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Electrophilic properties of nitroheterocyclic compounds. Potential hypoxic cells radiosensitizers

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Abstract

Investigation of the reduction potential and calculation of the partition coefficient *n*-octanol/water allow the assessment of the potential suitability of nitropirydine N-oxide compounds in radiotherapy of cancer. Experiments were carried out using cyclic voltammetry with HMDE as working electrode. The electrode reduction of the investigated compounds is quite irreversible and strongly dependent on pH.

Keywords: Radiosensity; Nitropirydines; Nitroimidazoles; Reduction potentials

1. Introduction

It is known that many nitroheterocycles and aromatic substrates can function as radiosensitizers and as cytotoxins in hypoxic cells [1]. Hypoxic (oxygen deficient) cells occur predominantly in tumors and seem to be indicators of a more aggressive disease [2]. They are virtually absent in normal tissues thus creating conditions for a selective bioreductive therapy of tumors. Radiosensitization refers to an enhancement of radiation damage by compounds, preferably under oxygen deficient conditions [3]. Hypoxic toxicity refers to an inherent cytotoxicity in the absence of O_2. The mechanism of action for these two biological effects involves usually the reduction of a nitro group via single or multiple reduction steps with one, two, four, or six electrons [4].

Until now many nitroheterocycles have been examined with respect to their radiopotentiating properties, and the most promising compounds proved to be nitrofurans and nitroimidazoles. Their nitro groups are "electron-affinic" and thus may interact with damages on DNA induced by radiation in a manner analogous to oxygen, hence they are called oxygen mimetic radiosensitizers or classic radiosensitizers [3,5]. Electron transfer from a damaged DNA site to the NO_2 group prevents charge recombination and produces the radical anion ($RNO_2^{\cdot -}$). As a consequence, the subsequent irreversible reactions may lead to a DNA strand breakage and cause the fixation of the damages [6].

Although in principle the properties which determine radiosensitization and hypoxic cytotoxicity are dependent on the reduction potential of the nitroimidazole group, the final factors evoking the two effects (radiosensitization and hypoxic toxicity) may not be the same. The selective toxicity of nitroaromatics toward hypoxic cells is due to the production of reactive intermediates, such as nitroso and hydroxylamine derivatives. Their reactivities, and thus cytotoxicities, are modulated by aromatic ring substituents as well as by the pH of the medium [7].

The search for new hypoxic cell-specific radiosensitizers is still focused on nitroimidazole analogues, however, new findings emerging from structure–activity relationships (SAR) used to design more efficient or effective agents are now implemented [8]. In particular, a correlation

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between the polarographic reduction potential and electron affinity was reported for nitroimidazole derivatives [9], which also correlates with the radiosensitizing efficiency [10].

It follows from this correlation that more positive reduction potentials may cause more effective radiosensitization. Further SAR studies confirm this assumption and, moreover, indicate that the electron affinity E_A, defined as the negative value of the energy of the lowest unoccupied molecular orbital (LUMO) obtained with molecular orbital (MO) calculation, correlates with the radiosensitizing activity as assessed by the sensitizing enhancement ratio (SER). SER is usually determined as the ratio of X-ray doses, which yield a 1% cell survival, applied under hypoxic conditions in the presence and absence of the drug [11]. A simple correlation between calculated E_A values and cathodic peak potentials obtained by cyclic voltammetry has also been noticed [8].

Apart from nitroimidazole, other compounds based on quinone or nitroaromatic structures were found to have bioreductive activities (mitomycin C, nitracrine) [12]. More recently, agents with N-oxide functionality (tirapazamine; antraquinone derivative AQ4N) were also described [13].

Based on the above considerations we have tried to evaluate the group of nitropirydine derivatives, including N-oxides, for electron-affinic (electrophilic) properties, which would allow us to assess their potential bioreductive properties with the aim of searching, among these compounds, for new potential hypoxic cells radiosensitizers.

