# Kinetics and thermodynamics of reversible disproportionation–comproportionation in redox triad oxoammonium cations – nitroxyl radicals – hydroxylamines

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Kinetics and equilibrium of the acid-catalyzed disproportionation of cyclic nitroxyl radicals $R_2NO^{\bullet}$ to oxoammonium cations $R_2NO^+$ and hydroxylamines $R_2NOH$ is defined by redox and acid–base properties of these compounds. In a recent work (*J. Phys. Org. Chem.* 2014, 27, 114-120), we showed that the kinetic stability of $R_2NO^{\bullet}$ in acidic media depends on the basicity of the nitroxyl group. Here, we examined the kinetics of the reverse comproportionation reaction of $R_2NO^+$ and $R_2NOH$ to $R_2NO^{\bullet}$ and found that increasing in $-I$-effects of substituents greatly reduces the overall equilibrium constant of the reaction $K_4$. This occurs because of both the increase of acidity constants of hydroxyammonium cations $K_{3H+}$ and the difference between the reduction potentials of oxoammonium cations $E_{R2NO+/R2NO\bullet}$ and nitroxyl radicals $E_{R2NO\bullet/R2NOH}$. pH dependences of reduction potentials of nitroxyl radicals to hydroxylamines $E_{1/3\Sigma}$ and bond dissociation energies D(O–H) for hydroxylamines $R_2NOH$ in water were determined. For a wide variety of piperidine- and pyrrolidine-1-oxyls values of $pK_{3H+}$ and $E_{R2NO+/R2NO\bullet}$ correlate with each other, as well as with the equilibrium constants $K_4$ and the inductive substituent constants $\sigma_I$. The correlations obtained allow prediction of the acid–base and redox characteristics of redox triads $R_2NO^{\bullet}$–$R_2NO^+$–$R_2NOH$. Copyright © 2014 John Wiley & Sons, Ltd.

**Keywords:** comproportionation; free-energy relationships; hydroxylamines; nitroxyl radicals; oxoammonium salts; reduction potentials

## INTRODUCTION

Nitroxyl radicals **1**, oxoammonium cations **2** and hydroxylamines **3** form a stable organic redox triad with efficient one and two electron transfer (Scheme 1).

Because of these properties, nitroxyl radicals provide, inter alia, new opportunities in the synthesis of advanced materials,[1] 'green' catalysts' design for the oxidation of organic compounds,[2,3] active materials for organic batteries[4,5] and electronic devices.[6] Just like their inorganic congener – nitric oxide[7] – nitroxyl radicals at submillimolar concentrations exhibit antioxidant and cytoprotective properties,[8,9] but at concentrations $\geq 10^{-3}$ M, they increase oxidative stress and exert a cytotoxic effect on tumor cells.[10–12] Analogously to other redox active agents,[13] nitroxyl radicals modulate the activity of clinically used anticancer drugs and may improve their chemotherapeutic properties.[14–16]

For effective use of nitroxyl radicals in such applications, it is important to know the redox and acid–base characteristics of a wide variety of structures **1**–**2**–**3**. A convenient way to accomplish this is to study in detail the acid catalyzed disproportionation of nitroxyl radicals. For many radicals, this reaction is ~100% reversible[17,18] (Scheme 2).

It includes half reaction of reduction of nitroxyl radicals $1 \rightarrow 3$ and oxoammonium cations $2 \rightarrow 1$, as well as acid–base equilibria of protonation of radicals **1** and hydroxylamines **3**. The overall equilibrium constant of disproportionation $K_4$ is an integral characteristic, which reflects changes of the values that characterize these processes, and provides information on the structure–property relations. For each nitroxyl radical, there is the equilibrium value $pH_{eq}$

wherein the ratio of concentrations $[\mathbf{2}][\mathbf{3}]_{\Sigma}/[\mathbf{1}]^2 = 1$ (refer to Supporting). Direct determination of $K_4$ from the concentrations of reagents near $pH_{eq}$ cannot be carried out with sufficient accuracy as a result of the low rate of achievement of the equilibrium. Constant $K_4$ may be determined with good accuracy from the data on the kinetics of disproportionation of **1** in strongly acidic solutions and comproportionation of **2** and **3** at pH $\gg pH_{eq}$.[19]

In the previous work,[18] we studied the influence of the structure of 21 nitroxyl radicals on the kinetics of disproportionation in aqueous $H_2SO_4$ and found a correlation between the basicity of nitroxyl groups and reduction potentials of oxoammonium cations $E_{2/1}$. In the present study, we investigated the kinetics of comproportionation of eight pairs of oxoammonium **2** and hydroxyammonium salts $3H^+$ and for the first time revealed the effect of substituents and heterocyclic ring structure on the equilibrium constant $K_4$. pH dependences of reduction potentials of

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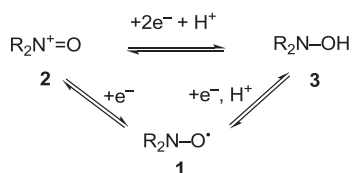
**Scheme 1.** Redox–triad oxoammonium cation **2** – nitroxyl radical **1** – hydroxylamine **3**
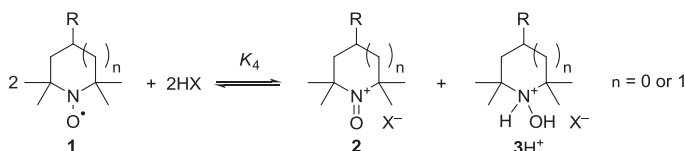


**Scheme 2.** Acidity-dependent reversible disproportionation–comproportionation in redox triad **1–2–3**

nitroxyl radicals $E_{1/3\Sigma}$ and bond dissociation energies D (O–H) for hydroxylamines **3** in water were determined. The linear free-energy relationships between the reduction potentials $E_{2/1}$, dissociation constants of hydroxyammonium cations $K_{3H+}$ and the equilibrium constant $K_4$ were found. For the radicals of piperidine and pyrrolidine series, values of $pK_{3H+}$ and $E_{2/1}$ show good correlations with the inductive substituent constants $\sigma_I$.

