

Mutual Effect of Functional Groups and the Radical Center on the Reactivity of Nitroxyl Radicals

A. D. Malievskii and A. B. Shapiro

Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, ul. Kosygina 4, Moscow, 119991 Russia

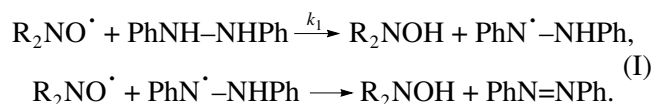
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Abstract—This review considers the correlation between the reactivity of nitroxyl radicals (piperidine, pyrroline, pyrrolidine, imidazoline, dihydroquinoline, tetrahydroquinoline, diphenyl nitroxide, etc.) and their chemical structure in terms of the rate constants of reactions between these radicals and hydrazobenzene. 4,4'-Di(*tert*-butyl)diphenyl nitroxyl has the highest reactivity, and the nitroxyl radical of benzoindolopyrrolidine is the least reactive (the difference is a factor of $\sim 10^4$). The effects of the metal atom in stable organometallic nitroxyl radicals and of the halogen atom in halogenated nitroxyl radicals on the reactivity of the nitroxyl center are considered. Data on the effect of the nitroxyl center on the reactivity of functional groups in the piperidine nitroxyl radical are generalized. Nitroxyl radicals with an activated double bond are shown by quantum chemical calculations to form cyclic transition complexes with amines, involving both the paramagnetic center and a double bond. This explains why the activated double bond in nitroxyl radicals is more reactive in nucleophilic additions of amines than the same bond in their diamagnetic analogues. The rate constants of nitroxyl reduction with hydrazobenzene and of nitroxyl oxidation with tetranitromethane are related to the σ_{ESR} constant derived from isotropic hyperfine coupling constants $\text{HFC}_{(a_N)}$, and their correlation with Hammett constants is demonstrated. The role of solvents in the reduction and oxidation of the nitroxyl radicals is considered. The influence of hydroxyl radical–polar solvent complexes and hydroxylamine–polar solvent H complexes on the course of reactions is considered for hydrogen atom transfer in systems of a sterically hindered nitroxyl radical and hydroxylamine.

One of the characteristic properties of stable nitroxyl radicals (NRs) is their ability to act as both one-electron oxidants and reducing agents [1]. The influence of structural factors on the redox properties of NRs have been studied [2–12] by different methods for a wide range of oxidants and reducing agents in various solvents and at various temperatures.

In these studies, the reactivity of an NR was estimated, for example, from Gibbs energy (ΔG) data for the reaction between the NR and 1-hydroxy-2,2,4,5,5-pentamethyl-3-imidazoline-3-oxide in chloroform [11], from rate constant data for the reaction between the NR and hydrazobenzene in an alcoholic solution (k_{alc}) [4], and in an N-(*para*-methoxybenzalidene)-*para*-butylaniline mixture [7], from electrochemical potentials ($-E_{1/2}$) data for NR reduction in aqueous ethanol, dimethylformamide, and a benzene–methanol mixture [12], as well as from the extent of the reaction between the NR and ascorbic acid in a phosphate buffer at a given time point [6].

Since the reduction of NRs was studied under different conditions and by different methods, the reactivities of NRs cannot be compared using the results of those studies. We proposed [13] comparing the reactivities of NRs in terms of the rate constants (k_1) of NR–hydrazobenzene reactions in hexane (a neutral solvent) at room temperature:

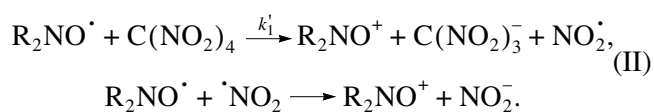


The reactivities of more than 40 nitroxyl radicals (including piperidine, pyrroline, pyrrolidine, hydrogenated γ -carboline, benzoindolopyrrolidine, imidazoline, dihydroquinoline, tetrahydroquinoline, and diphenylamine) were thus characterized.

Furthermore, we suggested [13] equations relating the rate constants (k_1) of reaction (I) for the above-listed NRs to the physicochemical parameters of NR reduction measured by other authors under different conditions [2–12]. Using these correlation equations, we characterized [13] the reactivities of about 50 other nitroxyl radicals with various structures in terms of k_1 .

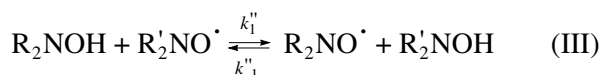
Thus, the use of k_1 provided a unified basis for the reactivity analysis of more than 90 different nitroxyl radicals and allowed a more general consideration of the dependence of NR reactivity on various structural factors, including the size and nature of the ring, coordination bonds with an organometallic moiety, and the electronic and steric effects of functional groups in different positions of the ring.

It was suggested to compare the reductive properties of NRs in terms of the rate constant k_1' of the NR–tetranitromethane reaction in an aqueous medium at room temperature [13–15]:



In an earlier work [14], we related the rate constants of reactions (I) and (II) (k_1 and k_1') to the Hammett constant σ and to the isotropic HFC constant a_N , which reflects the spin density distribution in the nitroxyl fragment.

Hydrogen atom exchange between sterically hindered hydroxylamines and nitroxyl radicals,



was studied by kinetic methods in a wide temperature range [16]. This reaction provides additional information on NR reactivity and makes it possible to estimate the NO–H bond dissociation energy for a series of hydroxylamines.

For reactions (I)–(III), we studied [14] the effect of the solvent, including specific interaction resulting in the formation of NR–solvent complexes. The participation of NRs in cyclic mechanisms of chain termination was studied in [17]. There have been reports on specific reactions of nitroxyl radicals in polymer matrices [18–26].

Here, we review our earlier results and the literature concerning the reactivity of nitroxyl radicals. The earlier data on the influence of the nitroxyl center on the reactivity of functional groups of imidazoline NRs [2] are supplemented by our new results (including unpublished data) for piperidine NRs in the Diels–Alder, Michael, Tollens, Favorskii, and Trofimov reactions and some other processes.

The participation of the paramagnetic center and a functional group in the formation of a transition complex is discussed for the reaction of 3,5-dimethylene-2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl with a secondary amine with reference to quantum chemical calculations. The structure of the transition complex of the diamagnetic analogue of this NR in the reaction with amine is considered for comparison.

INFLUENCE OF STRUCTURAL FACTORS ON THE REACTIVITY OF NITROXYL RADICALS

The rate constants (k_1) of reaction (I) for many NRs are presented in Table 1. The values experimentally obtained by the authors are labeled with an asterisk. For other NRs, k_1 data were calculated using correlations between k_1 and the parameters characterizing the reactivity of these NRs ($-E_{1/2}$, ΔG , k_{alc}):

$$\log k_1 = 3.78 - 0.2\Delta G, \quad (1)$$

$$\log k_1 = 1.65 + 2.9E_{1/2}, \quad (2)$$

$$k_1 = 46.3k_{\text{alc}}. \quad (3)$$

Thus, the reactivity of a large group of stable nitroxyl radicals with different structures was estimated.

Based on the k_1 data, we constructed a unified scale of reactivity (oxidative properties) for stable nitroxyl radicals with various structures. In this group of stable radicals, 4,4'-di(*tert*-butyl)diphenyl nitroxyl (**20**), with $k_1 = 5 \times 10^3 \text{ l mol}^{-1} \text{ s}^{-1}$, and the nitroxyls of hydrogenated quinoline (**21**, **22**), with $k_1 = (0.3\text{--}3.1) \times 10^3 \text{ l mol}^{-1} \text{ s}^{-1}$, show the highest reactivity. For nitroxyls of the piperidine and imidazoline series, $k_1 = 5\text{--}60 \text{ l mol}^{-1} \text{ s}^{-1}$. Benzoindolopyrrolidine nitroxyl (**3**), with $k_1 = 0.2 \text{ l mol}^{-1} \text{ s}^{-1}$, is the least reactive of the nitroxyls considered.

The high reactivity of the di(*tert*-butyl)diphenyl nitroxyl and hydrogenated quinoline nitroxyls (NRs with a system of conjugated bonds) compared to the reactivity of the piperidine, imidazoline, pyrrolidine, pyrroline, and tetrahydro- γ -carboline NRs (Table 1) is explained by the fact that the former are sterically less hindered near the nitroxyl center.

The delocalization of the unpaired electron exerts a substantially weaker effect on the reactivity of the NRs than the steric factor.

The low reactivity of NR **3** can be explained by the strong steric hindrance near all atoms of the pyrrolidine ring and by the possibility of the partial delocalization of the unpaired electron on benzoindole nuclei.

The nitron group in the 3-imidazoline NR contributes considerably to the reactivity of this radical (Table 1). According to quantum chemical calculations, the spin density on the oxygen atom (ρ_O) is 0.0136 higher in **6a** than in **5a** and the spin density on the nitrogen atom (ρ_N) is 0.0125 lower in **6a** than in **5a** (Table 2) [2]. As for experimental data, NRs **5a** and **6a** are characterized by markedly different a_N constants: for CHCl_3 and aqueous solutions, a_N for **5a** is larger than a_N for **6a** by 0.15 and 0.72 G, respectively [2]. It turned out that the imidazoline nitroxyl with a nitron group **6a** is six times more reactive than its imidazoline analogue **5a** in reduction with hydrazobenzene (Table 2). A similar difference in the rate of NR reduction with hydrazobenzene is observed for the following pairs of NRs (without and with a nitron group, respectively): **5c–6j**, **5d–6k**, **5e–6i**, **5f–6m**, and **5l–6e** (Table 1). This unusual fact is worth explaining. According to ESR data, the unpaired electron in 3-imidazoline-3-oxides is localized on the nitroxyl center. However, it can be assumed that a substantial spin density appears on the nitron group at the instant of reaction [2]. This may cause a reduction of the nitron group. If this is the case, the reduction rate will increase, because the nitron group is less screened than the nitroxyl center. The deoxygenation of the nitron group of the 3-imidazoline-3-oxide NR with hydrazine, presented in [2] and in the last section of this review, confirms this hypothesis.

