Voltammetric oxidation of Hantzsch 1,4-dihydropyridines in protic media: substituent effect on positions 3,4,5 of the heterocyclic ring

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Abstract

A detailed study was done of the electrochemical oxidation of some 1,4-dihydropyridine (1,4-DHP) derivatives in order to determine the influence of the substituents in the heterocyclic ring. Two types of derivatives were synthesized, namely, 3,5-(substituted)-4-(5′-nitro-2′-furyl)-1,4-DHP for series A, and 3,5-dicarboethoxy-4-(substituted or non-substituted)-1,4-DHP for series B. Voltammetry, coulometry, controlled potential electrolysis, UV–vis spectroscopy and GC–MS techniques were employed to collect data that permitted to postulate oxidation mechanisms in a protic medium. In acid media, at pH < 4, all derivatives follow oxidation mechanisms obeying the ECE sequence. However, at pH > 4, series A derivatives follow an ECEC sequence, while series B derivatives obey a DISP1 mechanism. In both cases, the uptake of proton at N-1 by the OH^- ion of the media was the rate-determining step.

Keywords: 1,4-Dihydropyridines; Oxidation; Voltammetric

1. Introduction

The 4-aryl-substituted 1,4-dihydropyridines (1,4-DHP), analogues of NADH coenzymes have received most attention because of their relevant applications in various cardiovascular diseases [1–3]. In addition, recently preceding studies have suggested [4–9] that 1,4-DHP derivatives also provide an antioxidant protective effect that may contribute to their pharmacological activity. This effect is not due to the Ca^{2+} antagonist effect, but is related to the reactivity of these compounds towards radical species [5]. On the other hand, the oxidation of the dihydropyridine ring is the main metabolic route for these compounds.

Although 1,4-DHPs vary markedly in their chemical structure and their antihypertensive effect, the basic features of the pharmacological activity of 1,4-DHPs are both the secondary nature of the nitrogen in the dihydropyridine ring and the presence of ring substituents, including aromatic substituents at position 4, which seem to play an important role. The analysis of different aromatic substituents at position 4 indicated that the optimal structural features generate the most favorable conformation for binding site, where the aromatic ring is almost perpendicular to the 1,4-DHP ring [10].

Investigations on 1,4-DHP electrochemical oxidation have been previously performed in both aprotic and protic media, however, the more detailed mechanistic information has been obtained in aprotic media [8,11–15]. These investigations were generally done by using mainly rotating ring disk electrode (RRDE), linear and cyclic voltammetry and ESR spectroscopy, and have revealed that, in non-aqueous solutions, 1,4-dihydropyridine derivatives are oxidized in a two electron reaction, in particular, in an ECE mechanism. On the other hand, investigations in protic media are rather scarce, but in the last years some evidences have contributed to shed light on this mechanism. Rodriguez Mellado and coworkers [16,17] studied the oxidation of diethyl 1,4-dihydro-2,4,6-trimethyl-3,5-piridinedicarboxylate and 1,4-dihydro-2,6-dimethyl-3,5-piridinedicarboxylate and reported that the mechanism differs depending on the acid or basic character of the medium used. Those authors have

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demonstrated that, in a basic medium, the mechanism consisted of a DISP1 scheme in which the rate determining step was the uptake of a proton by either the OH^- ion or the basic components of the buffer. Recently, in a previous report [18], we found that H-substituent at position N-1 of 1,4-DHP derivatives affects considerably the electrochemical behavior. In fact, derivatives having an ethyl group instead of the H-substituent follow the same mechanism in protic (pH independent mechanism) or aprotic media. However, derivatives bearing H-substituent follow a different mechanism depending on whether acid, basic or aprotic media are involved. Derivatives having ethyl substituent at position N-1 follow an oxidation mechanism obeying the ECE sequence. On the other hand, derivatives with H at position N-1 follow the same ECE sequence only in acid media. In basic media, the mechanism consisted of a DISP1 scheme where the rate-determining step was the uptake of the proton at position N-1 by the OH^- ion present in the electrolytic solution.

In the process of finding new 1,4-DHP derivatives with new or improved pharmacological activities we explored different structural changes inserting a five-membered heterocyclic nucleus at C-4 instead of the traditional aromatic substituent. We also synthesized new derivatives changing the ester groups at C-3 and C-5.

Considering that the state-of-the-art in electrochemical oxidation of 1,4-DHP derivatives revealed the importance of some substituents, mainly at N-1 and C-4 [18,19], the aim of this work was to contribute to the study of the electrochemical oxidation mechanism of 1,4-DHP derivatives in protic media in order to establish how the different substituents at C-3, C-4 and C-5 affect the oxidation mechanism.