2. Experimental

In present work, the properties of the following compounds were investigated: 4-nitropyridine N-oxide (**1**), 2-methyl-4-nitropyridine N-oxide (**2**), 3-methyl-4-nitropyridine N-oxide (**3**), 2,3-dimethyl-4-nitropyridine N-oxide (**4**), 2,5-dimethyl-4-nitropyridine N-oxide (**5**), 3,5-dimethyl-4-nitropyridine N-oxide (**6**), 2,6-dimethyl-4-nitropyridine N-oxide (**7**), 2,6-dimethyl-4-nitropyridine (**8**), 2,3,6-trimethyl-4-nitropyridine N-oxide (**9**), 2-(*N*′-methyl-*N*′-nitroamino)-6-methyl-4-nitropyridine N-oxide (**10**), 1-methyl-4-nitroimidazole (**11**), and 1-methyl-5-nitroimidazole (**12**). The methyl derivatives of 4-nitropyridine N-oxide used in the study were synthesized by previously described methods [14–19]. Calculation of electronic spectra and electronic structure of the studied compounds were performed within the framework of the modified all-valence electrons INDO method, utilizing some of its modifications and including 100 single excited configurations in the configuration interaction procedure [20–24]. The ground state geometry of species was optimized using the ab initio method in the base 3-21GHF.

Voltammetry measurements were performed with Autolab PGSTAT12. A hanging mercury drop with a surface of 1.5 mm^2, a Ag/AgCl|KCl (3 M) electrode, and a platinum wire were used as working electrode, reference electrode, and auxiliary electrode, respectively. Before each measurement the solution was purged with N_2 gas. Measurement of pH was carried out with a Beckman Φ72 pH Meter.

3. Result and discussion

Electron affinity and hydrophobicity are both indicators for a radiosensitizing activity. Calculated values of the partition coefficient *n*-octanol/water (*P*) for the investigated compounds are listed in Table 1. Introducing a methyl group into nitropyridine N-oxide increases the partition coefficient. Both one-methyl derivatives of 4-nitropyridine N-oxide have *P*=0.02291. The introduction of a second methyl group causes a further increase of *P* to a value of 0.07568. The introduction of an N-oxide group to 2,6-dimethyl-4-nitropyridine decreases the partition coefficient. Methyl nitroimidazolium derivatives have higher *P* values as compared to N-oxide nitropyridine derivatives. Compound

Table 1
Physicochemical parameters of 4-nitropyridine derivatives and nitroimidazole compounds

No.	Compound	Mp/°C	*P*	E_{pc}/V	E_A/eV	E_{LUMO}*/eV
(**1**)	4-nitropyridine N-oxide	161	0.00693	−0.330	1.608	−2.982
(**2**)	2-methyl-4-nitropyridine N-oxide	158	0.02291	−0.300	1.555	−3.128
(**3**)	3-methyl-4-nitropyridine N-oxide	136	0.02291	−0.277	1.532	−3.174
(**4**)	2,3-dimethyl-4-nitropyridine N-oxide	92	0.07568	−0.285[a]	1.468	−3.093
(**5**)	2,5-dimethyl-4-nitropyridine N-oxide	152	0.07568	−0.371	1.477	−3.110
(**6**)	3,5-dimethyl-4-nitropyridine N-oxide	179	0.07568	−0.411	1.456	−3.051
(**7**)	2,6-dimethyl-4-nitropyridine N-oxide	163	0.07568	−0.392	1.502	−3.059
(**8**)	2,6-dimethyl-4-nitropyridine	47	0.76384	−0.301	1.361	−2.178
(**9**)	2,3,6-trimethyl-4-nitropyridine N-oxide	114	0.25003	−0.531	1.417	−3.020
(**10**)	2-(*N*′-methyl-*N*′-nitroamino)-6-methyl-4-nitropyridine N-oxide	188	0.01079	−0.239	1.766	−3.231
(**11**)	1-methyl-4-nitroimidazole	137	0.53940	−0.714	0.636	−1.468
(**12**)	1-methyl-5-nitroimidazole	52	0.66085	−0.506	1.015	−1.959

Mp, melting point; *P*, partition coefficient *n*-octanol/water; E_{pc}, potential of cathodic peak (υ=0.050 V s^{-1}, phosphate buffer pH=6.833); E_A, electron affinity of ground state ($E_A=-E_{LUMO}$); E_{LUMO}*, LUMO energy of excited state.

