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Mendeleev Commun., 2024, **34**, 676–679

Mendeleev Communications

Competition between n → π* interactions and H-bonding: a way to stabilize aminoxyl anions and to improve electron transfer kinetics

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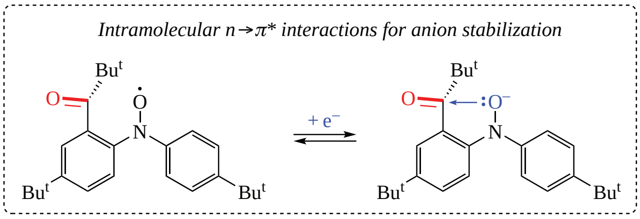
DOI: 10.1016/j.mencom.2024.09.016

A new approach to stabilization of the reduced state of nitroxides in solution is suggested. Thermodynamic stabilization of the strongly basic aminoxyl anions toward protonation and hydrogen bond formation with the solvent was achieved by intramolecular n → π* interactions. A new stable nitroxide radical bearing *ortho*-acyl group was synthesized to demonstrate this effect by means of cyclic voltammetry.



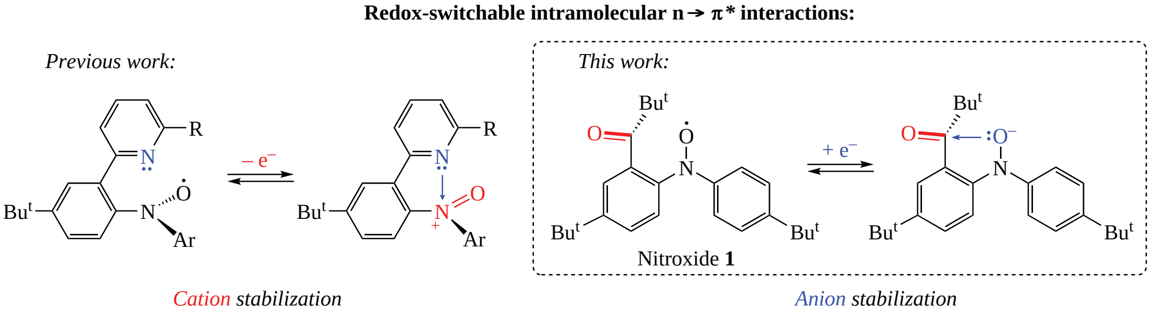
Keywords: intramolecular n → π* interactions, anion stabilization, diaryl nitroxides, hydrogen bonding, voltammetric testing.

Stabilization of various redox states of a molecule using switchable intramolecular interactions is a promising route to novel materials. One of the possible approaches is the using of intramolecular n → π* interactions, *i.e.*, the through-space donation of electron density from a lone electron pair of a donor (n) to a low-lying antibonding molecular π*-type orbital of an acceptor.[1,2] This approach may efficiently work for stabilization of either cationic or anionic species. Recently, it was also recognized that the n → π* interactions are one of the key forces governing the molecular structure and functionality of biomolecules.[2–5] An interesting but as yet underinvestigated aspect is cooperativity or competition between two different types of weak interactions (*e.g.*, between hydrogen bonding and n → π* interactions), when one weak interaction leads to strengthening or weakening of the other one. This approach may be useful for a 'dynamic' stabilization of the different oxidation states of molecules, to improve their functioning as redox-active materials.

Nitroxides are well known type of redox-active molecules widely used in catalysis, energy conversion and storage devices, as redox mediators and initiators, *etc*.[6] Alkylnitroxides, *e.g.*, TEMPO, form stable cations under oxidation whereas its reduction is chemically irreversible and leads to aminoxyl anions which are strong bases.[7,8] The situation with diarylnitroxides is more complicated: stability of the anionic and cationic species formed under reduction or oxidation, respectively, may be different and strongly depends on the structure. The most interesting are ambipolar molecules capable to form stable anionic and cationic species. For this purpose, the dynamic stabilization using redox-switchable weak interactions is one of the most promising approaches.[9]

Diaryl nitroxides are a convenient platform for insertion of the substituents in the close vicinity to the NO group capable for dynamic stabilization of its redox states *via* switchable weak interactions. Recently, we demonstrated how the *ortho*-pyridyl group inserted in the diarylnitroxide stabilizes the oxoammonium cation due to donation of the pyridyl lone pair to the $\pi^*_{N=O}$ orbital in the cation[10,11] (Scheme 1), thus switching on the fluorophoric properties.[11] Can the similar strategy be used for the anionic stabilization? Could the nitroxide group serve as an electrogenerated lone pair donor, participating in the redox-switchable n → π* interactions?

