of alkyl halides [116–119]. It has been established that the essential factor in all catalytic processes is the reduction of the transition metal to a low oxidation state and that the catalytic efficiency depends on the capacity of the reducibility of the metal center as well as on the reactivity of the reduced metal complex. In particular, numerous Ni(II)-**salen** complexes have been evaluated via voltammetry electropolymerization [120]. Several of these studies have essentially focused on the electrocatalytic reduction activity of Schiff base complexes in a large number of homogeneous and heterogeneous reactions [121–123].

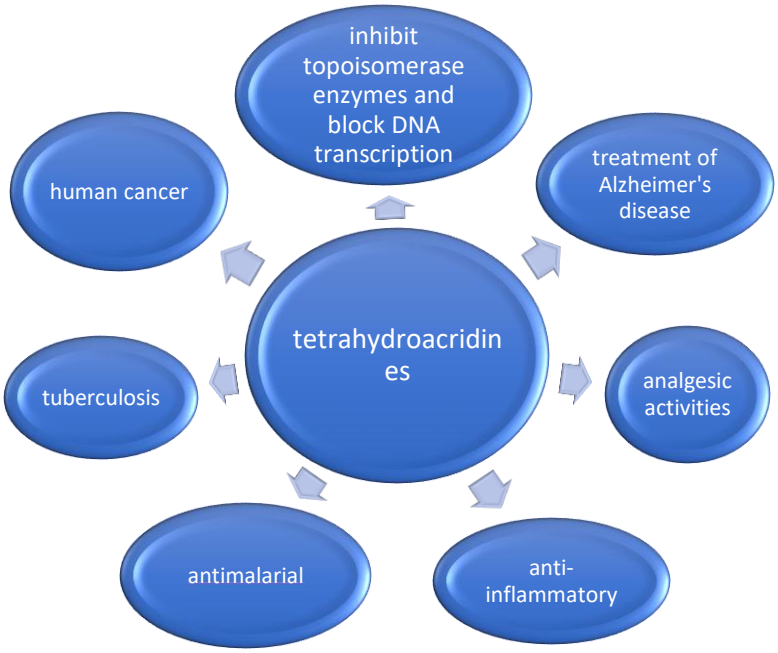


Figure 1. Tetrahydroacridines – scheme of medical applications.

Precisely from this perspective, this paper focuses on the characterization of **L** and its tetradentate Ni(II)L complex using different physicochemical and spectroscopic methods.

An in-depth electrochemistry characterization of **L** and Ni(II)**L** was carried out to study the electropolymerization mechanism and characteristics of the polymer films deposited on the electrode surface, as well as the behavior of the modified electrodes covered by the electroactive polymer films. The biological properties of these compounds were also tested for antibacterial and antifungal activities against several usual pathogenic strains. The radical scavenging method was used to put in evidence the efficiency of their antioxidant activity. Conductivity studies were also performed.

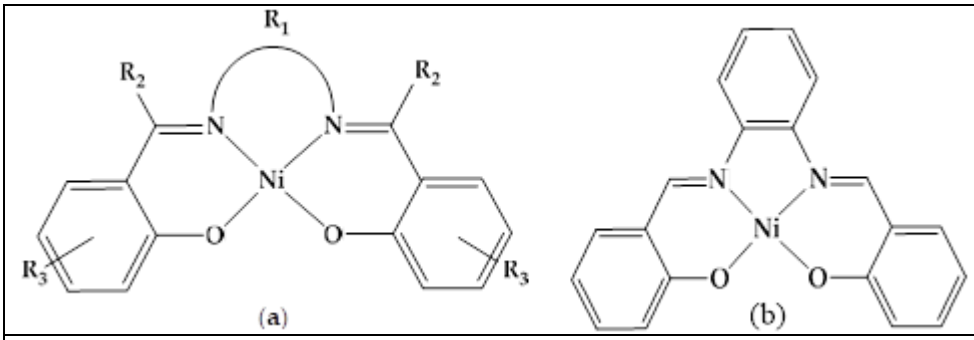


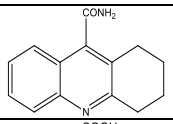
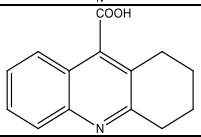
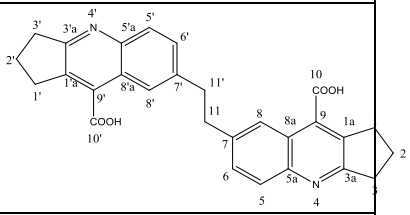
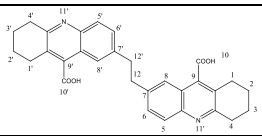
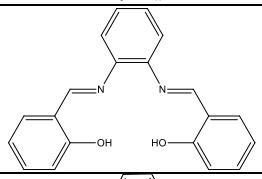
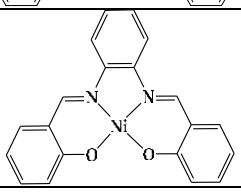
Figure 2. (a) Structure of Ni(II)-salen complexes, where R1 is a two–four carbon-atom-saturated bridge or a substituted aromatic moiety, R2 is H or an alkyl substituent, and R3 is a halogen or another substituent to the aromatic ring; (b) Ni(II)-salophen complex studied in the present paper (R1 = C_6H_4, R2 = H, and R3= H).

In the Laboratory of Electrochemical Processes in Organic Solvents (PESO) of the National University of Science and Technology POLITEHNICA Bucharest, research was initiated on the electrochemical properties of these compounds [124–127] and the properties were evaluated by quantum mechanical calculations [124, 125]. This doctoral thesis was developed within the Departments of Analytical Chemistry and Bioengineering and Physical Chemistry and Electrochemistry of the Faculty of Chemical Engineering and Biotechnology of the National University of Science and Technology POLITEHNICA Bucharest. The thesis is part of the concerns related to the testing of new organic compounds in order to establish their electrochemical properties and for the development of new sensors based on chemically modified electrodes (CME).

The thesis brings original contributions related to the electrochemical characterization of some tetrahydroacridine derivatives recently synthesized at the C. D. Nenițescu Institute of Organic and Supramolecular Chemistry of the Romanian Academy. In the thesis, 2 new tetrahydroacridine derivatives (**MM11** and **MM12**) were synthesized, characterized by spectral methods, and the electrochemical and optical properties of 4 tetrahydroacridine derivatives (**MM1**, **MM4**, **MM11**, **MM12**) were investigated. DFT quantum mechanical calculations and properties were performed for 4 compounds (**MM1**, **MM4**, **MM11**, **MM12**), according to **Table 1.1**.

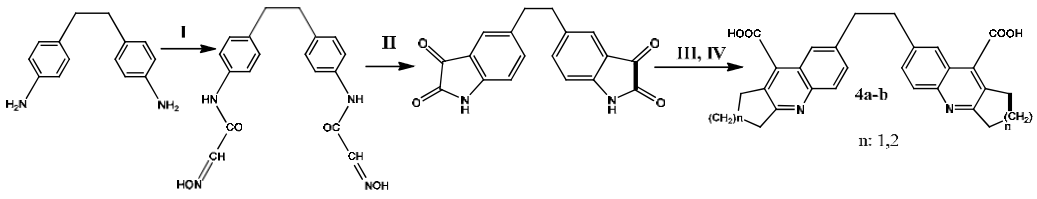
All tetrahydroacridine derivatives in **Table 1.1**. were synthesized according to the literature, in accordance with the cited references

Table 1.1. Compounds investigated in this work.

No. Crt.	Organic ligand code	Organic ligand name (IUPAC)	Structure
1.	**MM1**	1,2,3,4-tetrahydroacridine-9-carboxamide	
2.	**MM4**	1,2,3,4-tetrahydroacridine-9-carboxylic acid	
3.	**MM11 4a**	7,7'-(ethane-1,2-diyl)bis(2,3-dihydro-1H-cyclopenta[b]quinoline-9-carboxylic acid) (**4a**)	
4.	**MM12 4b**	7,7'-(ethane-1,2-diyl)bis(1,2,3,4-tetrahydroacridine-9-carboxylic acid) (**4b**)	
5.	**H2L**	2,2'-((1E,1'E)-(1,2-phenylenebis(azanylylidene))bis(methanylylidene))diphenol (Salophen)	
6.	**Ni(II)L**	Ni(II) salophen	

1.2. METHODS USED TO IDENTIFY AND CHARACTERIZE THE COMPOUNDS INVESTIGATED IN THE THESIS

1.2.1. Synthesis of the tetrahydroacridines studied in this thesis



Scheme 1. Synthesis of tetrahydroacridines analogous with 4,4′-(ethane-1,2-diyl)dianiline skeleton; I. CCl_3-CHO, NH_2OH, Na_2SO_4, T = 95–100 °C; II. H_2SO_4, T = 70 °C; III. KOH alcoholic solution, cyclanone (cyclohexanone or cyclopentanone for **4a** and **4b**, respectively).

Starting from 4,4′-(ethane-1,2-diyl)dianiline (**1**), chloral and hydroxylamine, bis-isonitrosoacetanilide (**2**) were prepared by Sandmayer reaction (step I) in low yield (30%).

In step II of the reaction, compound (**2**) was heated at 87–95 ◦C in H2SO4 for twenty

minutes, to obtain the corresponding bis-indoline-tetraone (**3**) by cyclocondensation in good yields. In step III, the corresponding bis-acids 7,7′-(ethane-1,2-diyl)bis(2,3-dihydro-

1H-cyclopenta[b]quinoline-9-carboxylic acid) (**4a**) and 7,7′-(ethane-1,2-diyl)bis(1,2,3,4-tetrahydroacridine-9-carboxylic acid) (**4b**) were obtained by Pfitzinger condensation of bisisatine(**3**) with cyclanones in a solution of KOH in ethanol. The final compounds have low solubility in organic solvents and melting points above 240 ◦C with decomposition [128,129]. In the following paragraphs, the specific working conditions for the compounds resulting from each step, the yields of the steps, and the spectral data for the newly synthesized compounds are presented.

1.2.2. Spectral methods for characterization of the investigated compounds

The synthesized tetrahydroacridine compounds were characterized by: NMR, IR, MS, elemental analyses.

1.2.2.1. Nuclear magnetic rezonance investigations (MR)

^{1}H and ^{13}C-NMR spectra were recorded using a Gemini 300 BB spectrometer operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C in DMSO-d_6, using TMS as the internal reference.

The ^{1}H-NMR and ^{13}C-NMR spectra were indicative of the compound's formation.

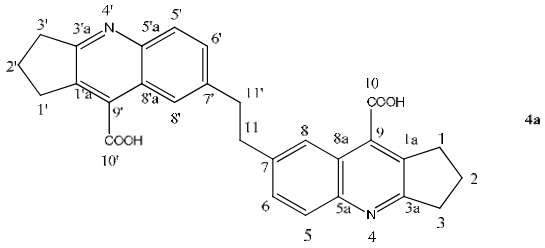


Figure 3. Molecular structure of 7,7′-(ethane-1,2-diyl)*bis*(2,3-dihydro-1H-cyclopenta[b]quinoline-9- carboxylic acid) (**4a**).