[a] Potential measured at pH=6.665.

(**10**), which has simultaneously a hydrophilic and a methyl group, has a smaller *P* value in comparison with the one-methyl derivative. For compound (**12**), in which the methyl and the nitric group are closer to each other, the value of *P* is increased in comparison with (**11**), in which both groups are more distant. It is known that less lipophilic analogs are both less neurotoxic and more rapidly excreted [25], hence nitropyridines N-oxides should be less toxic than nitroimidazoles, but this has to be confirmed experimentally.

Nitroimidazoles at a concentration of 1 mM with an E_A value of more than 0.9 eV and a partition coefficient larger than 0.021 showed satisfactory enhancement ratios (E_R>1.60) [8]. The molecular diagrams of the investigated compounds (**1**), (**2**), (**3**), (**4**), (**5**), (**6**), (**7**), (**8**), (**9**), (**10**), (**11**), (**12**) are shown in Fig. 1. Values of C^2, the square of atomic orbital coefficients (eigenvectors), obtained with LUMO and the highest occupied molecular orbital (HOMO) are assigned to the structure. In nitroimidazoles, the minimum

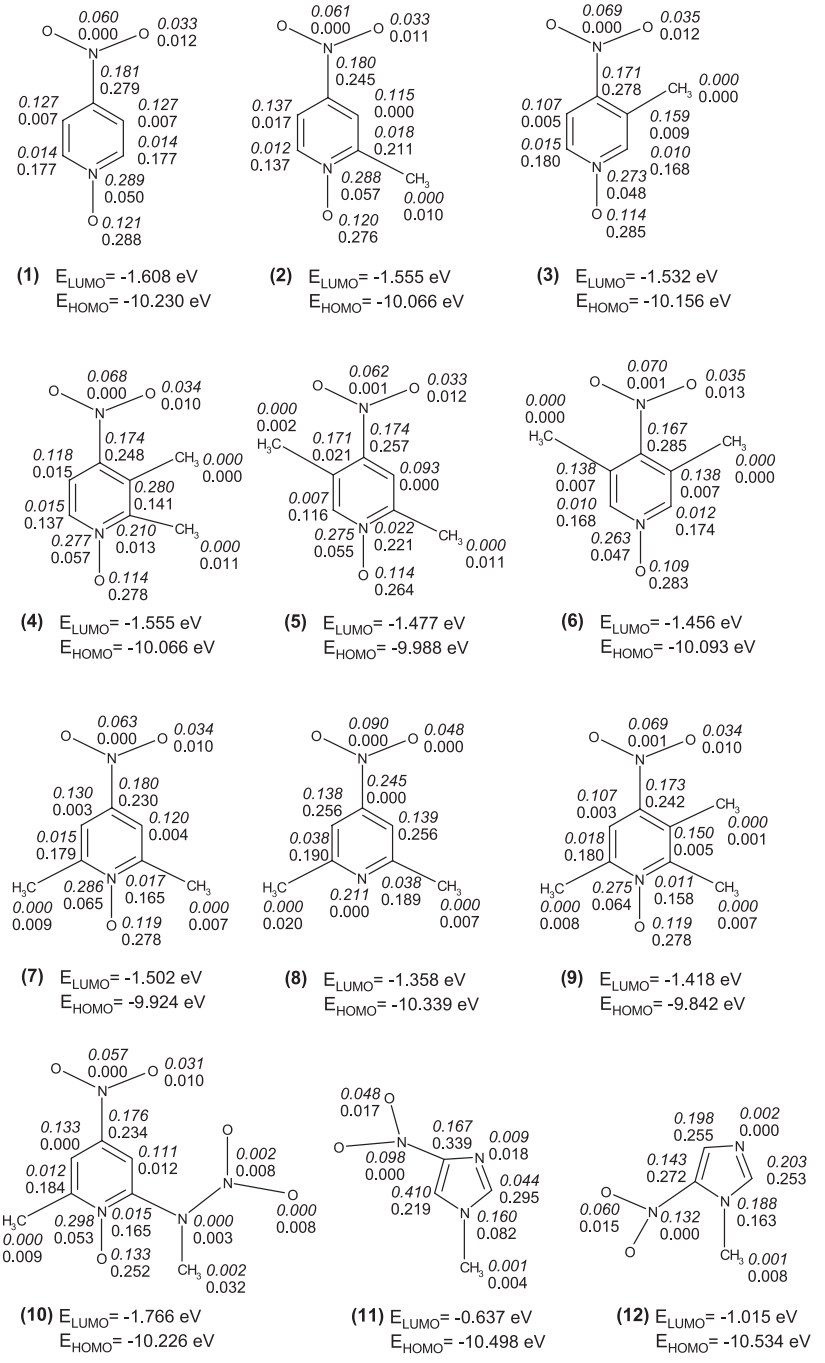

Fig. 1. The molecular diagram, orbital energy of LUMO (E_{LUMO}) and HOMO (E_{HOMO}) of compounds (**1**), (**2**), (**3**), (**4**), (**5**), (**6**), (**7**), (**8**), (**9**), (**10**), (**11**), (**12**). The squares of atomic orbital coefficients (eigenvectors) C^2 of LUMO (in italic) and HOMO are shown in the molecular diagram.