## EXPERIMENTAL

References on methods for the synthesis of nitroxyl radicals **1** are listed in Supporting Information. Oxoammonium perchlorates **2b–i** were synthesized by oxidation of radicals **1** with $Cl_2 + NaClO_4$ solution using adapted method.[20] Hydroxyammonium salts **3H+** were synthesized by reduction of radicals **1** in MeOH/EtOH – HCl solution[21] either by hydrogenation ($H_2$/Pd/C) or reduction with $Na_2S_2O_4$[22] of radicals **1** yielding hydroxylamines **3**, which then were transformed to **3H+** salts by reacting with acids (refer to Supporting).
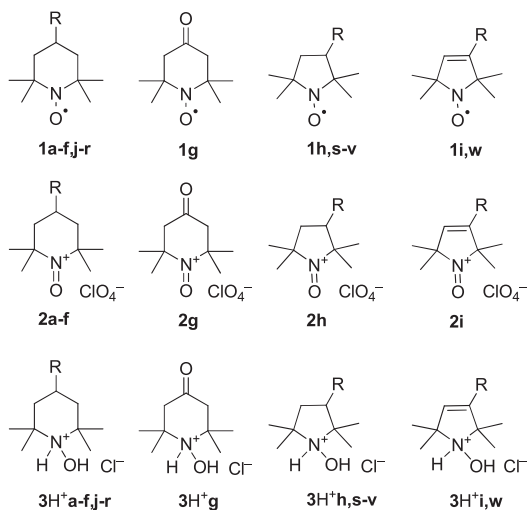


R = H (**a**), $CH_2C(O)NH_2$ (**b**), OMe (**c**), NHAc (**d**), Cl (**e**), CN (**f,v**), $C(O)NH_2$ (**h,w**), COOEt (**i,l**), COOH (**j**), OH (**k**), NHMs (**m**), NHC(O)$CF_3$ (**n**\*), OAc (**o**), OMs (**p**), $NH_3^+$ (**q**), $NMe_3^+$ $MeOSO_3^-$ (**r**), $CH_2OH$ (**s**), $CH_2NHAc$ (**t**), COOMe (**u**)     \* **3H+n** as oxalate

The kinetics of comproportionation of **2** and **3H+** salts in buffer solutions was studied by following the increase of electron paramagnetic

resonance (EPR) signal of radicals **1** at 20 °C. EPR measurements were performed with Adani CMS 8400 spectrometer using glass ampoules of ~1 mm internal diameter. Spectra of all radicals **1** in aqueous solutions represent triplets of equal intensities. Intensity of central line of the spectrum was used as an analytic signal. At $[1] \leq 2 \times 10^{-3}$ M, the intensity of EPR signal (*I*) was found to be a linear function of [1]. The unique calibration curve in coordinates of log $[1] = a \times \log I + b$ was used for each radical. At that, the slope *a* is close to 1 in all cases.

The chemicals used for buffer solutions preparation were reagent grade. Buffer solutions were prepared by mixing of 0.1 M glycine or 0.1 M KCl with 0.1 M HCl. In case of **2** + **3H+** pairs with low $pK_{3H+}$ values, the kinetics of comproportionation was studied in HCl or $HClO_4$ solutions. Reaction mixtures were prepared by mixing of $10^{-1}–10^{-2}$ M solutions of **2** and **3H+** in suitable buffer system. Comproportionation of **2** and **3H+** proceeds with reasonable rate at $pH_{eq} \ll pH \ll pK_{3H+}$ and is first order with respect to both cations. For each **2** + **3H+** pair, the reaction kinetics was studied for pH interval wider than 0.5 pH units. Because the consumption of one mole of **2** is accompanied by the formation of two moles of **1**, the current concentration of **2** is equal to $[2] = [2]_0 - 0.5[1]$. At $[3H^+]_0 \gg [2]$, the processing of the experimental data was performed in the coordinates of the pseudo-first-order kinetic equation:

$$ln\left\{[2]_0 / ([2]_0 - 0.5[1])\right\} = k_{ef}t$$

where $[2]_0$ is initial concentration of the oxoammonium salt and [1] is current concentration of radical **1**. Effective rate constants $k_{ef}$ are given in Table S1.

Data on the kinetics of disproportionation of radicals[18] were supplemented by the results for **1f, i**. The obtained $k_2^0/K_{1H+}$ values are listed in Table 1. Estimated $pK_{1H+}$ (±0.3) values were found to be −7.0 (**1f**) and −8.4 (**1i**).

The $pK_{3H+}$ values (refer to Table 1) were determined by potentiometric titration of **3H+** salts according to Albert and Sergeant.[23] Initial concentrations of **3H+** salts were 0.010–0.015 M. Titration was performed with 0.2 N NaOH carbonate-free solution in an argon atmosphere at 20 °C using Mettler Toledo FE20 pH meter, which was calibrated with standard buffer solutions.

Voltamperometric studies were performed using an IPC-Pro computer-controlled potentiostat (Econix). Curves were recorded using a three-electrode circuit with a disk glassy carbon electrode ($d = 1.70$ mm) as a working electrode, platinum wire as a counter electrode, and saturated calomel electrode as a reference electrode. Oxidation of radicals **1** was studied at scan rates of 0.05, 0.1, 0.2, 0.3 and 0.4 V s$^{-1}$ at $[1] = 5 \times 10^{-3}$ M in 0.1 M $LiClO_4$ aqueous solution at 25 °C in argon flow. Peak potentials were approximated to zero current (Fig. S1). Difference between the potentials of cathodic and anodic peaks in all cases did not exceed 70 mV, which corresponds to a reversible process. Obtained midpoint potentials $E_{2/1} = (E_p{}^c + E_p{}^a)/2$ were corrected by +244 mV to assign to the normal hydrogen electrode (Table 1).

Letter designations of points in the figures correspond to the numbering of compounds.

## RESULTS AND DISCUSSION

### Kinetics

According to EPR and potentiometric titration, solutions of hydroxylamines **3H+** are stable for more than 1 week under conditions of comproportionation reaction (pH < 4). The studied oxoammonium salts **2** (except for **2g**[24]) in the same solutions do not undergo any significant changes during more than 1 day. Stoichiometry and kinetics of the comproportionation **2** + **3H+** was studied at $[3H^+]_0 \gg [2]_0$. Except for the pair **2g** + **3H+g**, within the limits of experimental error, the final concentrations of radicals **1** formed in the reaction are equal to $2[2]_0$. This is consistent with previous data for the reaction of **2a** + **3a**.[19] In the case of reaction **2g** + **3H+g**, the final concentration of **1g** is less than $2[2g]_0$ because of parallel autoreduction of **2g** and partial destruction of piperidine ring.[24]