2. Experimental

2.1. Compounds

All compounds (Fig. 1) were synthesized in our laboratory. General procedure: 10 mmol enamine (ethyl 3-aminocrotonate and/or 3-aminocrotononitrile) and 5 mmol aldehyde (5-nitro-2-furaldehyde, formaldehyde, acetaldehyde, 3-nitrobenzaldehyde) were dissolved in glacial acetic acid (30 ml). Water was added until precipitation of the dihydropyridine occurred. The crude solid product was filtered off and washed with ether. The compounds were recrystallized twice from absolute ethanol. Compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy using a 300 MHz spectrometer (Bruker, WM 300), infrared spectroscopy (FT-IR Paragon Spectrometer, 100PC) and an elemental analysis (Perkin-Elmer, 240 B).

2.1.1. Ethyl 4-(5′-nitro-2′-furyl)-2,6-dimethyl-1, 4-dihydropyridine-3,5-dicarboxylate (**I**)

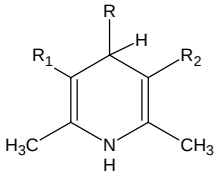
IR (KBr): ν_{max} 3346.7, 1704.3, 1656.0, 1517, 1487.9, 1400, 1355.0, 1211.9, 1114.4. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (dd, 6H, J = 7.1, J = 7.1); 2.36 (s, 6 H); 4.15 (dq, 2H, J = 10.9, J = 7.1); 4.21 (dq, 2H, J = 10.9, J = 7.1); 5.27 (s, 1H); 6.19 (brs, 1H); 6.26 (d, 1H, J = 3.4), 7.21 (d, 1H, J = 3.4). ^{13}C NMR (75 MHz, $CDCl_3$): 166.8 (C2), 162.7 (C2), 146.4 (C2), 113.2, 108.9, 99.0 (C2), 60.2 (C2), 34.6, 19.6 (C2), 14.3 (C2) ppm. Anal. Calc. for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found: C, 55.85; H, 5.54; N, 7.72.

2.1.2. Ethyl 3-cyano-4-(5′-nitro-2′-furyl)-2,6-dimethyl 1, 4-dihydropyridine-5-dicarboxylate (**II**)

IR (KBr): ν_{max} 3317.9, 2199.4, 1664.3, 1638.5, 1527.1, 1493.1, 1383.0, 1355.5, 1257.0, 1115.7. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (dd, 3H, J = 7.1, J =7.2); 2.18 (s, 3H); 2.38 (s, 3H); 4.12 (dq, 1H, J_3 = 10.9, J = 7.1); 4.16 (dq, 1H, J = 10.9, J = 7.2); 4.90 (s, 1H); 6.04 (brs, 1H); 6.38 (d, 1H, J = 3.7), 7.24 (d, 1H, J = 3.7). ^{13}C NMR (75 MHz, $CDCl_3$): 166.2, 160.0 (C2), 147.6, 146.3, 118.6, 113.0, 109.5, 97.6, 81.8, 60.5, 35.9, 19.7, 18.5, 14.2 ppm. Anal. Calc. for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.76; N, 13.24. Found: C, 56.56; H, 4.77; N, 13.19.

2.1.3. 3,5-Dicyano-4-(2′-furyl-5′-nitro)-2,6-dimethyl-1, 4-dihydropyridine (**III**)

IR (KBr): ν_{max} 3369.2, 2205.9, 1665.8, 1536.3, 1505.1, 1393.1, 1358.8. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.07 (s, 6



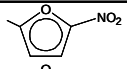
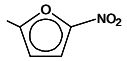
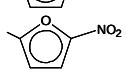
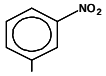
	Compounds	R1	R2	R	Ep /mV (p H 3.0)	Ep/mV (pH 10.6)
A	**I**	-CO_2Et	-CO_2Et		932	536
A	**II**	-CN	-CO_2Et		956	484
A	**III**	-CN	-CN		988	436
B	**IV**	-CO_2Et	-CO_2Et	-H	404	214
B	**V**	-CO_2Et	-CO_2Et	-CH_3	804	440
B	**VI**	-CO_2Et	-CO_2Et		908	520

Fig. 1. Chemical structures of synthesized 1,4-DHPs with their corresponding peak potential values.

H); 4.92 (s, 1H); 9.81 (brs, 1H); 6.82 (d, 1H, $J = 3.8$), 7.70 (d, 1H, $J = 3.8$). ^{13}C NMR (75 MHz, DMSO-d_6): 159.7 (C2), 158.0 (2), 121.8 (C2), 114.9, 111.9, 73.8 (C2), 33.9, 20.8 (C2) ppm. Anal. Calc. for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73. Found: C, 57.75; H, 3.73; N, 20.65.

