Effect of Solvent Polarity on the One-electron Oxidation of Cyclic Nitroxyl Radicals

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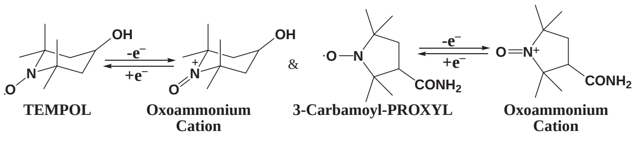
The one-electron oxidation potentials of two cyclic nitroxyl radicals determined by the differential pulse voltammetry and cyclic voltammetry were found to shift negatively with the increased solvent polarity.

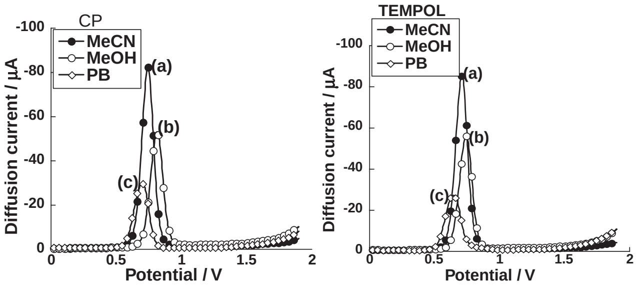
Cyclic nitroxyl radicals, spin probes for in vivo ESR measurements,[1–4] have attracted much attention over the years due to their radical-scavenging activity against reactive oxygen species (ROS), such as hydroxyl radical ($^{\bullet}OH$)[5,6] and superoxide ($HO_2^{\bullet}$/$O_2^{\bullet-}$),[7,8] as well as secondary radicals derived from ROS, such as carbon-centered radicals,[9–11] nitrogen dioxide ($^{\bullet}NO_2$),[12] and nitric oxide ($^{\bullet}NO$).[13] Tendency to loose an electron i.e., the ease of oxidation of nitroxyl radicals to the corresponding oxoammonium cations (Scheme 1) have also been found to be a key factor in various biological studies.[14–16]

Recently, we have reported that 3-carbamoyl-2,2,5,5-tetramethylpyrrolidine-*N*-oxyl (3-carbamoyl-PROXYL, CP) can act as an electron donor to scavenge a reactive oxygen radical.[17] Thus, the one-electron oxidation potentials of nitroxyl radicals, which are affected by the structure of compounds as well as by solvents, are of great importance to evaluate their radical-scavenging activity. However, very little is known about the interaction between the cyclic nitroxyl radicals and solvent molecules during the electrochemical oxidation. We report herein the electrochemical behavior of two different nitroxyl radicals, CP and 4-hydroxy-2,2,6,6-tetramethylpiperidine-*N*-oxyl (4-hydroxy TEMPO, TEMPOL) in various solvents during the differential pulse voltammetry and cyclic voltammetry.

Differential pulse voltammograms (DPV) for the one-electron oxidation of CP in three different solvents, phosphate buffer (PB) (10 mM, pH 7.2), methanol (MeOH) (0.1 M Bu_4NClO_4), and acetonitrile (MeCN) (0.1 M Bu_4NClO_4) were obtained and different electrochemical parameters such as peak potential, peak height, and peak width were analyzed to assign the oxidation potential and magnitude of diffusion current for the one-electron oxidation of nitroxyl radicals. The DPVs for CP (Figure 1) showed clearly defined and symmetric peak at $E_{pa} =$ 0.70, 0.74, and 0.81 V vs Ag/AgCl in PB, MeCN, or MeOH, respectively. A significant negative shift in the one-electron oxidation potentials was found with the increase in solvent polarity (polarity order: PB > MeCN > MeOH). DPVs for TEMPOL (Figure 1) were also obtained in the same manner to validate the effect of solvent polarity on the one-electron oxidation of TEMPOL. However, TEMPOL was found to be oxidized at comparatively negative potential than CP ($E_{pa} = 0.64$, 0.71, and 0.74 V vs Ag/AgCl in PB, MeCN, or MeOH, respectively).



Scheme 1. One-electron oxidation of cyclic nitroxyl radicals.

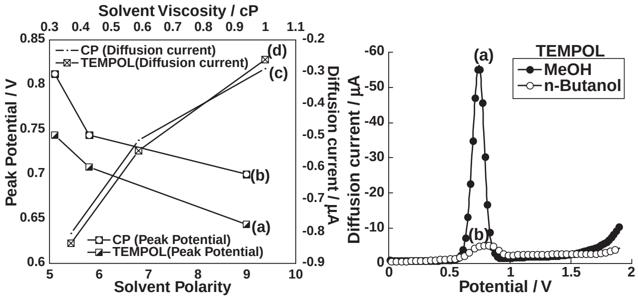


(I) (II)

Figure 1. DPVs of CP (I) and TEMPOL (II) (2.0×10^{-3} M) in (a) MeCN (0.1 M Bu_4NClO_4), (b) MeOH (0.1 M Bu_4NClO_4), and (c) PB (10 mM, pH 7.2) at 298 K. Scan rate: 2 mV s^{-1}; amplitude: 25 mV.