**Table 1.** Kinetic and thermodynamic parameters of the disproportionation/comproportionation reactions for redox triads **1–2–3**

| 1–2–3 | $10^2 \cdot k_2^0/K_{1H+}$, $M^{-2} s^{-1}$ [18] | $k_{-2}$, $M^{-1} s^{-1}$ | $pK_{3H+}$ ($\pm0.03$) | $K_4$, $M^{-2}$ | $E_{2/1}$, V versus NHE ($\pm0.003$)[a] | D(O–H), kJ/mol ($\pm1.0$) |
|---|---|---|---|---|---|---|
| **a**[19] | $21 \pm 1$[19]; $18$[17] | $51 \pm 1$ | 6.90 | $33000 \pm 2000$ | 0.734 | 294.7 |
| **b** | $7.4 \pm 0.5$ | $135 \pm 10$ | 6.31 | $1400 \pm 200$ | 0.784 | 295.0 |
| **c** | $8.9 \pm 1.2$ | $156 \pm 18$ | 5.82 | $380 \pm 70$ | 0.818 | 297.9 |
| **d** | $3.0 \pm 0.2$ | $207 \pm 15$ | 5.83 | $98 \pm 7$ | 0.843 | 296.0 |
| **e** | $3.9 \pm 0.3$ | $234 \pm 21$ | 5.48 | $50 \pm 7$ | 0.865 | 299.4 |
| **f** | $1.3 \pm 0.1$ | $310 \pm 22$ | 5.17 | $6.2 \pm 1.0$ | 0.890 | 298.4 |
| **g** | $0.83 \pm 0.13$ | $396 \pm 43$ | 4.18 | $0.35 \pm 0.07$ | 0.920 | 299.8 |
| **h** | $0.26 \pm 0.11$ | $3640 \pm 190$ | 5.27 | $0.14 \pm 0.06$ | 0.877 | 287.2 |
| **i** | $0.062 \pm 0.007$ | $19100 \pm 500$ | 4.50 | $0.00103 \pm 0.00002$ | 0.972 | 289.7 |
| **j** | $4.4 \pm 0.4$ | — | 6.20[b] | 440[c] | 0.813 (pH ~3) | 295.6[e] |
| **k** | $4.4 \pm 0.4$ | — | 6.00 | 340[c]; 480[d] | 0.818 | 296.6[e] |
| **l** | — | — | 5.79 | 180[d] | — | — |
| **m** | — | — | 5.57 | 67[d] | — | — |
| **n** | — | — | 5.55 | 63[c]; 61[d] | 0.850 | 298.1[e] |
| **o** | — | — | 5.55 | 61[d] | — | — |
| **p** | — | — | 5.02 | 14[c]; 5.4[d] | 0.879 | 300.1[e] |
| **q** | $1.1 \pm 0.1$ | — | 4.86[b] | 3.0[c]; 2.6[d] | 0.908 (pH ~3) | 300.1[e] |
| **r** | $0.89 \pm 0.14$ | — | 3.83 | 0.17[c]; 0.02[d] | 0.962 | 304.1[e] |
| **s** | $0.55 \pm 0.08$ | — | 5.85 | — | 0.809 | — |
| **t** | — | — | 5.67 | — | 0.805 | — |
| **u** | — | — | 5.22 | — | 0.883 | — |
| **v** | — | — | 4.25 | — | 0.970 | — |
| **w** | — | — | 4.71 | — | 0.972 | — |

[a]Data of this work. Known literature values of $E_{2/1}$ potentials are listed in Table S3.
[b]The carboxyl group of **3**H$^+$**j** is titrated first, p$K$ 4.34; p$K$ value of amino group is $10.1 \pm 0.1$ in case of **3**H$^+$**q**.
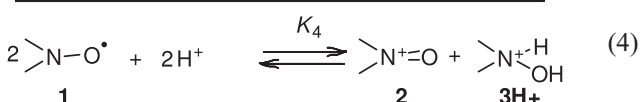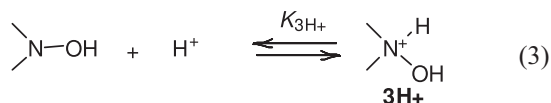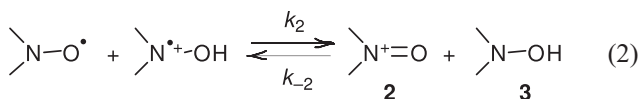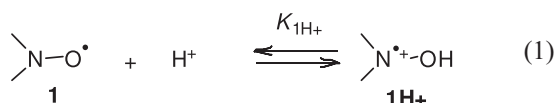[c]Found from $K_4$ versus $E_{2/1}$ correlation (Eqn 18).
[d]Found from $K_4$ versus $K_{3H+}$ correlation (Eqn 17).
[e]Values of $K_4$ were used from $K_4$ versus $E_{2/1}$ correlation (Eqn 18).

The rate constant for **2g** + **3**H$^+$**g** was determined by subtracting the contribution of **2g** autoreduction in studied buffer systems.

According to the previously proposed mechanism (1–3),[17,19] the rate-limiting step of comproportionation is the oxidation of base **3** by cation **2**.

$$\begin{array}{c} \text{N–O}^\bullet \ + \ \text{H}^+ \ \underset{}{\overset{K_{1H+}}{\rightleftharpoons}} \ \text{N}^{\bullet+}\text{-OH} \end{array} \qquad (1)$$

$$\quad \mathbf{1} \qquad\qquad\qquad\qquad \mathbf{1H+}$$

$$\text{N–O}^\bullet \ + \ \text{N}^{\bullet+}\text{-OH} \ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \ \text{N}^+\text{=O} \ + \ \text{N–OH} \qquad (2)$$

$$\qquad\qquad\qquad\qquad \mathbf{2} \qquad\qquad \mathbf{3}$$

$$\text{N–OH} \ + \ \text{H}^+ \ \underset{}{\overset{K_{3H+}}{\rightleftharpoons}} \ \text{N}^+\!\!\begin{smallmatrix}H\\OH\end{smallmatrix} \qquad (3)$$

$$\qquad\qquad\qquad\qquad\qquad \mathbf{3H+}$$

$$2\,\text{N–O}^\bullet \ + \ 2\text{H}^+ \ \underset{}{\overset{K_4}{\rightleftharpoons}} \ \text{N}^+\text{=O} \ + \ \text{N}^+\!\!\begin{smallmatrix}H\\OH\end{smallmatrix} \qquad (4)$$

$$\mathbf{1} \qquad\qquad\qquad\qquad \mathbf{2} \qquad\qquad \mathbf{3H+}$$

Given that $[\mathbf{3}] = [\mathbf{3}\text{H}^+]_0 K_{3H+}/(K_{3H+} + a_{H+})$ (refer to Supporting), the comproportionation rate is determined by Eqn 5.

$$-d[\mathbf{2}]/dt = 0.5 \ d[\mathbf{1}]/dt = k_{-2}[\mathbf{2}][\mathbf{3}] \qquad (5)$$
$$= k_{-2}K_{3H+}\,[\mathbf{2}][3H^+]_0/(K_{3H+} + a_{H+})$$

When $[\mathbf{3}\text{H}^+]_0 \gg [\mathbf{2}]_0$, the dependence of $\ln\{[\mathbf{2}]_0/([\mathbf{2}]_0 - 0.5[\mathbf{1}])\}$ on time is linear to a conversion of $\geq 90\%$ (Fig. 1) and corresponds to the reaction of first order in [**2**].

