Electrochemical and ESR Characterization of Free Radicals from C-4 Nitroso Phenyl 1,4-Dihydropyridines in Aprotic Media

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The present paper deals with the electrochemical and electron spin resonance (ESR) characterization of a number of nitroso phenyl 1,4-dihydropyridines in aprotic media on a hanging drop mercury electrode (HDME). The electrochemically generated nitroso radical anions decayed by a second-order reaction. Kinetic rate constants varied between k_2, 4906 ± 43 $(M\,s)^{-1}$ and 17,955 ± 159 $(M\,s)^{-1}$ depending on the chemical structures. An increase in the bulk of the alkyl substituents from methyl—to isopropyl in 3- and 5-positions on the dihydropyridine ring stabilized the free radicals. Also, the electrochemically generated nitro radical anions from the parent nitrophenyl 1,4-dihydropyridines (1,4-DHP) derivatives were kinetically characterized and were significantly more stable than nitroso derivatives. The time-course of controlled potential electrolysis of the different compounds was followed electrochemically by differential pulse voltammetry, cyclic voltammetry, and spectroscopically by UV-visible and ESR. There is an intermolecular consecutive reaction during electrolysis, which gives the nitranion products. Formation of the one-electron reaction product, i.e., the nitroso radical anion, was confirmed by ESR experiments, and the corresponding hyperfine coupling constants were calculated for all the nitrosophenyl 1, 4-DHP derivatives studied.

1, 4-Dihydropyridines (1,4-DHP) have been broadly studied due to their relevance in cardiovascular therapy.[1,2] These were first synthesized by Hantzsch[3] and successive structural modifications were later developed. These modifications were on the 1-, 3-, 4-, and 5-positions of the dihydropyridine ring, which gave important results, and in 1977 the Bayer group synthesized the drug nifedipine, revolutionizing the antihypertensive therapy.[4] Attempts to find improved bioavailability, longer therapeutic action and new pharmacological applications have encouraged the synthesis of many structural analogues of nifedipine.[5,6]

At present, compounds related to the 1,4-DHPs are being synthesized to examine new pharmacological properties.[7-10] In this scope, we have now synthesized a novel series of C-4 nitrosophenyl 1,4-dihydropyridines.[11] Our interest in the synthesis of these compounds is based on earlier evidence that some commercial nitrophenyl 1,4-dihydropyridines undergo photolysis when exposed to short-wavelength, visible or UV-*C* radiation in aqueous solution, giving the corresponding nitroso derivatives.[12-15] Also, formation of free radicals during the reduction of nitroso compounds[16,17] and the potential participation in cytotoxic reactions in human beings being used in cancer chemotherapy[6,18,19] has stimulated our interest in the electrochemistry of these compounds. Also, they are recognized as potentially reactive metabolites of a variety of toxicologically interesting compounds, which become carcinogenic and/or mutagenic after covalent binding to proteins and DNA.[20,21] Some nitro aromatic compounds are of pharmacological interest and are as administered drugs, i.e., antibiotics such as chloramphenicol, nitroimidazoles used in cancer treatment, or nitrofurans or nitrothiazoles used as antifungicidal agents, and they can be reduced to nitroso intermediates.[16] Therefore, reductions of the nitroso group are of prime importance but have not received great attention mainly because of difficulties in syntheses of nitroso compounds and their chemical instability. Furthermore, much of the literature has been devoted to nitrosobenzene[22-24] and in particular, to the electrochemical reduction of aromatic nitroso compounds.[25,26] Furthermore, in earlier work[27] the electrochemical characterization of a photodegradation product from nifedipine, named the nitrosopyridine derivative (NPD), has been reported which gave anionic nitroso free radicals.

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As far as we know there is little evidence on the effect of inclusion of a nitroso group on the electrochemical properties of 1,4-DHP, and a systematic study on the electrochemical reduction in aprotic media of nitrosophenyl 1,4-DHP derivatives by cyclic voltammetry is reported. Also, UV-visible and electron spin resonance (ESR) spectroscopy were used to follow the electrolytic behavior of these compounds. In the synthesized 1,4-DHP derivatives we varied both the position of the nitroso group and the bulk of the alkyl groups at 3- and 5-positions on the dihydropyridine ring.

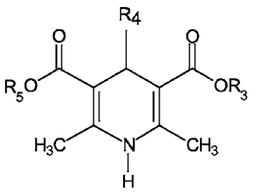
Experimental

Nitro- and nitroso phenyl 1,4-dihydropyridines were synthesized according to literature procedures[28-30] and chemical structures are shown in Fig. 1.

