

Electrochemical and Spin-Trapping Properties of *para*-substituted α -Phenyl-*N*-*tert*-butyl Nitrones



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ARTICLE INFO

Article history:

Received 5 October 2015

Received in revised form 22 January 2016

Accepted 7 February 2016

Available online 9 February 2016

Keywords:

Nitrones

Antioxidants

Electrochemistry

Spin-Trapping

Free Radicals

Oxidative Stress

ABSTRACT

Nitrones are known both as therapeutic antioxidants and efficient spin-traps. In this work, the redox behavior of various *para*-substituted α -phenyl-*N*-*tert*-butyl nitrones (PBN) was studied by cyclic voltammetry. The polar effect of the substituents was found to correlate with the electrochemical properties of the nitronyl function. Compounds bearing an electron-withdrawing group were more easily reduced than those having an electron-donating group and an opposite trend was observed for the oxidation. Ease of oxidation was also computationally rationalized using DFT approach showing increased ease of oxidation with electron donating functionalities. Since electrochemical properties of nitrones are known to correlate with biological properties, this work provides insights in the design of potent nitrone antioxidants. Using cyclic voltammetry the relative rate of superoxide trapping by nitrones was investigated and compared to the classical antioxidant BHT. The determination of the relative rate of phenyl radical trapping was also carried out but showed no clear correlation with the nature of the substituents. This indicates the absence of a polar effect in agreement with previous data and further supports the intermediate nature, that is, non- or weakly nucleophile, of phenyl radical. On the contrary kinetics of hydroxymethyl radical trapping was found to correlate with the nature of the substituents, demonstrating the nucleophilic nature of its addition onto nitrones.

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Introduction

Oxidative stress has been implicated in several pathophysiological disorders such as cardiovascular diseases [1], cancer [2], stroke and neurodegenerative diseases [3]. The ability of nitrones to prevent oxidative stress-mediated damage in *in-vitro* and *in-vivo* models has made them promising synthetic antioxidants with considerable potential in therapeutics [4–6]. For instance, nitrones have shown excellent neuroprotection [7]. Among other properties, one can cite cardioprotection [8], anti-cancer activity [9], as well as anti-ageing effect [10]. Aside from their use as therapeutic antioxidants, nitrones are used in spin-trapping experiments where the nitronyl group reacts with a free radical to form a stable

and identifiable aminoxyl radical that is detected by EPR spectroscopy [11]. The spin trapping technique was developed in the late 1960s and, since then, nitrones have been widely used as analytical reagents to identify biologically relevant free radicals such as oxygen-, carbon- or sulfur-centered radicals. Although there are several evidences to support that radical trapping and antioxidant properties of nitrones are not dependent of each other, the precise mechanism by which these compounds act in different biological models has not yet been fully elucidated [6].

The nitronyl moiety exhibits electrochemical activity both in aqueous and non-aqueous media. Because of the redox behavior of nitrone spin-traps, the “inverted spin-trapping” has been reported [12,13]. In this process, there is an inversion of the electron distribution between the two reacting species, leading to a classical aminoxyl spin adduct whose formation arises from the capture of a polar nucleophile by the radical cation form of the spin-trap. It is therefore important to know the redox behavior of nitrones in order to determine in which conditions spin-trapping

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reactions occur. In addition, the ease of oxidation of nitronone derivatives has been found to correlate with antioxidant properties [14,15]. The low oxidation potential of azulenyl-based nitrones is thought to provide enhanced radical scavenging [14,16,17] and neuroprotective antioxidant activities [18] vs. that of PBN. In a recent report, we showed a correlation between the oxidation potentials of *N*-*tert*-butyl substituted phenylnitrones and their ability to prevent H₂O₂-induced cell death [15]. Similar to this, correlation of the ease of reduction of indolone-*N*-oxide and their anti-malarial activity has been established [19].

One strategy in the design of efficient nitronone-based spin-traps is to deliver the nitronyl group to the relevant sites of radical production in the cell by conjugating it to specific target ligands. The choice of linker groups for optimal spin-trapping properties is highly desirable [20,21] and it has been demonstrated that its nature also affects its bioactivity [15]. Over the past years, we have explored the reactivity of various *para*- and *N*-*tert*-butyl-substituted phenyl nitrones [15,20] so as to identify the most promising linker groups and design selective targeted nitronone-based spin-traps for improved and optimal reactivity towards free radicals.

In this work, we report the redox properties of *para*-substituted nitrones (Fig. 1) using cyclic voltammetry in aqueous and organic media. The relationship between the electrochemical behavior of the nitronyl group and the nature of the substituent, *i.e.* electron-donating vs. electron-withdrawing, was studied. Using cyclic voltammetry the relative rate of superoxide trapping by nitrones was investigated. Finally, the rate constant of phenyl and hydroxymethyl radical trapping was also determined using EPR competition kinetic experiment.