Equation for the effective rate constant $k_{ef} = k_{-2}\,K_{3H+}[3H^+]_0/(K_{3H+} + a_{H+})$ under the actual experimental conditions ($a_{H+} \gg K_{3H+}$) simplifies to $k_{ef} = k_{-2}\,K_{3H+}[3H^+]_0/a_{H+}$. Accordingly, the effective rate constant $k_{ef}$ is proportional to $[\mathbf{3}\text{H}^+]_0$ (refer to Supporting, Table S1, the data for the reaction **2d** + **3**H$^+$**d**) and inversely proportional to $a_{H+}$. The oxidation of **3**H$^+$ cation or hydroxylamine **3**$^-$ anion, which is possible theoretically, does not make any substantial contribution to the rate of the process in the studied range of pH. Using stopped-flow technique, the rate constant of cation **2a** with anion **3a**$^-$ was found to be $3.3 \times 10^4\,\text{M}^{-1}\,\text{s}^{-1}$ and **2a** + **3a**$^-$ comproportionation contributed to the rate of reaction only at pH > 9.[25] Calculated at different pH values of $k_{-2} = k_{ef}a_{H+}/(K_{3H+}[3H^+]_0)$ are listed in Table S1. Mean values of $k_{-2}$ and its standard deviations are given in Table 1.

Complete set of constants characterizing mechanism (1)–(4) was obtained only for radical **1a**.[17] For other studied radicals, acidity constants $pK_{1H+}$ are calculated using the rate constant $k_2^0$ found for radical **1a**.[18] The rate constants of the forward
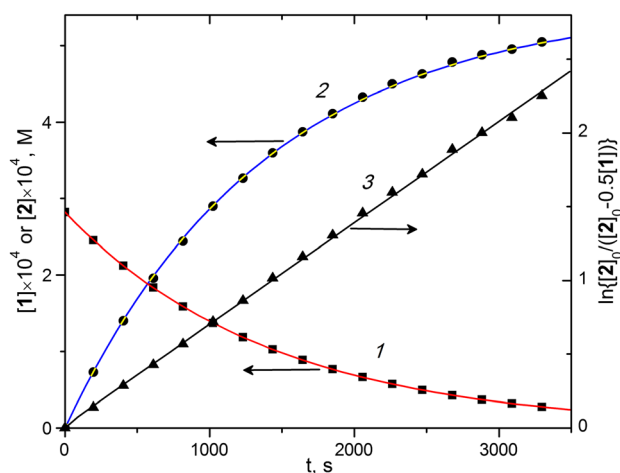
**Figure 1**. Kinetic curves of the consumption of **2d** (*1*), accumulation of **1d** (*2*), and the dependence of $\ln\{[2]_0/([2]_0 - 0.5[1])\}$ (*3*) on time for the comproportionation of **2d** and **3H⁺d** at 20 °C in glycine buffer solution, pH 2.97, $[2d]_0 = 2.8 \times 10^{-4}$, $[3H^+d]_0 = 3 \times 10^{-3}$ M



**Figure 2**. Comparison of voltammetric curves for the oxidation (*1*) and reduction (*2*) of radical **1a** ($5 \cdot 10^{-3}$ M) in aqueous 0.1 M LiClO₄ at 20 °C and scan rate 0.1 V s⁻¹

and reverse reactions of equilibrium (2) depend on the difference between the reduction potentials of cation radicals $1H^+$ to hydroxylamines **3** ($E_{1H+/3}$) and reduction potentials of oxoammonium cations $E_{2/1}$. Weak dependence of constants $k_{-2}$ on the nature of substituents R for compounds **a–g** indicates small changes in the difference $E_{1H+/3} - E_{2/1}$ for piperidine derivatives. Growth of $k_{-2}$ for pyrrolidine **h** and pyrroline **i** derivatives is likely because of a significant increase in $E_{2/1}$ caused by a high strain in the five-membered rings of oxoammonium cations.

The equilibrium constants $K_4$ were calculated from effective rate constants of disproportionation $k_2^0/K_{1H+}$, rate constants $k_{-2}$ and acidity constants of hydroxyammonium cations $K_{3H+}$: $K_4 = k_2^0/(K_{1H+}k_{-2}K_{3H+})$. The values of $K_4$ strongly depend on the structure of nitroxyl radicals and in the studied series of compounds **1a–i** change by more than seven orders of magnitude (Table 1). The values of $K_4$ for radicals **1k–r** were found from $K_4$ versus $E_{2/1}$ and $K_4$ versus $K_{3H+}$ correlations (refer to the succeeding texts).

### Reduction potentials $E_{1/3\Sigma}$

Figure 2 shows the voltammetric curves of reversible oxidation (*1*) and irreversible reduction (*2*) for radical **1a**. The irreversibility of electroreduction of radicals **1** on a timescale of this method (refer to also[26,27]) follows from the absence of a peak on the reverse part of the curve, a significant (~two times) decrease of the reduction peak current, its broadened shape and large slope (Fig. S2).