Yield 41% (18.55 g); M.p.: over 240 ◦C. Anal. calcd. $C_{28}H_{24}N_2O_4$ (452.51): C 74.32, H 5.35, N 6.19. Found: C 75.11, H 5.48, N 6.25;

IR(solid, ATR, cm^{-1}): 3359 m, 2949 m, 2881 m,1699 vs, 1594 vs, 1510 w, 1427 w, 1224 s, 886 w, 823 m, 664 w;

^{1}H-NMR (DMSO-d6+ TFA,δ ppm, *J* Hz): 8.07(d, 2H, *J* = 8.8, H5, H5′); 7.91(dd, *J* = 8.8, *J* = 1.6, 2H, H6, H6′); 7.86(d, = 1.6, 2H, H8, H8′); 3.40(t, *J* = 7.2, 4H, H3, H3′); 3.18(t, *J* = 7.4, 4H, H1, H1′); 2.50(s, 4H, H11, H11′); 2.16(cv, *J* = 8.0, 4H, H2, H2′);

^{13}C-NMR (DMSO-d6 + TFA, δ ppm): 165.80(C10, C10′); 165.70(C9, C9′); 142.42(C3a, C3′a); 140.60(C5a, C5′a); 137.34(C7, C7′); 136.36(C1a,C1′a); 134.24(C8, C8′); 124.98(C6, C6′); 123.67(C8a, C8′a); 120. 68(C5, C5‘); 36.49(C3, C3′); 31.82(C11, C11′); 30.01(C1, C1′); 22.75(C2, C2′).

Positive ESI-MS *m/z*: 453 [M + H]$^{+}$; 409 [M + H CO_2]$^{+}$; 365 [M + H $2CO_2$]$^{+}$; 183 [M + 2H $2CO_2$]$^{2+}$. Negative ESI-MS *m/z*: 451 [M H]$^{-}$; 407 [M H CO_2]$^{-}$; 363 [M/2 H $2CO_2$]$^{-}$; 182 [M/2 2H $2CO_2$]$^{-}$.

UV (λ_{max}, nm): 270, 311, 325.

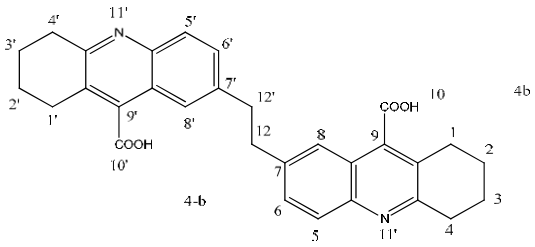


Figure 4. Structure of 7,7'-(ethane-1,2-diyl)*bis*(1,2,3,4-tetrahydroacridine-9-carboxylic acid) (**4b**).

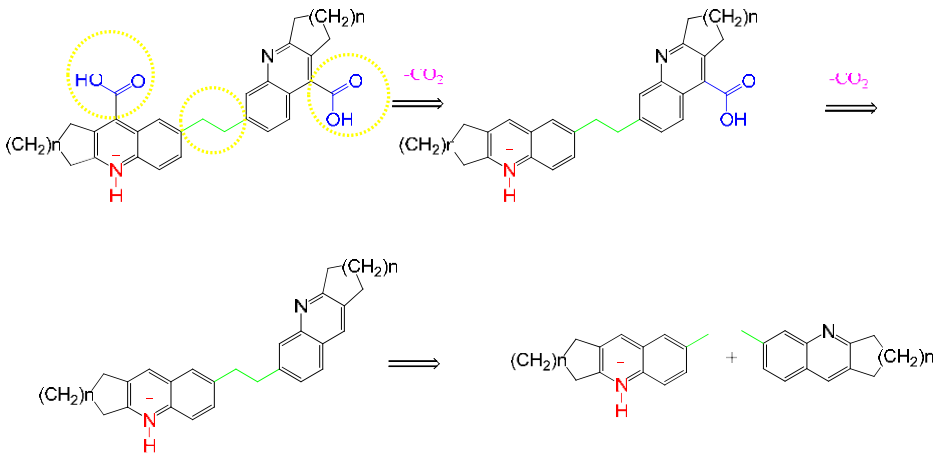
7,7'-(Ethane-1,2-diyl)*bis*(1,2,3,4-tetrahydroacridine-9-carboxylic Acid) (**4b**) According to Yield 41% (19.7 g); M.p.: over 240 °C Anal. calcd. $C_{30}H_{28}N_2O_4$ (480.56), C, 74.98; H,5.87; N, 5.83. Found: C 75.2, H 5.13, N 5.24;
IR(solid, ATR, cm^{-1}): 3485 s, 3367 s, 2941 s, 2865 s, 1590 s, 1397 s, 1369 m;
^{1}H-NMR (DMSO-d6 + TFA, δ ppm, *J* Hz): 8.14(d, 2H, *J* = 8.8, H5, H5'), 8.03(dd, 2H, *J* = 1.7, *J* = 8.8, H6, H6'), 7.57(d, 2H, *J* = 1.7, H8, H8'), 3.29(t,4H, *J* = 6.3, H4, H4'), 2.91(t, 6.2, 4H, H1, H1'), 2.50(s, 4H, H12, H12')1.95–1.84(m, 8H, H2, H3, H2', H3');
^{13}C-NMR (DMSO-d6 + TFA, δ ppm): 166.47(C10, C10'), 157.72(C9, C9'), 146.55(C4a, C4'a), 142.76(C5a, C5'a), 135. 64(C1a, C1'a), 135.35(C8, C8'), 128.02(C7, C7'),124.09 (C6, C6'), 36.40(C12, C12'); 28.81(C1, C1'); 25.40(C4, C4'); 20.68(C2, C2'); 20.16(C3, C3');
Positive ESI-MS *m/z*: 481 $[M + H]^+$; 393 $[M + H - 2CO_2]^+$; 197 $[M/2 + 2H - 2CO_2]^{2+}$;
Negative ESI-MS *m/z*: 479 $[M - H]^-$; 435 $[M - H - CO_2]^-$; 391 $[M - H - 2CO_2]^-$;
195 $[M/2 - 2H - 2CO_2]^{2-}$, UV (λ_{max}, nm): 268, 311, 326.

1.2.2.2. Infra-red spectrometry investigation (IR)

Infrared spectra were recorded using a Bruker FT-IR tensor 27 spectrometer directly on small samples of the compounds in the range of 4000–400 cm^{-1}.

1.2.2.3. Mass spectrometry investigations

Varian 310–MS LC/MS/MS triple quadrupole mass spectrometer fitted with an electrospray ionization interface (ESI) was used. Air was used as the drying gas at a pressure of 19 psi and temperature according to the experiment. The nebulizing gas was nitrogen of 40 psi for positive ionization and air of 55 psi for negative ionization. The needle voltage was established to the potential 5000 V for positive ionization and 4500 V for negative ionization. The substances were solubilized in DMSO and diluted with MeOH. The solution thus obtained was injected directly into the interface using a syringe pump Harvard 11PLUS, with a 0.010 mL/min flow. Thus, the protonated or deprotonated molecular ion obtained was selected using the first quadrupole. In the second quadrupole, the protonated or deprotonated molecular ion was fragmented via collision with inert gas (argon) to a pressure of 1.5 mTorr. Fragments were analyzed using the third quadrupole. Prior to these experiments, the tuning of the mass spectrometer was performed using PPG for both positive and negative.



Scheme 2. Fragmentation pattern for ethylene bridged *bis*-acids.

1.2.2.4. Investigation by thermogravimetric methods

Thermogravimetric analysis of the Ni(II)-salophen complexes was carried out using a Perkin-Elmer Pyris 6 TGA thermal analyser in a closed perforated aluminum pan simultaneous thermal analyzer. Thermogravimetric analysis of the complexes was performed under nitrogen atmosphere, in parallel with differential thermogravimetric analysis (DTG) and differential scanning calorimetry (DSC).

The TGA/DTG curves are shown in Figure 5.

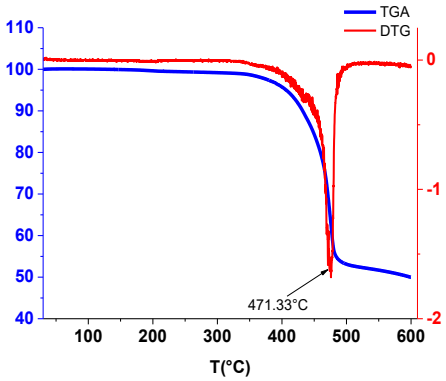


Figure 5. TGA/DTG of Ni(II)**L** (M = 374.06); M(NiO) = 74.69.

The thermal study of Ni(II)**L** was carried out according to the model described by El-Sawaf et al., following the evaluation of the percentages of mass loss according to the temperature ranges and the nature of the phenomena (endothermic or exothermic). The TGA/DTG curves of the Ni(II)**L** show its thermal decomposition occurring in a single step, while that of H_2**L** occurs in two steps [130]. The decomposition of Ni(II)**L** takes place over a temperature range and is coupled with an endothermic phenomenon on the DTG curve at 471.33 °C, corresponding to a mass loss of approximately 42% (calculated as 48%), associated with the elimination of [$2C_6H_4 + H_2 + N_2$]. Above 500 °C, the final residue can be attributed to [C_7H_5 + CO + NiO], with a mass loss percentage of about 50% (calculated as 51%).

1.2.1.5. Conductivity studies

Conductometric measurements were made on Digital Conductivity model Labtech. The molar conductivity (Λm) value for the H_2**L** and Ni(II)**L** metal complex measured

in dimethylsulphoxide (DMSO) was 0 in the range of 0–45 ohm^{-1} cm^2 mol^{-1}.and indicates that the Ni(II)**L** complex is non-electrolytic in DMSO, contrary to its behavior in other solvents [131; 132].

1.2.3 Electrochemical studies for tetrahydroacridine and salen compounds

In order to investigate the electrochemical properties of the newly synthesized organic compounds, the following methods were used: cyclic voltammetry (CV), differential pulse voltammetry (DPV) and rotating disk voltammetry (RDE). Chronoamperometry and cyclic voltammetry were used to prepare chemically modified electrodes (CME). Cyclic voltammetry was used for their characterization.