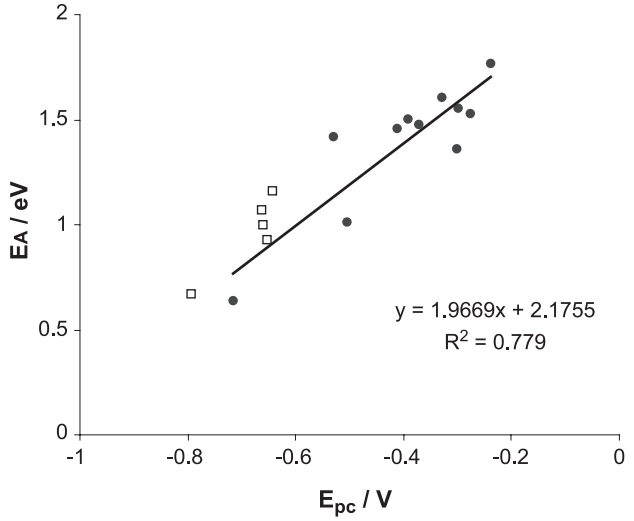

Fig. 2. Correlation between calculated E_A and measured E_{pc} at scan rate υ=0.05 V s^{-1}; pH=6.665. Closed circles represent data from this work, while open squares correspond to nitroimidazole derivatives described by Kasai et al. [8].

requirements for biological response modifiers were not only a high E_A value but also a localized C^2 of LUMO on the electron-deficient heteroaromatic group and C^2 of HOMO on a functional group of the side-chain [8]. Nitropyridine N-oxides have two groups, the nitro and N-oxide group, which can be reduced. The distribution of C^2 values of HOMO showed a trend opposite to that of LUMO, higher C^2 values of LUMO correspond to a higher susceptibility to reduction. For most investigated N-oxides except compound (**10**) the sum of C^2 values of LUMO for the nitro group is larger than that for the N-oxide group, hence reduction should occur on the nitro group. Compound (**10**) should be reduced at the N-oxide group. The sum of C^2 values of LUMO for the nitro group in nitroimidazoles is larger in compound (**12**) than in (**11**), hence compound (**12**) should be easier to reduce and should have a more positive reduction potential, as was confirmed by cyclic voltammetry. Some authors use the electron affinity determined by MO calculations to predict the radiosensitizing activity, but

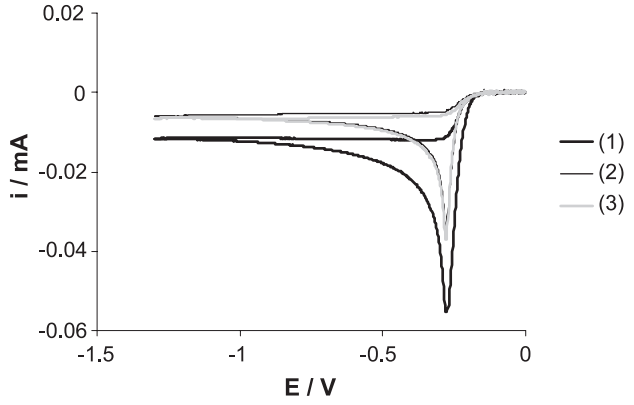

Fig. 3. Voltammograms of compound (**1**) c=1.00 mM, (**2**) c=1.95 mM, and (**3**) c=1.78 mM, scan rate υ=0.050 V s^{-1}, pH=6.833.