Herein, we report molecular design, synthesis, electrochemical and quantum chemical study of a new functionalized diarylnitroxide with the *ortho*-pivaloyl group (nitroxide **1**, Scheme 1, right) capable to provide intramolecular n → π* interactions stabilizing the aminoxyl anion. Bulky *tert*-butyl group of the pivaloyl fragment prevents planarization and direct conjugative interactions between the carbonyl and the aryl fragments. Using voltammetry and DFT calculations, we demonstrated that weak intramolecular n → π* interactions in the aminoxyl anion can be additionally strengthened by the



Scheme 1

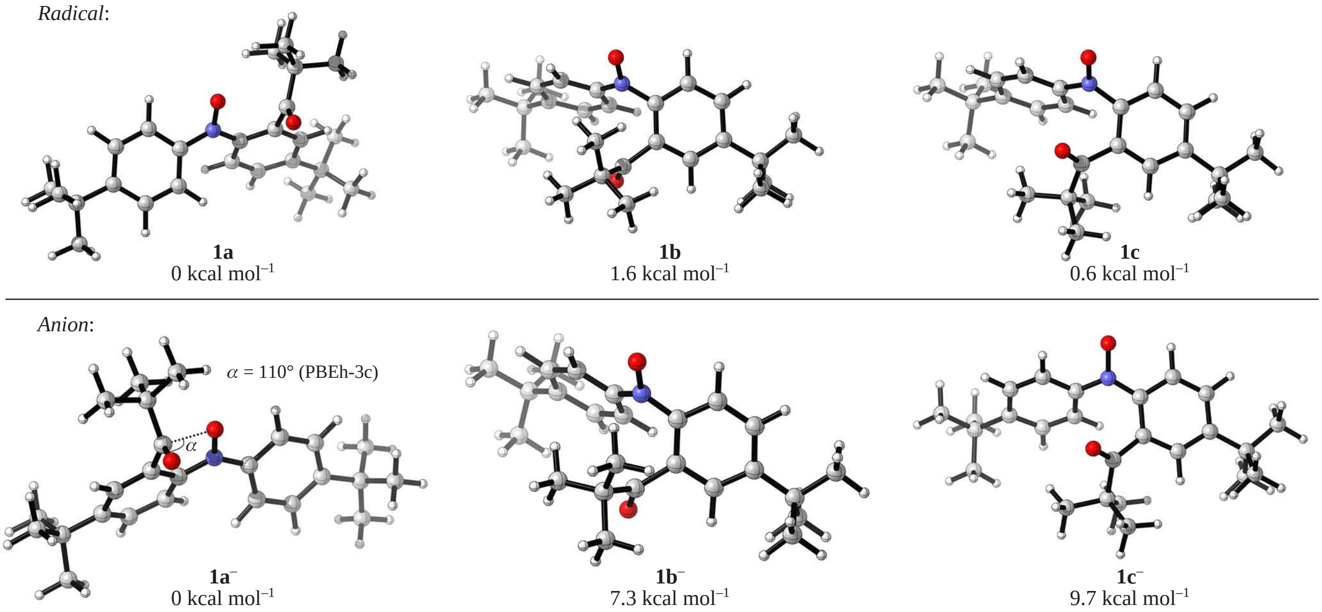


Figure 1 Relative electronic energies for the conformers of the nitroxide **1** (top) and the aminoxyl anion (bottom) in acetonitrile solution.

cooperative effect of the H-bonding with the carbonyl group, thus stabilizing the anionic species. Moreover, the competition between the $n\to\pi^*$ interactions and H-bonding with a solvent increases the ET kinetics, decreasing the solvent reorganization energy. Both points are of primary importance for the efficient functioning of redox-active materials.

Nitroxide **1** was synthesized in 49% yield by oxidation of the corresponding amine with mCPBA solution (28% of the starting amine was also recovered from the reaction mixture). The synthesis of the amine was described previously.[12] Notably, no competing Baeyer–Villiger oxidation was observed probably due to steric shielding of the carbonyl. Formation of the nitroxide was confirmed by high-resolution ESI mass spectrometry and ESR spectroscopy (see Online Supplementary Materials). The purity of the nitroxide was controlled by a spin counting method.

As follows from the quantum-chemical conformational analysis, nitroxyl radical **1** exists in solution as a mixture of three conformers **1a–c** with approximately the same energy (Figure 1). This indicates that there is no significant interaction between the nitroxyl group oxygen and the carbonyl carbon. In contrast to the radical, the anion demonstrates a clear conformational preference (Figure 1): conformer **1a**$^-$ has of *ca*. 7 kcal mol^{-1} smaller energy than two other conformers **1b**$^-$ and **1c**$^-$. Moreover, a significant pyramidalization of the carbonyl carbon atom is observed. Notably, the aminoxyl oxygen atom approaches the carbonyl center exactly along the Bürgi−Dunitz trajectory:[13] the O···C=O angle is equal to 110° (see Figure 1). These structural features clearly indicate the $n\to\pi^*$ interaction between the aminoxyl lone pair and the *ortho*-carbonyl group.