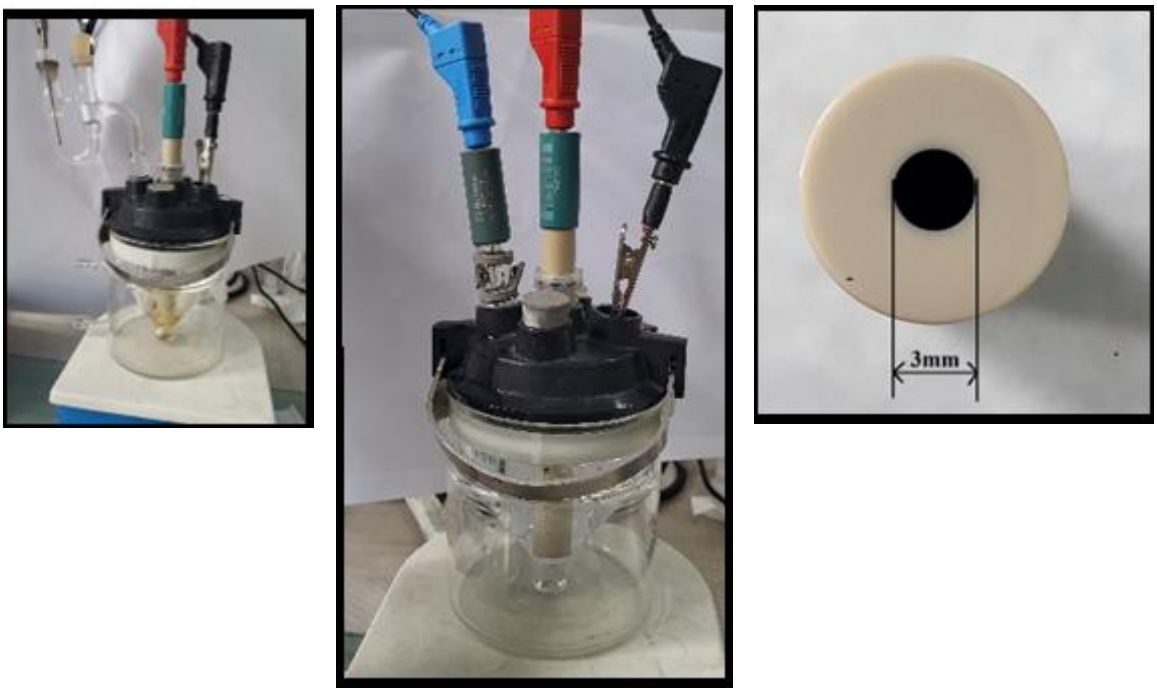
To perform the electrochemical experiments, an AUTOLAB 302N potentiostat (Figure 6a) was used coupled to a three-electrode electrochemical cell (Figure 7a.) after a prior setting of the experimental parameters, and the experimental data were acquired using a NOVA software interface (Figure 6b). As working electrodes (WE) were used glassy carbon (GC) electrodes with a diameter of 3 mm, supplied by Methrohm (Figures 7b,c), and chemically modified electrodes (CME). The reference electrode (RE) for the organic medium (Figure 7a) was Ag/Ag+ (10 mM $AgNO_3$ in CH_3CN + 0.1 M TBAP), and for the aqueous medium (Figure 7b) it was Ag/AgCl (3M KCl). A platinum wire was used as the auxiliary electrode (AE). Before each experiment, the GC was cleaned with diamond paste (0.25 μm) and then rinsed with acetonitrile.

In the case of experiments carried out in an organic medium, the potentials were reported relative to the redox potential of the ferrocene/ferricinium couple (Fc/Fc+), while those for the aqueous medium were reported relative to the potential of the Ag/AgCl reference electrode (3M KCl).



(a) (b)

Fig. 6. AUTOLAB 302N potentiostat (a) and NOVA interface (b) used for electrochemical experiments.



(a) **(b)** **(c)**

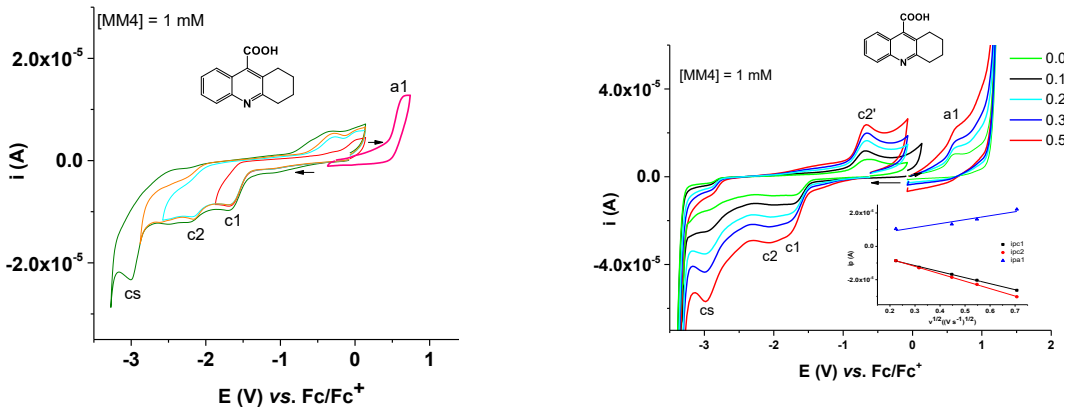
Fig. 7. Electrochemical cells used in electrochemical experiments for organic media (a), for aqueous media (b) and detail for GC electrode used (c).

To conduct the investigations on electrochemical studies of tetrahydroacridine derivatives, millimolar solutions of the investigated compounds were prepared in the supporting electrolyte. In the case of studies performed in organic medium, acetonitrile (CH3CN) was used as solvent, and tetrabutylammonium perchlorate (TBAP) was used as supporting electrolyte.

1.2.3.1. Cyclic voltammetry (CV) investigations

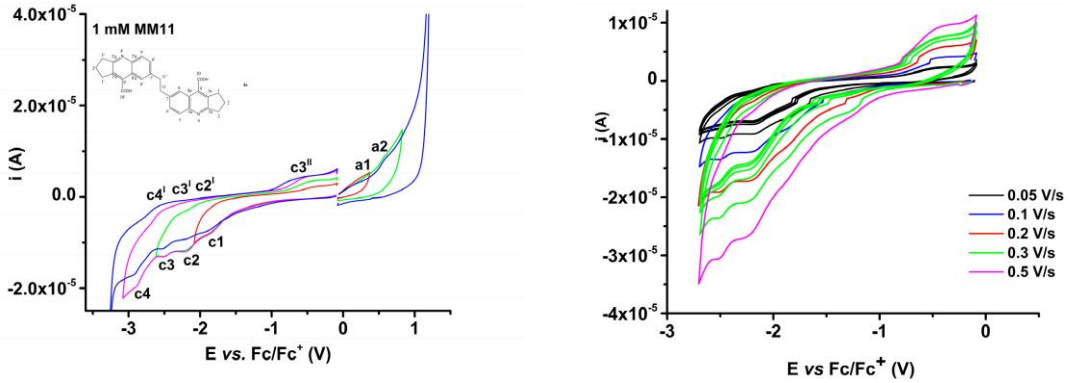
Among the most extensively employed electrochemical methods has been CV, due to its anatytical performancies. Using this method, we can gain insight into electrode mechanism and regarding of the reactions that take place near the active surface of the electrode, as well as the reactivity of electrochemically active species. Therefore, CV is used to study and understand the electrochemical processes of boundary systems, monitor reactions, and characterize electrodes [133].

The characterization for all compounds by CV was performed at different scan rates, over different potential ranges using their millimolar solutions in CH_3CN + 0,1 M TBAP suport electrolyte. Experiments were performed at 25°C temperature under argon atmosphere. Voltammograms were recorded starting from the stationary potential towards more positive potentials for the characterization of anodic processes. After the electrode is cleaned, it was polarized towards more negative potentials for cathodic processes characterization. Unless otherwise specified, a scan rate of 0.1 V/s was applied, showing thus the voltammograms for the compounds under study for different compounds concentrations. The obtained voltammograms are prezented in Figures **8a,b,c,d** for compound MM4, in Figures **9a,b** for compound MM11, in Figures **10** for H2**L** and Ni(II)**L**2. [124–127].



C d

Figure 8. CV (0.1 V/s) curves for: MM4 at different concentrations (a); comparison between MM1 and MM4 (b) CV curves at the same concentrations of 1 mM; MM4 (1 mM) on different potential domains (c); CV curves for MM4 (1 mM) at different scan rates (d); (d) inset: linear dependences of the peak currents for a1, c1 and c2 processes on the square root on the scan rates



(**a**) (**b**)

Figure 9. CV curves in anodic and cathodic scans on variable domains at 0.1 V/s (**a**) and at variable scan rates in 5 successive CV (0.1 V/s) cathodic scans (**b**) for **[MM11]** = 1 mM.

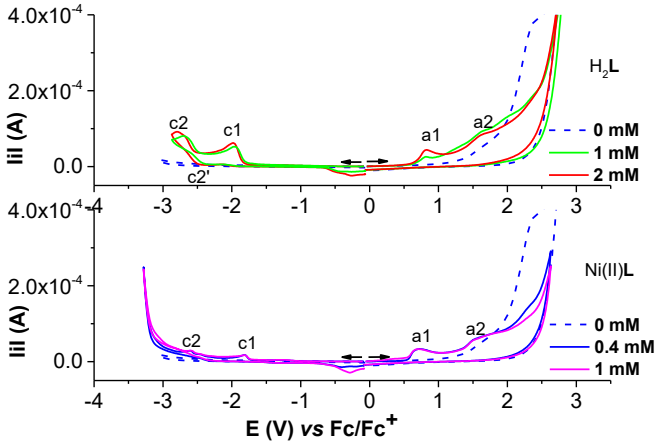
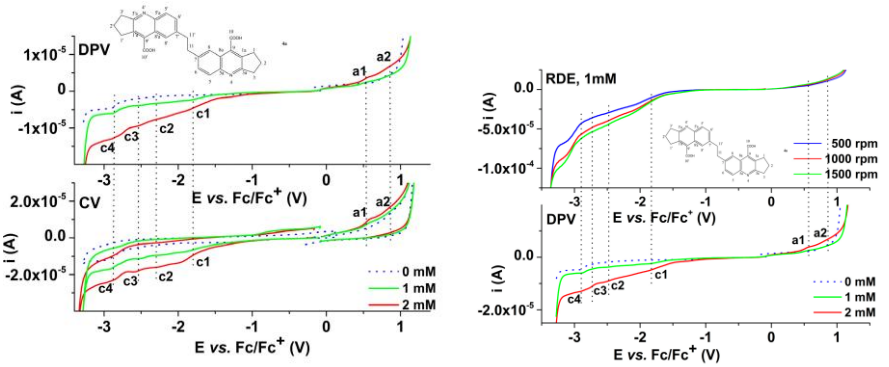


Figure. 10. CV curves (0.1 V/s) for anodic and cathodic on GC of H2L and Ni(II)L at different concentrations (mM) in TBAP (0.1 M)/ CH_3CN; the cathodic currents are shown in absolute values.

1.2.3.2. Differential pulse voltammetry (DPV) investigations

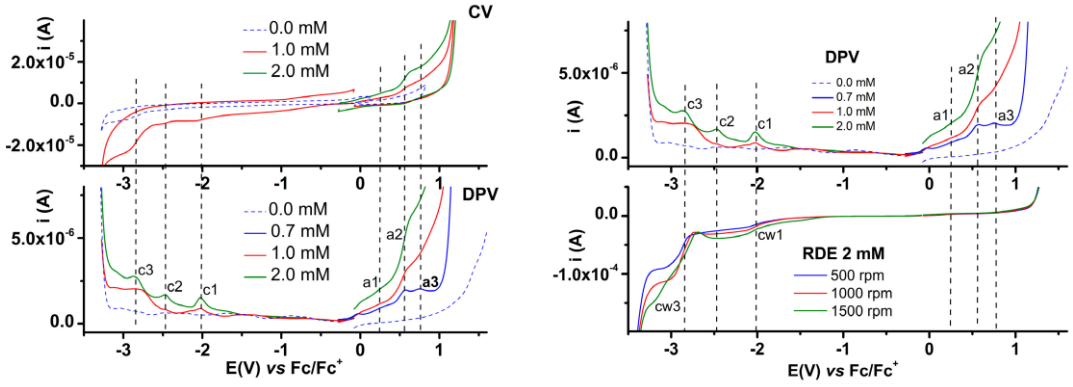
DPV is an electrochemical pulse technique able to minimize the background currents and can be used for the simultaneous analyses of more than one analyte. The voltammogram in DPV consist of a sequence of pulses in which a base potential is holded for a certain period of time before a potential pulse is applied [134].