*2.1.4. Ethyl 2,6-dimethyl-1,4-dihydropyridine-3, 5-dicarboxylate (***IV***)*

IR (KBr): ν_{max} 3350.3, 1693.1, 1651.6, 1212.0, 1116.5. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19 (t, 6H, $J = 7.1$); 2.19 (s, 6 H); 4.17 (q, 4H, $J = 7.1$); 3.27 (s, 2H); 5.17 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 168.0 (C2), 144.7 (C2), 99.6 (C2), 59.7 (C2), 24.8, 19.2 (C2), 14.5 (C2) ppm. Anal. Calc. for $C_{13}H_{19}NO_4$: C, 61.64; H, 5.53; N, 7.56. Found: C, 61.40; H, 5.55; N, 7.59.

*2.1.5. Ethyl 2,4,6-trimethyl-1,4-dihydropyridine-3, 5-dicarboxylate (***V***)*

IR (KBr): ν_{max} 3345.3, 1697.1, 1641.9, 1215.0, 1134.2. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (d, 3H, $J = 6.4$), 1.30 (dd, 6H, $J = 7.0$, $J = 7.0$.); 2.27 (s, 6 H); 4.16 (dq, 2H, $J = 11$, $J = 7.0$); 4.22 (dq, 2H, $J = 11$, $J = 7.0$); 3.83 (q, 1H, $J = 6.4$); 5.57 (brs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 167.9 (C2), 144.2 (C2), 104.7 (C2), 59.6 (C2), 28.5, 22.3, 19.6 (C2), 14.5 (C2) ppm. Anal. Calc. for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 62.97; H, 7.91; N, 5.26.

*2.1.6. Ethyl 4-(3′-nitrophenyl)-2,6-dimethyl-1, 4-dihydropyridine-3,5-dicarboxylate (***VI***)*

166.7 °C. IR (KBr): ν_{max} 3344.9, 1704.8, 1645.5, 1524.7, 1487.9, 1370.4, 1347.6, 1212.9, 1118.8. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (dd, 6H, $J = 7.1$, $J = 7.2$); 2.37 (s, 6H); 4.1 (dq, 2H, $J = 10.8$, $J = 7.1$); 4.11 (dq, 2H, $J = 10.8$, $J = 7.2$); 5.09 (s, 1H); 5.74 (brs, 1H); 7.37 (dd, 1H, $J = 8.2$, $J = 7.7$), 7.64 (ddd, 1H, $J = 1.2$, $J = 1.8$, $J = 7.7$), 8.00 (ddd, 1H, $J = 1.2$, $J = 2.3$, $J = 8.2$), 8.13 (dd, 1H, $J = 1.8$, $J = 2.3$). ^{13}C NMR (75 MHz, $CDCl_3$): 167.1 (C2), 149.9, 148.1, 144.6, 134.5, 128.6, 123.1, 121.4, 103.4 (C2), 60.0 (C2), 40.0, 19.7 (C2), 14.6, 14.2 (C2) ppm. Anal. Calc. for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; N, 7.48. Found: C, 61.01; H, 5.94; N, 7.51.

2.2. Electrolytic media

1,4-DHPs derivatives were dissolved in a mixture of 0.1 M aqueous Britton Robinson buffer and ethanol, 60/40, containing 0.3 M KCl (Merck). For all compounds concentrations between 0.1 mM and 0.5 mM were used.

2.3. Voltammetry

Differential pulse (DPV), cyclic (CV) and linear sweep voltammetry (LSV) were performed with BAS-CV 50 assembly. DPV experiments were carried out with 0.1 mM of 1,4-DHPs in ethanol/BR (30/70) solutions. On the other hand, for CV and LSV experiments solutions containing 0.5 mM of 1,4-DHPs in ethanol/BR (40/60) were used. A glassy carbon stationary electrode as working electrode for DPV and CV experiments was used. For hydrodynamic experiments, a glassy carbon rotating disk electrode was also employed. The surface of the disk was polished to a mirror finish with alumina powder (0.3 μm and 0.05 μm) before use and after each measurement. A platinum wire was used as auxiliary electrode and all potentials were measured against an Ag/AgCl electrode in saturated KCl.

2.4. Coulometric analyses

These studies were carried on exhaustive electrolysis at constant electrode potential (500–1200 mV) on a glassy carbon mesh electrode. Oxygen was removed with pure and dry pre-saturated nitrogen. A three-electrode circuit with an Ag/AgCl electrode was used as reference and platinum wire as a counter electrode. A BAS-CV 50 assembly was used to electrolyze the 1,4-DHPs solutions. The net charge was calculated by correction for the estimated background current.

2.5. UV–vis spectrophotometry

UV–vis spectra were recorded in the 200–600 nm range, using an UNICAM UV-3 spectrophotometer.

