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Quantum chemical calculations of hydration electrostatics and electrochemical oxidation potential of cyclic nitroxide radicals

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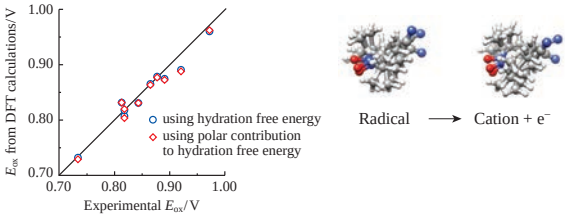
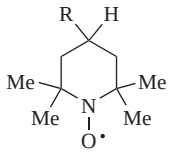
The oxidation potential E_{ox} of cyclic nitroxide radicals in water has been calculated using density functional theory methods and the polarizable continuum solvent model. Robust correlations were obtained between the calculated and experimental E_{ox} values with the lowest mean unsigned error of 10 mV. The electrostatic model was demonstrated as a useful approximation for the calculations of E_{ox}.

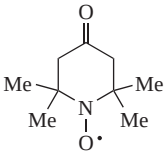


Nitroxide free radicals (nitroxides) possess distinctive chemical structure and reactivity and have diverse applications in biological, organic and material chemistry.[1–7] Multitude of chemical and biological functions of the nitroxides is related to their unique redox properties. The biological activities of nitroxides are generally attributed to the inhibition of pathological processes of the peroxidation of biomolecules.[2,4,8] The key reaction in the latter case is an oxidation of nitroxides $R_2N–O^•$ by peroxyl radicals in the aqueous surrounding, and the more easily are nitroxides oxidized the higher is their antioxidant activity.[9,10] In chemistry, nitroxides play a key role in the electrocatalytical oxidation of alcohols and other compounds.[1,7] Aqueous medium is essential in the aforementioned redox processes. For comparison, the oxidation potentials of nitroxides in nonpolar solvents are higher than that in water by about 100 mV.[11] For these reasons, the reliable prediction and interpretation of oxidation propensity of the nitroxides in water is of great importance.

A number of works on the quantum chemical calculations of electrochemical potentials E_{ox} for the liquid-phase oxidation of nitroxides are reported.[11–16] Quantitative structure–activity relationships (QSAR) for the redox properties of nitroxides have been explored,[11,14,15,17,18] including effects of intramolecular electrostatic interactions.[15,18] In this work, we have calculated E_{ox} values in water for a series of ten prototypic cyclic nitroxides **1**–**10** with varying rings and substituent groups, and with sufficiently broad distribution of experimental E_{ox} values.[11,19] Thus, our major goal was to explore the role of solvent electrostatics and solute conformations in the computational assessment and interpretation of E_{ox} of the nitroxide radicals.



1 R = H
2 R = COOH
3 R = OH
4 R = OMe
5 R = NHC(O)Me
6 R = Cl
7 R = CN



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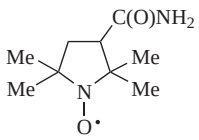

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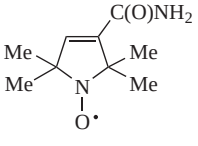

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The absolute standard oxidation potential E^0_{ox} (1 M ideal solution) for the half-reaction $R_2N–O^• \rightarrow R_2N^+=O + e^-(g)$ was determined relative to a standard hydrogen electrode (SHE) from the Nernst equation.[20] The underlying free energies $G^0_{sol}(X)$ of reactants X in a solution were calculated using the gas phase and solvation free energies $G^0_{sol}(X) = G^0_{gas}(X) + \Delta G^0_s(X)$ in the Born–Haber thermodynamic cycle. In the quantum chemical free-energy calculations,[†] we considered all the low-energy conformations of radicals and cations. The $G^0_{sol}(X)$ value was obtained from the free energies of separate conformations of the reactants according to equation (1):

$$G^0_{sol}(X) = G^0_{sol,1}(X) - kT\ln\sum_{i=1}^{n}\exp[-\Delta G^0_{sol,i}(X)/kT], \quad (1)$$

where k is the Boltzmann constant, T is the absolute temperature, and $\Delta G^0_{sol,i}(X) = G^0_{sol,i}(X) - G^0_{sol,1}(X)$.