Parent nitrophenyl 1,4-dihydropyridines.— 4-(3-nitrophenyl)-2, 6-dimethyl-3, 5-dimethoxycarbonyl-1, 4-dihydropyridine, (*meta*-NO_2-Me); 4-(3-nitrophenyl)-2,6-dimethyl-3,5-diethoxycarbonyl-1, 4-dihydropyridine, (*meta*-NO_2-Et); 4-(3-nitrophenyl)-2,6-dimethyl-3,5-diisopropyloxycarbonyl-1,4-dihydropyridine, (*meta*-NO_2-iPr); 4-(4-nitrophenyl)-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine, (*para*-NO_2-Me); 4-(4-nitrophenyl)-2,6-dimethyl-3,5-diisopropyloxycarbonyl-1,4-dihydropyridine, (*para*-NO_2-iPr); and 4-(4-nitrophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine, (*para*-NO_2-Me).

Nitrosophenyl 1,4-DHPs.— 4-(3-nitrosophenyl)-2, 6-dimethyl-3, 5-dimethoxycarbonyl-1, 4-dihydropyridine, (*meta*-NO-Me); 4-(3-nitrosophenyl)-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine, (*meta*-NO-Et); 4-(3-nitrosophenyl)-2,6-dimethyl-3,5-diisopropyloxycarbonyl-1,4-dihydropyridine, (*meta*-NO-iPr); 4-(4-nitrosophenyl)-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine, (*para*-NO-Me); 4-(4-nitrosophenyl)-2,6-dimethyl-3,5-diisopropyloxycarbonyl-1,4-dihydropyridine, (*para*-NO-iPr); and 4-(4-nitrosophenyl)-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridine, (*para*-NO-Me).

Solvents and reagents.— Dimethylformamide (DMF) and acetonitrile for UV spectroscopy were from Merck. Solutions of nitroso phenyl 1,4-DHP were prepared in the solvents, presaturated under a pure N_2. Tetrabutylammonium hexafluorophosphate (TBAHFP) was from Sigma-Aldrich, and tetrabutylammonium hydroxide solution (TBAOH) in 2-propanol/methanol 0.1 mol/L was from Merck.



Compound	R_3	R_4	R_5
meta-NO-iPr	$-CH(CH_3)_2$	3-NO	$-CH(CH_3)_2$
para-NO-iPr	$-CH(CH_3)_2$	4-NO	$-CH(CH_3)_2$
meta-NO-Et	$-CH_2CH_3$	3-NO	$-CH_2CH_3$
para-NO-Et	$-CH_2CH_3$	4-NO	$-CH_2CH_3$
meta-NO-Me	$-CH_3$	3-NO	$-CH_3$
para-NO-Me	$-CH_3$	4-NO	$-CH_3$

Figure 1. Chemical structures of C-4 nitroso phenyl 1,4-dihydropyridines.

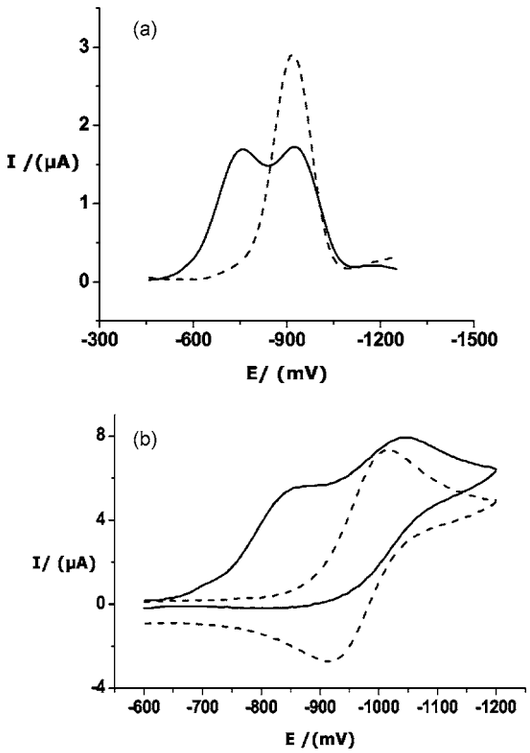


Figure 2. (a) dp polarograms and (b) CVs of 1 mM *meta*-NO-Me solutions in DMF in the (—) absence and (---) presence of 1 mM TBAOH. Scan rate for CV is 1 V/s.

Drug solutions.— For the spectrophotometric measurements stock solutions of 10 mM 1,4-DHP either in DMF or acetonitrile were prepared in the dark. Aliquots to give concentrations between 0.05 and 1 mM were diluted in the corresponding solvent, with 0.1 M TBAHFP as supporting electrolyte.

Electrochemical measurements.— Cyclic voltammetry (CV) was carried out in a BAS CV-100 voltammetric analyzer. A BAS CGME controlled-growth mercury electrode with a drop surface area of 1.93 mm^2 was the working electrode and a platinum wire was also used as a counter electrode. All potentials were measured against an Ag|AgCl|NaCl 3 M electrode supplied with a bridge for aprotic solvents. A drug concentration of 1 mM was used in all the experiments.