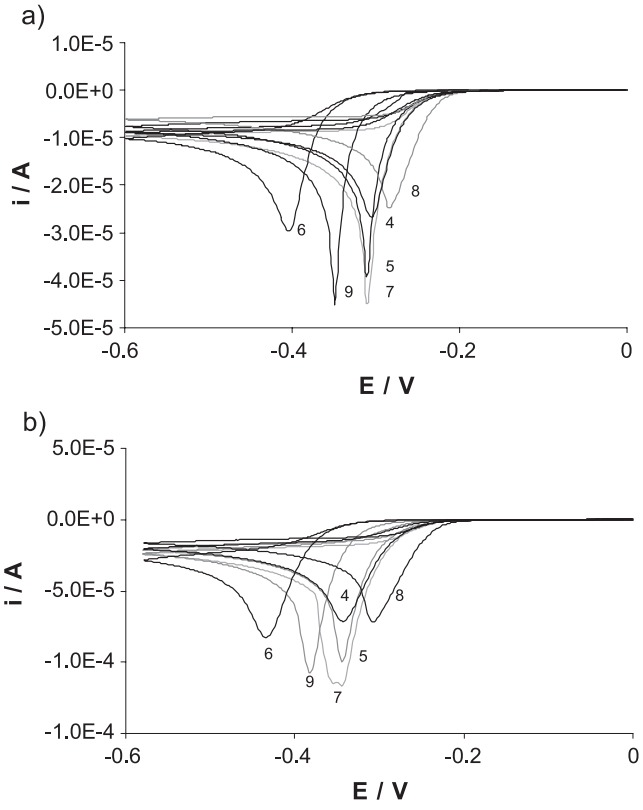

Fig. 4. Voltammograms of compounds (**4**), (**5**), (**6**), (**7**), (**8**), (**9**), c=1.37 mM for all species, scan rate (a) υ=0.050 V s^{-1}, and (b) υ=0.500 V s^{-1}; pH=6.786.

the correlation between E_A and E_{pc} is weak (see Fig. 2). Comparing E_A and E_{pc} values for the investigated compounds with data in the literature [8] lead us to postulate that nitropyridine N-oxides should be better radiosensitizers than nitroimidazole derivatives for which such a property was described.

The orbital energy of LUMO and HOMO for the investigated compounds is given in Fig. 1. Most compounds except (**11**) have an electron affinity above 0.9 eV. Moreover, it is evident that 4-nitropyridine compounds have larger electron affinities than nitroimidazole. The correlation between calculated electron affinities E_A and measured potentials of cathodic peak E_{pc} is presented in Fig. 2. The latter were determined with nitropirydines and nitroimidazoles in phosphate buffer at concentrations between 1 and 6 mM. However, the solubility of 2-(N'-methyl-N'-nitroamine)-6-methyl-4-nitropyridine N-oxide is much less than 1 mM and a saturated solution of this compound was used. E_{pc} values determined at a scan rate of 0.05 V s^{-1} are given in Table 1.

4-Nitropyridines in phosphate buffer do not exhibit an anode current peak in return scans even at fast scan rates up to 50 V s^{-1}, and some cathodic peaks have not a simple structure. Voltammograms of compounds (**1**), (**2**), (**3**) and of compounds (**4**), (**5**), (**6**), (**7**), (**8**), (**9**) recorded in the first cycle are presented in Figs. 3 and 4, respectively. In subsequent cycles a decrease of the cathodic peak current is