An opposite effect is exerted by the nitron group in the α -nitronyl nitroxyl **18**, where this group is conjugated with the nitroxyl group. Radical **18** (with a

Table 1. Rate constants k_1 of reactions between nitroxyl radicals and hydrazobenzene

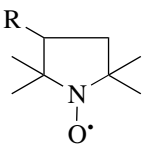
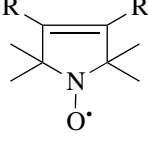
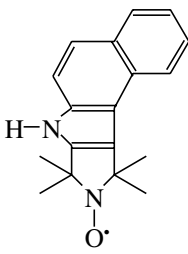
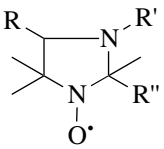
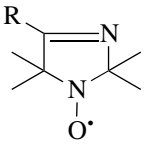
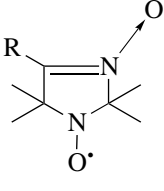
| Radical | | R | R' | R'' | $k_1, \text{l mol}^{-1} \text{s}^{-1}$ |
|---|-----------|---|-------------------|--------------------------------|--|
|  | 1a | CONH ₂ | — | — | 2.22* |
| | 1b | COOH | — | — | 2.69* |
| | 1c | OH | — | — | 1.37* |
|  | 2a | H | CONH ₂ | — | 3.45 |
| | 2b | H | COOMe | — | 4.4 |
| | 2c | H | Cl | — | 3.6 |
| | 2d | H | COH | — | 1.7 |
| | 2e | Br | Br | — | 3.2 |
| | 2f | Br | COOMe | — | 3.6 |
|  | 3 | — | — | — | <0.2* |
|  | 4a | Me | Me | Me | 1.50* |
| | 4b | Ph | Me | Me | 2.17* |
| | 4c | <i>para</i> -FC ₆ H ₄ | Me | Me | 2.80 |
| | 4d | <i>para</i> -MeC ₆ H ₄ | Me | Me | 2.10 |
| | 4e | Me | Me | C ₆ H ₁₃ | 0.37* |
|  | 5a | Me | — | — | 6.74* |
| | 5b | CCl ₃ | — | — | 9.80 |
| | 5c | Ph | — | — | 4.90* |
| | 5d | <i>para</i> -FC ₆ H ₄ | — | — | 7.70 |
| | 5e | <i>para</i> -MeC ₆ H ₄ | — | — | 9.20 |
| | 5f | ClC ₆ H ₄ | — | — | 6.95 |
| | 5g | CH=NOH | — | — | 8.40* |
| | 5h | CH=NC ₄ H ₉ | — | — | 5.40* |
| | 5i | CONH ₂ | — | — | 10.85* |
| | 5j | COMe | — | — | 10.10* |
| | 5k | <i>iso</i> -C ₃ H ₇ | — | — | 5.7 |
| | 5l | CHCl ₂ | — | — | 7.1 |
|  | 6a | Me | — | — | 43.8 |
| | 6b | CH ₂ Br | — | — | 48.4 |
| | 6c | MeCHBr | — | — | 43.0 |
| | 6d | CH ₂ I | — | — | 53.5 |
| | 6e | CHCl ₂ | — | — | 97.9 |
| | 6g | CHBr ₂ | — | — | 134.0 |
| | 6h | <i>para</i> -MeOC ₆ H ₄ | — | — | 26.0 |
| | 6i | <i>para</i> -MeC ₆ H ₄ | — | — | 28.0 |
| | 6j | Ph | — | — | 31.5* |
| | 6k | <i>para</i> -FC ₆ H ₄ | — | — | 43.8 |
| | 6l | <i>para</i> -BrC ₆ H ₄ | — | — | 46.0 |
| | 6m | <i>para</i> -ClC ₆ H ₄ | — | — | 48.4 |
| | 6n | CN | — | — | 196* |

Table 1. (Contd.)

| Radical | | R | R' | R'' | $k_1, \text{l mol}^{-1} \text{s}^{-1}$ |
|---------|------------|---|--|-----|--|
| | 7a | NHMe | — | — | 92 |
| | 7b | OH | — | — | 101 |
| | 8a | Me | — | — | 156 |
| | 8b | Ph | — | — | 209 |
| | 9a | Ph | — | — | 32 |
| | 9b | <i>para</i> -FC ₆ H ₄ | — | — | 37 |
| | 9c | <i>para</i> -MeC ₆ H ₄ | — | — | 32 |
| | 10a | H | H | — | 8.70* |
| | 10b | H | OH | — | 14.15* |
| | 10c | H | NH ₂ | — | 12.00* |
| | 10d | H | N(CH ₂ CH ₂) ₂ NH | — | 12.90* |
| | 10e | H | OCOPh | — | 14.60 |
| | 10f | H | Cl | — | 13.50 |
| | 10g | OH | Ph(C≡C) ₂ C ₆ H ₄ C≡C | — | 5.15 |
| | 10h | H | MeOC ₆ H ₄ CH=N— | — | 6.50 |
| | 10i | OH | Et | — | 5.15 |
| | 10j | OH | PhC≡C—C≡C— | — | 5.70 |
| | 11a | H | — | — | 13.90* |
| | 11b | Br | — | — | 27.0 |
| | 11c | Cl | — | — | 67.0 |
| | 12 | — | — | — | 14.50* |
| | 13 | — | — | — | 12.20* |
| | 14a | N(CH ₂ CH ₂) ₂ NH | — | — | 9.00* |
| | 14b | HgCl | — | — | 11.70* |
| | 14c | H | — | — | 5.00* |
| | 14d | J | — | — | 14.00* |
| | 14e | C≡CPh | — | — | 8.80* |
| | 14f | Ph | — | — | 6.60* |

Table 1. (Contd.)

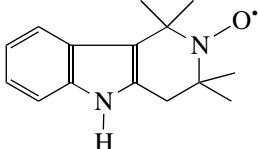
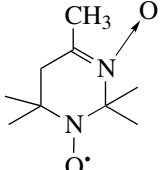
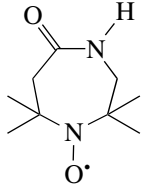
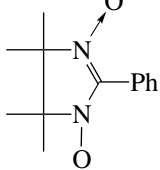
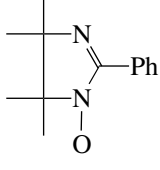
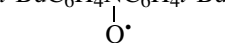
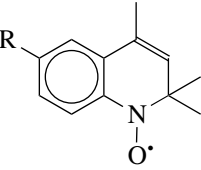

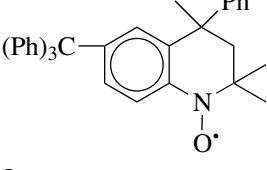
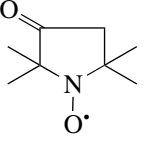
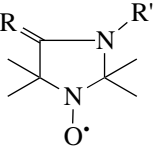
| Radical | | R | R' | R'' | $k_1, \text{l mol}^{-1} \text{s}^{-1}$ |
|---|------------|--|-----|-----|--|
|  | 15 | — | — | — | 8.30* |
|  | 16 | — | — | — | 80 |
|  | 17 | — | — | — | 32.5 |
|  | 18 | — | — | — | 7.70 |
|  | 19 | — | — | — | 158 |
| $t\text{-BuC}_6\text{H}_4\text{NC}_6\text{H}_4t\text{-Bu}$  | 20 | — | — | — | 5×10^3 * |
|  | 21a | (Ph) ₃ C HO(CF ₃) ₂ C | — | — | 366* |
|  | 21b | | | | 3.1×10^3 * |
|  | 22 | — | — | — | 420* |
|  | 23 | — | — | — | 19.0* |
|  | 24a | CH ₂ | CHO | — | 18.20* |
| | 24b | O | OH | — | 45.6 |
| | 24c | CHC(Ph)O | H | — | 18.45* |

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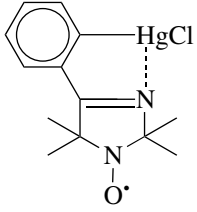
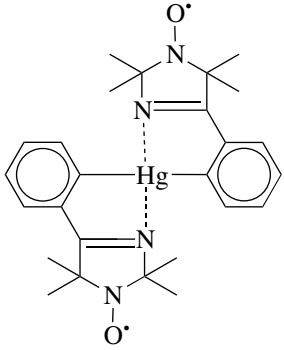
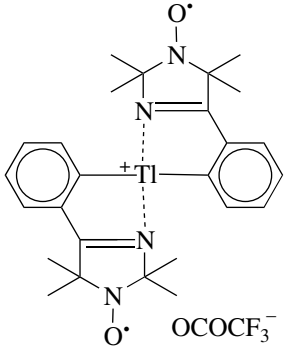
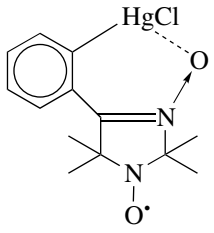
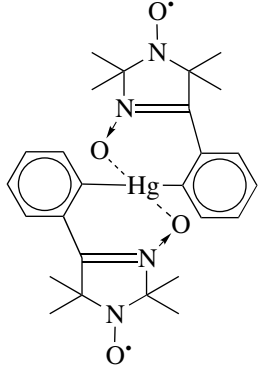
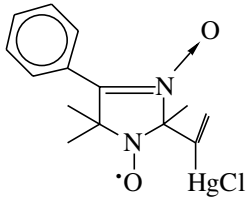
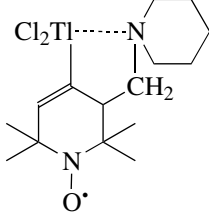
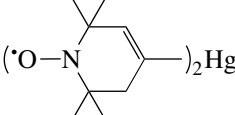
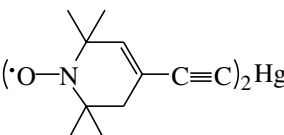
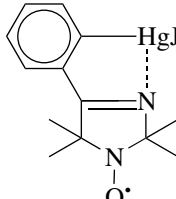
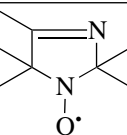
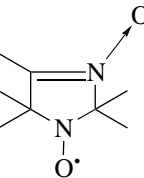
| Radical | R | R' | R'' | $k_1, \text{l mol}^{-1} \text{s}^{-1}$ |
|---|---|----|-----|--|
|  | — | — | — | 11.70 |
|  | — | — | — | 10.60 |
|  | — | — | — | 16.60* |
|  | — | — | — | 108* |
|  | — | — | — | 1090* |

Table 1. (Contd.)

| Radical | R | R' | R'' | $k_1, \text{l mol}^{-1} \text{s}^{-1}$ |
|--|---|----|-----|--|
|  30 | — | — | — | 38.0* |
|  31 | — | — | — | 14.40* |
|  32 | — | — | — | 7.40* |
|  33 | — | — | — | 11.50* |
|  34 | — | — | — | 11.50* |

* The starred k_1 values are obtained experimentally using reaction (1), and the other k_1 values are calculated using relationships (1)–(3) [13, 38].

Table 2. Some physicochemical constants of nitroxyl radicals of the imidazoline series

| Radical | a_N, G | ρ_O | ρ_N | $k_1, \text{l mol}^{-1} \text{s}^{-1}$ | $-E_{1/2}(\text{red.}), \text{V}$ |
|---|---|----------|----------|--|-----------------------------------|
|  5a | 14.60 (CHCl_3) 15.88 (H_2O) | 0.6674 | 0.3105 | 6.74 | 0.60 |
|  6a | 14.45 (CHCl_3) 15.16 (H_2O) | 0.6810 | 0.2980 | 43.80 | 0.39 |

nitron group) is less reactive ($k_1 = 7.70 \text{ l mol}^{-1} \text{s}^{-1}$) than radical **19** ($k_1 = 158 \text{ l mol}^{-1} \text{s}^{-1}$), which is similar in structure but contains no nitron group. The unpaired electron in NR **18** is distributed between two equivalent N–O groups ($a_{N1} = a_{N3} = 7.2 \text{ G}$) [27], unlike the

unpaired electron in NR **19**, whose nitrogen atoms are not equivalent ($a_{N1} = 10 \text{ G}$ and $a_{N3} = 4 \text{ G}$). The fact that the N–O group in NR **18** is characterized by a lower spin density than the N–O group in NR **19** explains why the nitronyl nitroxyl radical is less reactive.

The reactivity of the NR increases with an increase in the electron-withdrawing properties of the functional groups in the positions separated from the radical center by two or more σ bonds: **6n** > **6a**, **5i** > **5c**, and **5j** > **5k**.

The presence of $N \rightarrow Hg$, $N \rightarrow Tl$, and $O \cdots Hg$ coordination bonds has been demonstrated for organometallic nitroxyl radicals [28–30]. The $N-Hg$ and $N-Tl$ distances in NRs **25–27** (Table 1) were found to be approximately 2.6 Å, which exceeds the length of the ordinary covalent bond (2.05 Å) but is substantially shorter than the sum of the van der Waals radii. Calculations revealed strong coordination bonds $N-O \cdots Hg$ and $N-O \cdots Tl$ in orthomercurated and orthothalliated 2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline nitroxyl radicals [31, 32]. The interaction between the unpaired electron of the NR and the mercury and thallium atoms in the organomercury and organothallium nitroxyl monoradicals and biradicals was discovered and studied in [31–37]. The spin exchange in these cyclometallated NRs occurs through $N \rightarrow Hg$, $N \rightarrow Tl$, and $O \cdots Hg$ bridges [28–30].