Methods.— The experimental I_{pa}/I_{pc} ratios were calculated according to the procedure of Nicholson and Shain using individual CVs.[31,32] Kinetic reaction orders for loss of the nitroso radical anions were quantitatively assayed for first- and second-order coupled reactions according to a previously published study.[32,34]

Controlled potential electrolysis.— Controlled potential electrolysis (CPE) was carried out either on a mercury pool electrode or a reticulated vitreous carbon electrode (BAS no. MF-2077) at −1200 mV in anhydrous DMF or acetonitrile containing 0.1 M TBAHFP as supporting electrolyte under pure, dry presaturated nitrogen. A three-electrode circuit with an Ag/AgCl electrode was reference and a platinum coil in a separated fritted chamber was the counter electrode. A Wenking potentiostat, model POS 88, was used to electrolyze the solutions.

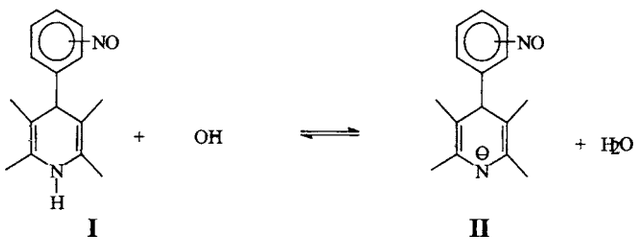
UV-Visible spectroscopic studies.— A UNICAM UV-3 spectrophotometer was used to examine the mechanism and progress of the electrolysis of nitrosophenyl 1,4-DHPs electrolysis in acetonitrile in the 220–700 nm range at different intervals. Acquisition and data treatment were carried out with Vision 2.11 software. An electrolytic cell of our own construction,[35] based on a 1 cm UV cuvette, with a platinum coil or a glassy carbon as working electrode was used for the in situ generation of the reduction species. Constant stirring was used which was stopped before each measurement.

ESR measurements.— The nitro and nitroso radical anions from the parent nitro- and nitrosophenyl 1,4-DHP derivatives were generated in situ by electrochemical reduction in an electrochemical flat quartz cell (Wilmad WG-810) inside the microwave chamber of an X-band spectrometer with platinum electrodes. The following experimental conditions were used for the electrochemical reduction: 1 mM solutions of nitroso phenyl 1,4-DHP derivatives in DMF containing 0.1 M TBAHFP as supporting electrolyte. Solutions were nitrogen degassed for 10 min, and during the electrochemical reduction ESR spectra were recorded with a Bruker ECS 106 X-band spectrometer with 50 kHz field modulation. ESR spectra were recorded at room temperature in the following conditions: center field = 3440 G, sweep field = 40 G, conversion time = 40, 96 ms, and time constant = 20, 48 ms. Hyperfine splitting constants are given in G, and were estimated to be within ±0.05 G.

Results and Discussion

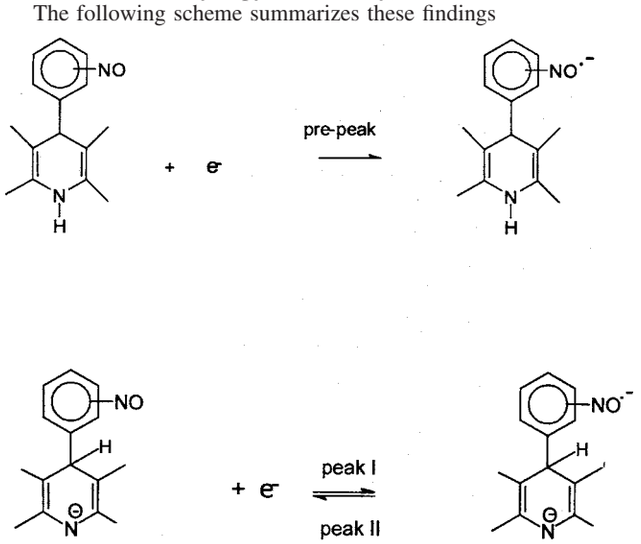
Reduction of nitroso phenyl 1,4-DHP derivatives on HMDE in an aprotic medium.— A CV characterization of all compounds at different sweep rates (0, 1–50 V/s) was carried out. In this medium, the first characteristic in the reductions was appearance of prepeaks at more positive potentials that those corresponding to the R–NO/R–$NO^{\cdot}$ couple. These prepeaks completely disappeared after addition of TBAOH. In Fig. 2, this type of behavior is illustrated by both differential pulse polarography (dpp) and CV measurements for the *meta*-NO-Me derivative. The 1,4-DHP compound exhibited two differential pulse (dp) polarographic peaks at −760 and −920 mV,

respectively (Fig. 2a). However, the dp polarographic signal at −760 mV disappeared when base was added, but the peak height at −920 mV increased. In CV experiments (Fig. 2b), the prepeak at −861 mV disappeared after addition of 1.0 mM TBAOH, permitting isolation of the reversible couple. Furthermore, a gradual disappearance of the prepeaks was directly proportional to the quantity of added base and there was a drastic color change in the solutions, from colorless to light yellow. Thus, this change can be due to the ionized form of the dihydropyridine ($R–N^-$), because TBAOH acts as a Lewis base. Such changes were observed in all the studied compounds. Thus, the equilibria among these forms are



Therefore, to avoid the prepeaks the base was always added to the medium, giving only one reduction. The appearance of the prewaves indicated the presence of two different electroactive species.[36,37] Thus, the prewave would correspond to reduction of the nitroso group in neutral dihydropyridine ring (R–N–H), whereas the most cathodic signal (reversible) would correspond to the reduction of the nitrosophenyl group in the anionic dihydropyridine ($R–N^-$). Therefore, for further descriptions in this paper, R–NO indicates the anionic form of the dihydropyridine moiety, II.