To carry out the multi-conformation free-energy calculations, we have performed a systematic conformational analysis of the studied nitroxides. The piperidine cycle in the nitroxides adopts

[†] Treatment of the free radicals was based on unrestricted wave functions. The quantum mechanical part was performed with the Gaussian-09 program. The gas-phase geometries and thermal contributions were computed using the B3LYP[21,22] density functional and the 6-31G(d) basis set. $G^0_{gas}(X)$ and $\Delta G^0_s(X)$ values were calculated at T = 298.15 K using the gas-phase optimized geometries. The total energies $E_{tot}(X)$ in gas phase were determined using the B3LYP, M05-2X[23] and M06-2X[24] functionals that are widely used in calculations of molecular structures and thermochemistry, and the correlation consistent cc-pVTZ[25] basis set augmented with diffuse functions in Gaussian-09. $\Delta G^0_s(X)$ were obtained using the 'standard model density' (SMD)[26] version of polarizable continuum model (PCM). The accepted free-energy difference in equation (1) was $G^0_{sol,i}(X) \leqslant 6kT$. The experimental values of E_{ox} were determined relative to SHE;[19] in the calculations we used $E^0_{abs}(SHE) = -4.44$ V.[20]

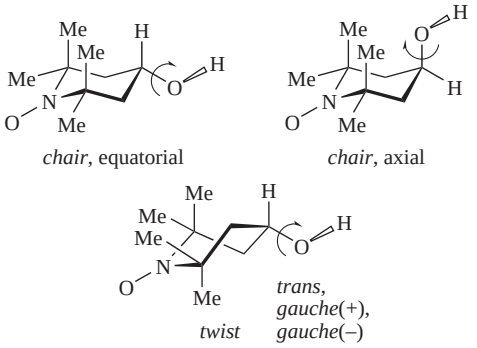

Figure 1 Possible conformations of nitroxide **3**.

chair and twist conformations as depicted for structure **3** (Figure 1) and, for the chair structure, the side group occupies an either equatorial or axial position of the ring. The chair conformation is the most stable one for the majority of piperidine-*N*-oxyls, except for compound **8** that prefers the twist form. The energy difference between the twist and chair conformations of the radicals and cations **1** and **8** is in general less than 12 kJ mol^{-1}, whereas the activation energies for the rearrangement between these conformations are about 11–17 kJ mol^{-1}. The majority of the studied conformational transitions are thermally allowed at room temperature. Overall, the computed conformational properties of nitroxides are consistent with the previously reported data.[12,14,15,18,27,28]

The density functional theory (DFT) calculations using equation (1) have provided generally good linear correlations between the computed and experimental E^0_{ox} values for nitroxides **1**–**10**. In particular, the M05-2X/aug-cc-pVTZ scheme reproduced the experiment with the mean unsigned error (MUE) of only 10 mV, R = 0.98 and a = 0.903 (Figure 2). This scheme employs the largest basis set among those used in the present work and the accurate hybrid meta exchange-correlation M05-2X functional, whose development[23] had relied on the B3LYP optimized geometries. The accuracy of results shown in Figure 2 can be compared to that of the G3(MP2,CC)(+) multiple-conformation calculations of E_{ox} in MeCN for 21 cyclic nitroxides with MUE = 33 mV.[15] The correlation coefficients R and the slopes a of computed linear dependencies vary in the ranges of 0.93–0.98 and 0.90–1.02, respectively (see Figure 2 and Table S1 in Online Supplementary Materials). The MUE of calculated E_{ox} values changes from 10 to 192 mV and in this case, the use of B3LYP renders largest inaccuracies. The calculated data revealed that the slope of straight lines is more sensitive to the level of treatment of solvent than that of gas term. The calculations of G^0_{sol}(X) using B3LYP/6-31G(d) and PBE/6-31G(d) yielded linear plots

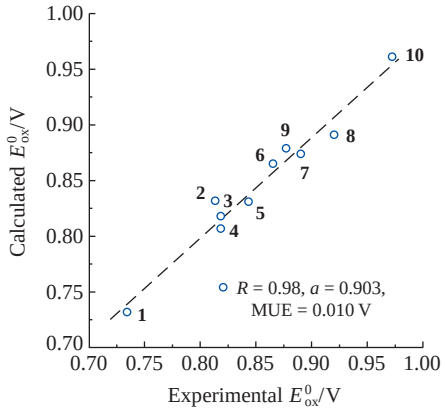

Figure 2 Correlation between the experimental[19] and calculated E^0_{ox} values for nitroxides **1**–**10** in water. E_{tot} and ΔG^0_s were calculated at the M05-2X/aug-cc-pVTZ level of theory.