The high reactivity of the cyclometallated radicals as compared to the reactivity of similar radicals containing no metal can be explained by the enhancement of the electron-withdrawing properties of the nitroxyl caused by the intramolecular coordination bonds $N \rightarrow Hg$, $N \rightarrow Tl$, and $O \cdots Hg$ (Table 1) [38]. Comparison of the reactivities of the cyclomercurated imidazoline monoradical **25** and biradical **26**, the cyclothalliated biradical **27**, and the starting phenylimidazoline nitroxyl **5c** suggests that the mercury and thallium atoms increase the reactivity of **25–27** by a factor of 2–3 and the oxidative reactivity of cyclothalliated biradical **27** is higher than that of the corresponding organomercury biradical **26**. The reactivities of the organomercury monoradicals and biradicals are nearly equal (the biradicals are characterized by a rate constant per reaction center).

The reactivity of *N*-oxides **6**, **28**, and **29** exceeds the reactivity of the corresponding nitroxyl radicals containing no nitron group **5**, **25**, and **26**. It was demonstrated by X-ray crystallography that the $N-O \cdots Hg$ coordination bond in NRs **28** and **29** is weak. However, for NRs **6j**, **28**, and **29** the rate constant ratio is 1 : 3.4 : 35, while it is 1 : 2.4 : 2.2 for **5c**, **25**, and **26**. High rate constants are observed for NRs **28** and **29**. We explain this high reactivity of the cyclomercurated 3-imidazoline-3-oxide NR by the possibility of a spin density appearing on the oxygen atom of 3-oxide at the instant of reaction, as considered above.

Like metal atoms, halogen atoms increase the reactivity of nitroxyl radicals. For example, the iodinated NR **14d** is almost three times as reactive as its piperidine analogue **14c**. The monohalogenated and particularly dihalogenated derivatives of the 3-imidazoline-3-oxide NR (**6b**, **6c**, **6d**, **6g**, **6k**, **6l**, and **6m**) are more reactive than their halogen-free analogues (Table 1). Fluorine atoms in

2,2,4-trimethyl-1,2-dihydroquinoline NRs exert a strong effect on the reactivity of these radicals. For instance, **21b** is almost one order of magnitude more reactive than **21a**.

The bis(trifluoromethyl) NR is extremely reactive towards toluene, cyclopropane, halogenated olefins, anthracene derivatives, and other compounds [39–41]. Nitroxyl radicals **8a** and **8b**, with a positive charge on the nitrogen atom of the imidazoline cycle, are 20–40 times more reactive than their uncharged analogues **5a** and **5c**.

Analysis of reactivity data for stable piperidine, pyrroline, pyrrolidine, and imidazoline NRs allows us to relate the rate constants k_1 of hydrogen atom addition to an NR (reaction (I)) to the $NO-H$ bond dissociation energy (D) of the hydroxylamine resulting from this radical:

$$\log k_1 = -14.53 + 0.22D_{NO-H}. \quad (4)$$

It follows from Eq. (4) that, the stronger the $NO-H$ bond in the hydroxylamine, the more reactive its NR.

Using Eq. (4) and k_1 data for the types of NR listed above [13, 38], we determined the $NO-H$ bond dissociation energies for the hydroxylamine series. The discrepancy between the D_{NO-H} values calculated for hydroxylamines in earlier studies [42, 43] and the same data obtained using Eq. (4) does not generally exceed 1–1.5 kcal/mol.

KINETICS AND MECHANISM OF THE REDUCTION OF NITROXYL RADICALS WITH HYDRAZOBENZENE

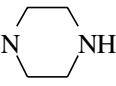
The rate constant k_1 of the reduction of piperidine NRs with hydrazobenzene (I) in hexane depends weakly on the substituent in the NR (Table 3): the difference in k_1 between the most and least reactive NRs is ~50% at 25°C. The following equation is valid:

$$\log(k_1/k_{10}) = 0.047 + \rho\sigma'', \quad (5)$$

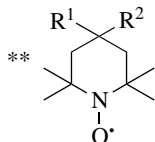
where k_{10} is the reduction rate constant of NR **10a** [14], σ'' is the Hammett constant, and ρ is the measure of the sensitivity of the reaction to induction effects (see Table 3). The low value of $\rho = 0.4$ indicates a low-polarity transition state, which is characteristic of hydrogen atom transfer. Furthermore, a high kinetic isotope effect is observed for the reduction reaction (Table 4), suggesting that the transition state is asymmetric and, perhaps, nonlinear [44].

Several mechanisms can be suggested for NR reduction with hydrazobenzene, considering that different types of NR complex with a proton-donor compound [14, 45] having a lone electron pair at the heteroatom can be formed. In our opinion, one of the possible variants is as follows: hydrazobenzene reacts with the NR via the interaction of the π orbital of the NR with the σ orbital of the hydrogen atom of the NH group to form a $\pi-\sigma$ complex. In this case, steric hindrance is less pro-

Table 3. Isotropic constants $HFC_{(a_N)}$, g factor, and reaction rate constants (k_1 and k'_1) for the reduction of NRs with hydrazobenzene and for the oxidation of the NRs with tetranitromethane in water at room temperature

| NR* | R ^{1**} | R ^{2**} | NR reduction | | | | NR oxidation | | | | | |
|------------|------------------|---|--------------------------------|----------------------------------|---|---------------------|---------------------|----------------------------------|--|---------------------|-----------------|-------------------|
| | | | C ₆ H ₁₄ | | | | H ₂ O | | | | | |
| | | | $a_N(\pm 0.02)$, G | $\sigma_{ESR}^{***} \times 10^2$ | k_1 , l mol ⁻¹ s ⁻¹ | g factor (0.0001) | $a_N(\pm 0.02)$, G | $\sigma_{ESR}^{***} \times 10^2$ | k'_1 , l mol ⁻¹ s ⁻¹ | g factor (0.0001) | σ^{****} | $E_{p/2}$, V [2] |
| 10a | H | H | 15.27 | 0 | 8.7 | 2.0060 | 17.14 | 0 | 10.0 | 2.0056 | 0 | 0.29 |
| 10b | H | OH | 15.10 | 0.49 | 14.2 | 2.0060 | 16.99 | 0.38 | 1.70 | 2.0057 | 0.23 | 0.34 |
| 10c | H | NH ₂ | 15.13 | 0.40 | 12.0 | 2.0060 | — | — | — | — | — | — |
| 10d | H |  | 15.16 | 0.31 | 12.9 | 2.0060 | 16.88 | 0.66 | 1.35 | 2.0057 | — | — |
| 10f | H | Cl | — | — | 13.5 | — | 16.36 | 2.02 | 0.40 | — | 0.34 | 0.40 |
| 11a | — | =O | 14.21 | 3.12 | 13.9 | — | 15.96 | 3.10 | 0.10 | 2.0056 | 0.51 | 0.44 |
| 12 | — | =NOH | 14.61 | 1.92 | 14.5 | 2.0057 | 16.46 | 1.76 | 0.30 | — | 0.38 | 0.40 |
| 35 | H | OCH ₃ | — | — | — | — | 16.78 | 0.92 | 1.14 | — | 0.25 | 0.35 |
| 36 | OH | C≡CH | 14.88 | 1.12 | 10.8 | 2.0058 | 16.73 | 1.05 | 1.40 | 2.0057 | — | — |

*NRs are numbered as in Table 1.

***For σ_{ESR} , see Eq. (12) in the text.**** σ " is the Hammett constant [2].

nounced than in other variants. Although π complexes are intermediates in the hydrogen atom transfer step, the system moving along the reaction coordinate can pass over the state of a complex [45].

The correlation between the rate constant of the reduction of NR **10a** with hydrazobenzene and the dielectric constant ϵ for aprotic solvents (hexane, chlorobenzene, and their mixtures), which was established in the form

$$\log k_{11} = 2.27 \times 10^{-2} - 3.0 \times 10^{-2}(\epsilon - 1)/(2\epsilon + 1), \quad (6)$$

confirms the absence of a polar effect of the medium. At the same time, the ~50-fold decrease in k_1 on going from hexane to ethanol ($\epsilon = 24.3$) indicates that ethanol is involved in this reaction [14]. This might be due to the formation of a hydrogen bond between the NR and an EtOH molecule. This would decrease the spin density on the oxygen atom of the nitroxyl moiety [27]. In turn, this would impede the transfer of the hydrogen atom from the NH group of hydrazobenzene to this oxygen atom.

KINETICS AND MECHANISM OF THE OXIDATION OF NITROXYL RADICALS WITH TETRANITROMETHANE

The rate constant k'_1 of reaction (II) for the oxidation of piperidine, pyrroline, pyrrolidine, and imidazoline nitroxyls with tetranitromethane in an aqueous medium at 25°C ranges between 0 and 13 l mol⁻¹ s⁻¹ and depends on both the nature of the cycle and substituents (Table 5). The greatest difference between k'_1 values in the piperidine series is ~10², which is observed for NRs **37** and **11a**. In the pyrroline series, the effect of electron-withdrawing substituents on the reactivity of an NR is much stronger than this effect in the corresponding pyrrolidine NR. For instance, the rate constant for the pyrrolinecarboxylic acid NR **38** is 28 times lower than the rate constant for the pyrrolidinecarboxylic acid NR **1b** (Table 5). In the imidazoline series, strong electron-withdrawing substituents decrease the reactivity of NRs to near zero (Table 5).

For the rate constants of the oxidation of piperidine NRs with tetranitromethane in water at 25°C, the following equation is valid:

$$\log(k'_1/k'_{10}) = 0.04 - \rho\sigma, \quad (7)$$

where k'_{10} is the rate constant of the oxidation of NR **10a** and σ'' is the Hammett constant (Table 3) [14]. The high absolute value of $\rho = 4.02$ indicates an important role of polar effects of the substituents in the radicals and is consistent with the concept that a cation is formed in reaction (II) via electron transfer from the NR to the electron acceptor (tetranitromethane).

These facts can be explained qualitatively on the basis of the limiting structures of the nitroxyl radical presented in [1, 2]:



With an increase in the electron-withdrawing properties of the substituent, the negative charge on the oxygen atom decreases and the spin density on this atom increases, whereas the electron density and spin density on the nitrogen atom of the nitroxyl fragment increases and decreases, respectively. As this takes place, the isotropic constant $\text{HFC}_{(a_N)}$ decreases [14, 27, 45].

The electrochemical oxidation potential ($E_{p/2}$) increases in the same way, and, hence, electron transfer is impeded and the rate constant decreases:

$$\log k'_1 = 3.83 - 10.55E_{p/2} \quad [14]. \quad (8)$$

It is shown in [46, 47] for several systems that $E_{p/2}$ is a linear function of the ionization potential, which directly determines the reactivity.

The replacement of an aprotic substituent by a proton-donor substituent raises the negative charge and decreases the spin density on the oxygen atom of the nitroxyl group owing to the formation of an H bond [2, 27, 45]. This increases the isotropic $\text{HFC}_{(a_N)}$ constant [14, 27, 45] (Table 3).