The investigation of compounds by DPV method was realized by a scan rate of 0.01 V/s, with a pulse amplitude of 0.025 V and a step of 0.2 s using their millimolar solutions in CH_3CN + TBAP 0,1 M suport electrolyte. The experiments were performed at 25°C temperature under argon atmosphere. For the characterization of anodic processes voltammograms were recorded going first from the stationary potential towards more positive potentials. After the electrode was cleaned, it was polarized towards more negative potentials for the characterization of cathodic processes. Figures **11a,b** for compound **MM11,** Figures **12a,b** for compound **MM12**, and Figure **13** for L2**H** and L2**Ni(II)** reprezent the voltammograms obtained for the respective compounds [124–127].



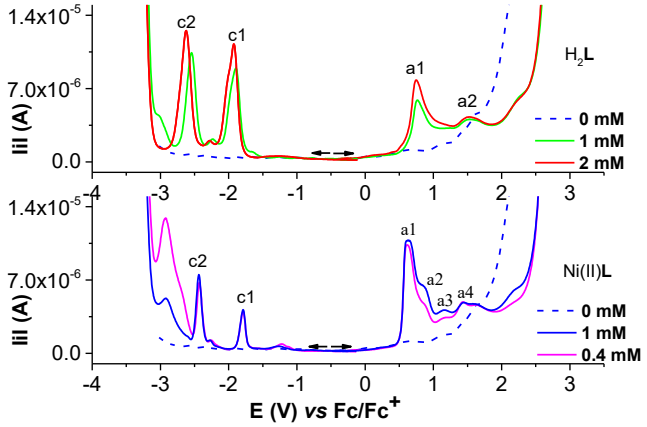
(a) (**b**)

Figure 11. Voltammograms of DPV vs. CV (0.1 V/s) (**a**) and RDE vs. DPV (**b**) curves at different concentrations of **MM11**.



(a) (**b**)

Figure 12. CV (0.1 V/s) vs. DPV (**a**) and DPV vs. RDE (**b**) curves at different concentrations of **4b** and variable electrode rotation rates



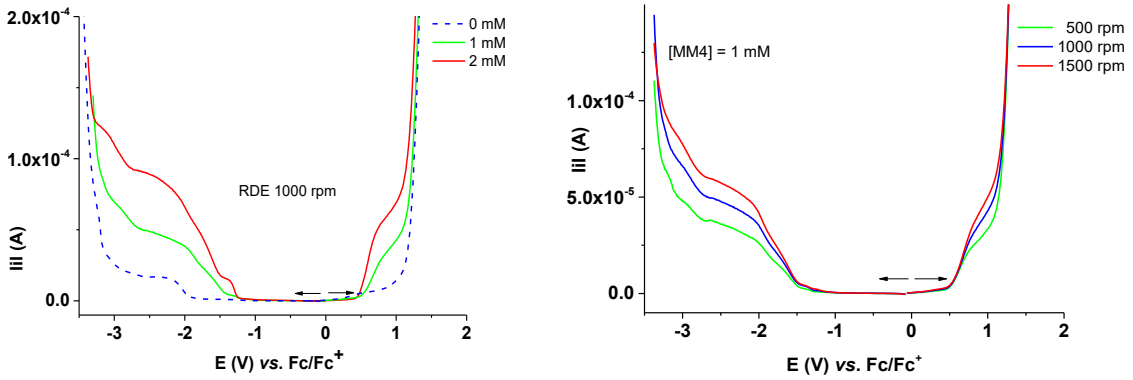
Figures. 13. Anodic and cathodic DPV curves (0.01 V/s) on GC of H2**L** and Ni(II)**L** at different concentrations (mM) in TBAP (0.1 M)/ CH_3CN; cathodic currents are indicated in absolute values.

1.2.3.3. Rotating disk electrode voltammetry investigations (RDE)

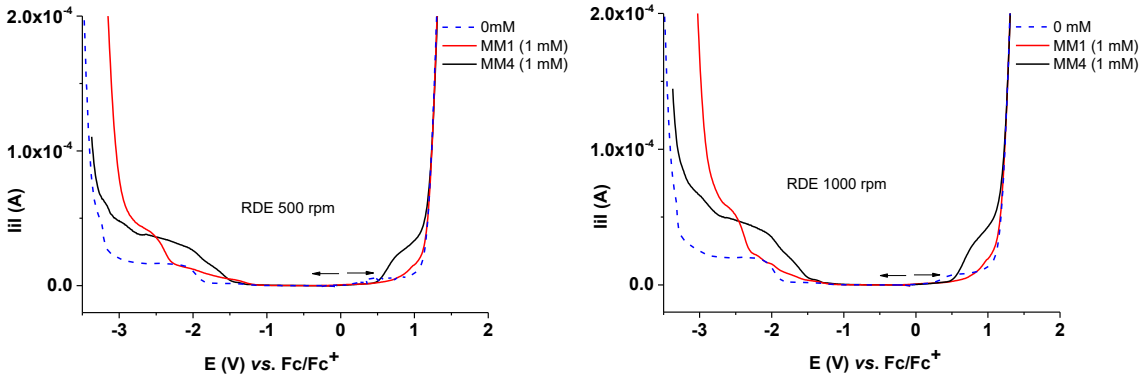
The RDE technique uses a rotated electrode as working electrode in a three-electrode cell for hydrodynamic voltammetry. During experiments the disk electrode rotates and induces a flux of the studied compound to the surface of electrode. Since there is a thin layer that rotates with the disk electrode, the increasing of rotation speed of the electrode conducts to the increasing of the convection of the solution at the disk surface. The diffusion rate of the substrate will be adjusted by controlling the electrode rotation speed [135].

For the characterization of the compounds by RDE, the experiments were performed at a scan rate of 0.01 V/s and at several rotation speeds (500, 1000 and 1500 rpm) using millimolar solutions in CH_3CN + 0.1 M TBAP support electrolyte. The experiments were performed at 25°C temperature under argon atmosphere.

For the characterization of the anodic processes (oxidation) the voltammograms were recorded starting from the origin potential to the extremities, in the positive side. For the characterization of the cathodic processes (reduction) the electrode was polarized in more negative potentiale, the electrode being previous cleaned. In Figures 14a,b,c,d the voltammograms are obtained for **MM1** and **MM4**. The voltammograms for [H2**L**] and [Ni(II)**L**] are given in Figure 15. [124-127].



a b



c d

Figure 14. RDE curves for MM4 at diferent concentrations (a) and rotation rates (b), and comparison between MM1 and MM4 at two rotation rates (c, d) for the same concentration of MM4 (1 mM)

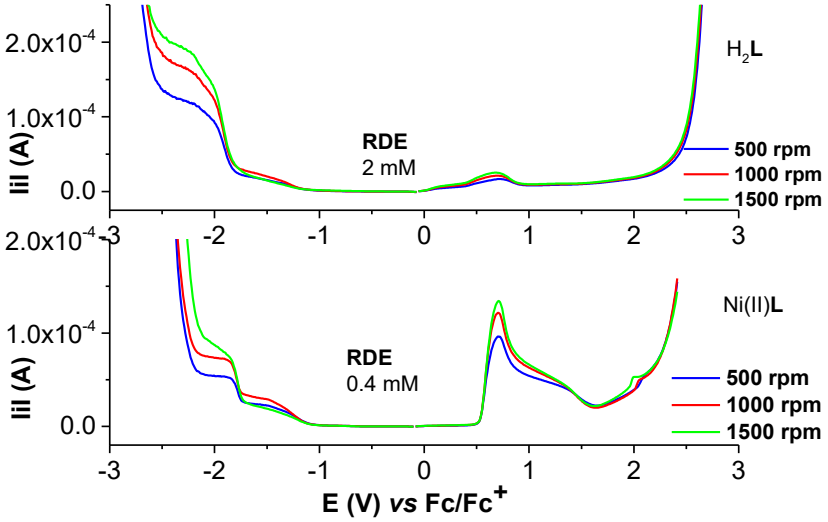


Figure **15**. RDE curves on GC at different rotation speeds (rpm) for [H_2L] = 2 mM and [Ni(II)L] = 0.4 mM in TBAP (0.1 M)/ CH_3CN; the cathodic currents are indicated in absolute values

1.2.4. Optical methods for investigation of tetrahydroacridine derivatives

The optical properties of the ligands were studied by UV-Vis spectroscopy of micromolar solutions of each ligand in acetonitrile. UV-Vis spectrometry studies were performed on a JASCO V-670 spectrometer (Figure **16**a) in quartz cuvettes with an optical path length of 10 mm and a volume of approximately 3.5 mL (Figure **16**b) in freshly dried acetonitrile for [H2**L**] and [Ni(II)**L**] and in DMF for **MM1** and **MM4**. The experimental parameters were established and the experimental data were acquired using the Spectra Manager interface (Figure **16**c).



(a) (b) (c)

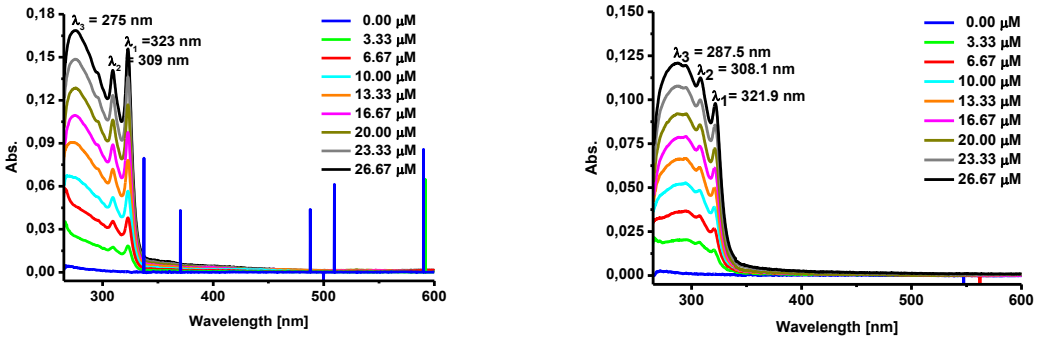
Figure 16 .JASCO V-670 dual-beam spectrometer (a), quartz cuvette with an optical path of 10 mm (b), and the Spectra Manager interface (c) spectra manager to conduct UV-Vis experiments.

1.2.4.1 Characterization of organic ligands properties by UV-Vis spectrometry

For the characterization of the studied compounds the following procedure was followed: into each of the two cuvettes of the spectrophotometer, 3 mL of solvent, respectively CH_3CN or DMF were introduced and the baseline in the range 800-200 nm of wavelengths was recorded. UV-Vis spectrum at 0 ligand concentration was recorded in the range of 800-200 nm, in CH_3CN or DMF in both cuvettes. In on vessel equipped with a magnetic stirrer, 5 µL of 2 mM ligand solution in CH_3CN were added, and the spectrum was recorded after the solution was stirred for 1 minute.

