Article

Electrochemical Properties of Biologically Active Heterocyclic Naphthoquinones

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Uma série de naftoquinonas heterocíclicas naturais e sintéticas, algumas delas com atividades anti-plasmódio e tripanosomicida comprovadas, foi estudada através de voltametria cíclica em meio aprótico (DMF/TBAP). Os voltamogramas apresentaram dois pares de ondas, relativos a processos reversíveis ou quase-reversíveis de transferência monoeletrônicos, formando, no ramo catódico, o ânion-radical semiquinônico ($Q^{\bullet-}$) e, em seguida, o diânion (Q^{2-}). *Orto*-naftoquinonas sofreram redução mais facilmente do que *para*-naftoquinonas similares. *Para*-naftoquinonas fundidas a um heterociclo aromático mostraram-se mais facilmente redutíveis do que *orto*-naftoquinonas ostentando heterociclos não aromáticos. Efeitos dos substituintes correlacionam-se bem com os valores de potencial de redução de primeira onda (Ep_{c1}) e de potencial de meia onda ($E_{1/2}$). Eletrólises realizadas em presença de anidrido acético forneceram hidroquinonas acetiladas em alto rendimento. Comparação dos dados eletroquímicos com atividades anti-plasmódio evidenciou ausência de correlação, diferentemente do registrado em relação às atividades tripanosomicidas.

A series of natural and synthetic heterocyclic naphthoquinones, some of them with anti-plasmodial and trypanocidal activities, were studied by cyclic voltammetry in aprotic media (DMF/TBAP). In this solvent, the voltammograms of the quinones show two pairs of waves, corresponding to reversible or quasi-reversible one-electron transfer processes to form the semiquinone anion radical ($Q^{\bullet-}$) and the dianion (Q^{2-}). Within the studied series, *ortho*-quinones undergo reduction easier than isomeric *para*-quinones. However, *para*-naphthoquinones fused to an aromatic heterocyclic ring are more easily reduced than the corresponding *ortho*-naphthoquinones with a non aromatic heterocycle. Substituents effects correlated very well with the first reduction potential (Ep_{c1}) and the half wave potential ($E_{1/2}$). High yield reductive acetylation was achieved by electrolyses in the presence of acetic anhydride. Comparison of electrochemical data with reported antimalarial activities showed no correlation, differently from the already reported trend in relation to trypanocidal activities.

Keywords: *cyclic voltammetry, quinone reduction, heterocyclic naphthoquinones, substituent effects, biological activities*

Introduction

Several natural and synthetic heterocyclic naphthoquinones have important biological activities such as antitumoral, anti-protozoan and antibiotic[1-9]. In cancer chemotherapy, they are considered the second more important group[8]. After an initial bioreduction step, their mode of action normally involves the generation of active oxygen species by redox cycling[8], intercalation in the DNA double helix[10] or alkylation of biomolecules[11]. As the bioreduction of quinones is influenced by their redox properties, the understanding of how structural features of the quinones are related to these properties is an important step to comprehend their mechanism of action and predict modifications to improve their biological activity[12].

A plethora of quinones is known, the electrochemistry of which has been widely studied[13,14]. There are, however, few reports on electrochemical studies of heterocyclic naphthoquinones[1,13-16]. Recently, we observed a contribution of the easiness of reduction on the trypanocidal activity of seventeen synthetic and natural naphthoquinones[17]. Correlation between antimalarial activities and redox potential was earlier observed[9]. As the electrochemistry of these quinones have not yet been published, we report here their electrochemical parameters, including Ep_c and $E_{1/2}$ values of for their cathodic waves, in aprotic medium, along with results from electrolyses for some of them. We also compare antimalarial activities and electrochemical data. The aprotic medium was chosen because it mimics the hydrophobic cell environment[18].