Cyclic voltammograms (CV) of CP and TEMPOL (see Supporting Information, Figure S1[18]) in PB, MeCN, and MeOH also showed a similar correlation between the one-electron oxidation potentials and solvent polarity. Linear plot of anodic (I_{pa}) and cathodic (I_{pc}) diffusion currents vs scanrate ($v^{1/2}$) (Figure S2[18]) and constant values for half wave potential ($E_{1/2}$) with different scan rates indicates that both the one-electron oxidation and corresponding reduction processes were faradic-natured. The peak separation, $E_{pa} - E_{pc}$ of 65 ± 5 mV for scan rates less than or equal to 0.1 V s^{-1} and the oxidation peak current equal to the accompanying reduction peak current confirm diffusion controlled, and the reversible one-electron redox process.

These electrochemical data indicate that the oxoammonium cations generated via one-electron oxidation of the nitroxyl radicals interact with solvent molecules comparatively stronger than the nitroxyl radicals and the oxidation of nitroxyl radicals becomes favorable in terms of free energy of reaction. Both polarity and viscosity of the medium had significant effect on the oxidation of nitroxyl radicals (Figure 2). For example, highly polar PB caused negative shift in the oxidation potentials and its comparatively highly viscous nature limited the diffusion of nitroxyl radicals at electrode surface, resulted in the declination of oxidation.



(I) (II)

Figure 2. (I) Plots of solvent polarity (Phenomenex) vs the E_{pa} values of nitroxyls (a and b) and viscosity (Phenomenex) vs diffusion current (c and d) during the differential pulse voltammetry in MeCN (polarity = 5.8, viscosity = 0.37 cP at 293 K), MeOH (polarity = 5.1, viscosity = 0.60 cP at 293 K), and PB (polarity = 9.0, viscosity = 1 cP at 293 K) at 298 K. Scan rate: 2 mV s^{-1}; amplitude: 25 mV. (II) DPVs of TEMPOL (2.0×10^{-3} M) in (a) MeCN (0.1 M Bu_4NClO_4) and (b) *n*-butanol (0.1 M Bu_4NClO_4) at 298 K. Scan rate: 2 mV s^{-1}; amplitude: 25 mV.

Furthermore, the negative shift in the one-electron oxidation potentials with increase in the solvent polarity validate comparative ease of oxidation in relatively polar medium. It might be due to stabilization of the oxoammonium cations by dipolar attraction in polar media. Inverse relationship between anodic diffusion current and solvent viscosity (Figure 2) was observed in case of both radicals. Reduction in diffusion current in the protic solvent like MeOH and PB as compared to the aprotic solvent like MeCN can be accounted for the interaction between nitroxyl radicals and solvent molecules. Strong hydrogen bonding between nitroxyl radicals and hydroxylic solvents has also been reported[19,20] and it has been found that the nitroxyls–water interactions are approximately 30% stronger than the H_2O–H_2O hydrogen bond.[21,22] However, the solvents interact comparatively stronger with the oxoammonium cations than the nitroxyl radicals themselves. Therefore, the viscosity of the solvent is the only factor for reduced diffusion current in MeOH and PB. It is also evidenced by the difference in anodic diffusion current for TEMPOL in *n*-butanol and methanol. Both the solvents are protic, but highly viscous nature of butanol retards diffusion of TEMPOL molecules towards the electrode surface, which not only caused the decrease in current, but also the broadening of peak in the DPV (Figure 2) of TEMPOL in *n*-butanol. Moreover, the comparative negative one-electron oxidation potential of TEMPOL than CP may be explained on the basis of stereochemical hindrance around the N–O$^{\bullet}$ moiety in these molecules. Transformation to the chair conformations in six-membered ring molecule, TEMPOL, could stabilize the oxoammonium cation, resulted in the easier oxidation of TEMPOL than the five-membered nonflexible ring molecule, CP, in which the stabilization of oxoammonium cation was absent. Since the stabilization of the oxoammonium cations was found to have a significant effect on the one-electron oxidation of both nitroxyl radicals, the parameters that affect the stabilization of the oxoammonium cations must be an important factor to control the oxidation and hence the radical-scavenging efficiency of nitroxyl radicals. Solvent was the one factor, however, many other parameters like structure of the compounds, and presence of chelating metal ions, also may give interesting results.

In conclusion, reaction medium plays an important role in the oxidation of nitroxyl radicals. This is not to say that various other thermodynamic and kinetic aspects of reaction in solution are not important. However, we cannot assess correctly the electron-donating ability of a compound and also the mechanism for oxidation reaction until we consider effect of reaction medium. Furthermore the ease of oxidation of a radical scavenger imitates their scavenging efficiency, therefore the parameters, affecting oxidation process would be helpful while assessing the scavenging mechanism and relative scavenging efficacy of nitroxyl radicals.

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