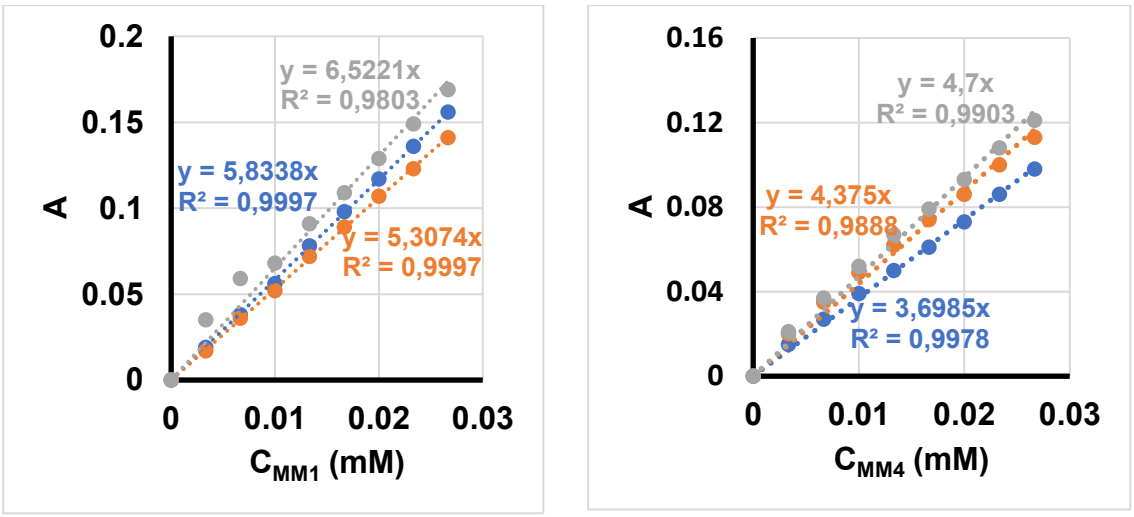
After adding another 5 µL of 2 mM ligand in the existed solution in the cuvette, this solution was stirred for another one minute and the spectrum was recorded. The procedure was repeated after each addition, up to a total amount of 25 µL of 2 mM ligand solution in the working tank (Figure 16b).

The absorption picks were identified and the calibration curves were obtained for each resulting solution as it is represented in Figures 17a,b and 18a,b, The UV-Vis specta data are figured in chapter 2.1 for MM1 and MM4 in the reference [125]; in chapter 2.2. for H2**L** and Ni(II)**L** in the reference [127], respectively.



a b

Figure 17. UV-Vis spectra in DMF for MM1 (a) and MM4 (b) at different concentrations [125]



a b

Figure 18. Absorbance dependencies upon concentration of MM1 (a) and MM4 (b) in DMF at the main peak wavelengths [125]

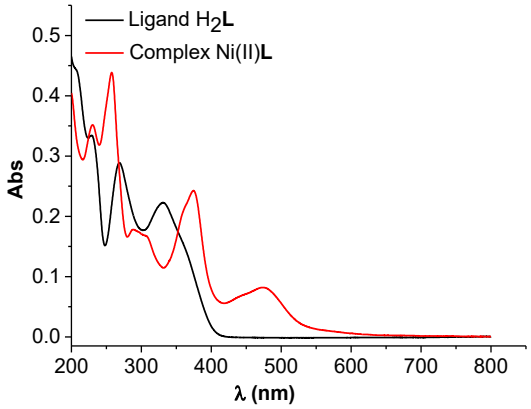
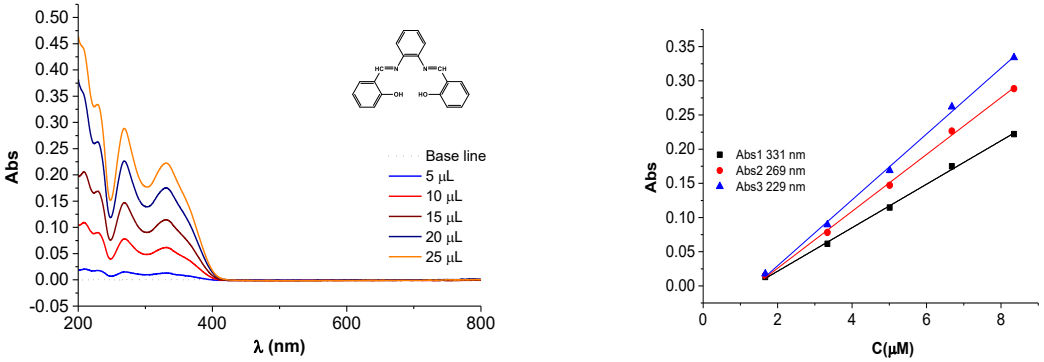
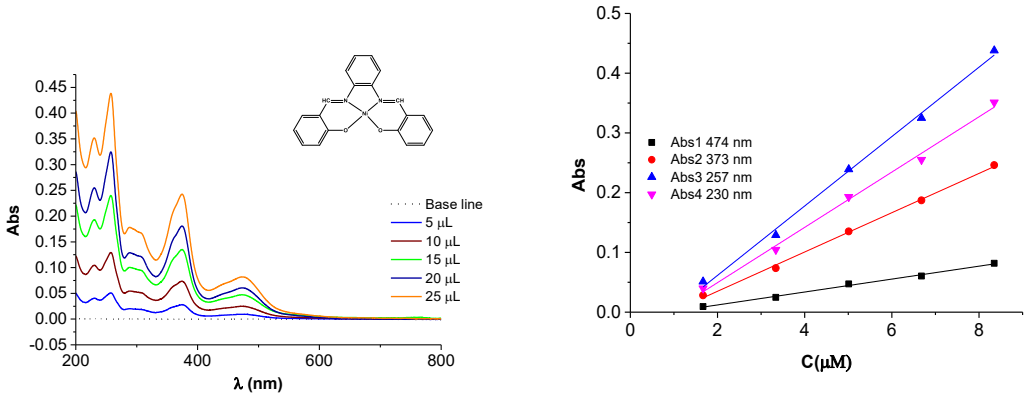


Figure 19. UV-Vis spectra of H2**L** (2 mM) and complex Ni(II)**L** (1 mM) in acetonitrile.



(**a**) (**b**)

Figure 20. (**a**) UV-Vis spectra of the H_2**L** in acetonitrile for different amounts of solution (2 mM) in acetonitrile; (**b**) calibration curves at different wavelengths [127].



(**a**) (**b**)

Figure 21 (**a**) UV-Vis spectra of the Ni(II)**L** in acetonitrile for different amounts of solution (1 mM) in acetonitrile; (**b**) calibration curves at different wavelengths [127].

1.3. DFT CALCULATION METHODS FOR INVESTIGATION OF TETRAHYDROACRIDINES

To calculate the structural parameters and properties of a molecule, density functional theory (DFT) calculation methods were applied. This has led to the development of a wide variety of different procedures or models, divided into two categories: quantum chemistry models and molecular mechanics models. Quantum chemistry models are derived from the Schrödinger equation, which treats molecules as collections of nuclei and electrons, without any reference to "chemical bonds"[136]. The Schrödinger equation are solved only for only for a single-electron system (the hydrogen atom), and for other atoms approximations must be made. Obviously Quantum models differ in the nature of these approximations.

1.3.1. Principles and algorithms in DFT calculation

Density functional theory (DFT) is a computational quantum mechanical modeling method widely applied in physics, chemistry, and materials science to investigate the electronic structure of atoms, molecules, and condensed phases. In this study, the properties of the proposed compounds were calculated using Spartan'18 software (Wavefunction, Inc., Irvine, USA). The calculations employed DFT and the hybrid functional B3LYP [137] with the 6-31G (d, p) polarization basis set [138], for structures optimized at equilibrium geometry in the ground state or in different media (polar or non-polar solvents).

The computation protocol includes the following steps:

a) Construction of the structure of the investigated compounds.

b) Obtention of the lower energy conformer of the above-generated structure by energy minimization and geometry optimization, using Merck molecular force field (MMFF).

c) Set up the algorithm and basis set for properties computations

d) Perform property calculation, data collection, and data analysis.

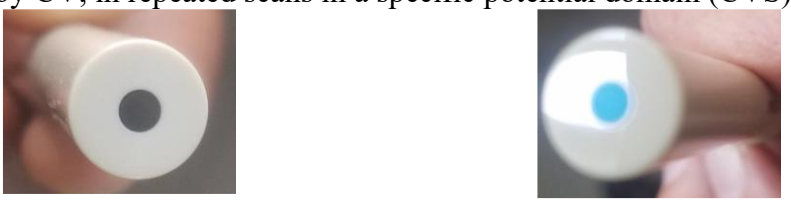
1.3.2 Examples of properties calculated using DFT

The predictions based on the electronic structure theory for the newly synthesized compounds were completed using the density functional theory (DFT) method. The

geometric optimization of the structure was performed based on model structures, the results being used for subsequent geometric optimization. The frontier molecular orbitals FMO, HOMO - the highest occupied molecular orbital and LUMO - the lowest unoccupied molecular orbital were investigated energetically to estimate the stability/reactivity of the studied compounds [92]. Then the isosurface maps of all FMOs were drawn. The quantum reactivity parameters were calculated: chemical potential (μ), ionization potential (I), electron affinity (A), electronegativity (χ), hardness (η), softness (σ) [126]. The energy gap value (Eg) was obtained as the difference between the HOMO and LUMO energy levels from the analysis of the FMO orbitals. The results are shown in reference [126] for 4a and 4b respectively. A high value of Eg indicates higher stability and lower reactivity, while a low value of Eg indicates higher reactivity and lower stability [93, 94].

1.4. PREPARATION OF CHEMICALLY MODIFIED ELECTRODES (CMEs) BASED ON Ni(II)-SALOPHEN

Chemically modified electrodes (CMEs) are conducting or semiconducting materials coated on electrode surfaces in monomolecular, multimolecular, ionic or polymeric films. These films change the interface properties [138]. The films could be colored, as in case of using Salophen ligand, where they have blue color (Figure 16). CMEs were prepared within PESO Laboratory on a glassy carbon electrode (GC) by electropolymerization of Ni(II)-Salophen ligand. The electropolymerization was achieved either by controlled potential electrolysis (CPE) or by CV, in repeated scans in a specific potential domain (CVS).



a b

Figure 22. GC electrode (3 mm in diameter) before (a) and after (b) deposition of poly Ni(II)-Salophen

1.4.1. Preparations of CMEs based on Ni(II)-Salophen by CV scanning (CVS)

The electrochemical behaviour of millimolar solutions of the Ni(II)-L complex with film formation in the presence of 0.1 M TBAP/CH_3CN was studied by cyclic voltammetry (CV). All potential is referenced against the couple ferrocenium/ferrocene, used as an internal standard. The corresponding chronoamperograms are shown in Figures 10, 12, 14 and 18. The modified electrodes obtained by CPE, transferred into the ferrocene solution, have the CV curves represented in the Figures 11, 13, 15 and 17.