The following scheme summarizes these findings



The existence of this equilibrium was also proved by using UV-visible (UV-vis) spectroscopy. In Fig. 3 the effect on the electronic absorption spectra of adding a TBAOH solution for a 0.08 mM *meta*-NO-Me solution in acetonitrile is shown. The spectra pattern indicates a transition from neutral, I, (λ = 351 nm) to ionized, II, (λ = 440 nm). The peak at 310 nm does not change by the addition of the base, the shoulder at 350 nm disappears while the band at 440 nm is formed. If we compare Fig. 3 with Fig. 6, the peak at 310 nm decreased probably due to the electrochemical reduction reactions.

To study the electrochemical behavior of the R–NO/R–NO· couple in isolation, the change in the voltammetric response with the scan rate was analyzed for all the compounds studied. For *para*-NO-Me compound, the current ratio I_{pa}/I_{pc} increases as the scan rate is increased, reaching a limiting value which tends to the unity (Fig. 4a). The behavior is similar for the CVs at different sweep rates. These results demonstrate an irreversible chemical reaction

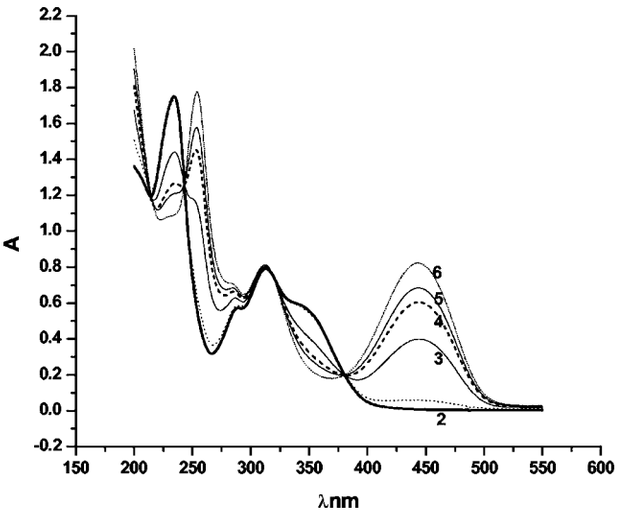


Figure 3. UV-vis absorption spectra of 0.08 mM *meta*-NO-Me solution in acetonitrile, in the (—) absence and (---) presence of TBAOH. Curves (2–6) = 0.1, 0.15, 0.2, 0.25, and 0.3 mM TBAOH.

following a reversible charge transfer, i.e., an electrochemical (EC) process.[34] As predicted by Olmstead et al.[34] for a second-order reaction, the I_{pa}/I_{pc} ratio decreased with increasing concentration of the nitroso phenyl 1,4-DHP compounds. Furthermore, the cathodic peak potential also depends on the derivative concentrations and sweep rates, with $dE_{pc}/d \log c$ and $dE_{pc}/d \log v$ average values of 22 ± 3 mV, in agreement with the theoretical value of 24.5 mV for an EC_i process where the chemical step follows second-order kinetics.[33,34]

The experimental ΔEp average value of 67 ± 5 mV is relatively close to the theoretical value of 60 mV for monoelectronic transfer. The independence of the $I_{pc}/v^{1/2}$ ratio of the logarithm of sweep rate shows that there are no adsorption processes complicating the reduction process, as confirmed by the linear dependences of $\log I_p$ on $\log v$. The experimental average slope for such plots was 0.509 (c. coeff. 0.995).

In addition, the experimental results show that the one-electron transfer process to giving the nitroso radical anion is followed by an irreversible chemical reaction, which can be represented by the following equations

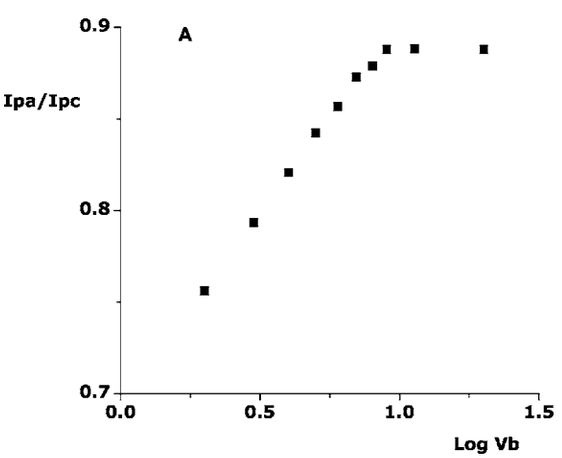


Figure 4. Dependence of the current ratio, I_{pa}/I_{pc}, on the logarithm of sweep rates for 1 mM *para*-NO-Me solution.