Therefore, a reliable determination of pH-dependent reduction potentials of nitroxyl radicals to hydroxylamines $E_{1/3\Sigma}$ by cyclic voltammetry is not feasible.[25,28,29] However, the dependences of $E_{1/3\Sigma}$ on pH may be calculated using the values of $E_{2/1}$, $K_4$ and $K_{3H+}$ obtained in this work (Table 1). The reduction of **1** to the sum of $3H^+$, **3** and $3^-$ includes half-reaction (6) and acid–base equilibria (3) and (7).
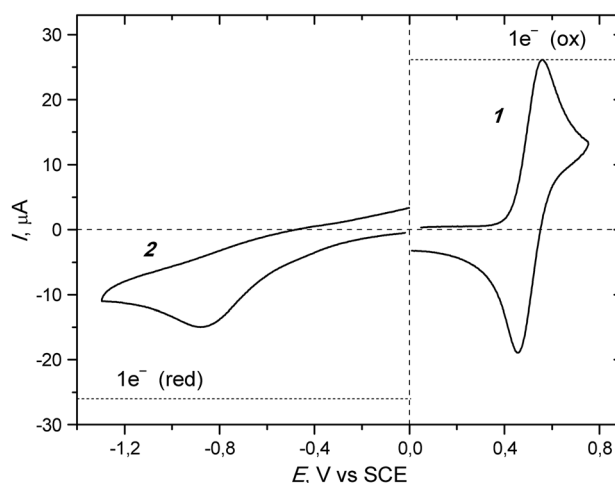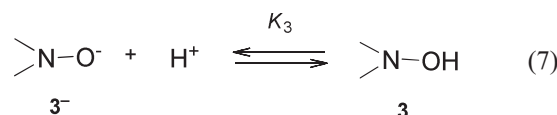
$$\ce{>N-O^{\bullet} + e^- <=> >N-O^-} \qquad (6)$$

$$\mathbf{1} \qquad\qquad\qquad \mathbf{3^-}$$

$$\ce{>N-O^- + H^+ <=>[K_3] >N-OH} \qquad (7)$$

$$\mathbf{3^-} \qquad\qquad\qquad\qquad \mathbf{3}$$

Given that $[3]_\Sigma = [3H^+] + [3] + [3^-] = [1]$, the dependence of $E_{1/3\Sigma}$ on $a_{H+}$ can be written in the form:[17]

$$E_{1/3\Sigma} = E^0_{1/3-} - (RT/F)\ln K_3 K_{3H+}$$
$$+ (RT/F)\ln\left(K_3 K_{3H+} + a_{H+}K_{3H+} + a_{H+}^2\right) \qquad (8)$$

Under standard conditions ($a_{H+} = 1$ M), the equilibrium constant $K_4$ is determined by the difference of pH-dependent potential $E_{1/3\Sigma}$ and pH-independent potential $E_{2/1}$: $E_{1/3\Sigma} - E_{2/1} = (RT/F)\ln K_4$. At pH 0, the last term in Eqn 8 is negligible; hence, it follows that $E_{1/3\Sigma} = E^0_{1/3-} - (RT/F)\ln K_3 K_{3H+} = E_{2/1}^0 + (RT/F)\ln K_4$. It is reasonable to suggest that $K_3$ values for hydroxylamines **3** are close enough to known value $K_3 = 2 \times 10^{-14}$ M for H₂NOH,[30] so that at pH < 12 is true $K_3 K_{3H+} + a_{H+}K_{3H+} + a_{H+}^2 \approx a_{H+}K_{3H+} + a_{H+}^2$. As a result, we obtain Eqn 9 for $E_{1/3\Sigma}$ versus pH dependence at pH < 12 based on the found values of $E_{2/1}$, $K_4$ and $K_{3H+}$.

$$E_{1/3\Sigma} = E_{2/1} + 0.059\ \log K_4 + 0.059\ \log\left(a_{H+}K_{3H+} + a_{H+}^2\right) \qquad (9)$$

These dependencies for radicals **1a–c**, **g–i** are shown in Fig. 3. The values of $E_{1/3\Sigma}$ for radicals **1a–i**, **k**, **n**, **p–r** at selected pH are given in Table S2. Taking into account the experimental errors of used constants, the errors of $E_{1/3\Sigma}$ values does not exceed ±10 mV.

The intersections of plots $E_{1/3\Sigma}$ versus pH and $E_{2/1}$ lines correspond to pH$_{eq}$ values at which the ratios of concentrations $([2][3]_\Sigma)/[1]^2 = 1$. The values of $K_{3H+}$ shift the inflections on the $E_{1/3\Sigma}$ versus pH plots, so that of the two radicals (for example, **1a** and **1c**) one may be more potent oxidant at high and the other at low pH. At pH 7, radicals **1h** and **1g** exhibited the lowest (0.103 V) and the highest (0.234 V) values of $E_{1/3\Sigma}$ among the studied radicals **1a–i**. The pH-dependent potentials for two-electron reduction of oxoammonium cations to hydroxylamines may be calculated as $E_{2/3\Sigma} = E_{2/1} + E_{1/3\Sigma}$.
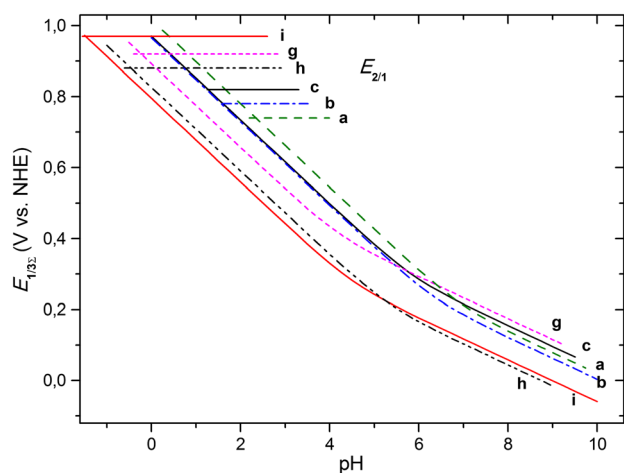
**Figure 3**. Plots of $E_{1/3\Sigma}$ versus pH and pH-independent potentials $E_{2/1}$ for selected radicals **1**. Lettering of lines corresponds to designation of compounds (refer to Experimental)



**Figure 4**. Plot of $pK_{3H+}$ versus $\sigma_I$ for piperidine (*1*) and pyrrolidine hydroxylamines (*2*)

## Correlations for acid–base and redox properties in the triad 1–2–3

For aliphatic compounds, the linear free-energy relationship is most developed as linear dependencies of properties of the compounds on inductive substituent constants $\sigma_I$. Inductive effect is defined as the difference of the measured parameters for the substituted and unsubstituted molecules. Mathematically, it is expressed by Eqn 10 where the constant $\sigma_I$ depends on the variable substituent only, and the constant $\rho_I$ depends on the system under study.[31]

$$\Delta E - \Delta E^\circ = \rho_I \sigma_I \qquad (10)$$

The $E$ value may stand for the reaction energy, Gibbs energy or the activation energy. A similar equation can also be formulated for the other physical properties. Using the literature data and the data obtained in this work, we analyzed the possible correlation in the triad of **1–2–3** for such parameters as substituent constants $\sigma_I$, acidity constants $pK_{3H+}$, reduction potentials $E_{2/1}$ and equilibrium constants $K_4$. The free-energy differences of the one-electron reduction of oxoammonium cations **2** and equilibriums (3) and (4) are derived as: $\Delta G_{2/1} = -zFE = -96500$ (C mol$^{-1}$) $\times E_{2/1}$ (V) $= -96.5 \times E_{2/1}$ and $\Delta G_K = -RT \times \ln K = -5.7 \times \log K$ (kJ/mol).