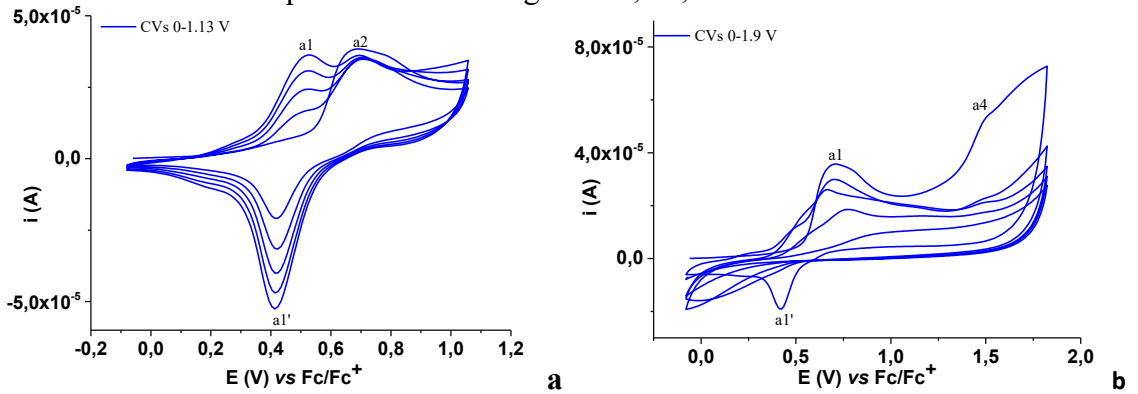


Figure 23. CVs of complex Ni(II)-L (0.4 mM) in TBAP/CH_3CN at 1.13 V (a) and (1mM) in TBAP/CH_3CN at 1.9 V(b).

The CV curves (5 cycles) of the electropolymerisation process of the Ni(II)-L complex (Figure 19) display two successive reversible redox waves at 0.887 V and 0.633 V, which can be attributed to the Ni(II)/Ni(III) redox couple [**139**]. The results of this electropolymerisation process are blue coloured films on the electrode surfaces [**140**]. The electrodes thus obtained proved to be electroactive in the carrier (TBAP/CH_3CN) and ferrocene electrolyte solutions.

1.4.2. Preparations of CMEs based on Ni(II)-salophen by controlled potential electrolysis (CPE)

The preparation of CMEs by electrolysis at controlled potential (CPE) was carried out at different electrodeposition potentials on the vitreous carbon electrode (GC) with a diameter of 3 mm using a solution of 2 mM of each ligand in CH_3CN + 0.1 M TBAP.

For the immobilization of Ni(II)-salophen on the GC surface by CPE, millimolar solutions of it in CH_3CN + 0.1 M TBAP at different charges and different potentials were used, as in the following Figures. Electrodeposition was performed on a vitreous carbon (GC) electrode with a diameter of 3 mm.

After performing the 0.9 V amperometry, the CPE-complex becomes an efficient electrode for the oxidation of Ni(II)/Ni(III) according to the literature [**141**], the increase in the efficiency of the CPE-complex of Ni(II)/Ni(III) oxidation can be attributed to the formation of a blue-coloured solid on the surface of the electrode.

Amperometry (0.9 V, 0.5 mC, 1 mC and 1.5 mC) for a fresh carbon paste electrode reveals an increase in activity for each potential (Figures. 10, 12, 14 and 18), a CPE-complex shows an increase in potential attributed to redox couple of Ni(II)/Ni(III). Thus, current increases are observed when transferred into the ferrocene solution (Figures. 11, 13, 15 and 17).

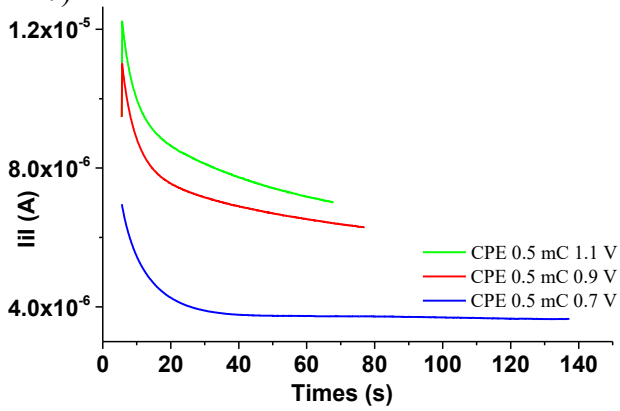


Figure 24. Chronoamperograms during the preparation of Ni(II)-L-CMEs in 0.4 mM solution of Ni(II)-L in 0.1 M TBAP/CH_3CN, by CPE at different potentials.

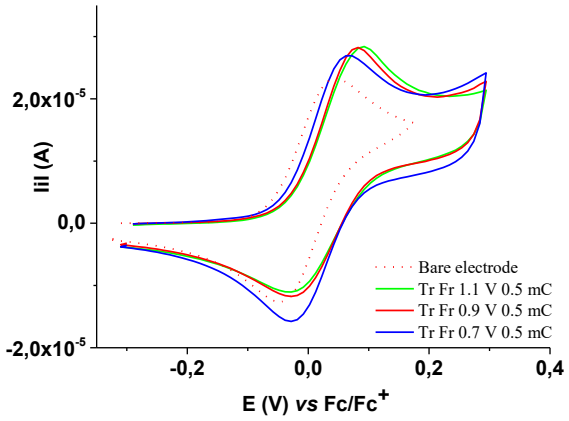


Figure 25. CV curves (0.1 V/s) after the transfer of Ni(II)-L-CMEs in ferrocene solution (1 mM) in 0.1 M TBAP/CH_3CN vs. bare electrode.

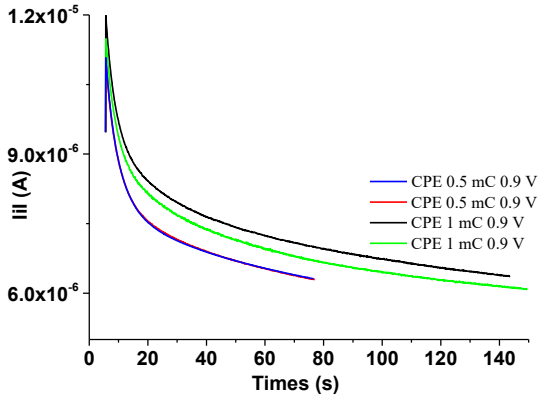


Figure 26. Chronoamperograms during the preparation of Ni(II)-L-CMEs in 0.4 mM solution of Ni(II)-L in 0.1 M TBAP/CH_3CN, by CPE at different charges.

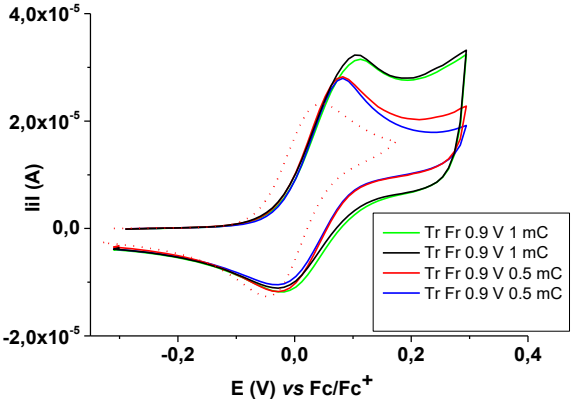


Figure 27. CV curves (0.1 V/s) after the transfer of Ni(II)-L-CMEs in ferrocene solution (1 mM) in 0.1 M TBAP/CH_3CN vs. bare electrode.

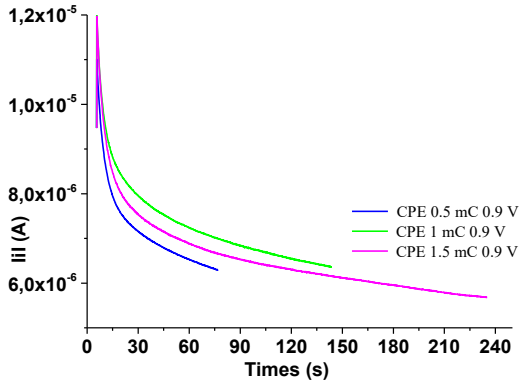


Figure 28. Chronoamperograms during the preparation of Ni(II)-L-CMEs in 0.4 mM solution of Ni(II)-L in 0.1 M TBAP/CH_3CN, by CPE at different charges.

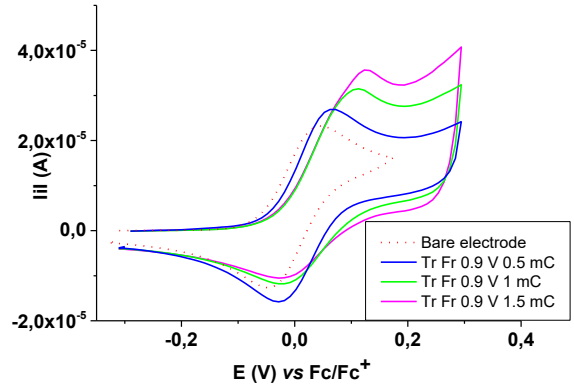


Figure 29. CV curves (0.1 V/s) after the transfer of Ni(II)-L-CMEs in ferrocene solution (1 mM) in 0.1 M TBAP/CH_3CN vs. bare electrode

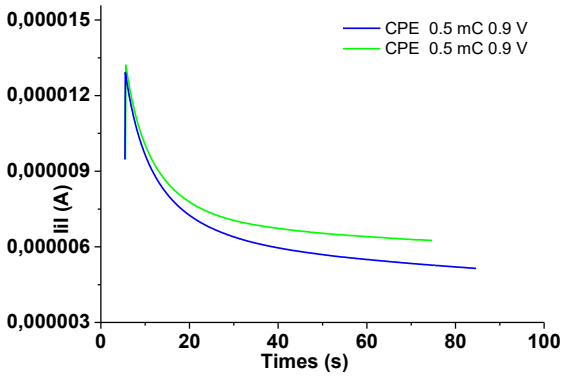


Figure 30. Chronoamperograms during the preparation of Ni(II)-L-CMEs in 0.4 mM solution of Ni(II)-L in 0.1 M TBAP/CH_3CN, by CPE at 0.5 mC.