2.6. GC–MS

A gas chromatograph/mass selective detector (5890/5972) combination (Hewlett-Packard, Palo Alto, CA, USA) and a Hewlett-Packard 7673 autosampler were used for the analyses. The *m/z* range monitored was 45–550 with a scan rate of 1 scan/s; the normal energy electron was set at 70 eV. A Hewlett-Packard Ultra-1 column, 25 cm × 0.2 mm i.d. × 0.11 μm film thickness (Little Falls, Wilmington, Delaware, USA), was used.

3. Results and discussion

A long series of 1,4-DHP derivatives (Fig. 1) were synthesized to investigate the effect of the substituents at positions C-3, C-4 and C-5 on the oxidation of the 1,4-DHP ring. In order to study the effect of C-4 substitution we shall compare compounds **I**, **IV–VI** and with the objective of inquiring about the effect of C-3, C-5 substitutions we will use compounds **I–III**. All the compounds **I–VI** were oxidized at the glassy carbon electrode showing only one irreversible oxidation peak when submitted to a DPV experiment. This peak was observed in the entire range of pH analyzed (2–11). Fig. 2 displays the evolution of the voltammograms of compound **I** at different pH values, but all the studied compounds followed a similar behavior. The Ep-pH plot shows that at pH > 4 the oxidation process

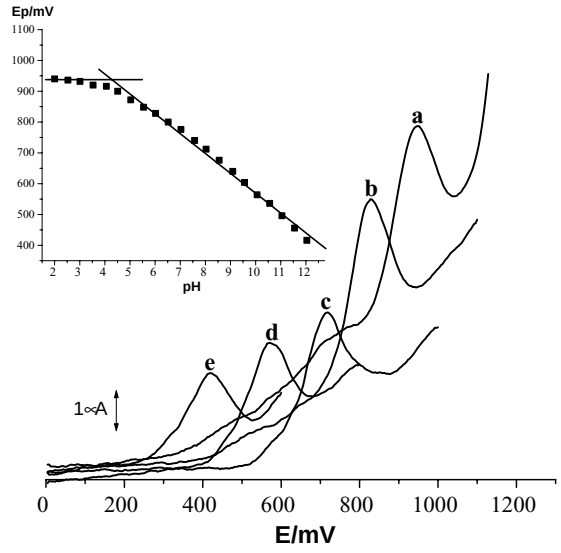


Fig. 2. Differential pulse voltammograms of compound **I** at different pH values, insert: Potential peak dependence on pH a–e implies pHs of: 2.0, 6.0, 8.0, 10.0, and 12.0, respectively.

is pH-dependent, however, at pH $\leq$ 4 the process is pH independent. A similar behavior for other related compounds had been previously reported [18]. At pH $>$ 8, the slopes of the Ep versus pH straight lines were 71.6, 67.2, 80.5, 50.9, 59.7 and 63.5 mV/pH for derivatives **I**–**VI**, respectively. In the pH-dependent zone all compounds were more easily oxidized than at higher pH values. On the other hand, we have corroborated that a *N*-ethyl-1,4-DHP derivative shows an totally pH-independent oxidation process in all the pH scale as had been previously reported [18] (Fig. 3).

In order to obtain optimal conditions for the limiting current we also tried with hydrodynamic voltammetry on a rotating disk electrode. From this study, we obtained the

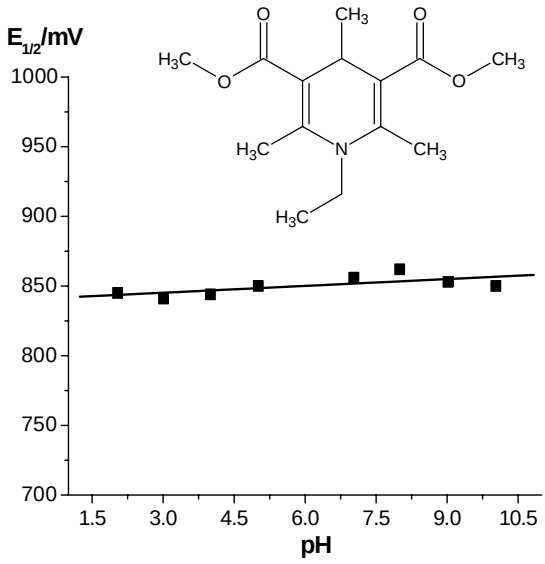


Fig. 3. Dependence of half wave potential on pH variation of methyl *N*-ethyl-4-methyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