Results and Discussion

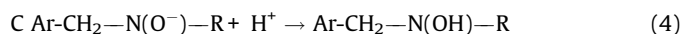
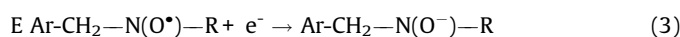
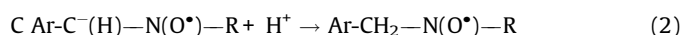
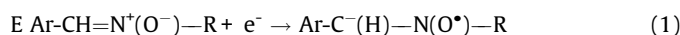
Cyclic Voltammetry. The electrochemical characterization of these nitrones was investigated using cyclic voltammetry and redox potentials are reported in Table 1. We first studied the electrochemical properties of nitrones in acetonitrile containing *tetra*-butylammonium perchlorate (TBAP) as electrolyte. In the electroactivity domain of the solvent, the cyclic voltammograms of the nitrones showed oxidation and reduction processes at vitreous carbon Cv and Pt electrodes, respectively. By calibrating vs. ferrocene (Fc/FeCp₂) it can be observed single- and two-electron transfers (Fig. S1 in supplemental data) [22]. The electrochemical systems concern the nitronone oxidation or reduction but additional processes are observed, the reduction of the nitrile for **6** and the oxidation of the amine for **1**. In the anodic domain, the voltammograms appeared more complicated. Moreover, electrode fouling occurred during the experiments.

Reduction in acetonitrile. PBN and nitrones **1**, **2**, **3** and **5** are reduced through two successive electron transfers. Nitrones **4** and **6** exhibit a similar behaviour but the first reduction peak is shifted towards anodic potentials and may be attributed to a two-electron transfer similar to the other derivatives but with redox potentials nearly equal. The anodic displacement is explained by the electron withdrawing effects of the substituents and the extension of the electronic delocalization. Fig. 2 shows representative

voltammograms for PBN and nitrones **2**, **4** and **6**. Correlation of Hammett constants (σ_p) with the first reduction peak potential of the nitrones (Fig. S2 in supplemental data) gave a linear relation except for nitronone **5**. This direct correlation suggests increased ease of reduction as the substituent becomes more electron-withdrawing. This observation is consistent with the normal trend expected from electron-donating substituents which could repel the addition of electrons leading to more negative potentials [23,24]. For nitrones **4** and **6**, a further electron transfer around -2.4 V was also observed. For nitronone **4**, this is very likely due to a two-electron reduction of the carbonyl group as already observed in the literature [25,26]. The potential of the carbonyl reduction depends on the electron delocalization [27], whereas the nature of the products formed depends on the medium: a pinacol through a single-electron transfer, or an alcohol through a two-electron transfer [27,28] that requires further protonation. For nitronone **6**, the one-electron reduction was found to be reversible, yielding the radical anion CN^{•-} [29], which was stable under the time scale of the cyclic voltammetry experiments.

Whatever the derivative, the two-electron reduction was irreversible and no backward peaks were observed. At Cv electrodes (Fig. S3-S4 in supplemental data), the backward peak appeared when the potential scan rate increased with values of ~ 50 V/s for PBN and 16 V/s for nitronone **2**. Fig. 3 shows the normalized voltammograms of PBN as a function of the potential scan rate v . The voltammograms are composed of two close peaks which are displaced towards negative potentials when the potential scan rate is increased, the peaks currents being decreased as well. The electron transfer may be represented by an ECEC scheme with E denoting a slow electrochemical reaction and C a fast chemical reaction which prevents the observation of a backward signal. This scheme was simulated with the first electrochemical reaction characterized by $E^{\circ}_1 = -2.00$ V, $k^{\circ}_1 = 0.1$ cm.s⁻¹ and the second one by $E^{\circ}_2 = -2.05$ V, $k^{\circ}_2 = 0.01$ cm.s⁻¹ (Fig. S5 in supplemental data). A good agreement was observed with the experimental voltammograms of PBN as depicted in Fig. 3. This ECEC scheme can be applied to the other PBN derivatives (data not shown).

Aldonitrones are known to undergo reduction in non-aqueous media [23,30,31] but the mechanism has not been well-established yet. PBN would be reduced into the non-electrochemically active hydroxylamine [30] and then into the amine form [23] through an overall 4 electrons exchange; the hydroxylamine might also undergo dehydration into imine. Taking into account the electrochemical results obtained here, the reduction of the nitronyl group may be described by an ECEC scheme, the final product would be the hydroxylamine:



Oxidation in acetonitrile. Considering the anodic behavior of the PBN derivatives, the PBN derivatives were studied at Pt electrodes in order to diminish the electrode fouling (Fig. 4). Only nitronone **1** exhibited a different behavior due to the amine group which is oxidized at ~ 0.7 V yielding the radical-cation Me₂N^{•+}Ar. This electrochemical system was found to be reversible when the potential scan was restricted to this system.

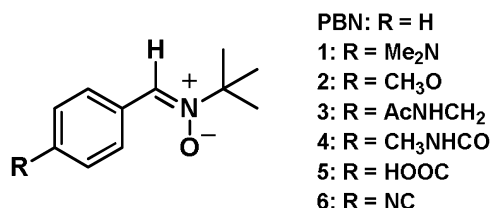


Fig. 1. Chemical structures of the *para*-substituted nitrones used in this work.

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