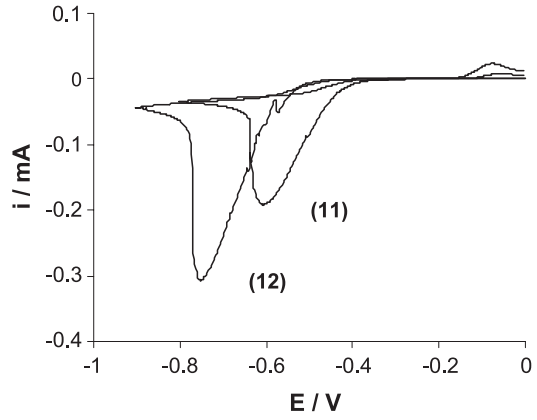

Fig. 5. Voltammograms of compounds (**11**) c=5.45 mM and (**12**) c=5.44 mM; scan rate υ=0.050 V s^{-1}; pH=6.833.

observed. As is evident from Fig. 3 the voltammograms of both one-methyl derivatives at a scan rate of 0.05 V s^{-1} have a similar shape and similar potentials of the reduction peak. Compounds with more substituents at the same concentration display different peak heights (Fig. 4). A complex shape of the peak for compound (**7**) at higher scan rates is also visible. Voltammograms of nitroimidazoles at similar concentrations (5.45 mM for 1-methyl-4-nitroimidazole and 5.44 mM for 1-methyl-5-nitroimidazole) show a complex cathodic peak and a very low anodic peak in reverse scan (see Fig. 5). Two minima of the cathodic current potential can be detected which both depend linearly on the logarithm of the scan rate (Fig. 6). For 1-methyl-4-nitroimidazole at low and high scan rates only one minimum is observed, which indicates that a coupled chemical reaction of the electroactive species occurs for this compound. The existence of an anodic peak depends on the scan rate, thus it was not observed for 1-methyl-5-nitroimidazole at a scan rate below 0.025 V s^{-1}. The height of this peak depends on the square root of the scan rate and

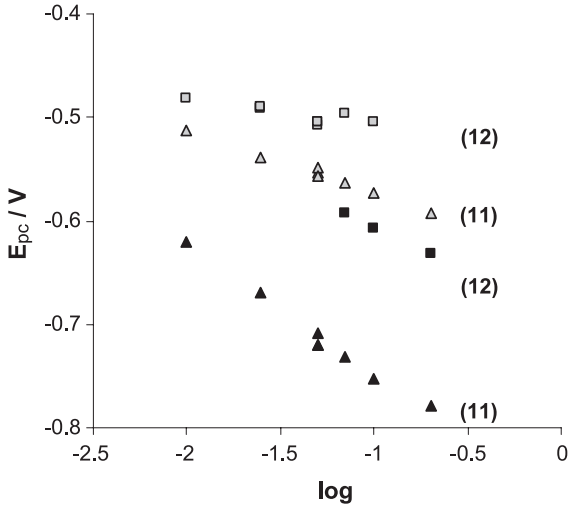

Fig. 6. Dependence of E_{pc} on log(υ) for nitrolmidazoles. Conditions of experiment were as described for Fig. 5.

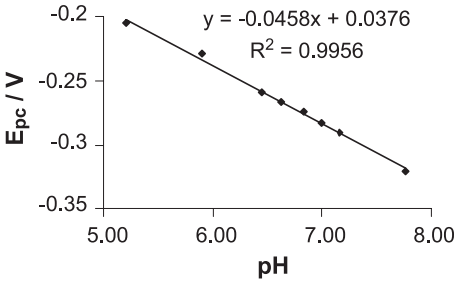

Fig. 7. Dependence of reduction potentials on pH for compound (**8**), concentration of ethanol 1% vol. Voltammograms were measured at υ=0.050 V s^{-1} in phosphate buffer.

on the potential range, i.e. if scanning is carried to more negative potentials its height is less. The ratio ipc/ipa decreases for larger scan rates, but because of the widening a peak and its shifting to more positive potentials it is not possible to obtain voltammograms under reversible or quasi-reversible conditions. Moreover, 1-methyl-4-nitroimidazole has a much higher peak current than 1-methyl-5-nitroimidazole and the first minimum is smaller than the second.