Experimental

Chemicals

The naphthofuranquinones (NFQ), naphthothiophenquinones (NTQ), naphthodihydropyranquinones (NDQ) used in this work were described elsewhere (**1-6**[19], **7-12**[20], **13-14**[19] and **15-17**[21-22]).

Solvents, electrolytes and solutions

N,N-Dimethylformamide (Merck, Uvasol Grade) was treated with cupric sulfate, filtered and distilled at reduced pressure through a glass Vigreux column (12 cm). Tetra-*n*-butylammonium perchlorate (TBAP) was prepared from the corresponding bromide (Aldrich or Lancaster Synthesis) and perchloric acid 70% (Aldrich). The resulting salt was washed with cold water until neutral pH, recrystallized from ethyl acetate and thoroughly dried before use (2 days, 70 °C, under high vacuum). Test solutions of the quinones (1 mM) were prepared just before electrochemical experiments and the dissolved oxygen eliminated by bubbling the solution with dry nitrogen. During the experiments the cell was covered with aluminum foil to minimize photoreactions.

Electrochemical Measurements

Cyclic voltammetry (CV) was performed using a PAR model 273 A/PAR EG & G potentiostat/galvanostat equipped with an HP 7090A measuring plotter system. The whole system was controlled by a 386 SX/Microtec compatible PC. A SMDE 303 A/EG & G PARC hanging mercury electrode (area 0.009664 cm^2) was used as the working electrode, together with a platinum counter-electrode and a home-built Ag/AgCl/NaCl (0.1 M) Luggin reference electrode, isolated from the solution by a Vycor rod. The scan rate was in the range 0.035 - 35 V s^{-1}.

Reduction

2, **3**, **7** and **14**, were electrolyzed at a potentiostat-galvanostat 371/PAR EG&G. The current was integrated electronically. Conventional glass cells were used with the anode and cathode compartments separated by medium porosity sintered glass. The electrolyte was pre-electrolyzed at -2.0 V until the background current reached a low steady value.

The following description is typical for electrolyses procedures and methods for work-up and isolation of products. 2-Methylfuran-*para*-naphthoquinone, **2** (0.0175 g, 0.08 mmol), dissolved in 40 mL of DMF/TBAP (0.1M) was electrolyzed at an Hg pool cathode held at -0.9 V. After consumption of 1 F/mol, the cell current reached residual current. The potential was then increased to the potential of the second wave (-1.6 V). After uptake of an additional 1 F/mol, the cell current was still 50% of the initial one. The decrease of the current turned very slow, and the electrolysis was finished. Addition of water, followed by ether extraction furnished a colorless compound that immediately suffered air oxidation to give back the original quinone. The electrolysis was then, carried out, using quinones **3** (0. O146 g, 0.065 mmol)/**7** (0.0216 g, 0.101 mmol) and **14** (0.0205 g, 0.086 mmol) in the presence of freshly distilled acetic anhydride (5 mL) as an electrophile, close to the potential of the second wave (-1.7 V). After reaching the residual current, with exact consumption of 2 F/mol, the acetylated compounds **18**, **19** and **20** were obtained, with yields of 100%, 82%, and 94%, respectively.

*4,9-Diacetoxy-2-ethylnaphtho[2,3-b]furan (***18***)*

Colorless crystals, m.p. 165-167 °C (CHCl$_3$); IR KBr/max$^{(cm-1)}$:1762 (νCO), 1600 (ν arom. ring), 1366 (δO-COC),1203, 1164, 1042 (δCO), 765, 735 (ν furan). ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 1.36 (t, J = 7.5 Hz, 3H, CH$_2$C̲H̲$_3$), 2.52 (s, 3H, COCH$_3$), 2.57 (s, 3H, COCH$_3$), 2.82 (dq, J = 7.5 Hz, J = 1.0 Hz, 2 H, C̲H̲$_2$CH$_3$), 6.38 (t, J = 1.0 Hz, 1H, furan ring), 7.42-7.52 (m, 2 H, arom. ring) 7.90-7.95 (m, 2H, arom. ring).