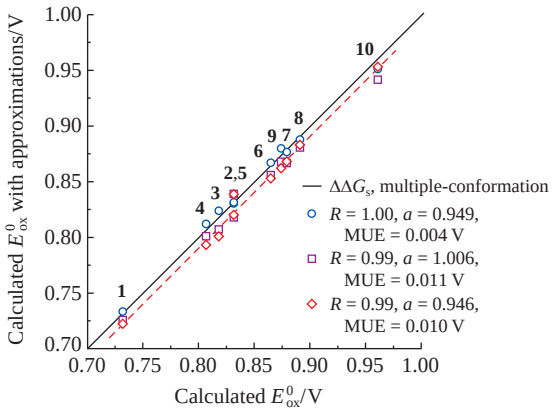

Figure 3 E^0_{ox} values for nitroxides **1**–**10** in water obtained from the multiple-conformation model *vs.* three models: (○) single-conformation model with full ΔG^0_s, (◇) multiple-conformation model with the $\Delta\Delta G_{s,el}$ term, and (□) single-conformation model with the $\Delta\Delta G_{s,el}$ term. The level of calculations is the same as in Figure 2.

with the closest to unit slopes. It can also be noted that the application of large aug-cc-pVTZ basis set in the calculations of ΔG^0_s reduces MUEs, but does not improve the slope as compared to smaller basis sets employed in the development of SMD (see Table S1).

We have then compared how different approximations may influence the calculated E^0_{ox}. Switching to the single-conformation approach in equation (1) only slightly changed the computed E^0_{ox} values and did not deteriorate the statistical fit with experiment (Figure 3 and Table S1). The correction onto G^0_{sol}(X) from the additional low-energy conformations reached several kJ mol^{-1} for the considered molecules; however, these contributions mostly canceled out in the free-energy calculation for the whole process. Yet, the found good performance of single-conformation model can be a limited case, while the multiple-conformation approach is in general the preferred method for calculating E^0_{ox}.[20]

The second model approximation replaces the solvation free energies ΔG^0_s in equation (1) by its polar contributions $\Delta G_{s,el}$. Electron transfer from the nitroxide radical roughly only rearranges its electron distribution without changing the chemical composition of the reactant. The corresponding change of hydration free energy $\Delta\Delta G^0_s$(X) is determined then by the difference of the electrostatic solute–solvent interactions of the cation and radical. Figure 3 shows that the use of only the polar hydration terms in calculation of G^0_{sol}(X) indeed yields the excellent correlation with the results based on non-truncated ΔG^0_s for both multiple- and single-conformation approaches.

The interplay of internal electronic energies and hydration electrostatics is illustrated by the energies of nitroxide **3**. In gas phase, the most stable conformation of its cations is the chair structure of piperidine with the axial *gauche*(±) position of substituent group (Table S2). The simple interpretation is that this conformer has a favorable intramolecular electrostatics due to the smaller distance between the positively charged atom N^+ and negatively charged O atom of hydroxyl group (see, *e.g.*, natural charges[11] for **3**). In water, the electrostatic solute–solvent interactions destabilize the axial *gauche* conformers as compared to the equatorial *gauche* structure by 17.9 kJ mol^{-1}. Similar conformational pattern was found for structure **4**. Overall, the polarized aqueous medium compensates electrostatic intramolecular interactions between the $N{=}O^+$ center and substituent groups in the nitroxide cations.

The effect of solvent electrostatics on the experimental and calculated E_{ox} of cyclic nitroxides had been demonstrated recently for three solvents of different polarity.[11] According to the solvent electrostatic models, the measured and calculated oxidation

potentials[11] grow upon decreasing the solvent polarity. Switching to microscopic water models can provide a more accurate description of the specific hydration of nitroxides, but will keep the found counter-balancing solvent influence on the conformations of nitroxide cations. It can be thus expected that the QSAR for E^0_{ox}, based only on the solute electron structure,[15] will be less pronounced in the aqueous environment. The rational approach to quantify substituent effects on E_{ox} of nitroxides should apparently consider combined contributions of the solute and solvent response. A useful approximate model would include considering only the electrostatic contribution $\Delta G^0_{s,el}$, in view of that the computational schemes for the calculation of polar term in ΔG^0_s are generally more developed than that for non-polar one.

In conclusion, we have determined the performance of several DFT and PCM(SMD) schemes in the calculation of E^0_{ox} values of nitroxides in water. The lowest MUEs of calculations were found for the M05-2X functional. The reliable description of changes in E^0_{ox} can be achieved from considering only the polar contribution to ΔG^0_s(X) of nitroxides. The electrostatic interactions with the polarizable water dielectric alter the conformational population as compared to the gas phase and overshadow through-space electrostatic interactions in the reactants. The calculation of only polar solvation free energies emerges as a useful approximation for the quantitative estimates of oxidation potentials of the cyclic nitroxides.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.026.

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