## $pK_{3H+}$ versus $\sigma_I$

The data on $pK_{3H+}$ obtained in this work are listed in Table 1, and literature constants $\sigma_I$ are given in Table S3. The values of $pK_{3H+}$ correlate very well with inductive constants $\sigma_I$ in the case of hydroxylamines with neutral and positively charged substituents R (Fig. 4). Lines *1* for 1-hydroxypiperidines and *2* for 1-hydroxypyrrolidines correspond to Eqns 11 and 12 with determination coefficients $R^2$ 0.985 and 0.975. At $\sigma_I = 0$, Eqns 11 and 12 give the expected $pK_{3H+}$ values for **3H⁺a** and 1-hydroxy-2,2,5,5-tetramethylpyrrolidine,[32] for which the experimental $pK_{3H+}$ value is apparently unknown.

$$pK_{3H+} = (-3.22\pm0.13) \times \sigma_I + (6.84\pm0.06) \qquad (11)$$

$$pK_{3H+} = (-3.30\pm0.30) \times \sigma_I + (6.18\pm0.10) \qquad (12)$$

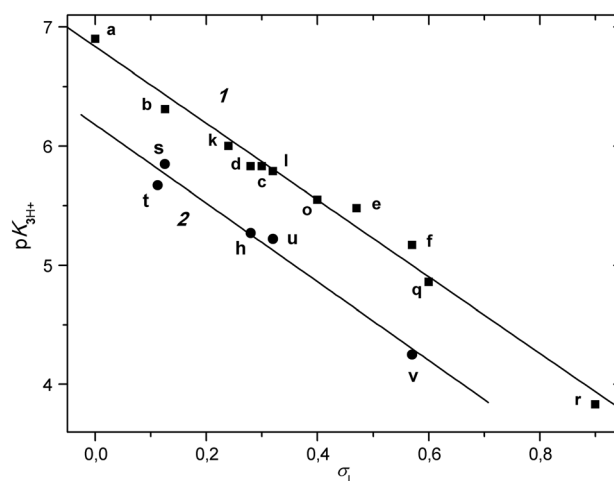Data concerning the salts **3H⁺m**, **n**, **p** are not included in Fig. 4 because we failed to find $\sigma_I$ values for their substituents R in the literature. Salt **3H⁺j** does not obey Eqn 11 probably because of the strong intramolecular interaction of the carboxylate and hydroxyammonium groups.

## $E_{2/1}$ versus $\sigma_I$

The values of reduction potentials $E_{2/1}$ obtained in this study and known from literature are listed in Tables 1 and S3. For the drawing of correlation dependences $E_{2/1}$ versus $\sigma_I$, the data from both tables were used. Piperidine and pyrrolidine derivatives with known constants of substituents $\sigma_I$ give a good linear correlation (Fig. 5, Eqns 13 and 14) with coefficients of determination $R^2 = 0.98$ (line *1*) and 0.99 (line *2*).

$$E_{2/1} = (0.262\pm0.010) \times \sigma_I + (0.742\pm0.004) \qquad (13)$$

$$E_{2/1} = (0.362\pm0.015) \times \sigma_I + (0.767\pm0.005) \qquad (14)$$

At $\sigma_I = 0$, Eqns 13 and 14 give the expected values of $E_{2/1}$ for redox couples **2a/1a** and 2,2,5,5–tetramethyl-1-oxopyrrolidinium
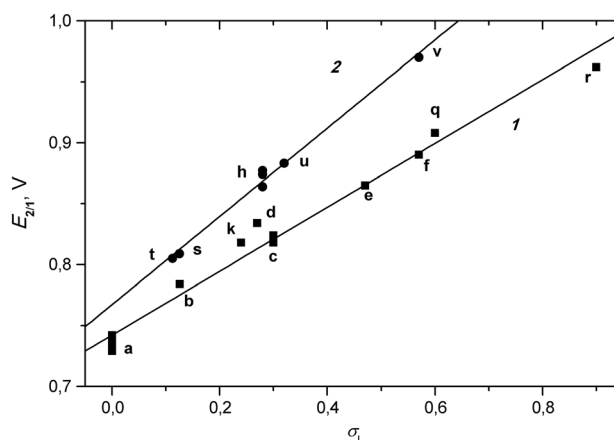


**Figure 5**. Plot of $E_{2/1}$ versus $\sigma_I$ for the piperidine (*1*) and pyrrolidine (*2*) derivatives

cation/2,2,5,5-tetramethylpyrrolidine-1-oxyl. Satisfactory correlation $E_{2/1}$ versus $\sigma_I$ for some pyrrolidine derivatives was first reported in work.[27]

### $E_{2/1}$ versus p$K_{3H+}$

Cross-correlation of $E_{2/1}$ versus p$K_{3H+}$ follows from the linear dependences of these parameters on inductive constants of substituents $\sigma_I$ (Figs. 4 and 5). Data on $E_{2/1}$ and p$K_{3H+}$ obtained in this study (Table 1), as well as literature data on $E_{2/1}$ (Table S3), were used to build this relationship. Compounds of the piperidine series with uncharged and single-bonded substituents R showed good correlation (Fig. 6, line 1), which corresponds to Eqn 15.

$$\Delta G_{E2/1} = (1.49\pm0.05) \times \Delta G_{K3H+} - (129\pm2) \quad (R^2 = 0.985) \quad (15)$$

The good quality of the same plot (Fig. 6, line *2*) for the studied series of pyrrolidine derivatives (Eqn 16) confirms the trend.

$$\Delta G_{E2/1} = (1.97\pm0.11) \times \Delta G_{K3H+} - (143\pm3) \quad (R^2 = 0.97) \quad (16)$$

The slopes of the dependences (15) and (16) are equal to 1.49 and 1.97 and reflect a greater influence of the substituents R on the free energy of the reduction $2 \rightarrow 1$ as compared with their influence on the dissociation equilibrium of hydroxyammonium cations $3H^+$. The most basic hydroxylamine **3a** corresponds to redox couple **2a**/**1a** with the lowest potential $E_{2/1}$. Also, electrophilic properties and stability of oxoammonium cations depend on the inductive effects of substituents R. Relative to water as a standard base, acidity constant p$K_5$ for **2a** is known to be 14.5 (Scheme 3).[33] *N*-oxide **4a** (R = H) have a limited stability and is a bit stronger protic acid with p$K_6$ 13.1. Salts **5**$^-$M$^+$ were obtained by treatment of **2a** with excess of alkalies MOH.[34]