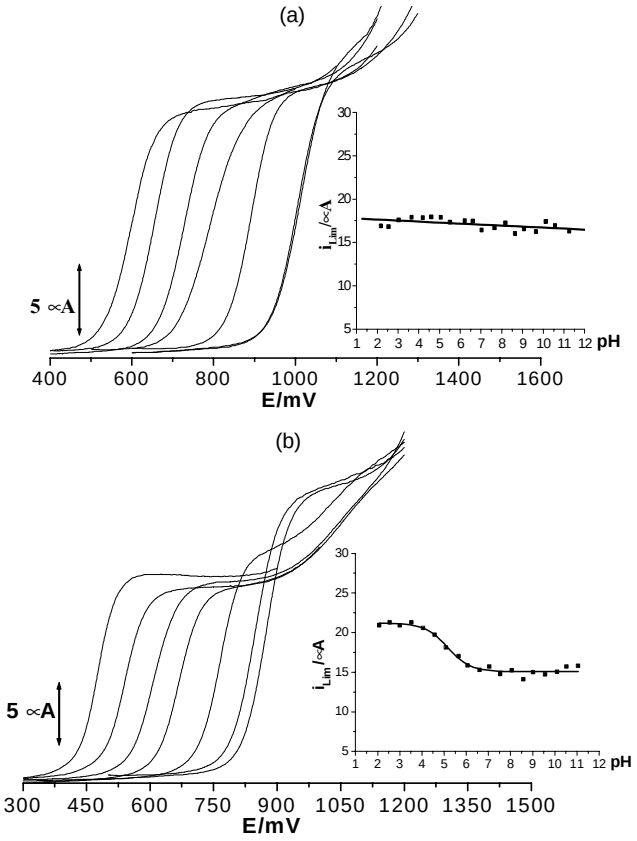


Fig. 4. Hydrodynamic voltammograms at different pH values. (a) Compound **I**, insert: i_{Lim} vs. pH plot. (b) Compound **V**, insert: i_{Lim} vs. pH plot.

dependence of the limiting current on pH giving important information about the oxidation process. The limiting current values of compounds of series A were pH-independent. However, the limiting current belonging to compounds of series B decreased as pH increased (Fig. 4). Since the limiting current is dependent on the number of transferred electrons during oxidation, we assumed that the mechanism of the compounds of series B involve different number of transferred electrons depending on the acid or basic character of the medium used. In order to validate this occurrence, we determined the number of electrons involved in the oxidation process. Coulometric analyses at pHs 3 and 11 were carried out. The results displayed in Table 1 reveal that compounds of series A follow a two-electron oxidation process in all pH range. On the other hand, derivatives of series B follow a two-electron oxidation process in an acid medium (pH = 3) and one-electron oxidation process at pH = 11.

Table 1
Apparent number of electrons transferred during the electro-oxidation process, obtained by coulommetric analyses, at pHs 3 and 11

	Series A			Series B		
	I	**II**	**III**	**IV**	**V**	**VI**
pH 3	2.4 ± 0.1	2.3 ± 0.1	2.3 ± 0.2	1.9 ± 0.1	2.0 ± 0.1	2.1 ± 0.1
pH 11	2.0 ± 0.1	1.9 ± 0.1		1.3 ± 0.1	1.1 ± 0.1	1.4 ± 0.1

To obtain additional information about the electrode process, we also carried out cyclic voltammetry. Cyclic voltammograms were registered at pHs 3, 7 and 11. In all cases only one irreversible anodic peak at different sweep rates (0.1–10 V/s) was observed. The potential peak values were dependent on sweep rate corroborating the irreversible character of the oxidation process. Furthermore, the slope of the log ip versus log v plots was between 0.73 and 0.87 showing that adsorption phenomena accompanied the electrode process [20].

UV–vis spectra at different pHs for the compounds were registered, exhibiting similar maxima about 240 and 350 nm. These absorption bands were pH-independent suggesting that the electroactive species is the same in the entire pH range under study. This result agrees with previous information where a pK_a of 19.8 was obtained for compound **IV** [21].

In order to isolate and identify the products of the oxidation reaction, we carried out exhaustive controlled potential electrolysis and then the products were monitored by gas chromatography combined with mass spectrometry (GC–MS). The mass spectra obtained from solutions containing compound **I** (before and after potential controlled electrolysis) after gas chromatographic separation are compared in Fig. 5. The retention times for solutions containing either non-electrolyzed or electrolyzed compound **I** are 11.7 and 10.2 min, respectively. All the studied compounds followed the same pattern, revealing the formation of the corresponding pyridine derivatives as products of the oxidation reaction [22–24].

According to the obtained values for peak potentials (Fig. 1), we can claim that, in series A derivatives, an increase in the electron-attracting character of substituents at C-3 and C-5 on the dihydropyridine ring favors oxidation at a basic pH; however, the opposite effect is observed at pH $\leq$ 4. This fact indicates that there is a change in the oxidation mechanism for these compounds depending on whether an acid or basic medium is involved.