Table I. Second-order rate constants (k_2) and lifetimes ($t_{1/2}$) for parent C-4 nitro phenyl- and corresponding nitroso phenyl 1,4-DHP derivatives. These values were calculated for DMF solutions containing an initial 1 mM concentration of compounds. Temperature: 20°C.

Compound	k_2 (M^{-1} s^{-1})	$t_{1/2}$, s
m-NO_2-Me	2909	0.34
p-NO_2-Me	2328	0.43
m-NO_2-Et	2202	0.45
p-NO_2-Et	2780	0.35
m-NO_2-iPr	367	2.5
p-NO_2-iPr	390	2.55
m-NO-Me	7284	0.138
p-NO-Me	17,954	0.054
m-NO-Et	5150	0.193
p-NO-Et	11,133	0.089
m-NO-iPr	4906	0.2
p-NO-iPr	6365	0.156

$$R\text{–}NO + e^- \leftrightarrows R\text{–}NO^{\cdot}\text{–}$$

$$2R\text{–}NO^{\cdot}\text{–} \xrightarrow{k_2} \text{Products}$$

The second-order rate constants were obtained from single CVs, according to Olmstead et al.,[34] by using the following relationship

$$\log \omega = \log(k_2 c_0 \tau)$$

the linearity (average c.c. of 0.990) of plots of the kinetic parameter ω vs the time constant. τ is added confirmation that the chemical step follows second-order kinetics for all the compounds. From plots of ω vs τ, assuming a dimerization process, the kinetic rate constants were calculated for all the nitro- and nitroso phenyl 1,4-DHP derivatives.

In Table I, the second-order kinetic rate constants (k_2) and the corresponding half-life times ($t_{1/2}$) for the parent nitro phenyl 1,4-DHPs and corresponding nitrosophenyl 1,4-DHP derivatives are shown, and the following general conclusions are drawn:

1. Free radicals electrochemically generated from the parent nitro phenyl 1,4-DHPs (nitro radical anions) are more stable than those of the corresponding nitrosophenyl 1,4-DHPs (nitroso radical anions).

2. In general, an increase in the bulk of the alkyl substituents in 3- and 5-positions on the dihydropyridine ring varying from methyl to isopropyl produced the more stable free radicals, i.e., decreased k_2 of both nitrophenyl and nitrosophenyl derivatives was observed (e.g., k_2 *meta*-NO_2-iPr = 367 $[M\ s]^{-1}$ vs k_2 *meta*-NO_2-Me = 2909 $[M\ s]^{-1}$). The results were similar for nitrosophenyl 1,4-DHP derivatives, i.e., k_2 *meta*-NO-Me = 7284 $[M\ s]^{-1}$ vs k_2 *meta*-NO-iPr = 4906 $[M\ s]^{-1}$. In contrast, compounds with a methyl substituent in the 3- and 5-positions gave the most unstable radicals in the reaction media.

3. The position of either the nitro or nitroso group on the aromatic ring seems not to be relevant with respect to the stability of the generated free radicals.

Controlled potential electrolysis.— CPE of nitroso phenyl 1,4-DHP derivatives in DMF giving the corresponding nitroso radical anions in bulk solution were performed with a reticulated vitreous carbon working electrode at a fixed potential of −1200 mV. The time-course of these reactions was followed electrochemically (dpp and CV) and spectroscopically (UV-vis).

Differential pulse polarography. The time-course of electrolysis followed by dp polarography for a 1 mM *para*-NO-iPr solution is shown in Fig. 5a. The initial dp polarogram (curve 1), corresponding to the nitroso compound, exhibits a prepeak at −818 mV followed by a second peak at approximately −1000 mV. After 5 min of electrolysis (curve 2), the prepeak disappeared, with the appearance of a new peak at −1657 mV. However, the height of the single signal at approximately −1000 mV decreased. At longer electrolysis times, 15 and 30 min (curves 3 and 4), there was a significant decrease in the main peak at approximately −1000 mV, but the height of the peak at −1657 mV remained practically constant. Similar results were found for the other nitroso phenyl 1,4-DHP compounds, i.e., parallel with a decrease of the original signals with the time-course of electrolysis, new signals at more negative potentials appeared between −1630 and −1700 V, depending on the compound studied.