Since protons participate in the stepwise reduction of nitro compounds according to

$$RNO_2 + e^- \rightarrow RNO_2^{\cdot -} \quad (1)$$

$$RNO_2^{\cdot -} + e^- + 2H^+ \rightarrow RNO + H_2O \quad (2)$$

$$RNO + 2e^- + 2H^+ \rightarrow RNHOH \quad (3)$$

$$RNHOH + 2e^- + 2H^+ \rightarrow RNH_2 + H_2O \quad (4)$$

the dependence of E_{pc} on pH in the range between 5.21 and 7.76 (0.1 M phosphate buffer) was determined for compound (**8**) at a concentration of 1 mM and in the presence of 1% vol. ethanol (Fig. 7). A linear dependence of the cathodic peak potential on pH was observed, however, its slope is different from the theoretical value of −0.059 V/pH unit for an electrochemical reaction involving equal numbers of electrons and protons. If the ratio of electrons

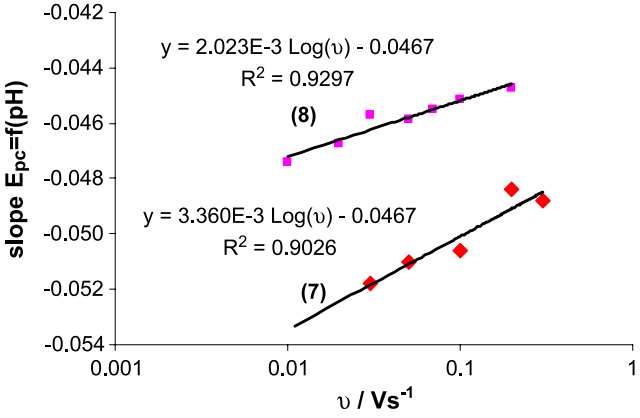

Fig. 8. Slope of the linear dependence E_{pc}=f(pH) as a function of scan rate (logarithmic scale) for compounds (**7**) c=0.2 mM and (**8**) c=0.98 mM.

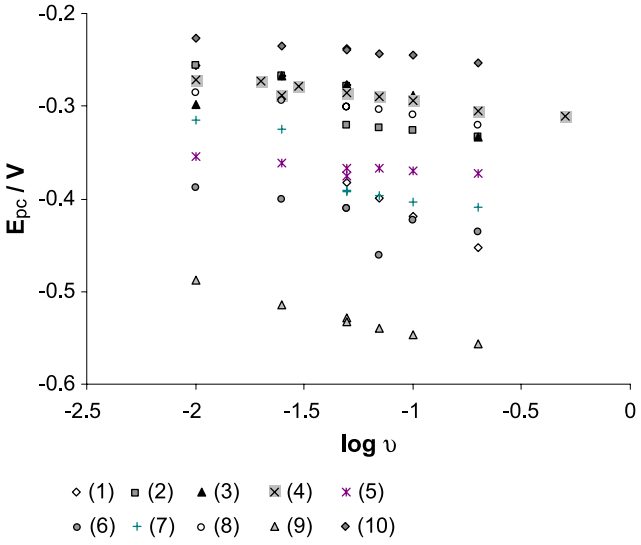

Fig. 9. Dependence of E_{pc} on log(υ) for compounds (**1**), (**2**), (**3**), (**4**), (**5**), (**6**), (**7**), (**8**), (**9**), (**10**); pH=6.665.

to protons for a sequence of electrochemical reactions varies between 1 and 2 the corresponding slope should fall in the interval between −0.059 and −0.030. Hence the value of −0.047 (at a scan rate 0.01 V s^{-1}) observed for compound (**8**) indicates such a situation with probably 4 protons being consumed per 5 electrons during the electrode reduction. Moreover, this slope was found to depend on scan rate in that it decreases with increasing rate (Fig. 8). Besides compound (**8**) only compound (**7**) was investigated with respect to the dependence of the cathodic peak potential on pH, and a similar behavior was observed, however, the dependence of the slope on scan rate was somewhat different (Fig. 8). This may be explained by different rate constants for the reactions (1)–(4) and by differences in the mixed processes.