^{13}C-NMR (CDCl$_3$, δ): 11.3 (Me), 20.6 (Me), 20.8 (Me), 22.0 (CH$_2$), 98.6 (CH), 120.9 (CH), 121.0 (CH), 123.5

(Cq), 123.6 (Cq), 124.4 (Cq), 124.7 (CH), 125.3 (CH), 126.2 (Cq), 134.5 (Cq), 144.3 (Cq), 164.4 (Cq), 168.3 (CO), 168.8 (CO).

4,9-Diacetoxynaphtho[2,3-b]thiophen (19)

Colorless crystals, m.p. 237 °C IR KBr/max$^{(cm-1)}$:1752, 1365, 1206, 1163, 1069, 1014, 758. ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 2.56 (s, 6H, COCH$_3$), 7.28 (bs, 1H, thiophen ring), 7.46 (bs, 1H, thiophen ring), 7.52-7.55 (m, 2H, arom. ring), 7.85-7.89 (m, 1H, arom. ring), 7.93-7.97 (m, 1H, arom. ring).^{13}C-NMR (CDCl$_3$, δ): 20.7 (Me), 20.7 (Me), 120.2 (CH), 120.6 (CH), 121.6 (CH), 124.5 (Cq), 124.8 (Cq), 125.9 (CH), 126.2 (CH), 128.8 (CH), 130.9 (Cq), 131.9 Cq), 138.4 (Cq), 138.6 (Cq), 168.2 (CO), 169.0 (CO).

4,5-Diacetoxynaphtho[1,2-b]furan (20)

Colorless crystals, m.p. 134-136 °C. IR KBr/max$^{(cm-1)}$: 1766, 1369, 1206, 1042, 1010, 764, 721. ^{1}H-NMR (CDCl$_3$, 400 MHz, δ): 1.39 (d, J = 7.1 Hz, 6H, CH(CH$_3$)$_2$), 2.41 (s, 3H, COCH$_3$), 2.46 (s, 3H, COCH$_3$), 3.17(m, 1H, CHCH$_3$)$_2$), 6.38 (s, 1H, furan ring), 7.4-7.51 (m, 1H, arom. ring), 7.53-7.59 51 (m, 1H, arom. ring), 7.84 (d, J = 8.1 Hz,

1H, arom. ring), 8.26 (d, J = 8.1 Hz, 1H, arom. ring). ^{13}C-NMR (CDCl$_3$, δ): 20.4 (Me), 20.6 (Me), 21.0 (2 x Me), 28.4 (CH), 98.9 (CH), 119.3 (Cq), 119.8 (Cq), 120.2 (CH), 121.9 (CH), 124.4 (CH), 125.5 (CH), 126.3 (CH), 132.8 (Cq), 133.3 (Cq), 148.2 (Cq), 165.0 (Cq), 167.9 (CO), 168.6 (CO).

Results and Discussions

The cyclic voltammograms of the naphthoquinones in DMF showed two typical waves corresponding to two sequential reversible or quasi-reversible one-electron transfer processes[13,14]. The first wave was related to the redox couple quinone (Q) / semiquinone anion radical (Q$^•$) and the second wave due to the semiquinone anion radical (Q$^•$) / quinone dianion (Q^{2-}).

The electrochemical parameters (Ep$_{c1}$ and Ep$_{c2}$, Ep$_{a1}$ and Ep$_{a2}$, E$_{(1/2)1}$ and E$_{(1/2)2}$, ΔEp$_c$, for both waves, and Ep$_{c2}$-Ep$_{c1}$), for seventeen heterocyclic naphthoquinones (Fig. 1) were measured from cyclic voltammograms registered with a scan rate of 0.100 V s^{-1}. These data are listed in Table 1.
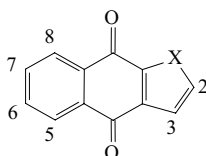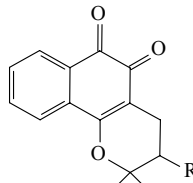