An increase in electronegativity of substituents R should lead to decrease in both p$K_5$ and stability of salts **2**. Among the oxoammonium salts studied here, **2g** is the less stable. Even in an acidic aqueous solution, it undergoes partial autoreduction to radical **1g**. Mechanism of the process involves the fragmentation of *N*-oxide **4g** and the reduction of **2g** to radical **1g** by fragmentation products.[24] In alkaline medium, the rate of reaction increases, and the composition of the products indicates that the main primary process is an attack of OH$^-$ on C–H bonds of the piperidine ring of **2g**.[35]

### $K_4$ versus p$K_{3H+}$

Formula for determination of $K_4 = k_2^0 / (K_{1H+}k_{-2}K_{3H+})$ suggests that, at least for the nitroxyl radicals with the same heterocycle, the relationship between log $K_4$ and p$K_{3H+}$ is linear. The data obtained for the piperidine derivatives **a–f** give a good correlation (Fig. 7) corresponding to Eqn 17.

$$\Delta G_{K4} = (-1.99\pm0.14) \times \Delta G_{K3H+} + (52.8\pm5) \quad (R^2 = 0.97) \quad (17)$$

Increasing in $-I$-effects of substituents in the series of **a–f** derivatives reduces the overall equilibrium constant by $\Delta(\log K_4) \approx -3.7$. This occurs because of increase in acidity constants of hydroxyammonium cations $\Delta(pK_{3H+}) \approx 1.7$ and decrease of the ratio of equilibrium constants characterizing the reactions (1) and (2): $\Delta[\log(K_2 / K_{1H+})] \approx -2$ (Table. 1). Any more detailed analysis of $K_2 / K_{1H+}$ ratio would be speculative because the difference $\Delta(pK_{1H+}) = -7.0 - (-5.8) = -1.2$ for the series of **a–f** derivatives is obtained assuming the same value of the rate constants $k_2^0$.[18] Equation 17 allows calculating the values of $K_4$ for the piperidineoxyls with known p$K_{3H+}$ values (Table 1). Data point for triad **g** was not included in the correlation. Carbonyl group causes the geometry of the cycle (the twist conformation for **1g**[36]) different from the chair conformation characteristic of piperidine derivatives with single-bonded substituents R. Probably, this is the reason for the deviation of $-5.7 \times \log K_4$ value for triad **g** in this and other (refer to Fig. 8) studied dependences. High-lying points of triads **h**, **i** in Fig. 7 correspond to low values of $K_4$ for the pyrroline and pyrrolidine derivatives.

### $K_4$ versus $E_{2/1}$

Values of $E_{2/1}$ obtained in this study and known from literature (Tables 1 and S3) were used to build this relationship. For a series
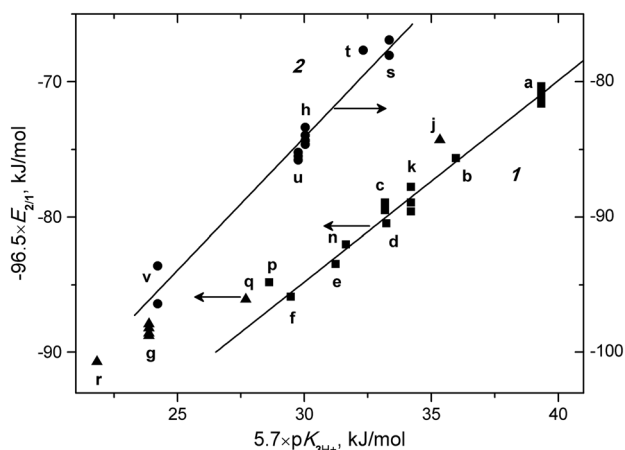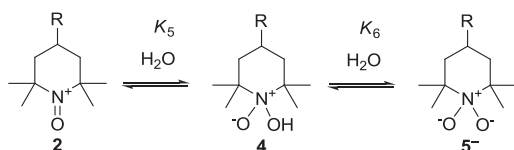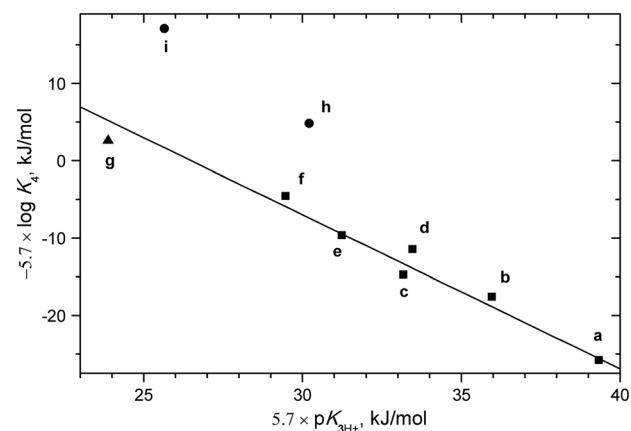


**Figure 6**. Plot of $-96.5 \times E_{2/1}$ versus $5.7 \times$ p$K_{3H+}$ for compounds of the piperidine (*1*) and pyrrolidine (*2*) series. To avoid overlapping, symbols of plot (*2*) are shifted upwards by 10 kJ/mol. Triangle symbols are for outliers



**Scheme 3**. Acidic properties of cations **2** and *N*-oxides **4**



**Figure 7**. Plot of $-5.7 \times \log K_4$ versus $5.7 \times$ p$K_{3H+}$ for redox triads **a–i**. Triangle and circus symbols are for outliers
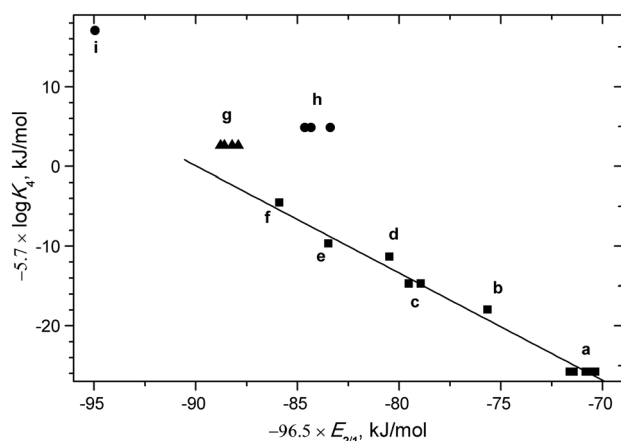
**Figure 8**. Plot of $-5.7 \times \log K_4$ versus $-96.5 \times E_{2/1}$ for redox triads **a–i**. Triangle and circus symbols are for outliers
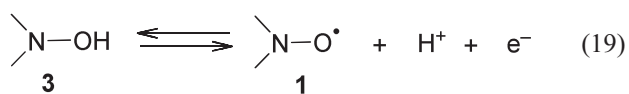
of compounds **a–f**, values of $\Delta G_{K4}$ correlate well with $\Delta G_{E2/1}$ (Fig. 8, Eqn 18).