A linear dependence of E_{pc} on logυ was observed for all compounds (Figs. 6 and 9). However, due to some

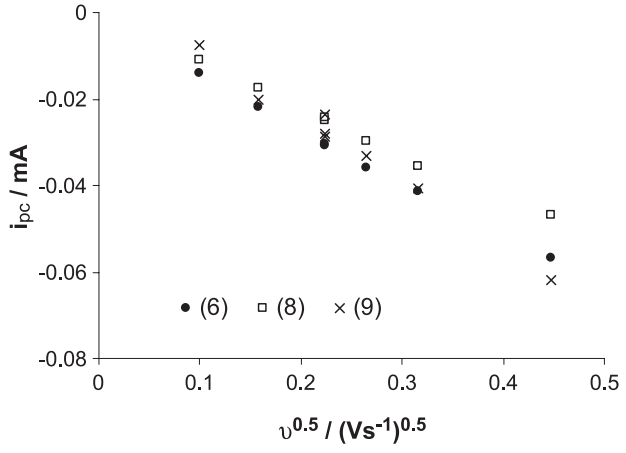

Fig. 10. Dependence of the cathodic peak current on $\upsilon^{0.5}$ for compounds (**6**) c=1.58 mM, (**8**) c=1.38 mM, and (**9**) c=1.29 mM; pH=6.833.

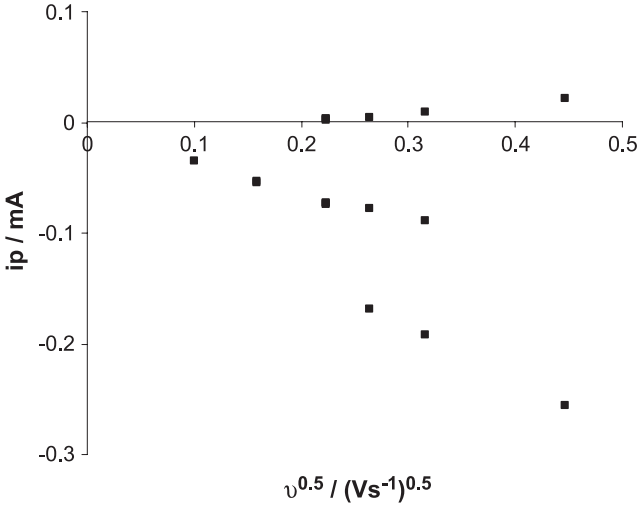

Fig. 11. Dependence of the peak current on $\upsilon^{0.5}$ for compound (**12**), c=5.44 mM, pH=6.833. Anodic and cathodic processes are presented.

reactions involved in the electrode processes, the corresponding currents ipc depend linearly on $\upsilon^{0.5}$ (see Fig. 10) for compounds (**6**) and (**8**), which have symmetrically substituted methyl groups, and for the barely visible first current minimum in the voltammogram of compound (**9**). For the other compounds, the dependences of the current on scan rate are not so simple, and sometimes even a switching occurs, as shown in Fig. 11 for compound (**12**). A similar behavior was observed for compounds (**1**), (**2**), and (**3**). At higher scan rates, an additional peak can appear very close to the first peak, and the current of this new peak is larger than that of the first peak. Generally, voltammograms of nitropyridine derivatives have similar shapes without any anodic signals, and no other changes were observed at higher scan rates up to 50 V s^{-1}.

4. Conclusion

Some authors use the electron affinity determined by MO calculations to predict the radiosensitizing activity, but the correlation between E_A and E_{pc} is weak due to complicated reduction reactions. A comparison of the obtained reduction potentials of nitropirydines and nitroimidazoles, electron affinity (Fig. 2) and hydrophobicity with data reported earlier [8] allows us to conclude that in both groups of compounds radiosensitizers could exist. Compound (**12**) should be a better radiopotentitator than compound (**11**), and nitopyridine N-oxides should be better radiopotentitators than nitroimidazoles, but this requires further investigations of the biological activity. The larger C^2 LUMO values for nitro than N-oxide groups in most of the presented N-oxides suggest that reduction should occur at the nitro group, but this depends also on the side chain for various analogues. The electrochemical reduction mechanism of the presented compounds is irreversible, involves protons and hence is pH-dependent.

Acknowledgements

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