Quinone	X	C-2	C-3	C-5	C-6	C-7	C-8
				Substituents			
1	O	H	H	H	H	H	H
2	O	Me	H	H	H	H	H
3	O	Et	H	H	H	H	H
4	O	CHMe$_2$	H	H	H	H	H
5	O	H	H	OMe	H	H	H
6	O	CH(OH)Me	H	H	OMe	H	H
7	S	H	H	H	H	H	H
8	S	H	H	OMe	H	H	H
9	S	H	H	H	OMe	H	H
10	S	H	H	H	H	H	OMe
11	S	H	H	H	H	OMe	OMe
12	S	H	H	OMe	H	OMe	H
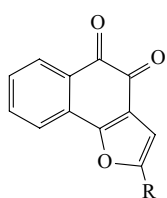
13: R=H
14: R=CHMe$_2$
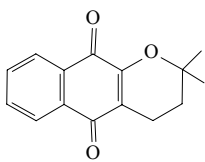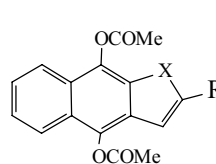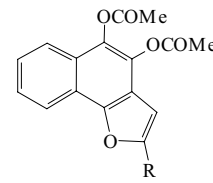
15

16: R=H
17: R=CH$_2$CH=CH$_2$

18: X=O, R=Et
19: X=S, R=H

20: R=CHMe$_2$

Figure 1. Structures of studied quinones.

Table 1. Voltammetric parameters* in DMF/TBAP 0.1M, $v = 0.100$ mV s^{-1}.

Q	1st wave				2nd wave				-(Ep$_{c2}$-Ep$_{c1}$)
	-Ep$_c$	-Ep$_a$	ΔEp	-E$_{1/2}$	-Ep$_c$	-Ep$_a$, ΔEp	-E$_{1/2}$		
1	0.762	0.680	0.082	0.721	1.419	1.345	0.074	1.382	0.657
2	0.784	0.726	0.058	0.755	1.450	1.386	0.064	1.418	0.666
3	0.784	0.724	0.060	0.754	1.426	1.366	0.060	1.396	0.642
4	0.789	0.719	0.070	0.754	1.464	1.390	0.074	1.427	0.675
5	0.828	0.774	0.054	0.801	1.439	1.366	0.073	1.403	0.611
6	0,817	0.741	0.076	0.779	1.405	1.341	0.064	1.373	0.588
7	0.793	0.718	0.075	0.756	1.471	1.393	0.078	1.432	0.678
8	0.832	0.769	0.063	0.801	1.400	1.331	0.069	1.366	0.568
9	0.817	0.751	0.066	0.784	1.466	1.395	0.071	1.431	0.649
10	0.847	0.780	0.067	0.814	1.404	1.329	0.075	1.367	0.557
11	0.855	0.792	0.063	0.824	1.410	1.320	0.090	1.365	0.555
12	0.871	0.795	0.076	0.833	1.476	1.380	0.096	1.428	0.605
13	0.659	0.579	0.080	0.619	1.213	-	-		0.554
14	0.708	0.635	0.073	0.671	1.290	1.180	0.110	1.235	0.582
15	0.899	0.821	0.078	0.860	1.503	1.406	0.097	1.455	0.604

The Ep$_{c1}$ of the *para*-naphthoquinone derivatives **1-12** is in the range -0.76 V 0.87 V while Ep$_{c2}$ varies from -1.40 V to -1.48 V (Fig. 2). In the case of the aromatic heterocyclic *ortho*-naphthoquinones **13** and **14**, Ep$_{c1}$ and Ep$_{c2}$ vary from -0.66 V to -0.71 V and from -1.21 V to -1.29 V, respectively (Fig. 3). The *ortho*-naphthoquinones with a non aromatic heterocyclic ring (**16** and **17**) showed their Ep$_{c1}$ (-0.80 V and 0.81 V) and Ep$_{c2}$ (-1.32 V to -1.38 V) close to those of *para*-naphthoquinone derivatives. The Ep$_{c1}$ and Ep$_{c2}$ of the *para*-derivative **15**, -0.90 V and -1.50 V, respectively, are the more negatives among the investigated quinones.