Cyclic voltammetry.— CVs corresponding to a 1 mM *meta*-NO-iPr solution at different electrolysis times are shown in Fig. 5b. Before the electrolysis (curve 1), only a prepeak at −876 mV, followed by a reversible couple corresponding to nitroso radical anion formation is observed, with the following potentials: E_{pc} = −1065 mV and E_{pa} = −963 mV. However, after 5 min electrolysis (curve 2), the prepeak disappeared and the decrease of the first reversible reduction process at E_{pc} = −1030 mV and E_{pa} = −963 mV corresponded to reduction of the nitroso radical anion, and a second reversible couple at E_{pc} = −1707 mV and E_{pa} = −1564 mV appeared. However, at 15 min (curve 3) and 30 min of electrolyis (curve 4), the reversible couple that appeared at more cathodic potentials was almost unaltered in parallel with the significant decrease of currents of the couple corresponding to the nitroso radical anion. The time-course of the electrolysis of the other nitroso phenyl 1,4-DHPs was similar, i.e., formation of the nitroso radical anion and its further consumption were concomitant with appearance of a new reversible couple at more cathodic peak potentials. This latter couple could correspond to formation of an azoxy derivative.[38] Consequently, we conclude that the chemical step in the reduction of nitrosophenyl 1,4-DHP derivatives in DMF corresponds to dimerization with elimination of water and presumably participation of hydrogen ions of the dihydropyridine moiety which produce the respective nitranion. As a final product, an azoxy derivative would be generated (second reversible couple). The mechanism can be summarized as follows

$$R\text{–}NO + e^- \leftrightarrows R\text{–}NO^{\cdot}\text{–} \qquad [1]$$

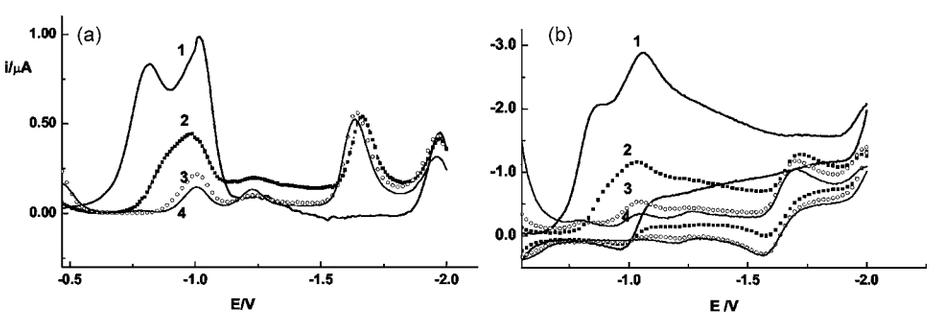


Figure 5. (a) dpp's and (b) CVs of 1 mM *meta*-NO-iPr in DMF. Time-course electrolysis (1–4) = 0, 5, 15, and 30 min, respectively.

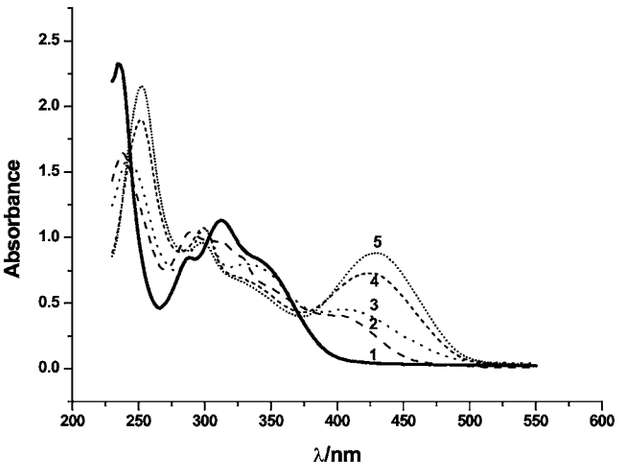
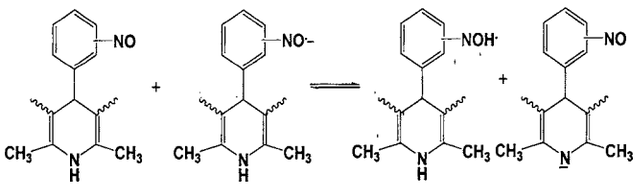


Figure 6. Time-course of CPE of 0.1 mM *meta*-NO-Me in acetonitrile at −1200 mV followed by UV-vis spectroscopy. Time-course electrolysis (1–5) = 0, 2, 4, 6, and 8 min.

$$2R\text{–}NO^{\cdot}\text{–} + 2H^{+} \rightarrow R\text{–}N = N\text{–}R + H_2O \quad [2]$$
$$\downarrow$$
$$O_{-}$$

UV-Vis spectroscopy.— The time-course of CPE for a 0.1 mM *meta*-NO Me solution followed by UV-vis spectroscopy is shown in Fig. 6. The original spectrum (1) of the compound exhibits two maxima at 235 and 312 nm and two shoulders at 288 and 351 nm. Spectra 2–5 show the time-course of the electrolytic reduction. At the beginning of the electrolysis (spectrum 2) two new signals appear at approximately 238 and 405 nm and shift to longer wavelengths concomitantly with increasing electrolysis time to give rise to new stable bands at 251 and 428 nm (spectra 4 and 5), respectively, indicating that there is a new species in solution. Parallel with these spectroscopic changes, the original maxima at 312 nm decreased, indicating that there was reduction of the nitroso group.