On the other hand, comparison of compounds **I**, **IV**–**VI** permits to state that an increase in the electron-attracting character of the C-4 substituent hinders the oxidation process. Compound **IV**, with an H-substituent at C-4 does not follow this order and is the most oxidizable derivative in the series. This may be explained, however, if we consider that C-4 substitution may destroy the coplanar feature of the dihydropyridine ring, or force the 3- and 5-carbonyl groups

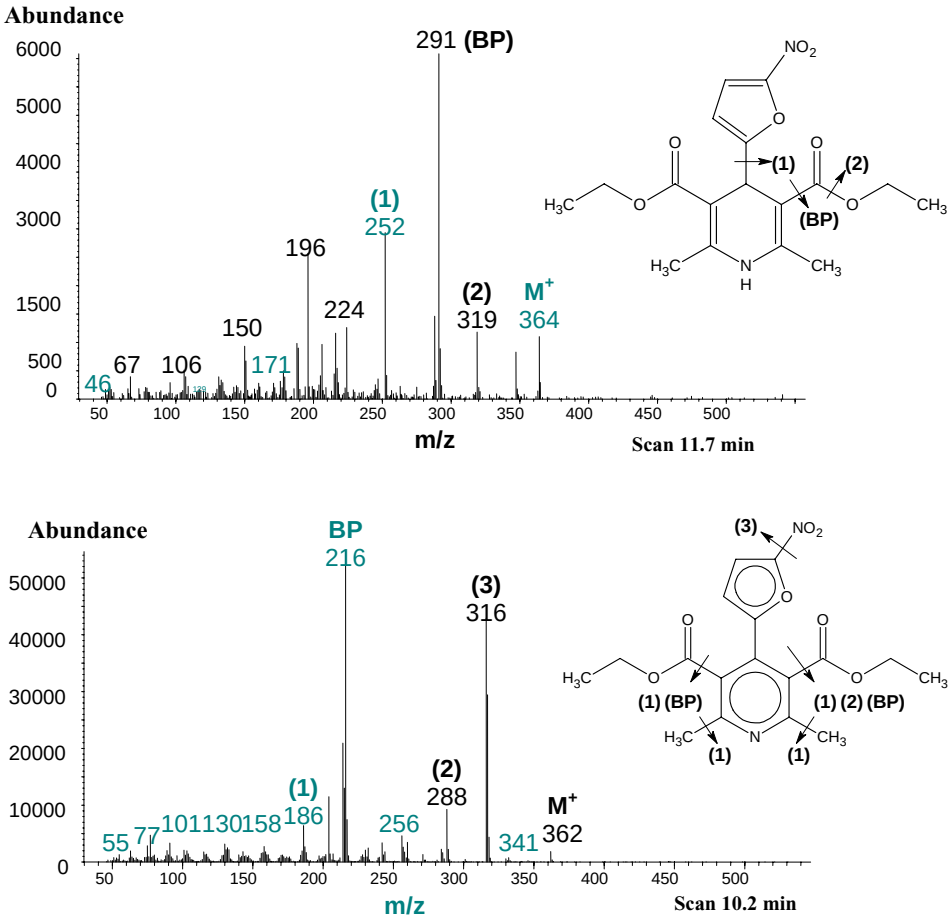
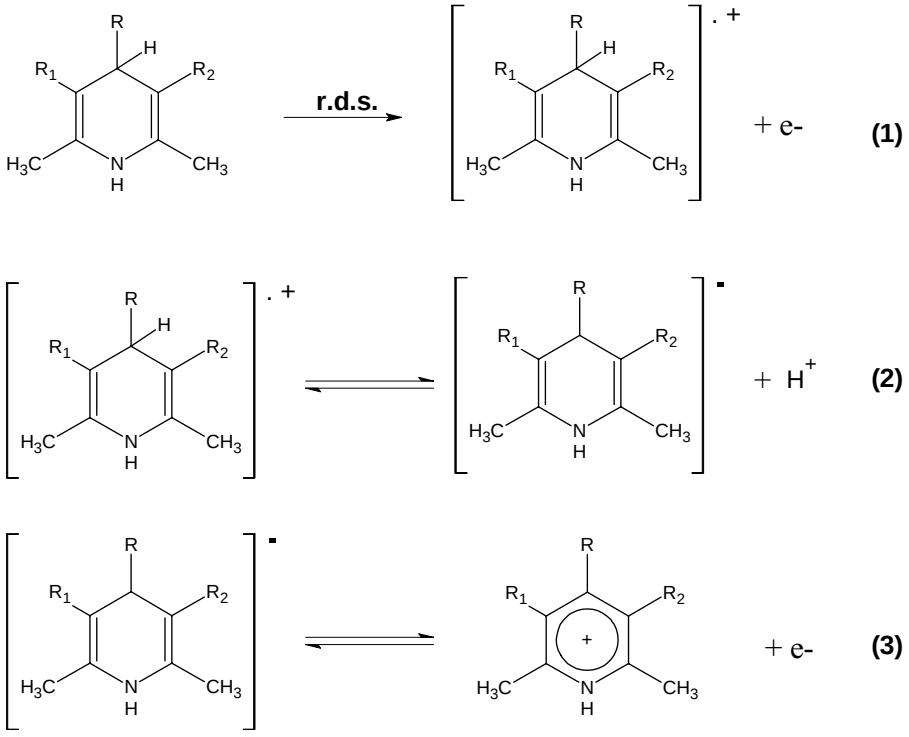


Fig. 5. GC–MS obtained from a solution of compound **I**: without electrolysis (retention time 11.7 min) and after electrolysis (retention time 10.2 min).