The peak current of the first (Ip$_{c1}$) and second reduction waves (Ip$_{c2}$) of the studied naphthoquinones are proportional to the square root of the scan rate, indicating diffusion controlled processes. In relation to the first cathodic wave, compounds **2**, **3**, **5**, **8-11**, **16** and **17** displayed an almost ideal electrochemical behavior: the separation between anodic and cathodic peak potentials (ΔEp) is close to that expected for a reversible one electron transfer (59 mV); the peak current ratio (Ip$_{a1}$/ Ip$_{c1}$) is close to unity and Ep$_{c1}$ and E$_{1/2}$ are independent of scan rates. These data and the one Faraday/mol consumption measured from electrolysis with quinone **2** (see experimental) are compatible with a reversible monoelectronic reduction wave (Figs. 2 and 3). The other quinones (**1**, **4**, **6**, **7**, **12-15**) showed a slight deviation
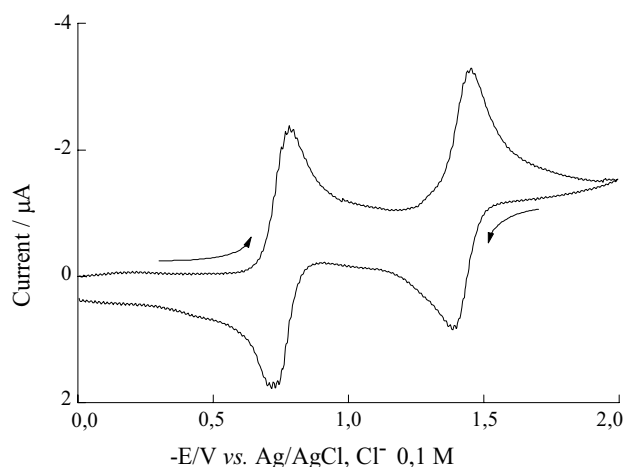

Figure 2. Cyclic voltammogram of *para*-quinone 2. [quinone] = ~1.0mM in DMF/TBAP (0.10M); 25 °C; $v = 0.100$ V s^{-1}; HMDE (0.97 mm^2).

from the ideal behavior: the ΔEp values varies from 70 mV to 80 mV and the Ep$_{c1}$ and E$_{a1}$ are constant only at low scan rates (≤ 2.0 V s^{-1}), changing slightly with the increase of scan rate, as expected for a quasi-reversible process.

Except for **2**, **3** and **6**, the profiles of the second reduction wave show characteristics of a less reversible monoelectronic processes: besides appearing broader and smaller than the first wave, their current ratios (Ip$_{a2}$/Ip$_{c2}$)
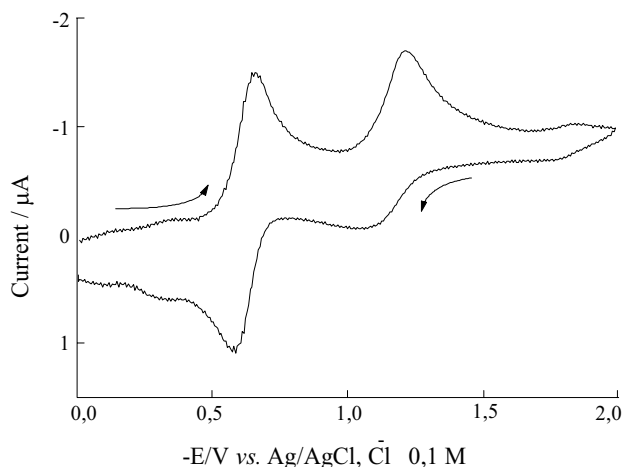
Figure 3. Cyclic voltammogram of *ortho*-quinone 13. [quinone] = ~1.0 mM in DMF/TBAP (0.10M); 25 °C; $v = 0.100$ V s^{-1}, HMDE (0.97mm^2).