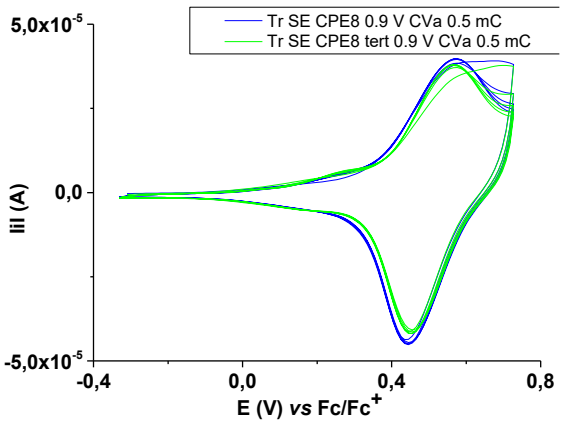


Figure 31. CV curves (0.1 V/s) after the transfer of Ni(II)-L-CMEs in supporting electrolyte 0.1 M TBAP/CH_3CN

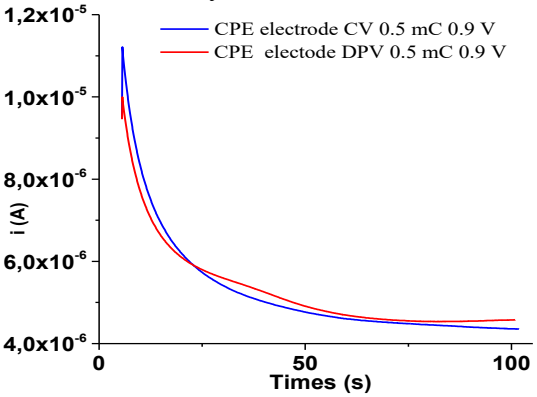


Figure 33. Chronoamperograms during the preparation of Ni(II)-L-CMEs in 0.11 mM solution of Ni(II)-L in 0.1 M TBAP/CH_3CN, by CPE at 0.5 mC

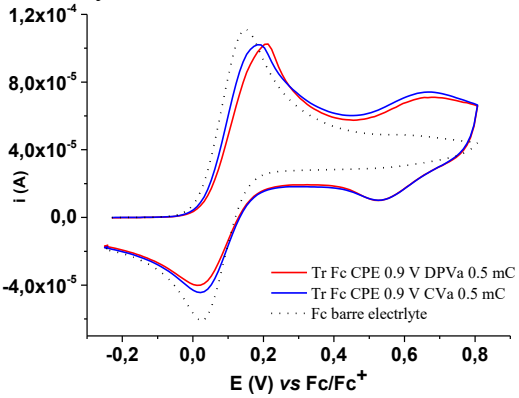


Figure 32. CV curves (0.1 V/s) after the transfer of Ni(II)-L-CMEs in ferrocene solution (1 mM) in 0.1 M TBAP/CH_3CN bare electrode

Table 8. Potential (E) and current (i) of the peaks in anodic (a1-a4) and cathodic (c1-c2) scans in CV experiments for Ni(II)-L (0.4 mM in 0.1 M TBAP/ACN) for Figure.27 for the 2 peaks obtained in Fc transfer.

Electrode	Ea (V)	Ec (V)	Ia (A)	Ic (A)	Ef=(Ea+Ec)/2 (V)	ΔE=Ea-Ec (V)
El nue	0.151	0.026	$1.107\ 10^{-4}$	$-6.1\ 10^{-5}$	0.0885	0.125
CME1(blue)	0.188	0.022	$1.029\ 10^{-4}$	$-4.435\ 10^{-5}$	0.1050	0.166
CME2(rouge)	0.209	0.0149	$1.026\ 10^{-4}$	$-4.019\ 10^{-5}$	0.1120	0.194
CME1 P2a	0.668	0.527	$7.4\ 10^{-5}$	$0.22\ 10^{-5}$	0.5975	0.141
CME2 P2c	0.674	0.527	$7.102\ 10^{-5}$	$0.22\ 10^{-5}$	0.6005	0.147
Figure 29 (Blue)	0.655	0.530	$3.98\ 10^{-5}$	$-4.18\ 10^{-5}$	0.5925	0.125
Figure 29 (red)	0.655	0.530	$3.98\ 10^{-5}$	$-4.18\ 10^{-5}$	0.5925	O.125

1.5. CHARACTERIZATION OF CMs BASED ON Ni(II)-Salophen

The characterization of the obtained CMEs was done by studying their interaction with solutions of known concentration of ferrocene in CH_3CN + 0.1 M TBAP or with the supporting electrolyte (CH_3CN + 0.1 M TBAP).

1.5.1. Characterization of CMEs based on Ni(II)-Salophen by redox probe

To make the redox probe, a system of two cells with three electrodes is used, as described in chapter 1.2. In one of the cells there is a solution of known concentration of Ni(II)-Salophen in CH_3CN + 0.1 M TBAP, and in the other a solution of ferrocene in CH_3CN + 0.1 M TBAP. CMEs obtained as described in chapter 1.4. were washed with acetonitrile. After that they were transferred to the cell with ferrocene solution in CH_3CN + 0.1 M TBAP of known concentration. The recorded voltammogram was compared with that of GC.

1.6. ELECTROCHEMICAL INVESTIGATION ON 1,2,3,4-TETRAHYDROACRIDINE-9-CARBOXAMIDE IN DIFFERENT ORGANIC SOLVENTS

The electrochemical investigations of 1,2,3,4-tetrahydroacridine-9-carboxamide (MM1) were carried out in two organic solvents, acetonitrile and dimethylformamide, using three methods: CV, DPV and RDE provided the basis for understanding the electrochemical properties of other tetrahydroacridines. And the study in mixture of these solvents could be the solution to see clearly peaks attributed to electroactive compound in the anodic domain, to avoid overlap with the solvent processes [124].

1.7. ELECTROCHEMICAL AND OPTICAL INVESTIGATION AND DFT CALCULATION ON TWO TETRAHYDROACRIDINES

New electrochemical and optical studies were carried out on 1,2,3,4-tetrahydroacridine-9-carboxamide and 1,2,3,4-tetrahydroacridine-9-carboxylic acid to understand the influence of the two functional groups grafted in position 9 on the behavior of these tetrahydroacridines. Their CV, DPV and RDE curves were examined and compared to explain the differences due the different substitution of tetrahydroacridine skeleton which can lead further to the design of their corresponding dimers intended for pharmaceutical purposes [125].

CHAPTER 2.
ARTICLES IN EXTENSO PUBLISHED AS SCIENTIFIC RESULTS OF DOCTORAL THESIS

CHAPTER 3.

3.. GENERAL CONCLUSIONS

3333New bis-tetrahydroacridines were synthesized and their structure was confirmed by specific spectral methods and a deep electrochemical study was performed. Fragmentation schemes in mass spectrometry for dimers have been developed.

The two tetrahydroacridines monomers 1,2,3,4-tetrahydroacridine-9-carboxamide (**MM1**), 1,2,3,4-tetrahydroacridine-9-carboxylic (**MM4**) were electrochemically studied in different solvents aimed to the understanding of the influence of the presence of functional groups on the electrochemical behavior of tetrahydroacridines.

The electrochemical experiments were extended to study two new bis-tetrahydroacridines, 7,7′-(ethane-1,2-diyl)bis(2,3dihydro-1H-cyclopenta[b]quinoline-9-carboxylic acid) (**4a**) and 7,7′(ethane-1,2-diyl)bis(1,2,3,4-tetrahydroacridine-9-carboxylic acid) (**4b**) in order to search their anodic and cathodic processes. This study revealed the formation of films with different properties, those from 4a being conducting films, while those from 4b were nonconducting. This last aspect could be connected to their use in anticorrosive protection.

The electrochemical and optical investigations carried out on two functionalized tetrahydroacridines at the position 9 of the skeleton with carboxyl and carboxamide groups allowed to put in evidence the effect of these functional groups on the properties of selected compounds

The electrochemical study was performed by cyclic voltammetry (CV), differential pulse voltammetry (DPV) and rotating disk electrode (RDE) voltammetry in acetonitrile/dimethylformamide in the presence of tetrabutylammonium perchlorate for different concentrations of each target, at different scan rates and electrode rotation rates.

The combination between electrochemical analysis and DFT simulations allowed to fiind the the effect of different structures on the tetrahydroacridine skeleton, which affects the electrochemical behavior.

The characteristics of electrode processes established by CV and DPV were underlined by RDE voltammetry.

The differences observed between the curves recorded in the two solvents (acetonitrile and dimethylformamide) were examined and mechanisms of electrochemical reduction and oxidation were proposed. The diffusion coefficients for **MM1** and **MM4** were calculated using Randles-Sevcik equation.

The results of electrochemical studies on **MM1** and **MM4** enlarge the known properties of these compounds and provide the basis for understanding the electrochemical properties of other tetrahydroacridines.

The UV-Vis study of these compounds allowed the evaluation of their optical properties in different solvents.

The DFT calculations for the two tetrahydroacridines revealed that the ionization potential and electronic affinity of the acid compounds are higher than those for carboxamide derivatives, together with the value of the HOMO-LUMO gap (ΔE). Carboxamide derivatives have lower electrostatic potential on heteroatoms regions, but overall, slight difference in reactivity, compared to acid derivatives.

Even if their structure is quite similar, research and calculations made possible to highlight different properties that can be used in the development of new drugs and corrosion inhibitors.

Complex characterization of **Salophen** ligand-**L** and its Ni(II) complex – **Ni(II)-salophen** (Ni(II)**L** - by UV-Vis and electrochemical methods, CV, DPV and RDE showed that this compound has the potential to build chemically modified electrodes (CMEs) based on this ligand for HMs analysis.

H_2**L** and Ni(II)**L** synthesized and confirmed using spectroscopic methods (NMR, FT-IR, UV-Vis, electrospray ionization mass spectroscopy, thermogravimetric analysis, and molar conductance measurements) demonstrated that H_2**L** acts as a tetradentate ligand and coordinates to the central metal through nitrogen and oxygen atoms.

Anodic electropolymerization used to form CMEs blue films on the electrode surfaces in the entire potential range studied either by scanning or controlled potential electrolysis (CPE) in the anodic domain of potential. Good reproducibility in film preparation via CPE was indicated by chronoamperometry.

Tests of antimicrobial and antifungal activity performed against the bacteria and fungi at different concentrations, showed a good activity on several Gram-negative bacteria..

All novelties on the studied compounds will be further exploited and extended to enlarge the field of modified electrodes for biological and anti-corrosion applications.