In order to explain the appearance of these new visible bands at 420–445 nm after electrolysis of nitroso derivatives, we propose formation of a nitranion on the nitrogen of the 1-position of the 1,4-dihydropyridine ring as a consequence of nitrogen deprotonation. There is formation of the nitranion from different compounds such as nitroaryl-substituted 1,4-DHP derivatives in aprotic media after the alkali addition[36,37] or reaction with electrogenerated superoxide anion.[39] It is plausible that the weakly acidic character of the dihydropyridine and the paucity of hydrogen ions in our electrolytic media favor an intermolecular acid–base reaction between the nitroso radical anion and the proton on the nitrogen of position-1 of the dihydropyridine ring. Thus, we suggest formation of the corresponding nitranion according to a father–son intermolecular reaction



Scheme 1. Father–son type intermolecular reaction between the parent nitroso compound and the electrogenerated nitroso radical anion to form the corresponding nitranion.

type as in Scheme 1. The nitroso radical anion behaves as a base, deprotonating the nitrogen of the position-1 of the dihydropyridine ring.

In order to test our previous hypothesis, we replaced the electrochemical generation of the nitroso radical anion by the addition of TBAOH to a 0.08 mM *meta*-NO Me solution in acetonitrile. Upon addition of TBAOH, an ion-paired OH^{-}, a new band appeared at approximately 420–440 nm depending on the derivative. This new visible band could be ascribed to a change in the acid–base equilibrium corresponding to the –NH group in the dihydropyridine ring. Thus, these experiments confirm that the spectral changes observed with both a TBAOH solution and the nitroso radical anion are due to changes in acid–base equilibria.

ESR characterization of free radicals generated from nitroso phenyl 1,4-DHPs.— The electrochemical reduction of nitroso phenyl 1,4-DHPs to the corresponding nitroso radical anions and its detection by ESR were carried out in 0.1 M TBAHFP in DMF.

As it has been observed for nitro-substituted benzene anions, the lines from the nitro-group nitrogen nuclei are broader on the high-field side than on the low side[40,41] of the spectrum. The same effect is observed here with the nitroso-group nitrogen nuclei. The linewidth variations, as asymmetric line broadening, are due by the anisotropies in the g and hyperfine tensors coupled with effects of molecular tumbling in solution. The structure of the radical is important in anisotropic line-broadening. For example, hyperfine anisotropy is important for nuclei in atoms such as ^{14}N with large local π-spin population. Tumbling rates depend on the molecules shape and size, on solvent interactions, and on the temperature.[42,43]

These spectra can be interpreted in terms of a triplet due to a nitroso-group nitrogen nucleus, four doublets attributed to four nonequivalent protons, and a doublet due to proton of the ring DHP at position-4′. This interpretation is supported by computer simulations of the experimental spectra. All simulated spectra had Lorentzian line shapes. The hyperfine pattern showed that the largest coupling constant can be assigned to the nitroso-group nitrogen nucleus. The assignments of the coupling constants to the specific protons can also be done by comparison with other nitro- and nitrosoaromatic anion radicals.[23,44,45] The comparison with nitroaromatic

Table II. Experimental hyperfine splitting constant values corresponding to nitroso radical anions from electrochemically generated C-4 nitrosophenyl 1,4-DHP compounds.

a (G)	*m*-NO-Me	*m*-NO-Et	*m*-NO-iPr	*p*-NO-Me	*p*-NO-Et	*p*-NO-iPr
N	9.4	8.8	7.0	8.4	8.1	10.0
H_2	3.7	4.0	3.55	5.8[a]	6.5[a]	4.0[a]
H_3	—	—	—	1.1[b]	1.0[b]	0.65[b]
H_4	3.8	6.0	4.3	—	—	—
H_5	1.14	1.05	1.07	0.4[b]	0.4[b]	0.45[b]
H_6	3.16	2.8	3.1	3.5[a]	2.8[a]	2.45[a]
H_{DHP}	0.52	0.4	0.45	1.2	1.2	1.2

[a] This value might correspond to the proton at positions 2- or 6-.
[b] This value might correspond to the proton at positions 3- or 5-.