The isotropic $\text{HFC}_{(a_N)}$ constants for piperidine NRs in water and hexane are interrelated by the linear expression

$$a_N(\text{H}_2\text{O}) = 0.89 + 1.06a_N(\text{hexane}) \quad [14]. \quad (9)$$

A similar relationship was obtained for nitroxyl radicals with different structures (five-, six-, and seven-membered rings) in water and chloroform:

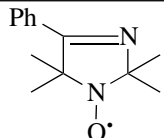
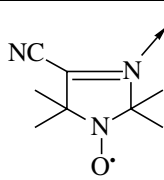
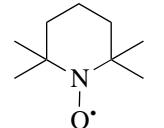
$$a_N(\text{H}_2\text{O}) = -2.82 + 1.26a_N(\text{CHCl}_3) \quad [14]. \quad (10)$$

A correlation between the isotropic $\text{HFC}_{(a_N)}$ constant, which is a measure of spin density on the nitrogen atom, and the Hammett constant σ , which reflects the change of electron density on the reaction center of the NR, was established [27] for several types of nitroxyl radical (in organic solvents) in the form $a_N/a_N^0 = -\rho\sigma$, where a_N^0 is the $\text{HFC}_{(a_N)}$ constant of NR **10a** and ρ is the measure of the sensitivity of the reaction to induction effects.

A similar correlation,

$$a_N/a_N^0 = 1.0 - 0.14\sigma'', \quad (11)$$

Table 4. Rate constants (k_1^H and k_1^D) of the reactions between nitroxyl radicals and non-deuterated and deuterated hydrazobenzenes and the kinetic isotope effect

| Nitroxyl radical | k_1^H , l mol ⁻¹ s ⁻¹ | k_1^D , l mol ⁻¹ s ⁻¹ | k_1^H/k_1^D |
|--|--|--|---------------|
|  5c | 4.9 | 1.75 | 2.80 |
|  6n | 196 | 45.7 | 4.29 |
|  10a | 8.70 | 3.43 | 2.54 |

was established for the piperidine series [14]. The relationship between the isotropic constant $\text{HFC}_{(a_N)}$ (for water as the solvent) and the Hammett constant σ'' for the piperidine series can be represented in a more convenient form:

$$\sigma_{\text{ESR}} = 5.32 \times 10^{-2}\sigma'' \quad [14], \quad (12)$$

where σ_{ESR} is the induction constant of the substituent and $\sigma_{\text{ESR}} = \log(a_N^0/a_N)$ (Table 3). Thus, k'_1 and a_N for the piperidine series are related by σ_{ESR} as

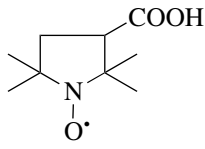
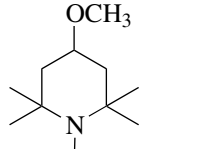
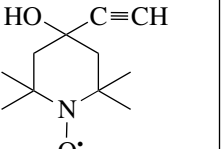
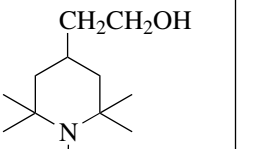
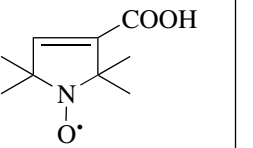
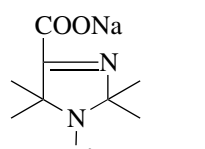
$$\log(k'_1/k'_{10}) = -0.34 - \rho\sigma_{\text{ESR}} \quad [14], \quad (13)$$

where $\rho = -56.4$.

According to data reported in [48], the other participant of the reaction (tetranitromethane) is a strong electron acceptor: its electron affinity is estimated at 1.7 eV. Quantum chemical calculations show that, in the tetranitromethane molecule, the electron density on the oxygen atoms of the nitro groups is much enhanced and that on the nitrogen and carbon atoms is substantially decreased.

In the oxidation reaction, the unpaired electron, delocalized over the molecular π orbital of the nitroxyl radical, interacts partially with the free orbital of one of the nitro groups of tetranitromethane, resulting in a weakening of one of the C–N bonds in tetranitromethane. Complete electron transfer from the nitroxyl radical to tetranitromethane results in the elimination of the $\cdot\text{NO}_2$ radical and the formation of reaction products, namely, the oxoammonium cation and the nitroform ion (reaction (II)).

Table 5. Rate constants (k'_1) of the reaction between nitroxyl radicals and tetranitromethane in an aqueous medium

| Radical | k'_1 , l mol ⁻¹ s ⁻¹ | $E_{p/2}$, V | Radical | k'_1 , l mol ⁻¹ s ⁻¹ | $E_{p/2}$, V |
|---|--|---------------|---|--|---------------|
|  1b* | 2.80 | — |  35 | 1.14 | 0.35 |
| 1c | 1.04 | — | | | |
| 2a | 0.16 | 0.38 |  36 | 1.40 [15] | — |
| 4b | 0.06 | 0.38 | | | |
| 6n | ~0 | 1.05 | | | |
| 10a | 10; 12.2 [15] | 0.25 |  37 | 13 [15] | — |
| 10b | 1.7 [15] | 0.34 | | | |
| 10c | 0.13 | — | | | |
| 10d | 1.35 | — |  38 | 0.10 | — |
| 11a | 0.10; 0.15 [15] | 0.44 | | | |
| 12 | 0.30 | 0.40 |  39 | ~0 | — |

Note: The absence of a reference means that k'_1 is obtained by the authors.

* Compounds are numbered as in Table 1.

The rate constant of the oxidation of the NR with tetranitromethane (reaction (II)) is solvent-dependent. This dependence arises primarily from the participation of reaction components in complex formation with solvent molecules [45, 49] and from the effect of the polarity of the medium. For instance, the reaction rate constant for NR **10a** in CCl₄–CH₃CN mixtures obeys the Kirkwood equation

$$\log k'_{11} = -5.71 + 10.64(\epsilon - 1)/(2\epsilon + 1), \quad (14)$$

although it cannot be excluded that the components of the CH₃CN–CCl₄ system itself are involved in complex formation with the NR [45, 49].

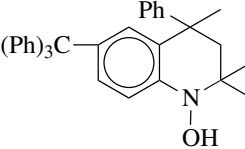
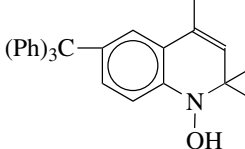
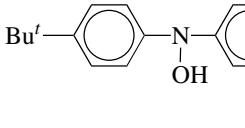
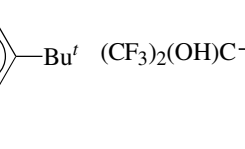
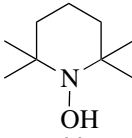
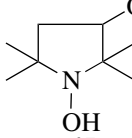
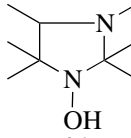
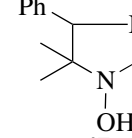
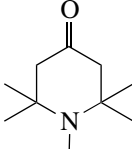
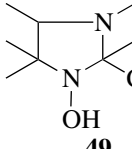
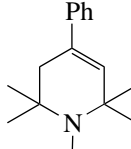
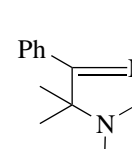
The reaction of NR **10a** with tetranitromethane in hexane ($\epsilon = 1.89$) almost does not occur, while for acetone ($\epsilon = 20.7$) and water ($\epsilon = 78.5$), the reaction rate

constant is 1.71 and 10 l mol⁻¹ s⁻¹, respectively. For acetone and water, Eq. (14) gives underestimated rate constant values. This is due to the participation of these solvents in the formation of complexes with the NR and tetranitromethane [46, 48, 49].

CYCLIC MECHANISMS OF CHAIN TERMINATION INVOLVING NITROXYL RADICALS

The high reactivity of NRs shows up as multiple chain termination via a cyclic mechanism in the oxidation of olefins, alcohols, and primary and secondary aliphatic amines. In this case, peroxide radicals possess both oxidative and reductive properties and the cyclic

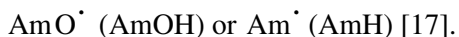
Table 6. Sterically hindered hydroxylamines and their bond dissociation energies $D_{\text{NO-H}}$ (kcal/mol)

| | | | |
|---|---|---|---|
|  |  |  |  |
| 40 | 41 | 42 | 43 |
| $D_{\text{NO-H}}$ 70.6 | 65.0 | 68.2 | 69.6 |
|  |  |  |  |
| 44 | 45 | 46 | 47 |
| $D_{\text{NO-H}}$ 69.7 | 66.4 | 66.5 | 66.7 |
|  |  |  |  |
| 48 | 49 | 50 | 51 |
| $D_{\text{NO-H}}$ 71.9 | 64.8 | 69.5 | 69.2 |

mechanism of multiple chain termination by NRs, as applied to a chain involving HO_2^\bullet , appears as follows:



Under polymer oxidation conditions, the cyclic mechanism includes the reactions $\text{R}^\bullet + \text{AmO}^\bullet$ and $\text{RO}_2^\bullet + \text{AmOR}$. At elevated temperatures, AmOR is thermally unstable and the mechanism includes the homolysis of the C–O or N–O bond of AmOR with the generation of



EFFECT OF THE MEDIUM ON THE REACTIVITY OF NITROXYL RADICALS IN POLYMERS

The specific character of the polymer matrix as a medium for bimolecular reactions involving nitroxyl radicals was revealed by analysis of the free-radical abstraction of a hydrogen atom from phenols, aromatic amines, and hydroperoxides and of the addition of an NR to methylenequinone in polymers (polypropylene, polyethylene, and polystyrene) and benzene [18–26].

Reactions in a polymer matrix proceed more slowly and with higher activation energies than reactions in the liquid phase. The reaction rate constant and molecular mobility of a nitroxyl radical are correlated. The faster the rotation of the radical in the polymeric matrix, the more rapidly it enters into the reaction. The introduction of benzene into a polymer increases the molecular mobility and thus accelerates the reaction.

The difference in reaction rate constants between polymers and solutions increases with an increase in the reactant volume: the larger the reactant volume, the lower the rate constant and rotation frequency in the polymer and the higher the activation energy.

All specific features of reactions in the solid phase can be explained in the framework of the “rigid cage” concept. The higher the rigidity of the cage walls, the larger the amount of energy required by an elementary step. The shape of the rigid cage sets up an additional hindrance for the orientation and chemical interaction of species. The mutual orientation of the reactants in the transition state causes changes in the shape of the polymer cage accompanied by an additional activation of the segments surrounding the pair of reacting species. As a consequence, the rate constant for the polymer is lower than the rate constant for the liquid phase.

HYDROGEN ATOM EXCHANGE IN THE STERICALLY HINDERED HYDROXYLAMINE–NITROXYL RADICAL SYSTEM

Hydrogen exchange in the hydroxylamine–nitroxyl radical system (reaction (III)) is generally reversible [2, 16, 27, 50], with few exceptions [51].

For the systems involving hydroxylamines **40–43** (Table 6) and nitroxyl radicals **1c**, **4a**, **4b**, **4e**, **10a**, **11a**, **14f**, **22** (Table 1), etc., the equilibrium state is achieved 50–200 ms after the reaction onset.

The forward and reverse hydrogen exchange reactions are characterized by low activation energies (Table 7) and low steric factors (10^{-6} – 10^{-4}).