Scheme 1. Oxidation mechanism of 1,4-DHP derivatives, in acid media/medium (pH 1–4).

to twist in relation to the central plane. It is known that both structural perturbations substantially reduce the effect of delocalization of substituents on stabilizing the radical [21].

Considering the above described results, some mechanisms may be postulated about the oxidation of the 1,4-DHP derivatives under study. According to both E_P versus pH and i_l versus pH plots, all compounds show a pH-independent behavior at pH $\leq$ 4. Consequently, all the studied compounds **I**–**VI** follow the same pH-independent mechanism as proposed in previous reports [17,18] at pH $\leq$ 4; i.e. in an acid medium, compounds **I**–**VI** follow an ECE sequence which is summarized in Scheme 1. This mechanism permits to explain the above described effect of the substituents in series A derivatives, since an increase in the electron-attracting character of the substituent at C-3 and C-5 diminish the electron density on the DHP ring thus hindering the electron transfer in step 1. A similar explanation is valid for compounds **I**, **V**, **VI** as to the electron-attracting power of the C-4 substituent.

In a basic medium the situation is different since experimental results show that all derivatives follow a pH-dependent mechanism as can be inferred from the E_P versus pH plot (Fig. 2); however, the studied compounds differ in the dependence of the limiting current on pH. In fact, series A derivatives, which have a 5-nitro-furyl substituent at C-4, show a pH-independent limiting current in all pH range (Fig. 4). On the other hand, series B derivatives show a decrease in the limiting current passing from acid (pH < 4) to basic pH (pH > 7) solutions (Fig. 4). At the same time, coulometric data (Table 1) indicate that the number of electrons required for the oxidation of the same compound decreases from 2 to 1 on passing from an acid to a basic medium. The comparison of these results strongly suggests a very slow reaction involved in the reaction pathway following the primary electron transfer, which cannot be the rate-determining step.

Thus, we postulate that the oxidation mechanism of derivatives **IV**–**VI**, at pH > 7, consists of a DISP1 scheme, as mentioned in previous reports [17,18]. A disproportionation reaction can explain the drop of the limiting current. In this case, the OH^- ion present in the electrolytic medium

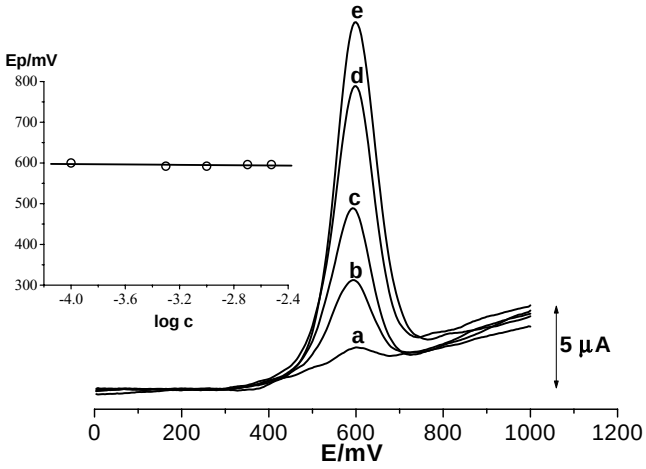
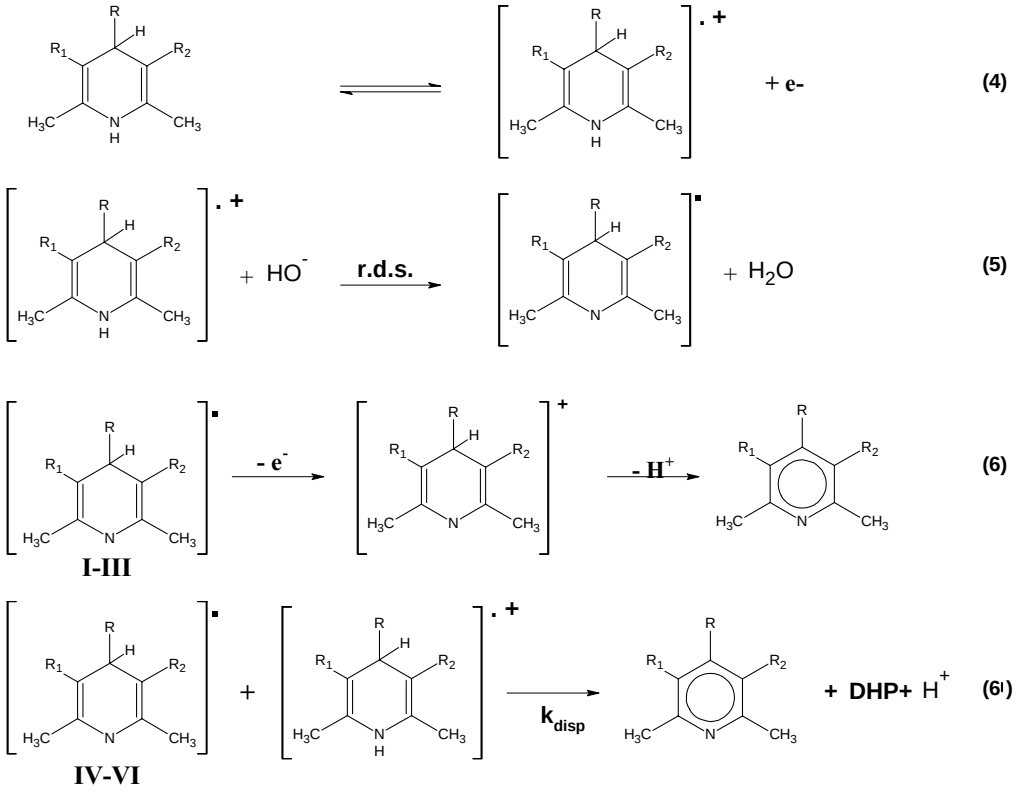