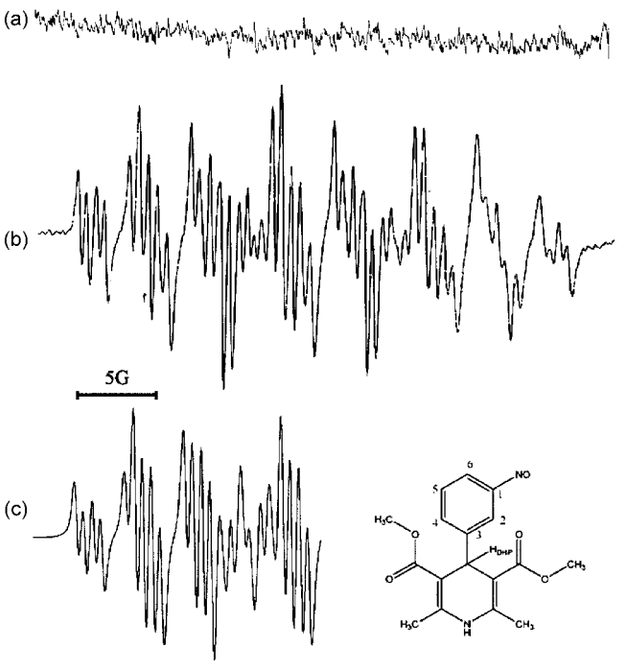


Figure 7. Experimental EPR spectra of (a) 0.1 M TBAHFP in DMF; (b) nitroso radical anion from 1 mM *meta*-NO-Me solution; and (c) simulated spectrum calculated by using constants from Table II.

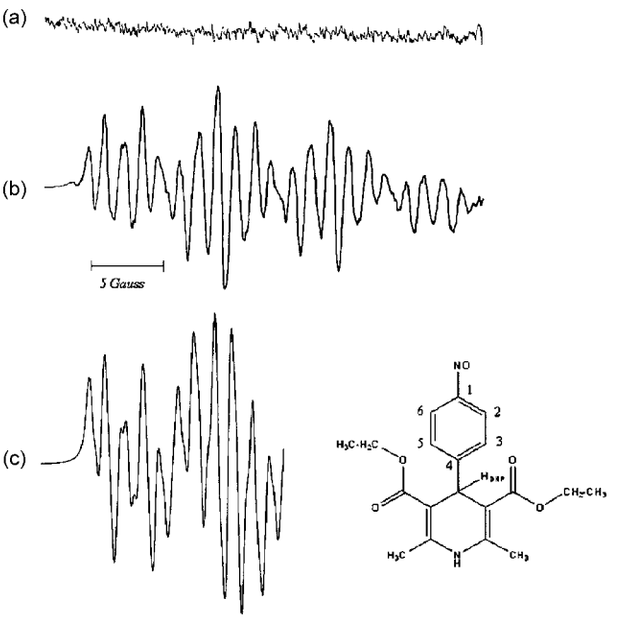


Figure 8. Experimental EPR spectra of (a) 0.1 M TBAHFP in DMF; (b) nitroso radical anion from 1 mM *para*-NO-Et solution; and (c) simulated spectrum calculated using constants from Table II.

anion radicals is justified as follows. The N = O group is electron-withdrawing, which is enhanced in the NO_2 group by the presence of an additional oxygen atom.[45] However, the coupling constants of nitrosobenzene and nitrobenzene anion radicals are similar. Therefore, we think that the comparison with nitroaromatic anion radicals is justified. The experimental hyperfine coupling constants of the anion radicals are in Table II. In general, the spectra of the *meta*-substituted derivatives are rather more complex than those of the *para*-substituted derivatives. The experimental spectra corresponding to these radicals are illustrated in Fig. 7b for the *meta*-NO-Me anion and Fig. 8b for the *para*-NO-Et anion, respectively. Furthermore, the corresponding simulated spectra shown in Fig. 7c and 8c, respectively, are in good agreement with the experimental spectra.

Conclusion

1. The electrochemical reduction in aprotic media of a number of synthesized nitroso phenyl 1,4-DHP derivatives gives rise to the one-electron reduction products, i.e., the nitroso radical anion in aprotic media.

2. The radical species decay by a second-order reaction corresponding to a dimerization, with formation of the azoxy derivatives.

3. Kinetic rate constants related to the stability of nitroso radicals varied depending on the structures of the studied compounds from $k_2 = 4906 \pm 43\ [\mathrm{M\ s}]^{-1}$ (*m*-NO-iPr) to $k_2 = 17{,}955 \pm 159\ [\mathrm{M\ s}]^{-1}$ (*p*-NO-Me). However, the parent nitro phenyl 1,4-DHP derivatives gave nitro radical anions significantly more stable than those of nitroso derivatives, i.e., with k_2 values varying between $367 \pm 11\ [\mathrm{M\ s}]^{-1}$ (*m*-NO_2-iPr) and $2909 \pm 43\ [\mathrm{M\ s}]^{-1}$ (*m*-NO_2-Me).

4. The increasing bulk of the alkyl substituents in positions 3- and 5- on the dihydropyridine ring from methyl- to isopropyl produced the most stable free radicals (nitroso radical anions).

5. The appearance of father–son type of reactions between the electrogenerated nitroso radical anions and the parent compounds, producing the corresponding nitranions, were established electrochemically and spectroscopically.

6. Nitroso radical anion formation was confirmed by ESR, and the corresponding hyperfine splitting constants were calculated with good agreement between the simulated and experimental spectra.

Acknowledgments

This work was supported by FONDECYT 1050761 and DI (University of Chile).

Universidad de Chile assisted in meeting the publication costs of this article.

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