Table 7. Rate constants of the forward and reverse reactions and equilibrium constants for hydrogen atom exchange in the sterically hindered hydroxylamine (HA)–nitroxyl radical system in hexane*

| HA | NR | k_1'' , l mol ⁻¹ s ⁻¹ | k_{-1}'' , l mol ⁻¹ s ⁻¹ | K_e |
|-----------|------------|---|--|-----------------------------------|
| 40 | 4e | 0.25×10^4 | 1.20×10^5 | 2.1×10^{-2} |
| 40 | 1c | 0.89×10^4 | 5.50×10^4 | 0.16 |
| 40 | 4b | 0.78×10^4 | 5.20×10^4 | 0.15 |
| 40 | 10a | 5.90×10^4 | 1.55×10^4 | 3.81 |
| 41 | 11a | — | — | 3.5×10^{-4} (exp6880/RT) |
| | | — | — | 36 |
| 41 | 4e | 0.80×10^4 | 1.00×10^5 | 0.08 |
| 41 | 10a | 1.50×10^5 | 1.35×10^4 | 11.1 |
| 42 | 4b | 5.20×10^5 (exp-2180/RT) | 6.80×10^5 (exp-400/RT) | 0.8 (exp-1780/RT) |
| | | 1.34×10^4 | 3.50×10^5 | 0.04 |
| 42 | 1c | 5.60×10^5 (exp-2200/RT) | 6.90×10^5 (exp-180/RT) | 0.8 (exp-2020/RT) |
| | | 1.40×10^4 | 5.10×10^5 | 2.7×10^{-2} |
| 42 | 11a | — | — | 8×10^{-3} (exp3660/RT) |
| | | 1.65×10^5 | 3.40×10^4 | 4.85 |
| 42 | 4e | 0.40×10^4 | 0.80×10^6 | 5×10^{-3} |
| 43 | 1c | 1.86×10^5 (exp-3300/RT) | 2.50×10^5 (exp-260/RT) | 7.4 (exp-3030/RT) |
| | | 7.33×10^3 | 1.62×10^5 | 4.6×10^{-2} |
| 43 | 4a | — | — | 6.1 (exp-3080/RT) |
| | | 0.50×10^4 | 1.40×10^5 | 3.5×10^{-2} |
| 43 | 4b | 1.94×10^6 (exp-3160/RT) | 2.10×10^5 (exp-330/RT) | 9.3 (exp-2830/RT) |
| | | 9.67×10^3 | 1.20×10^5 | 0.08 |
| 43 | 4e | 6.25×10^7 (exp-6130/RT) | 3.10×10^6 (exp-1350/RT) | 20.5 (exp-4780/RT) |
| | | 2.13×10^3 | 3.20×10^5 | 7×10^{-3} |
| 43 | 10a | 7.60×10^4 | 2.90×10^4 | 2.62 |
| 43 | 11a | 1.30×10^5 (exp-420/RT) | 5.10×10^5 (exp-2520/RT) | 0.2 (exp2260/RT) |
| | | 6.43×10^4 | 7.43×10^3 | 8.87 |
| 43 | 14f | 4.30×10^4 | 3.00×10^4 | 1.43 |
| 43 | 22 | 6.60×10^4 | 0.75×10^4 | 8.86 |

* At room temperature.

Comparison of the reactivities of NR **4b** towards hydroxylamine **43** and towards hydrazobenzene shows that $k_1'' = 1.94 \times 10^6 \exp(-3160/RT)$ in the first case and

$k_1 = 8 \times 10^4 \exp(-6300/RT)$ l mol⁻¹ s⁻¹ in the second case [16]. The higher reactivity of this NR towards hydroxylamine is due to the low activation energy.

Table 8. Isotope effect for the hydrogen exchange reaction in the sterically hindered HA–NR system

| HA | NR | $k_1'' \times 10^{-4}$ | $k_{-1}'' \times 10^{-4}$ | k_1^H/k_1^D | k_{-1}^H/k_{-1}^D |
|---------------|------------|-------------------------------------|---------------------------|---------------|---------------------|
| | | l mol ⁻¹ s ⁻¹ | | | |
| 43(H)* | 4a | 0.45 | 13.20 | 1.55 | 1.71 |
| 43(D)* | " | 0.29 | 7.70 | | |
| 43(H) | 14f | 4.30 | 3.00 | 1.71 | 1.56 |
| 43(D) | " | 2.52 | 1.92 | | |
| 43(H) | 4b | 0.86 | 13.70 | 1.51 | 1.38 |
| 43(D) | " | 0.57 | 9.90 | | |
| 41(H) | 4a | 1.37 | 6.16 | 1.88 | 2.06 |
| 41(D) | " | 0.73 | 3.00 | | |

Note: 20°C, hexane as the solvent, $[HA]_0 = (0.76-0.96) \times 10^{-4}$ mol/l, and $[NR]_0 = (1-10) \times 10^{-4}$ mol/l.

* HA(H) is non-deuterated HA, and HA(D) is deuterated HA (NO–H group).

Analysis of the rate constants of the forward and reverse hydrogen exchange reactions showed that the highest rate of hydrogen atom transfer at 25°C is $\sim 10^6$ l mol⁻¹ s⁻¹ and is observed for the systems hydroxylamine (HA) **49**–NR **20**, HA **45**–NR **20**, HA **49**–NR **21b**, and HA **47**–NR **20**. The lowest hydrogen transfer rate is 10^3 l mol⁻¹ s⁻¹ and is observed for the systems HA **40**, **42**, **43**–NR **4e**. The highest equilibrium constant is $K_e = 11$ and is observed for the HA **41**–NR **10a** system, and the lowest value of $K_e \approx 10^{-3}$ is observed for the HA **42**–NR **1c** system. For the HA **43**–NR **14f** system, the rate constants of the forward and reverse reactions are comparable (Table 7 [16]).

The NO–H bond dissociation energies for HAs **40**–**51** were derived from equilibrium constant data for the hydrogen exchange reaction (Table 6).

Replacement of the hydrogen atom in the NO–H group of hydroxylamine with a deuterium atom decreases the exchange rate by a factor of ~ 1.7 times

Table 9. Dependence of the kinetic parameters k_1'' and k_{-1}'' of the hydrogen atom transfer reaction in the HA **43**–NR **10a** system on the acetone (S) concentration

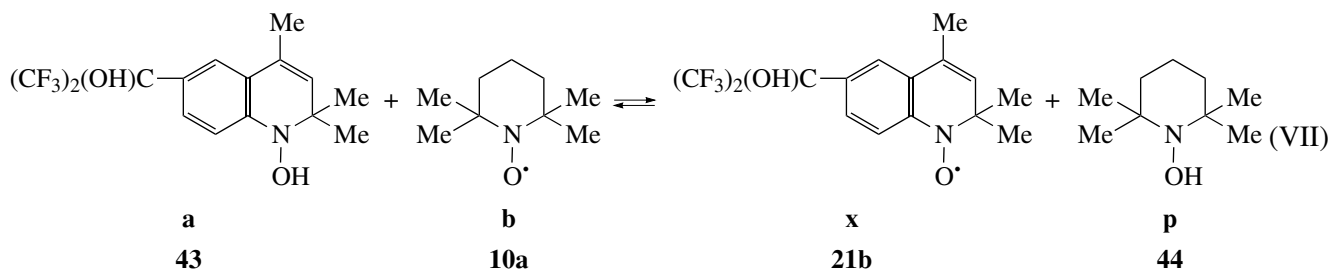
| No. | [S], M | $[a]_0 \times 10^5$, M | $[b]_0 \times 10^4$, M | $[x]_0 \times 10^6$, M | $k_1'', 1 \text{ mol}^{-1} \text{ s}^{-1}$ | $k_{-1}'', 1 \text{ mol}^{-1} \text{ s}^{-1}$ |
|-----|--------|-------------------------|-------------------------|-------------------------|--|---|
| 1 | 0.0 | 8.85 | 6.7 | 11.50 | 7.41×10^4 | 1.84×10^4 |
| 2 | 0.0 | 8.63 | 3.3 | 13.80 | 7.28×10^4 | 1.77×10^4 |
| 3 | 0.32 | 8.55 | 2.0 | 9.72 | 1.49×10^4 | 1.16×10^4 |
| 4 | 0.62 | 8.19 | 2.0 | 9.04 | 7.93×10^3 | 9.02×10^3 |
| 5 | 1.13 | 7.34 | 2.0 | 9.95 | 3.97×10^3 | 5.90×10^3 |
| 6 | 2.27 | 6.17 | 2.0 | 5.01 | 1.73×10^3 | 3.58×10^3 |
| 7 | 3.40 | 4.60 | 2.0 | 3.97 | 1.16×10^3 | 2.14×10^3 |
| 8 | 13.60 | 8.54 | 2.0 | 14.46 | 1.19×10^2 | 7.86×10^2 |
| 9 | 13.60 | 8.59 | 1.0 | 14.09 | 1.22×10^2 | 8.21×10^2 |
| 10 | 13.60 | 8.49 | 2.0 | 15.10 | 1.31×10^2 | 7.85×10^2 |
| 11 | 13.60 | 8.55 | 2.0 | 14.50 | 1.30×10^2 | 7.40×10^2 |

(Table 8) [16]. The weak isotope effect is explained by the cleavage of the initial bond and the formation of a new bond occurring synchronously. It is likely that the transition state is nearly symmetric and linear [44].

The role of the solvent in the hydrogen atom transfer reaction in the sterically hindered HA–NR system and possible variants of complex formation between the NR, HA, and solvent were studied for the HA **43**–NR **10a**

system in acetone (reaction (VII)). (Hereafter, the following designations are used: HA **43** = **a**, NR **10a** = **b**, NR **21b** = **x**, HA **44** = **p**, and Me₂CO (acetone) = S.)

If reaction (III) in hexane is not accompanied by any other reaction, a strong dependence of the rate constant on the solvent composition is observed for acetone and acetone–hexane mixtures [52] (Table 9).



The apparent rate constants k_1'' and k_{-1}'' decrease sharply with increasing Me₂CO concentration. Furthermore, on passing from an inert solvent (hexane) to acetone via hexane–acetone mixtures, the equilibration time lengthens (Fig. 1). According to reaction (VIII), Me₂CO (S) can perform several functions [45, 49, 53].

1. **b** + **a** \rightleftharpoons **x** + **p**
 2. **a** + S \rightleftharpoons c_1
 3. **b** + S \rightleftharpoons c_2
 4. **p** + S \rightleftharpoons c_3
 5. **x** + S \rightleftharpoons c_4
 6. c_2 + **a** \rightleftharpoons **p** + **x** + S
 7. c_4 + **p** \rightleftharpoons **a** + **b** + S
 8. **b** + S \rightleftharpoons c_5
 9. **x** + S \rightleftharpoons c_6
- (VIII)

The decelerating effect of acetone on hydrogen atom transfer in the NR–HA system is explained by the formation of NR and HA complexes with Me₂CO, which are not reactive or less reactive than the free (unbound) NR and HA. These include the dipolar radical–Me₂CO complexes c_2 and c_4 , in which electronic shells are not collectivized and the unpaired electron is not transferred from the radical to the ligand [45]. The dipolar complexes are involved in hydrogen atom transfer, reacting with the initial and resulting HAs. In the donor–acceptor complexes c_5 and c_6 , which are also formed from radicals and Me₂CO molecules, spin density is transferred from the radical to ligand and the electronic shells of the partners are collectivized. These complexes are not involved in the hydrogen atom transfer reaction [45]. Furthermore, the H complexes c_1 and c_3 result from the specific interaction between the carbonyl group of Me₂CO and the OH group of hydroxylamine. These complexes are not involved in hydrogen atom transfer. Processing of experimental data yielded

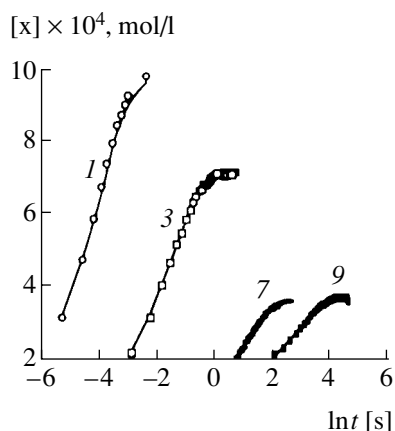


Fig. 1. Kinetics of quinoline radical **21b** (x) accumulation in the NR **10a**–HA **43** system for different initial concentrations of acetone (S) (the curve numbering is consistent with the compound numbering in Table 9): (1) $[S] = 0.0$ mol/l, $[a]_0 = 8.85 \times 10^{-5}$ mol/l, and $[b]_0 = 6.7 \times 10^{-4}$ mol/l; (3) $[S] = 0.32$ mol/l, $[a]_0 = 8.55 \times 10^{-5}$ mol/l, and $[b]_0 = 2.0 \times 10^{-4}$ mol/l; (7) $[S] = 3.40$ mol/l, $[a]_0 = 4.60 \times 10^{-5}$ mol/l, and $[b]_0 = 2.0 \times 10^{-4}$ mol/l; and (9) $[S] = 13.60$ mol/l, $[a]_0 = 8.59 \times 10^{-4}$ mol/l, and $[b]_0 = 1.0 \times 10^{-4}$ mol/l. The points are experimental data, and the lines represent calculated data.