Fig. 6. Differential pulse voltammograms of compound **V** at different concentrations, at pH 10. Insert: Dependence of the E_P on log c. (a–e) implies concentrations of: 0.1, 0.5, 1.0, 2.0, and 3.0 mM, respectively.



Scheme 2. Oxidation mechanism of 1,4-DHP derivatives at pH > 7.

uptakes the proton at N-1 position of the radical cation formed after the first one-electron transfer. Afterwards, this formed radical reacts with another molecule of the radical cation, re-establishing the 1,4-dihydropyridine and generating the pyridine derivatives. In relation to N–H bond energy, Cheng et al. [21] have proved that a deprotonation reaction following the first electron transfer is a favorable way to the oxidation of 1,4-DHPs. Furthermore, we claim that the oxidation mechanism follows a DISP1 instead of DISP2 scheme, because oxidation potentials do not depend on the concentration of the electro-active species, i.e. $dE_P/d \log c = 0$ (Fig. 6) [25].

On the other hand, compounds **I–III** do not fit well with a DISP1 scheme in basic media, because two instead one electrons are involved in the oxidation process. In accordance with this evidence, this type of compounds are oxidized following a different sequence involving the same rate determining step but with different subsequent reactions as shown in Scheme 2. Summing up, we postulate a mechanism (Scheme 2) where series B derivatives follow the route 4,5,6′, obeying a DISP1 scheme, while derivatives having 5-nitrofuryl substituent at C-4 follow the sequence 4, 5, 6 giving an ECEC mechanism.

This finding was totally surprising in relation to previous results [17,18] where the general rule appeared to be that all 1,4-DHP compounds having H at N-1 follow a DISP1 mechanism in which the rate determining step was the uptake of the proton at N-1 by the OH^- ion of the medium. In the present case series A derivatives despite having H at N-1 show a pH-independent limiting current incompatible with the previously reported DISP1 mechanism. Consequently, the 5-nitrofuryl substituent at C-4 seems to modulate a change in the mechanism of 1,4-DHP oxidations.

4. Conclusions

The electro-oxidation mechanism differs whether an acid or basic medium is involved. The N-1 proton is responsible for the mechanism change. In an acid medium, pH 1–4, all derivatives follow an oxidation mechanism obeying an ECE sequence. In this medium, an increase in the electron-attracting character of the substituents at C3, C4 or C5 hindered oxidation reaction.

On the other hand, at basic pH, the greater electron-attracting character of the nitrofuryl group in series A derivatives favored an ECEC mechanism; however, a DISP1 mechanism was found for series B derivatives. In both cases, the rate-determining step consisted of the uptake of the proton at N-1 in dihydropyridine ring by the OH^- ion of the media. Groups with greater electron-attracting character at C-3 and C-5 in the dihydropyridine ring favor oxidation at basic pH, however a contrary effect is shown with C-4 substituents.

Previous evidence on this topic seems to support the idea that all 1,4-DHP derivatives having H at N-1 follow a DISP1

mechanism in a basic medium however, the new findings of this work enable us to conclude that substitution at C-4 can generate changes in oxidation mechanism when passing from DISP1 to ECEC.

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