To reveal the influence of the *ortho*-pivaloyl group on the electrochemical properties of the radical **1**, the voltammetric study was performed. Both oxidation and reduction processes appeared to be reversible [Figure 2(*a*)]; the corresponding oxidation and reduction formal potentials ($E^{0\prime}$ = 0.95 and −0.69 V *vs*. Ag/AgCl, KCl$_{\text{(sat.)}}$, respectively) were anodically shifted relatively to the model bis(4-*tert*-butylphenyl)nitroxide[14] (+0.18 V shift for reduction and 0.14 V shift for oxidation processes) due to the electron withdrawing nature of the pivaloyl group.

More intriguing is fast electron transfer kinetics observed for the reduction process. A standard heterogeneous ET constant of the process (k_s = 0.01 cm s^{-1}) determined using the Nicolson method[15] is twice as high as the usual value for diarylnitroxides (k_s = 0.005 cm s^{-1}, regardless of the substitution motif[14]). This is rather significant improvement making both redox processes of nitroxide **1** suitable for practical application demanding fast ET kinetics (*e.g*., in supercapacitors). The probable reason for an increase in the k_s value is partial decrease in the localized negative charge in the aminoxyl anion due to the $n\to\pi^*$ interactions with neighboring carbonyl group. This diminishes basicity of the anion and its propensity to form hydrogen bonds with the solvent, thus decreasing the solvent reorganization energy. Importantly, the $n\to\pi^*$ interactions do not increase the inner reorganization energy since no bond breaking or bond formation occur. Notably, the similar competition between hydrogen bonding and $n\to\pi^*$ interactions is often observed in biomolecules, controlling their functioning.[1,2]

Not only the $n\to\pi^*$ interactions can influence the possibility for the hydrogen bonding; the inverse situation can also take place. To explore the interrelation, the voltammetric experiment with the acid additives was performed. It revealed that an addition of *ca*. 3 mol excess of acetic acid to the solution of nitroxide **1** in acetonitrile makes the reduction process electrochemically irreversible. In contrast, the chemical reversibility is reserved, as follows from multiple repetitive

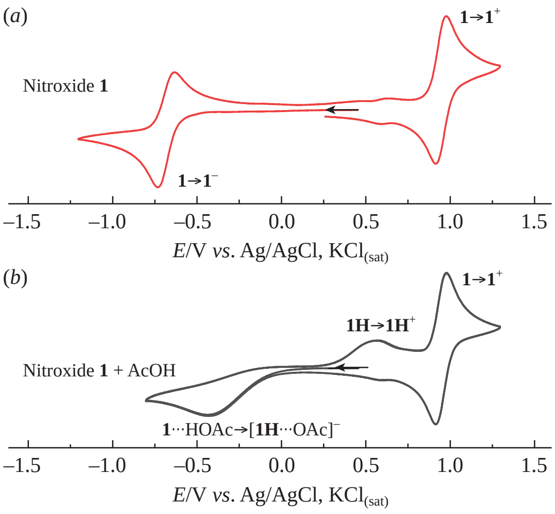


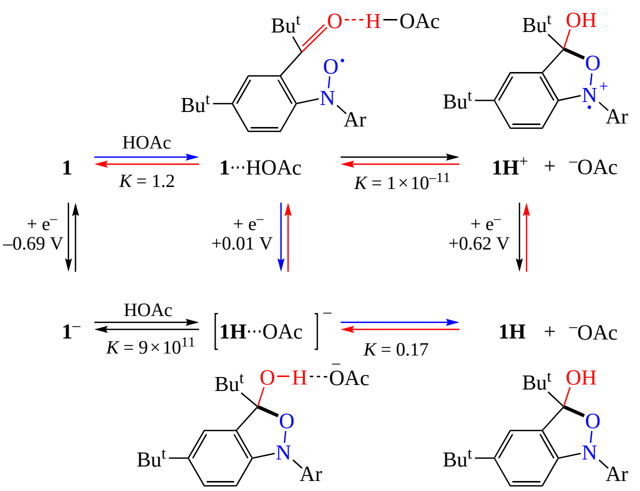
Figure 2 Voltammogramms of solutions of nitroxide **1** (3 mM, curve *a*) and nitroxide **1** with 10 mM AcOH added (curve *b*). MeCN, 0.1 M Bu_4NBF_4, glassy carbon electrode, 0.1 V s^{-1}.

scanning in the −0.8 to +1.3 V potential range. Huge anodic shifts of the reduction (by 0.3 V) and the reoxidation (by 1.19 V) peaks (compare curves *a* and *b* in Figure 2), together with large peak-to-peak separation (0.99 V at 0.1 V s^{-1} scan rate and 0.80 V at 0.01 V s^{-1}) are typical for the complex interplay of the protonation equilibria (in the anionic form) and the hydrogen bonding (in the neutral form). Strong anodic shifts of the reduction potentials in bis(4-methoxyphenyl)nitroxide under acetic acid addition (as a result of formation of the corresponding hydroxylamine or its hydrogen-bonded complex with acetate anion after reduction) were previously observed by Serve.[16] However, the peak separation observed in ref. 16 was much smaller than that for nitroxide **1** (0.45 V instead of 0.8 V) indicating an interplay of several effects in the latter case.