an array of rate constants for the forward and reverse reactions in the kinetic network (VIII). This array is consistent with the corresponding experimental data. The most probable array of rate constants is presented in Table 10. From the data listed in Table 10, it was reliably determined that $K_2 = 11$ and $K_4 = 2.5$ l/mol (these

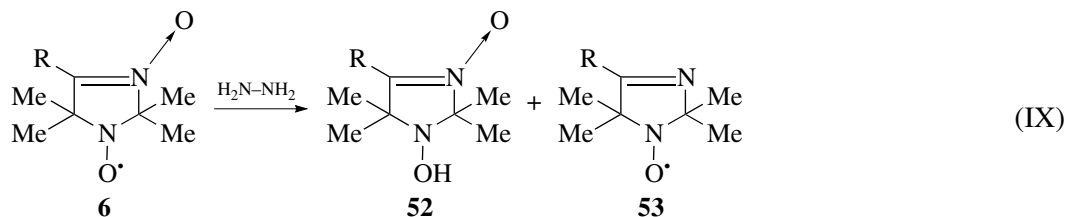
values are in agreement with the formation constants reported for complexes of proton donors with carbonyl compounds, alkylene oxides, and amines [53, 54]). Furthermore, we determined k_6 , k_1 , and k_{-1} (see Table 10). The values of K_3 and K_8 were determined previously [49]. The data listed in Table 10 suggest that the decrease in the rate of direct hydrogen atom transfer in the presence of Me_2CO is mainly due to the decrease in the concentration of unbound HA **43** and, to a much lesser extent, to the change in the concentration and reactivity of radical **10a** because of its transformation into the complex c_2 .

INFLUENCE OF THE NITROXYL CENTER ON THE REACTIVITY OF FUNCTIONAL GROUPS IN THE RING

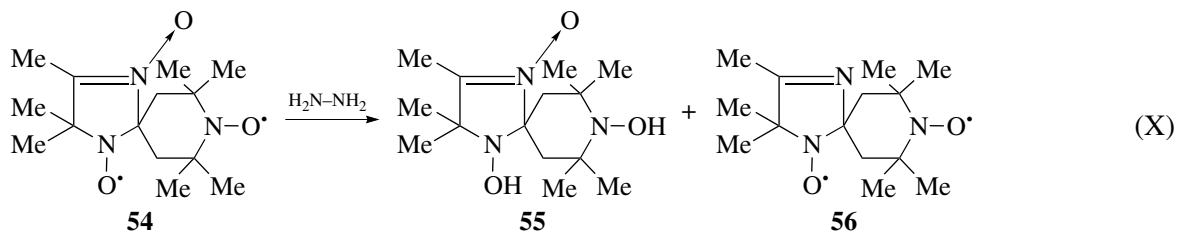
There are only a few works that deal with the influence of the nitroxyl group on the reactivity of a functional group in the NR, comparing the reactivities of the NR and its diamagnetic analogue, and consider the case of reactions proceeding via different pathways or at different rates.

Along with considering this problem for piperidine NRs, we present the most impressive examples from the chemistry of imidazoline radicals [2].

The reaction of the 3-imidazoline-3-oxide NR **6** with hydrazine hydrate in an alcoholic solution at room temperature includes the deoxygenation of the nitron group yielding an imidazoline nitroxyl **53**, which is further reduced by excess hydrazine to the corresponding hydroxylamine. The nitron group of the diamagnetic analogues is not deoxygenated under these conditions [2, 55].



In the reaction between hydrazine and biradical **54**,



the yield of the deoxygenation product **56** is twice as high as the same yield in the case of the imidazoline monoradical.

In all of the above examples, the nitroxyl radical in 3-imidazoline-3-oxide enhances the oxidative proper-

ties of the nitron group. According to Volodarskii *et al.* [2], the deoxygenation of the monoradicals and biradicals is caused by the spin density on the nitron group of these nitroxyls. Note that the difference between the constants $\text{HFC}_{(a_N)}$ of the 3-imidazoline-3-oxide and

Table 10. Rate constant arrays for the forward and reverse reactions in the kinetic network consistent with the experimental data for the hydrogen exchange reaction in the HA **43**–NR **10a** system

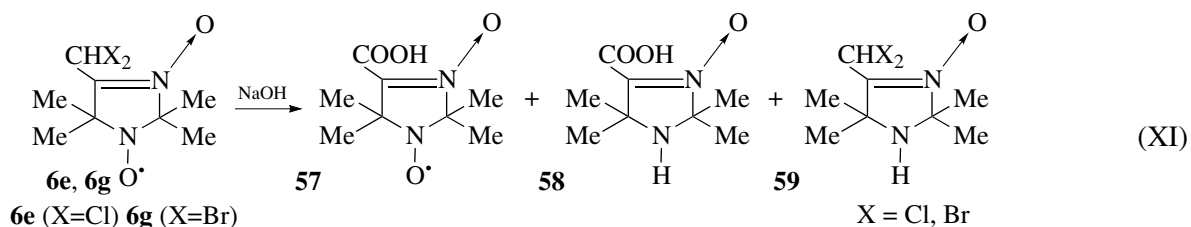
| Step no. | Reaction | Rate constant* |
|----------|-----------------------|-------------------|
| 1 | $b + a = x + p$ | 7.5×10^4 |
| –1 | $x + p = b + a$ | 2.3×10^4 |
| 2 | $a + S = c_1$ | 1.0×10^9 |
| –2 | $c_1 = a + S$ | 1.0×10^8 |
| 3 | $b + S = c_2$ | 2.5×10^7 |
| –3 | $c_2 = b + S$ | 1.0×10^8 |
| 4 | $p + S = c_3$ | 2.3×10^8 |
| –4 | $c_3 = p + S$ | 1.0×10^8 |
| 5 | $x + S = c_4$ | 0 |
| –5 | $c_4 = x + S$ | 0 |
| 6 | $c_2 + a = p + x + S$ | 4.7×10^4 |
| 7 | $c_4 + p = a + b + S$ | 0 |
| 8 | $b + S = c_5$ | 8.0×10^6 |
| –8 | $c_5 = b + S$ | 1.0×10^8 |
| 9 | $x + S = c_6$ | 0 |
| –9 | $c_6 = x + S$ | 0 |

* The dimensions of the rate constants of the bimolecular and monomolecular reactions are $\text{l mol}^{-1} \text{s}^{-1}$ and s^{-1} , respectively.

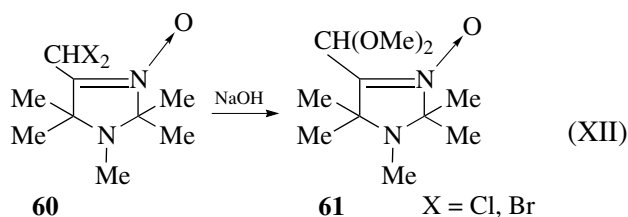
3-imidazoline nitroxyl radicals increases on passing to an aqueous or alcoholic media. The solvation of the nitron group apparently disturbs the electronic structure of the NR and results in electron density redistribution in the 3-imidazoline-3-oxide NR [2]. We believe that the nucleophilic attack of hydrazine on the 3-N–O

group in the 3-imidazoline-3-oxide NR can result in a greater spin density redistribution.

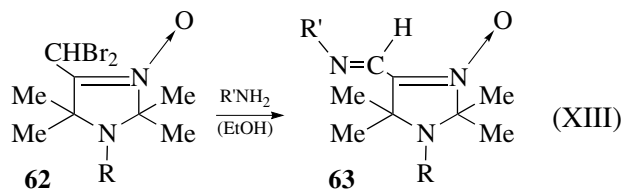
Dihalogen-substituted derivatives of the 3-imidazoline-3-oxide NR **6e**, **6g** react with NaOH in water–methanol solutions to form nitroxylcarboxylic acid **57** and several other products [2, 56]:



Under the same conditions, the corresponding diamagnetic analogues **60** form an acetal **61** as the main product:



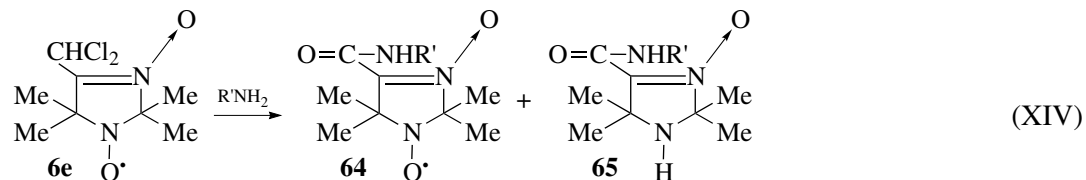
The diamagnetic dibromo derivatives of 3-imidazoline-3-oxides **62** react slowly with primary amines to form imines **63**:



The corresponding dichloro derivatives are less reactive under these conditions.

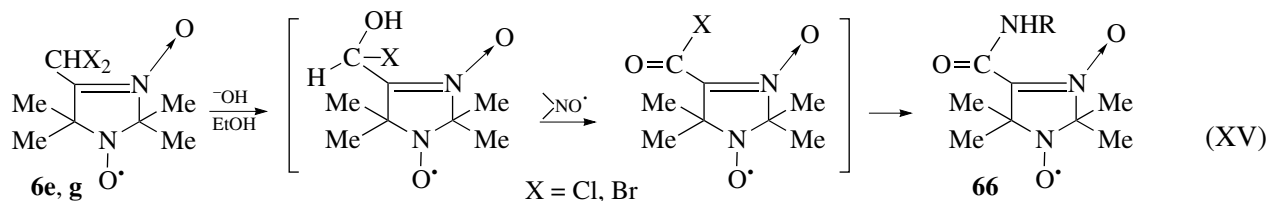
The paramagnetic dichloro derivative of 3-imidazoline-3-oxide **6e** reacts with a primary amine in an alco-

holic solution to form nitroxyl amide **64** in 35% yield and diamagnetic amide **65** in 45% yield [2, 57, 58]:



The formation of paramagnetic amides is explained [2] in terms of a mechanism according to which the reaction begins with the substitution of halogen in **6e**, **6g**

by hydroxyl followed by the fast oxidation of gem-halogenhydrin to an acid halide, which reacts with the amine to form amide **66**:

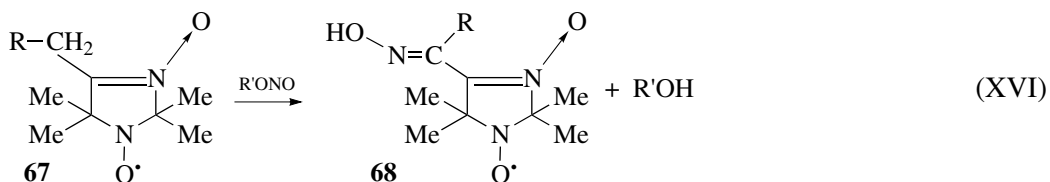


Here, the nitroxyl radical, whose nitroxyl group is reduced to a secondary amine, acts as an oxidant.