deviated significantly from unity. This fact is more evident for the *ortho* derivatives, **13** (Fig. 3), **16** and **17**, where the corresponding anodic waves are not discernible. This fact is indicative of kinetic or other complications. It is possible that the residual water present in the solvent and reagents could catalyze the disproportionation of the radical anion ($Q^{\bullet -}$) or be reduced by the electrogenerated dianion (Q^{2-})[23]. This *quasi*-reversible character of the second reduction process and the positive shift in Ep_{c2} could also be due to ion-pairing stabilization of the quinone dianion (Q^{2-}) by the tetra-*n*-butylammonium cation[15].

Except for **6** ($\Delta E = 0.588$ V), the difference between the two cathodic peaks (Ep_{c2}-Ep_{c1}, Table 1) is consistently smaller for the *ortho*-quinone derivatives (**13**, **14**, **16** and **17**) than for the *para*-quinones. As reported for aromatic dianions[24], charges dispersed over a large molecular framework are usually less affected or unaffected by counter ions. On the other hand, the proximity of the two charges in the *ortho*-naphthoquinone dianions could be more efficiently stabilized by counter-ions (n-Bu$_4$N$^+$Q^{2-}), causing a positive shift in the second wave. The vicinity of a charge and the nonbonding electrons of the *peri*-OMe substituent could have a similar effect and explain the intermediate values of Ep_{c2}-Ep_{c1} for the *para*-quinones **5**, **8**, **10-12**.

Using the Ep_{c1} values measured from CV recorded with $v = 0.100$ V s^{-1}, the seventeen quinones investigated can be arranged in the following order of easiness of reduction: **13 > 14 > 1 > 2 = 3 > 4 > 7 > 16 = 17 > 6 = 9 > 5 > 8 > 10 > 11 > 12 > 15**.

In spite of the possibility of comparison only on a qualitative basis, regular Ep_{c1} changes with the constant σ of the tethered substituent[25] were verified, always with the expected trend[26]. Thus, the introduction of a methoxy group at C$_5$ position (*peri*) of the *para*-NFQ skeleton (**1 →** **5**) provoked an Ep_{c1} shift of -0.066 V. The same substitution causes a less intense effect (-0.039 V) on the NTQ (**7 → 8**),

indicating an influence of the heteroatom. Interestingly, a methoxy group at the C$_8$ (*peri*) position of NTQ (**7 → 10**) induces a higher shift (-0.054 V). As expected on the basis of substituent constants for methoxy groups (σ_p-X = -0.12, σ_m-X = 0.10 and σ_o-X = -0.39)[25], their attachment to the C$_6$ position of *para*-NTQ (**7 → 9**) have a smaller influence on the Ep_{c1}, making the reduction only 0.024 V more negative. This reflects the dominant electrodonating mesomeric effect of the lone electron pair of the methoxy group. Although not additive, possibly due to changes in the molecule's planarity caused by the steric congestion[26], the introduction of a second methoxy group, as in (**7 → 11**) and (**7 → 12**), does lead to shifts of -0.062 V and -0.078 V, respectively. The location of the methoxy group on the benzenoid ring (C$_5$ *vs.* C$_8$, C$_6$ *vs.* C$_7$) and different heteroatoms in the attached ring (S or O) seems to influence the naphthoquinone carbonyls and thus Ep_{c1}, fact already demonstrated by ^{13}C-NMR data analysis[19,27].