To get a quantitative information about the proton transfer reactions in nitroxide **1**, digital simulation of the voltammograms of the **1** and AcOH mixture in the 0.01–5 V s^{-1} scan rate range was performed (see Online Supplementary Materials for details). For successful fitting of the experimental curves, three types of the redox-active species were considered: the protonated nitroxide (**1H**$^+$), the H-bonded adduct with AcOH (**1HOAc**) and the nitroxide **1** itself (Scheme 2). The selected thermodynamic parameters of the proton-transfer and redox equilibria found by the fitting of the voltammograms are given in Scheme 2. The processes occurring in the cathodic and anodic scans are marked in Scheme 2 in blue and red, respectively.

It turned that the reduction potential of the hydrogen-bonded complex of nitroxide **1** is 0.7 V more anodic than the reduction potential of **1** itself, similarly to that observed by Serve in the experiments with acetic acid addition to bis(4-methoxyphenyl)-nitroxide ($\Delta E_{1/2}$ = 0.67 V[16]). However, the peculiar feature of the voltammogram obtained for **1** + AcOH solution is a strong anodic shift of the reoxidation peak. According to Scheme 2, it corresponds to the oxidation of the protonated anion (**1H**). Notably, addition of more strong trifluoroacetic acid to nitroxide **1** solution makes its full protonation more thermodynamically feasible (the process in the upper right corner in Scheme 2), leading to well pronounced reversible redox couple at 0.62 (see Online Supplementary Materials). It should be noted here that digital simulation of the CVs reveals the involvement of direct **1H** oxidation at the reoxidation peak but tells nothing about its structure. The reasonable question is why oxidation of **1H** is so strongly anodically shifted with respect to oxidation of the hydrogen-bonded analog **1H**···$^-$OAc, as compared to bis(4-methoxyphenyl)nitroxide?

The answer was obtained by the quantum-chemical calculations that revealed the molecular structure of **1H** species responsible for the unusual voltammetric behavior of **1** in acidic solutions. Protonation of the aminoxyl oxygen atom typically yields the corresponding hydroxylamine, whereas protonation of **1**$^-$ at the carbonyl group leads to the isomeric cyclic hemiacetal (see Scheme 2). Surprisingly, the latter cyclic structure is much more stable than the hydroxylamine (6.9 kcal mol^{-1}). The cyclic nature of the *ortho*-acylated arylhydroxylamines was previously reported.[17–19] Thus, unexpectedly high oxidation potential of **1H** should be referred to its hemi-acetal rather than hydroxylamine structure.



Scheme 2

It should be noted that oxidation potentials of the free *N*,*N*-disubstituted hydroxylamines in aprotic media are *ca*. 0.5 V less anodic than that of the corresponding nitroxide radical oxidation.[20,21] The potential of **1H**$^+$/**1H** couple found from the CV simulation is closer to **1**$^+$/**1** couple redox potential ($E_{1^+/1} - E_{1H^+/1H}$ = 0.33 V) than one could expect for the hydroxylamine structure. This is consistent with the hemi-acetal structure, *i.e*. replacement of OH hydrogen atom in hydroxylamine by the CR_2OH group, which is an inductive acceptor.

To conclude, it is first demonstrated that competitive intramolecular n → π* interactions in diarylnitroxies can be used for thermodynamic stabilization of the aminoxyl anions formed under one-electron reduction, due to suppressing their protonation or hydrogen bonds formation with a solvent. Moreover, this also increases the electron transfer kinetics of the reduction process (due to a decrease in the solvent reorganization energy), which is important for possible application of redox-active nitroxides in energy conversion and storage systems.

As a convenient model, a new diarylnitroxide with an acyl group in the *ortho*-position (2-pivaloyl-4,4′-di-*tert*-butyldiphenylnitroxide) was proposed and synthesized. The competition between the n → π* interactions and H-bonding was first quantitatively estimated using electrochemical techniques. Voltammetric study of the nitroxide solution with the acid added, combined with the digital simulation of the experimental curves and quantum-chemical calculations, revealed the cyclic hemiacetal-type structure formation.

This work was supported by Russian Science Foundation (project no. 22-73-00040).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.09.016.

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Received: 7th May 2024; Com. 24/7492