The rate at which paramagnetic dihalomethyl derivatives react with amines is 2–3 orders of magnitude higher than the same rate for their diamagnetic counterparts. Dichloro derivatives in a paramagnetic series are more reactive than the corresponding dibromo deriva-

tives. Conversely, in a diamagnetic series, the dibromo derivatives are more reactive than their dichloro analogues [2, 56].

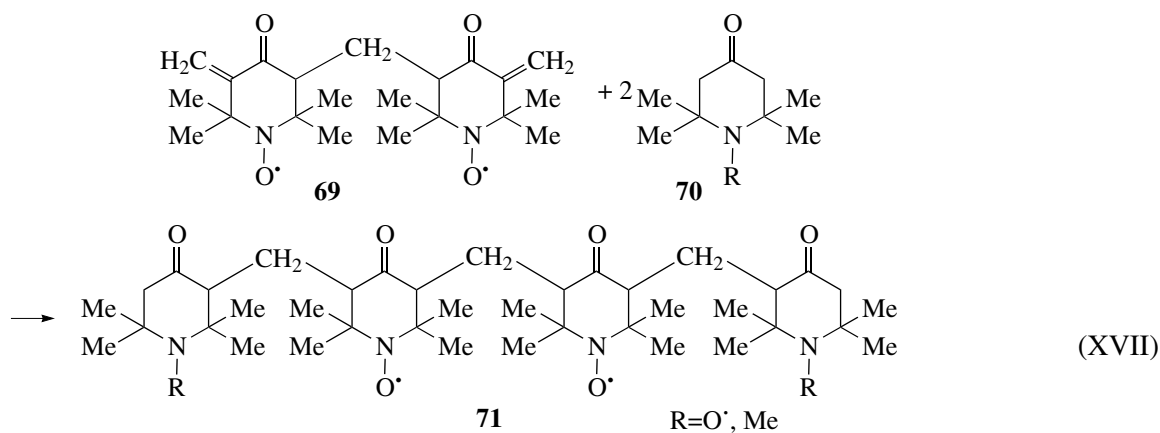
The nitroxyl radicals that are derivatives of 4-alkyl-3-imidazoline-3-oxide **67** are readily nitrosated at room temperature by alkyl nitrites in water–alcohol solutions of alkali to form the paramagnetic oxime **68** [2]:



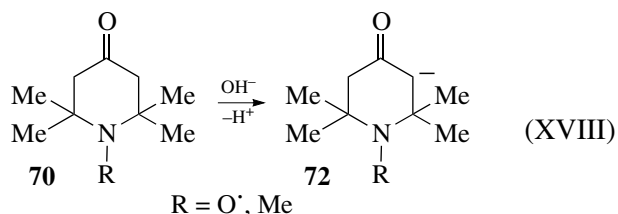
The electrophilic substitution reaction is caused by the high mobility of the α -CH₂-group, which is affected by the paramagnetic center via a mechanism that is unclear at present.

The closest diamagnetic analogues (1-nitroso derivatives of 4-alkyl-3-imidazoline-3-oxides) are not nitrosated under the same conditions.

The influence of the nitroxyl group on the reactivity of the functional group is also observed in a series of paramagnetic piperidine derivatives. For instance, according to our unpublished data, the rate of reaction of dinitroxyl **69**, which has two activated double bonds, with 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (Michael reaction) is ~200 times higher than the rate of reaction with 1,2,2,6,6-pentamethyl-4-oxopiperidine (the synthesis of biradical **69** was reported in [59]).

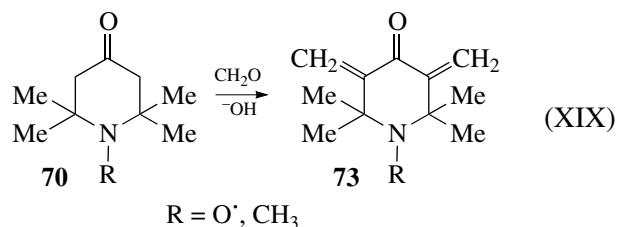


(The reaction is conducted in a system of CH₂Cl₂ and a 40% aqueous solution of alkali in the presence of the phase transfer catalyst tetrabutylammonium bromide at 20°C.) Carbanion **72** is formed in this reaction as an intermediate product:



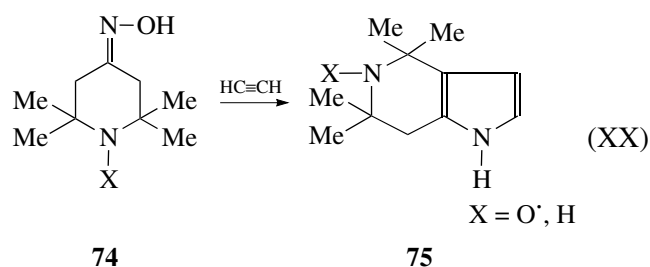
The formation of this carbanion is favored by the presence of a nitroxyl group, which enhances the acidity of the 3-methylene groups of the piperidone nitroxyl through a strong negative induction effect.

The reaction of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl with formaldehyde in an aqueous alkaline medium is more than two orders of magnitude faster than the reaction of its *N*-methyl analogue [60, 61]:

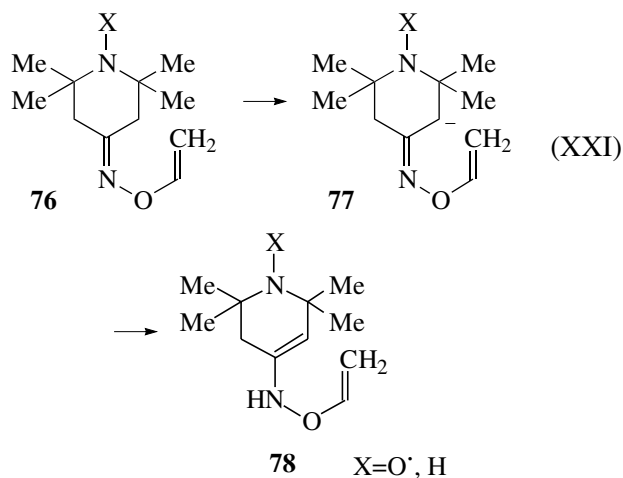


As in the previous example, this is explained by the higher rate of formation and the higher stability of the intermediate carbanion of nitroxyl **72** (reaction (XVIII)) as compared to its *N*-methyl analogue.

Data on the reactivity of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl and 2,2,6,6-tetramethyl-4-oxopiperidine oximes (**74**) towards acetylene in the KOH–DMSO system are presented in [62].

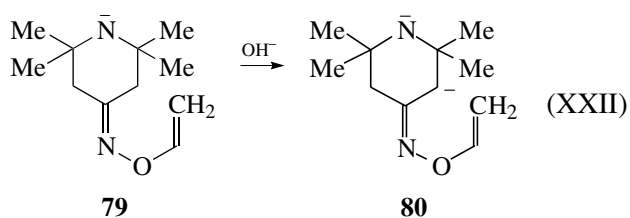


This nitroxyl ketoxime undergoes pyrrolization much more readily than its diamagnetic counterpart. According to the mechanism proposed for this reaction, *O*-vinyl oximes (**76**) are formed in the first step:



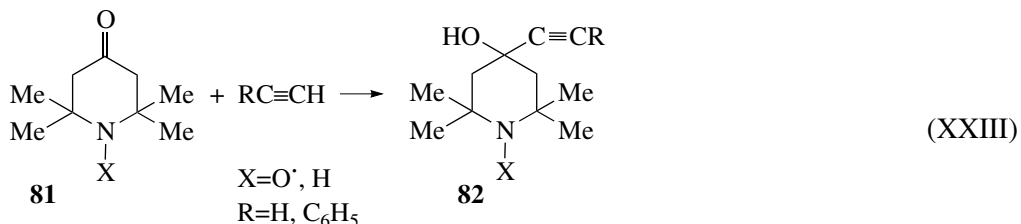
In the case of the nitroxyl, the isomerization of the intermediate *O*-vinyl oxime is favored by the acidity of the CH₂ groups increased by the induction effect of the N[•]–O group.

At the same time, in a superbasic medium, the ionization of the N–H group of *O*-vinyl oxime will probably prevent the deprotonation of the CH₂ group, because dianion **80** is thermodynamically unfavorable due to the repulsion of the closely arranged negative charges:



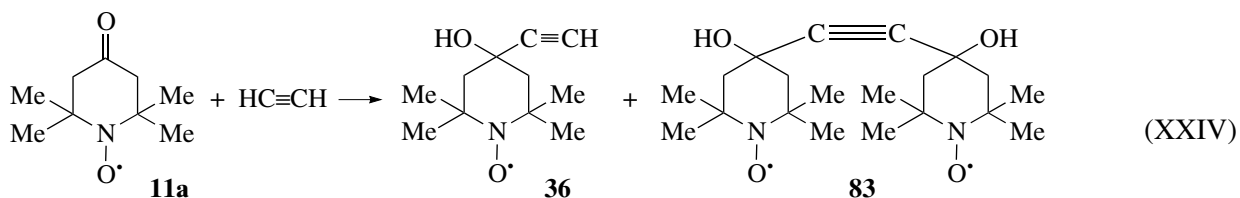
In the above reactions, the functional group in the nitroxyl radicals is more reactive than the functional group in the corresponding diamagnetic analogues. In the

examples presented below, we observe the inverse relationship. 2,2,6,6-Tetramethyl-4-oxopiperidine-1-oxyl **81** does not enter into the Favorskii reaction with acetylene or phenylacetylene in the presence of powdered KOH in THF at 0 to -5°C and atmospheric pressure, unlike its diamagnetic analogue triacetoneamine [63]. It is only when a modified Favorskii reaction is carried out (in liquid ammonia in the presence of a 20% alcohol solution of KOH at 20°C and a pressure of 16–18 atm) that the NR reacts with acetylene and phenylacetylene [64]:



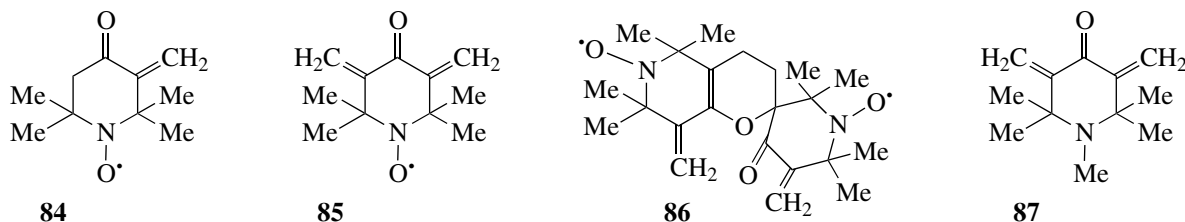
The reactions of the piperidone nitroxyl with acetylene and phenylacetylene [64] are complete within 100–120 h, while triacetoneamine reacts ~20 times as rapidly under similar conditions [65].

It is of interest that the reaction of 2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl with acetylene [64] affords biradical **83** as a by-product along with the ethynylcarbinol derivative **36**:



Under these conditions, the reaction between triacetoneamine and acetylene yields only an ethynylcarbinol derivative [65].