$$\Delta G_{K4} = (-1.35 \pm 0.05) \times \Delta G_{E2/1} - (121 \pm 4) \quad (R^2 = 0.99) \quad (18)$$
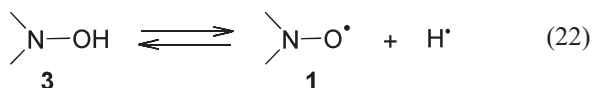
From the found correlations (Eqns 17 and 18), similar values of $K_4$ were obtained for piperidineoxyls **1k–r** (Table 1). Together with the data on potentials $E_{2/1}$ and values of $pK_{3H+}$, it allows one to calculate by Eqn 9 the expected dependences of potentials $E_{1/3\Sigma}$ versus pH for radicals **1k–r** (refer to Table S2).

**Bond dissociation energies D(O–H) for hydroxylamines 3**

In an analogous manner as it was performed for the hydroquinones,[37] for the reduction of radicals **1** to hydroxylamines **3**, a thermodynamic cycle can be constructed comprising the reaction (19)–(21). The sum of the free energies of these reactions correspond to the bond energies D(O–H) (reaction 22).

$$\text{\Large N—OH} \rightleftharpoons \text{\Large N—O}^{\bullet} + H^+ + e^- \quad (19)$$
$$\mathbf{3} \qquad\qquad\qquad \mathbf{1}$$

$$\Delta G = 96.5 \times E_{1/3}$$

$$H^+ + e^- \rightleftharpoons 0.5\, H_2 \quad \Delta G = 0 \quad (20)$$

$$0.5\, H_2 \rightleftharpoons H^{\bullet} \quad \Delta G = 203.1\ \text{kJ mol}^{-1} \quad (21)$$

$$\text{\Large N—OH} \rightleftharpoons \text{\Large N—O}^{\bullet} + H^{\bullet} \quad (22)$$
$$\mathbf{3} \qquad\qquad\qquad \mathbf{1}$$

Potential $E_{1/3}$ is related to potential $E_{2/1}$ and equilibrium constants $K_2 / K_{1H+} = K_4 \times K_{3H+}$ by equation $E_{2/1} - E_{1/3} = -(RT/F)\ln(K_2/K_{1H+})$. Consequently, it can be calculated from the known values of $E_{2/1}$, $K_4$ and $pK_{3H+}$ (Eqn 23).

$$E_{1/3} = E_{2/1} + 0.059 \cdot \log(K_4 \cdot K_{3H+}) = E_{2/1} + 0.059(\log K_4 - pK_{3H+}) \quad (23)$$

Calculated $E_{1/3}$ values are shown in Table S2. Equation 24 is obtained for calculation of bond dissociation energy D(O–H) in hydroxylamines **3** taking into account the approximately equal entropies for **1** and **3**, as well as T$\Delta$S corrections for atom H$^{\bullet}$, which at 25 °C is 34.3 kJ/mol.[37]

$$D(O–H) = 96.5 \left[ E_{2/1} + 0.059(\log K_4 - pK_{3H+}) \right] + 237.4 (kJ/mol) \quad (24)$$

The values of D(O–H) calculated by Eqn 24 are presented in Table 1. Error in determining $E_{1/3}$ (Eqn 23) does not exceed $\pm 10$ mV, thus corresponding to an error of $\pm 1$ kJ/mol for the calculated D(O–H). The obtained values of D(O–H) are by 0–4 kJ/mol higher for **3a**, **e**, **k**[38] and by 4–10 kJ/mol higher for **3a**, **c**, **g**[39] than values found from hydrogen atom exchange equilibria in non-polar solvents. Higher values of D(O–H) are characteristic for polar solvents and are because of hydrogen bonding between the solute and solvent.[40]

## CONCLUSIONS

(1) Comproportionation rate constants $k_{-2}$ in the series of piperidine derivatives **a–g** are weakly dependent on changes in reduction potentials of oxoammonium cations to nitroxyl radicals $E_{2/1}$. It is expected that the potentials of the second redox half reaction of equilibrium (2), that is, the reduction of radical cations **1**H$^+$ to hydroxylamines **3**, should change in parallel to the potentials $E_{2/1}$, so that the difference between them $(E_{1H+/3} - E_{2/1})$ and the equilibrium constant $K_2$ for nitroxyl radicals of the same heterocycle remain approximately constant.

(2) –I-Effects of substituents R increase the constants $k_{-2}$, $K_{1H+}$ and $K_{3H+}$ thus reducing the overall equilibrium constant $K_4 = k_2 / (k_{-2} \times K_{1H+} \times K_{3H+})$ in the studied series **a–i** by more than seven orders of magnitude.

(3) Pyrrolidine and pyrrolineoxyls are 0.1–0.15 V weaker oxidants than piperidine derivatives that is in agreement with their greater stability in biological samples. Values of $pK_{3H+}$ determine the position of inflections on $E_{1/3\Sigma}$–pH dependences, so that of the two radicals one may be more potent oxidant at high and the other at low pH.

(4) Values of reduction potentials $E_{2/1}$ and acidity constants $pK_{3H+}$ correlate well with the inductive constants of substituents $\sigma_I$. In addition, the free energies $-96.5 \times E_{2/1}$ and $-5.7 \times \log K_{3H+}$ are linearly related with each other, as well as with the free energy of a disproportionation–comproportionation equilibrium – $5.7 \times \log K_4$. These linear free-energy relationships allow predicting the redox and acid–base properties of triads **1–2–3**.

(5) The found bond dissociation energies D(O–H) for hydroxylamines in water are in the range 287–304 kJ/mol, which is 0–10 kJ/mol higher than the known values for non-polar solvents. This agrees with the expected increase in the values of D(O–H) in water as a result of the formation of hydrogen bonds.

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