CHAPTER 4.
4. PERSONAL CONTRIBUTIONS

1. New species of bistetrahydroacridines were synthesized and their structure was confirmed by several spectral methods NMR, IR, UV-Vis, ESI-MS.
2. Fragmentation schemes in mass spectrometry for dimers have been developed.
3. The electrochemical study was performed by cyclic voltammetry, pulse differential voltammetry and rotating disk voltammetry in acetonitrile/dimethylformamide in the presence of tetrabutylammonium perchlorate for different concentrations of each target, at different scan rates and electrode rotation rates. The combination of electrochemical analysis with DFT simulations allowed the systematic investigation of the effect of different structures on the tetrahydroacridine skeleton, which affect the electrochemical behavior.
4. The electrochemical investigation of 1.2.3.4-tetrahydroacridine-9-carboxamide (**MM1**) that was carried out in two organic solvents, acetonitrile (ACN) and dimethylformamide (DMF) in presence of 0.1 M tetrabutylammonium perchlorate put in evidence the reduction and oxidation peaks due to the electrochemical processes occurring during the potential scans.
5. The values of potential and current for the main peaks were obtained using cyclic voltammetry and differential pulse voltammetry, as well as their variations with concentration and scan rate.
6. Rotating disk electrode voltammetry underlined the characteristics of confirmed processes. The differences observed between the curves recorded by the same electrochemical method in the two solvents were examined and mechanisms of electrochemical reduction and oxidation were proposed to explain the processes seen on the experimental curves.
7. The behavior of **MM1** in ACN is like that in DMF in the cathodic domains. In the anodic domains two oxidation peaks are noticed in ACN, and no oxidation peak in DMF. The differences noted for the processes which occur in the anodic regions are due to the narrower potential limit of DMF compared to ACN. Therefore. The study of **MM1** oxidation processes is only possible in ACN. because the potential window of this solvent is wider.
8. The diffusion coefficients for **MM1** calculated using Randles-Sevcik equation. are favorable for ACN compared to DMF. being $4,61.82 \cdot 10^{-5}$ cm^2/s and $0.82 \cdot 10^{-5}$ cm^2/s, respectively.
9. The results of electrochemical studies on **MM1** enlarge the known properties of this compound and provide the basis for understanding the electrochemical properties of other tetrahydroacridines. Mixture of solvents could be the solution to see clearly peaks attributed to electroactive compound in the anodic domain, to avoid overlapping with the solvent processes.
10. The electrochemical and optical investigations carried out on two functionalized tetrahydroacridines at position 9 of the skeleton with carboxyl and carboxamide groups allowed to put in evidence the effect of these functional groups on the properties of selected compounds.
11. The electrochemical study performed by three methods leads to similar conclusions concerning the reactivity of 1,2,3,4-tetrahydroacridine-9-carboxylic acid and 1,2,3,4-tetrahydroacridine-9-carboxamide. The curves recorded by RDE highlighted the differences between them compared with those recorded by CV and DPV. However, the DPV curves let to get the potential values where oxidation and reduction processes occur, being in good agreement with the

potentials found by CV. Each method proved to be compulsory for the electrochemical characterization of these tetrahydroacridines.

12. The UV-Vis study of these compounds allowed the calculation of their extinction coefficients.
13. The DFT calculations for the two tetrahydroacridines revealed that the ionization potential and electronic affinity of the acid are higher than those for carboxamide derivative **MM1**, together with the value of the HOMO-LUMO gap (ΔE). The carboxamide derivative reveals lower electrostatic potential on heteroatoms regions, but overall, slight difference in reactivity, compared to acid derivative **MM4**.
14. .The range of tetrahydroacridines explored so far is extended to their dimers, the synthesis and properties of new tetrahydroacridine dimers:7,7′-(ethane-1,2-diyl)bis(2,3dihydro-1H-cyclopenta[b]quinoline-9-carboxylic acid) (**4a**) and 7,7′(ethane-1,2-diyl)bis(1,2,3,4-tetrahydroacridine-9-carboxylic acid) (**4b**).
15. The synthesized compounds were characterized, and their structure was confirmed by spectral analyses.
16. By DFT calculations, the main reactivity parameters were established and proved that compound **4a** is more reactive than **4b**. Compound **4a** has the lowest Eg value of 4.18 eV compared to compound **4b** which has a higher Eg value of 4.38 eV. This indicates that compound **4a** is less stable and more reactive than compound **4b**.
17. The electrochemical study allowed the evaluation of the potential at which oxidation or reduction processes take place for both compounds. In the case of compound **4a**, two non-diffusive anodic processes were highlighted, which can be attributed to the formation of film on the surface of the electrode, while at cathodic scanning reversible processes occur.
18. In the case of compound **4b,** the three anode processes are diffusive like the first cathodic process.
19. The comparison between **4a** and **4b** shows that **4a** is more reactive to film formation, and it can be used in such applications.
20. In the case of **4b**, the reduction processes could lead to the formation of non-conductive films. All these films will be examined further for protection against corrosion.
21. Even if their structure is quite similar, research and calculations have made it possible to highlight different properties that can be used in specific applications, such as the development of new drugs and corrosion inhibitors.
22. The detailed examination of the curves obtained by different electrochemical investigation methods brought complementary information and allowed the establishment of the potentials of some processes with possible applications of interest: the formation of films with conductive characteristics (at 0.3V potential for compound **4a**) or insulating (at 0.6V for compound **4a**). Compound **4b** can form non-conductive films at quite negative potentials (around −2.5V).
23. A deep exploration of the free Schiff base N,N'-Bis-(2-hydroxybenzylidene)-benzene-1,2-diamine (H_2**L**) and its Ni(II) complex (Ni(II)**L**,was performed in order to find broader applications not yet explored.
24. Complex characterization of **Salophen** ligand-**L** and its Ni(II) complex – **Ni(II)-salophen** (Ni(II)**L** - by UV-Vis and electrochemical methods, cyclic voltammetry (CV), differential pulse voltammetry (DPV) and rotating disk electrode voltammetry (RDE) was performed.

25. Investigation of **Ni(II)-salophen** by electrochemical (CV, DPV, RDE) and UV-Vis methods showed that this compound has the potential to construct electrochemical sensors for HMs analysis using chemically modified electrodes (CME) based on this ligand. Anode potentials around 1.4 V were found to be favorable for film deposition, as the processes occurring at this potential were found to be irreversible.
26. H_2**L** and Ni(II)**L** were synthesized and confirmed using spectroscopic methods (NMR, FT-IR, UV-Vis, electrospray ionization mass spectroscopy, thermogravimetric analysis, and molar conductance measurements). These analises demonstrated that H_2**L** acts as a tetradentate ligand and coordinates to the central metal through nitrogen and oxygen atoms.
27. For the electrochemical behavior of H_2**L** and Ni(II)**L** investigations in anodic and cathodic scan domains were done using DPV, CV, and RDE techniques to find new details for future applications. Ni(II)**L** exhibited an irreversible electron transfer and redox-diffusion-controlled processes in the anodic scans.
28. Anodic electropolymerization was used to form chemically modified electrodes (CMEs). The results of these electropolymerization processes were blue films on the electrode surfaces in the entire potential range studied. They were obtained either by scanning the potential in the anodic domain, or via controlled potential electrolysis (CPE).
29. The chronoamperometry indicated good reproducibility in film preparation via CPE. The CMEs' electrochemical tests showed excellent stability and an increase in current intensities after the transfer in ferrocene solutions.
30. H_2**L** and Ni(II)**L** were tested for their antimicrobial activity against the bacteria and fungi at different concentrations, showing good activities on several Gram-negative bacteria and also an antifungal effect.
31. All novelties on the studied compounds will be further exploited and extended to enlarge the field of modified electrodes for biological and corrosion applications.

CHAPTER 5.

5. DISSEMINATION OF RESULTS

5.1. PUBLISHED ARTICLES

(A) List of published articles of major interest for the PhD thesis

A1.F.A. Ngounoue Kamga, M.M. Hrubaru, O. Enache, E. Diacu, C. Draghici, E.-M. Ungureanu, Ni (II)-Salophen—Comprehensive Analysis on Electrochemical and Spectral Characterization and Biological Studies, Molecules, 2023, 28 (14), 5464.

A2.M.-M. Hrubaru, C. Draghici, F. A. Ngounoue Kamga, E. Diacu, C. E.ThankGod, A. C. Ekennia, , E.-M. Ungureanu ,Experiments and Calculation on New N,N-*bis*-Tetrahydroacridines, *Molecules* **2024**,*29*(17), 4082;doi.org/10.3390/molecules29174082.

A3.M.-M. Hrubaru, F. A. Ngounoue Kamga, N. Murat, A. Stefaniu, E.-M. Ungureanu, E. Diacu, Electrochemical and optical investigation and dft calculation on two tetrahydroacridines, U.P.B. Sci. Bull., Series B, Vol. 86, Iss. 2, 2024.

A4. F. A. Ngounoue Kamga, M.-M. Hrubaru, N. Murat, C. Draghici, M.-R. Bujduveanu, E.-M. Ungureanu, E. Diacu, Electrochemical investigation on 1,2,3,4-tetrahydroacridine-9-carboxamide in different organic solvents, U.P.B. Sci. Bull., Series B, Vol. 86, Iss. 1, 2024. ISSN 1454-2331.

5.2. PARTICIPATION IN INTERNATIONAL CONFERENCES

C1. M.-M. Hrubaru, M. R. Bujduveanu, E.-M. Ungureanu, C. Draghici, E. Bartha, E. DIACU, *Studies on tetrahydroacridines to investigate possible application in Alzheimer disease treatment,* Symmetry 2023 - The 4th International Conference on Symmetry, Barcelona.

C2. 1. M.-M. Hrubaru, A. Vasile (Corbei), A. Stefaniu, E.-M. Ungureanu, *Density functional, theory-based electrochemical models for tetrahydroacridines*, International *Conference CHIMIA 2024* "NEW TRENDS. IN APPLIED CHEMISTRY", Oral presentation , May 30th - June 1st,*2024,* Constanta. Oral presentation.

C3. N. Murat, A.-G. Brotea, M.-M. Hrubaru, E.-M. Ungureanu, *Chemically modified electrodes based on azulen-1-yl-2-phenyloxazol-5(4H)-one for heavy metal analysis*, Poster, Romanian International Conference on Chemistry and Chemical Engineering, RICCCE 23, Mamaia, 4 - 7 September, 2024.

C4. M.-F. Ticulescu, A. Burlacioc, M.-M. Hrubaru, F. Aurelien Ngounoue Kamga, E. Diacu, E.-M. Ungureanu, *Chemicaly modified electrodes based on several azulenyl-phenyloxazolone for Cu(II) analysis* , International *Conference CHIMIA 2024*"New trends. in applied chemistry", May 30th- June 1st, *2024,* Constanta.

C5. F. A. Ngounoue Kamga, M.-M. Hrubaru, O. Enache, E. Diacu, C. Draghici, V. Tecuceanu, E.-M. Ungureanu, S. Nkemone, P. Teke Ndifon, *Electrochemical study of nickel(II) complex with N2O2 Schiff base derived from N,N'-bis-(2-hydroxybenzylidene)-benzene-1,2-diamine*, Poster, 74th Annual Meeting of the International Society of Electrochemistry, 3 - 8 september 2023, Lyon, France.

C6. M.-M. Hrubaru, L. Mărunțescu, L. Pintilie, A. Stefaniu, C. D. Badiceanu, C. Draghici, E.-M. Ungureanu, *Electrochemical and biological studies of bis tetrahydroacridine derivatives,* poster, 9th, Regional Symposium on Electrochemistry - South-East Europe, Novi Sad, Serbia, June 3-7, 2024.

C7. M.-M. Hrubaru, C. Draghici, F. A. Ngounoue Kamga, R. Isopescu, E. Diacu, C. E.ThankGod, H. Louis, A. C. Ekennia, A. Stefaniu, E.-M. Ungureanu, *Experiments and calculation on new n,n-bis-tetrahydroacridines*, Oral presentation, 9th Regional Symposium on Electrochemistry - South-East Europe, Novi Sad, Serbia, June 3-7, 2024.

C8**.** M.-M. Hrubaru, A. Stefaniu, A. Vasile, F. A. Ngounoué Kamga, E.-M. Ungureanu, E. Diacu, *Electrochemistry and DFT calculation on tetrahydroacridines*, Oral presentation, Symposium S12 - Molecular Platforms and Electrochemistry for a Sustainable Society of the 75th Annual Meeting of the International Society of Electrochemistry in Montreal; August 2024.

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