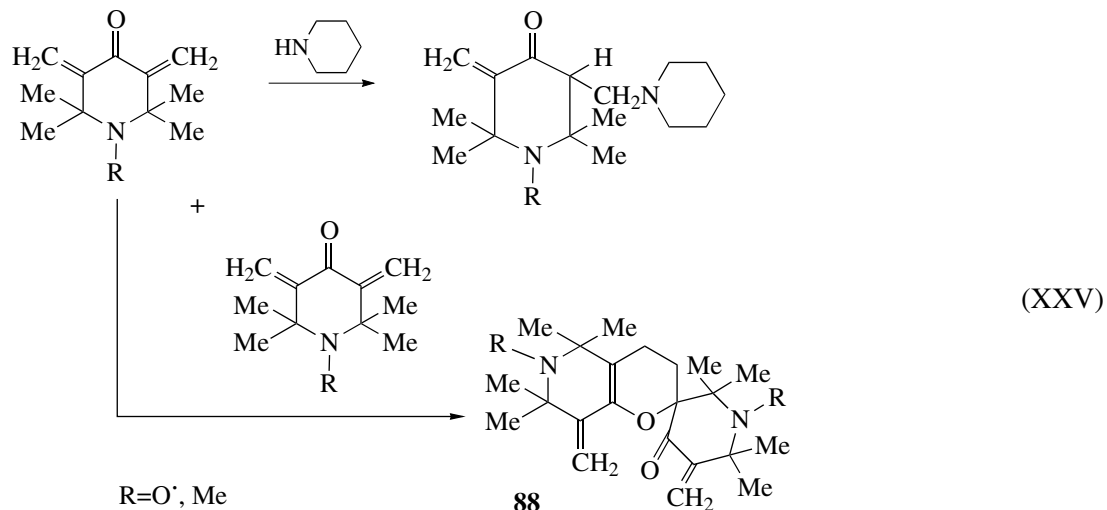
The high reactivity of the double bonds in piperidine NRs **84–86** is due to their conjugation with the carbonyl group and to the influence of the nitroxyl fragment [59, 60, 66–68]:



The rates of the addition of piperidine, morpholine, piperazine, and *N*-methylpiperazine to the methylene group of 3,5-dimethylene-2,2,6,6-tetramethyl-4-oxopiperidine-1-oxyl (**85**) with the formation of the mono-

substituted derivative are ~30 times higher than the addition rate of these amines to the methylene group of the diamagnetic analogue 3,5-dimethylene-1,2,2,6,6-pentamethyl-4-oxopiperidine **87** (reaction (XXV)).

The Diels–Alder dimerization rates of **85** and **87** also differ. Hydroxyl radical **85** is dimerized at room temperature, and compound **87** is dimerized above 100°C.



Three main factors can affect the difference in reactivity between compounds **85** and **87** in the nucleophilic addition of secondary amines and the Diels–Alder dimerization.

(1) Replacement of the strong electron acceptor O^\cdot in molecule **85** by an Me group, which possesses electron-donor properties. This decreases the polarization of the C=C bonds in **87** and can ultimately decrease the rates of the aforementioned reactions.

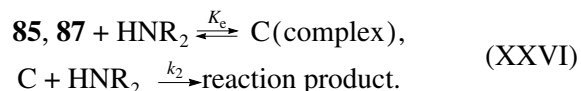
(2) A sufficiently strong steric interaction between the relatively bulky group N–Me and α -Me substituents in **87** (the so-called “presser” effect [61]). This can affect, for example, the conformation of the ring.

(3) Compounds **85** and **87** can react with secondary amines via different mechanisms involving, for instance, the NO^\cdot group of radical **85** in the formation of hydrogen bonds with the NH group of the amine.

We analyzed the causes of the different reactivities of compounds **85** and **87** towards piperidine using a kinetic method and quantum chemical calculations for

equilibrium structures and transition states in the addition of an amine to these nitroxyl radicals.

The reactions of **85** and **87** with piperidine at a piperidine concentration above 0.1 mol/l, when the reaction order with respect to amine is 2, appears as



The reaction begins with the formation of an H complex (C) involving the carbonyl group of the NR and the NH group of the amine. The equilibrium constants obtained by us for piperidine with NR **85** and molecule **87** at 20°C ($K_c = 3.0$ and 1.8 l/mol) correspond well with the equilibrium constants of similar H complexes [69–72].

The difference between the activation energies of the reactions of piperidine with molecule **87** and NR **85** is ~5 kcal/mol. One might assume that the induction factor dominates during these reactions. However, AM1 calculations [67] showed that radical **85** and mol-

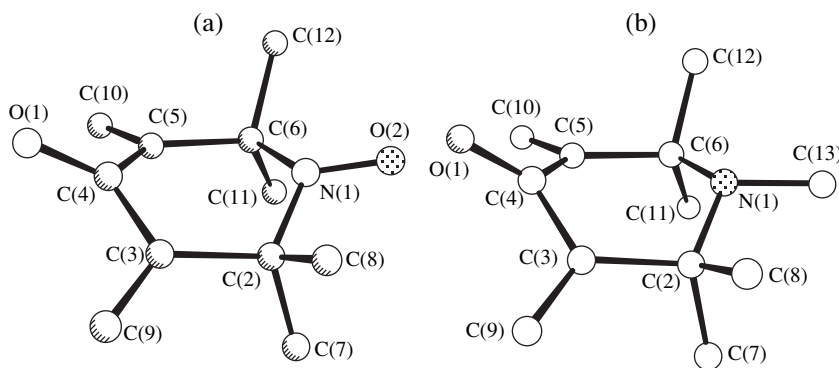


Fig. 2. Structures of (a) radical **85** and (b) molecule **87** according to the results of AM1 calculations.

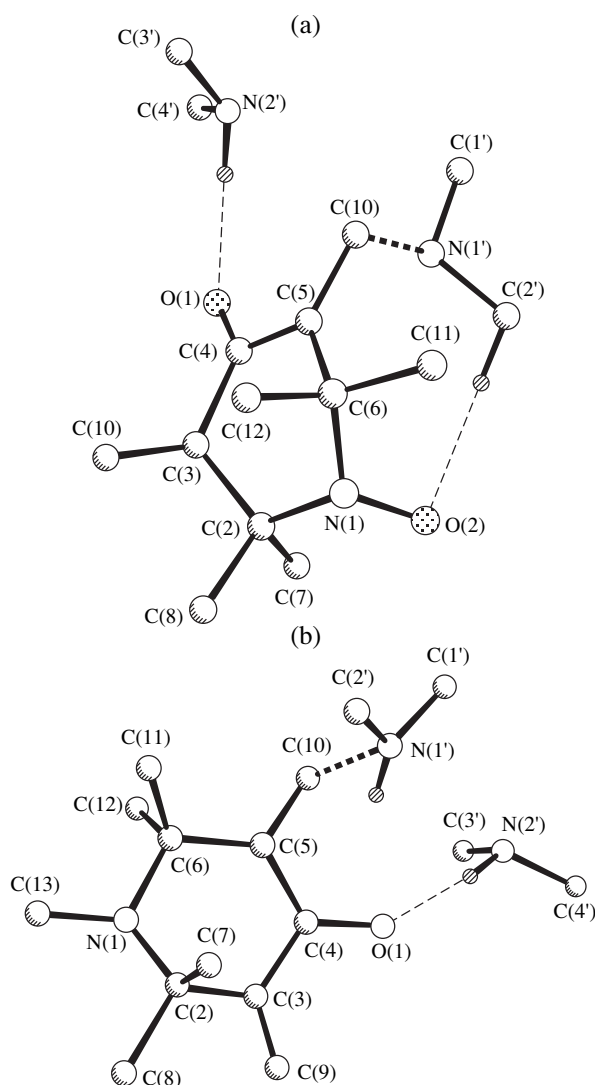


Fig. 3. Structures of the activated complexes in the reaction of dimethylamine with (a) radical **85** and (b) molecule **87** according to the results of AM1 calculations.

ecule **87** have nearly the same charges on the C atoms of the ring and exocyclic double bonds (Table 11, Fig. 2); that is, the induction factor can hardly affect the

Table 11. Charges on some atoms in NR **85** and molecule **87** as determined by quantum chemical calculations

| Atom | NR 85 | Molecule 87 |
|-------|--------------|--------------------|
| O(1) | -0.28 | -0.29 |
| N(1) | 0.06 | -0.27 |
| C(2) | 0.06 | 0.10 |
| C(3) | -0.18 | -0.16 |
| C(4) | 0.30 | 0.31 |
| C(5) | -0.18 | -0.16 |
| C(6) | 0.06 | 0.10 |
| C(9) | -0.14 | -0.16 |
| C(10) | -0.14 | -0.16 |

process. These calculations confirm the existence of a presser effect of the N-Me group; however, its influence on the equilibrium conformation of the ring in **87** is insignificant [67].

Elementary steps of the reactions of **85** and **87** with secondary amines were analyzed using dimethylamine as the model compound in calculations [67]. The difference in reactivity between compounds **85** and **87** in amine addition is due to the different structures of their transition complexes in this process. The reactions of both compounds are second-order with respect to amine, and the N-H group of one of its molecules forms a hydrogen bond with the oxygen atom of the carbonyl group.

A specific feature of the NR **85**-2[NH(CH₃)₂] transition complex compared to that in the case of molecule **87** is the presence of a C-H...O hydrogen bond between the O atom of the nitroxyl group and the H atom of the CH₃ group of the amine (Table 12, Fig. 3). The determining effect of these C-H...O contacts (the H...O distance usually ranges between 2.0 and 2.8 Å, and the C...O distance is 3.30–3.80 Å [73, 74]) on crystal packing and molecular organization in the liquid phase is presently recognized [75–77]. The C(5)...C(10) double bond in the transition complexes is elongated to 1.39 Å versus 1.34 Å in the starting compounds **85** and **87**. The C-N distance is 1.877 Å for **85**-2[NHMe₂] and 1.855 Å for **87**-2[NHMe₂].

The formation of the **85**-2[NHMe₂] transition complex is accompanied by profound changes in the shape of the six-membered ring, favoring the appearance of the above-mentioned C-H...O bond. The ring assumes the conformation of an asymmetrically flattened bath. The formation of the C-H...O bond in the **85**-2[NHMe₂] transition complex will increase its stability (versus its analogue **87**-2[NHMe₂]) and decrease the corresponding activation energy. Calculations showed that the activation energy of amine addition to radical **85** and molecule **87** is 23.3 and 25.3 kcal/mol, respectively.

For the Diels-Alder dimerization of compounds **85** and **87**, the exocyclic double bonds and carbonyl groups must lie in the same plane [78]. When molecule **87** is dimerized, this flattening is hindered as compared to

Table 12. Geometric parameters of X-H...O hydrogen bonds (X = N, C) and X-H bonds in activated complexes of NR **85** and in the complex between molecule **87** and NH(CH₃)₂

| Fragment | <i>d</i> , Å | | | φ, deg |
|--|--------------|-------|-------|---------|
| | X–H | H...O | X...O | X–H...O |
| 85 —2[NH(CH ₃) ₂] | | | | |
| N(2')–H(2')...O(1) | 1.007 | 2.164 | 3.165 | 172.5 |
| C(2')–H(2')...O(2) | 2.126 | 2.387 | 3.500 | 169.5 |
| 87 —2[NH(CH ₃) ₂] | | | | |
| N(2')–H(2')...O(1) | 1.007 | 2.150 | 3.152 | 173.2 |

the dimerization of radical **85**. This decrease in the reactivity of **87** is probably due to the presser effect of the N-Me group.

The above unified scale of reactivity for stable nitroxyl radicals can be used in the design of spin labels and probes.

Since nitroxyl radicals used in biological systems are rapidly reduced by cellular structures and lose their information content, it seems very important to use nitroxyls whose reduction rate constants are below $10 \text{ l mol}^{-1} \text{ s}^{-1}$ as spin labels and probes.

The rate constants of nitroxyl-hydrazobenzene reactions obtained by us were used in the calculation of NO-H bond dissociation energy for the corresponding sterically hindered hydroxylamines. These calculations were performed by E.T. Denisov and the authors with the use of different methods.

As for the influence of the unpaired electron on the reactivity of functional groups, this area of theoretical chemistry requires further kinetic studies and quantum chemical calculations.

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