Introduction of methyl, ethyl and *iso*propyl groups at C$_2$ of the *para*-NFQ skeleton (**2** and **3**) promoted small cathodic shifts of *ca* 0.025 V. All the negative increments are consistent with the increase of the negative charge at the reduction site[26].

Within the quinones investigated, the *ortho*-quinones were shown to be more easily reduced than the similar *para*-quinones, corroborating previous observations with other classes of quinones[13], in spite of the small number of systematic electrochemical studies comparing *ortho*- and *para*- pair of compounds[28]. By comparing the Ep_{c1} and Ep_{c2} values of **13** *vs.* **1**, **14** *vs.* **4**, and **16** *vs.* **15**, one observes that the differences are almost constant, around 100 mV and > 140 mV more negative, respectively, for *para*- derivatives. The larger difference on Ep_{c2} is related to higher *ortho*-Q^{2-} stability, as already reported. Very recently, Stoppani and coworkers[29] concluded, based on the calculated LUMO atomic charges, that electronic asymmetry and polarity of C=O bond are higher in *ortho*-naphthoquinones than in *para*-naphthoquinones. These aspects make the carbonyl carbon atom of *ortho* compounds more electron deficient and, hence, easier to reduce than those in symmetric *para*-naphthoquinone derivatives. They also observed that in tetrahydronaphthoquinones the eletrophilicity of the carbonyl oxygen was lowered[29]. Indeed, within the quinones investigated in the present study, the *ortho*-naphthodihydropyranquinones (**16**, **17**) are more difficult to reduce than *para*-naphthothiophenquinones and *para*-naphthofuranquinones, probably due to a smaller ability to stabilize the electrogenerated semiquinone (Q$^{\bullet -}$) and dianion (Q^{2-}) via conjugation.

Electrolyses of quinones, in the absence of electrophiles (acetic anhydride), lead, quite regularly to the starting material, by air oxidation. In our case, quinone **2** was recovered, after cathodic reduction, almost quantitatively.

In the presence of acetic anhydride, all the reactions occurred smoothly, with exact consumption of 2 F/mol and with high yields, reproducing earlier results[30].

It was shown recently that the trypanocidal activity was higher among quinones with more positive reduction potentials[17]. Earlier studies suggested a correlation between redox potentials and antimalarial activities[9]. It was also suggested that oxidative stress plays important role in malaria, being both beneficial and pathological[31]. Using the results published in the literature reporting the antiplasmodial activity assays for some of these quinones[5,19] we could see no apparent correlation, *ortho*- and *para*-quinones being equally active. This suggests that a different mechanism of drug action[31], independent of bioreduction is operating, as is the case for chloroquine and other alkaloids[32]. Among other possible mechanisms, the significant and similar antimalarial activity of *ortho*- and *para*-heterocyclic quinones could involve iron chelation[31].

Conclusions

Ortho-naphthoquinones are always easier to reduce than their *para*- isomers, reflecting the enhanced electrophylic character of the vicinal carbonyls in the former group. The Q^{2-} species generated by the reduction of *ortho*-quinones or *peri*-OMe substituted *para*-quinones are better stabilized by cations of the supporting electrolytes. This stabilization results in a positive shift of Ep_{c2}, turning ΔEp_c smaller than 0.600 V for these compounds. The heteroatoms (O and S) of heterocyclic naphthoquinones exert different effects over their carbonyl groups and, as consequence, over the carbons in the benzenoid ring. This fact causes different shifts in the reduction potential of quinones depending on the position of the substituent. The positions *ortho*, *meta* and p*ara* can not be considered similar and the effect is more pronounced when substituents are placed in the *peri*- position. Electrochemical reductive transformations of quinones in the presence of electrophiles are easily performed and may be useful for synthesis of several quinone derivatives or to protect the reactive carbonyl groups.

No correlation was evidenced between electrochemical parameters of quinones and published antiplasmodial activities. This finding suggests that, at least for the quinones evaluated, redox potential are not related to this biological activity.

Acknowledgments

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