The exchange reaction of hydrogen atoms in the system sterically hindered hydroxylamine—nitroxyl radical

A. D. Malievskii and S. V. Koroteev*

N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences,
4 ul. Kosygina, 117977 Moscow, Russian Federation.
Fax: +7 (095) 938 2156

The rate constants of the direct and reverse exchange reactions of the hydrogen atom in the system sterically-hindered nitroxyl radical—hydroxylamine of the quinoline, imidazoline, pyrrolidine, and piperidine series as well as diarylhydroxylamine were determined. A scale of the reductive abilities of the hydroxylamines was established. A low value of the isotope effect is typical of the reactions of hydrogen exchange in the systems hydroxylamine—nitroxyl radical.

Key words: hydroxylamine, nitroxyl radical; kinetics, isotope effect, rate constant, abstraction reaction.

Sterically-hindered hydroxylamines (HA) are of interest due to their use in chemical and biological systems. Previously,[1,2] HA were considered as a novel group of bioantioxidants capable of inhibiting free-radical processes by both HA and nitroxyls formed during oxidation of HA by oxygen, superoxide radicals, and enzyme systems. The hydroxylamines of piperidine and imidazoline series are commonly used for estimation of the rate of generation of superoxide radicals in microsomal membranes; HA of the quinoline series and diarylhydroxylamines participate in destruction of peroxides.[4] The H atom transfer reaction between nitroxyl and water-soluble HA of the pyrrolidine series has been proposed for controlling the state of a spin-traced lipid and its accessibility.[5] An intramolecular transfer of the H atom between the nitroxyl and hydroxylamine groups has been observed for bicyclic radical.[6] Systems HA—nitroxyl radical (NR) have been studied in the dynamic equilibrium state, and their dynamic characteristics have been determined.[7] Works on the study of the kinetic aspects of the chemical reactions involving sterically-hindered HA are few in number.[8]

In this work, the kinetics and mechanism of the H atom transfer between sterically hindered HA and NR were studied by a stop-flow method with a spectrophotometric registration:

$$R_2NOH + R_2'NO^{\cdot} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R_2NO^{\cdot} + R_2'NOH, \qquad (1)$$

The kinetic parameters and isotope effect were determined. The HA, including diarylhydroxylamines, and NR of quinoline, imidazoline, piperidine, and pyrrolidine series were used (Table 1).

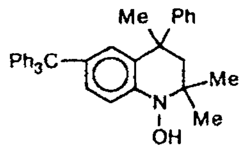
Experimental

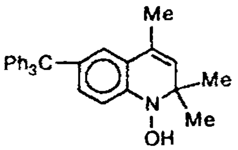
HA (**1**—**4**) and NR (**5**—**8** and **12**—**15**) were studied. The initial concentrations of HA were $(0.3-2.3) \cdot 10^{-4}$ mol L^{-1} and those of stable radicals were $(2.2-25) \cdot 10^{-4}$ mol L^{-1}. Hydroxylamines were obtained directly prior to the run according to reaction (2) from the corresponding radicals **9**, **11**, **13**, **16** and hydrazobenzene (HB) taken in a small deficit with respect to a radical based on the stoichiometry of reaction (2) in an absolute oxygen-free hexane purged with argon.

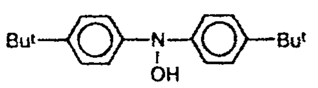
Table 1. The rate constants and equilibrium constants for the reactions of sterically-hindered hydroxylamines (HA) with NR (22 °C, hexane)

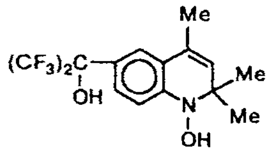
HA	NR	$k_1 \cdot 10^{-4}$	$k_{-1} \cdot 10^{-4}$	K_{eq}
		mol^{-1} L s^{-1}		
1	**5**	0.25	12.0	0.0208
1	**6**	0.89	5.5	0.1618
1	**7**	0.78	5.2	0.15
1	**8**	5.9	1.55	3.81
2	**5**	0.8	10.0	0.08
2	**8**	15.0	1.35	11.1
3	**5**	0.4	80.0	0.005
3	**6**	1.3	50.5	0.026
3	**7**	1.34	34.2	0.039
3	**9**	16.5	3.4	4.85
4	**5**	0.27	33.5	0.008
4	**6**	0.65	16.0	0.041
4	**7**	0.97	15.2	0.064
4	**11**	6.6	0.745	8.86
4	**13**	0.5	14.0	0.036
4	**14**	4.3	3.0	1.43

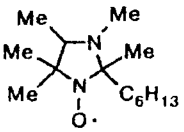
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 7, pp. 1324—1328, July, 1998.

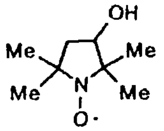

1

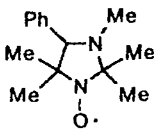

2

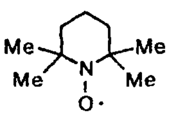

3

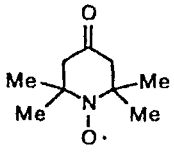

4

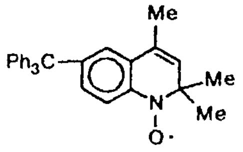

5

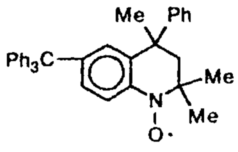

6

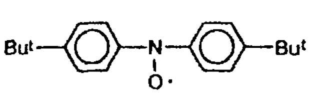

7

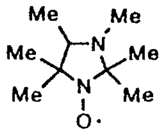

8

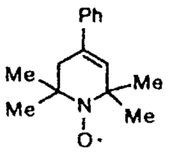

9

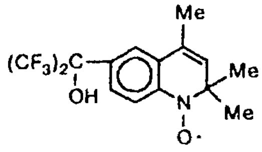

10

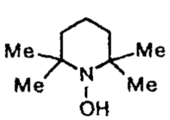

11

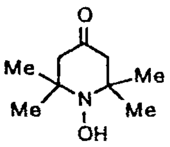

12

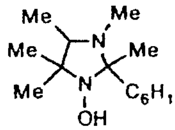

13

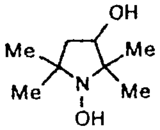

14

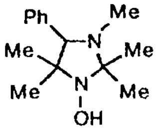

15


16


17


18


19


20

$$R_2NO^{\cdot} + PhNH{-}NHPh \xrightarrow{k_{HB}} R_2NOH + PhNH{-}N^{\cdot}Ph$$

$$R_2NO^{\cdot} + PhNH{-}N^{\cdot}Ph \longrightarrow R_2NOH + PhN{=}NPh \quad (2)$$

The reaction kinetics was studied by the change in the optical density of a solution in time (due to the accumulation of niroxyl radicals) at the specified wavelengths (nm): 465 for **9**, 382 for **11**, 365 for **13**, 376 for **16**. The temperature of the experiments was 22 °C. Calculations were processed according to a standard program for reversible second-order reactions. The rate constants for reaction (1) (k_1 and k_{-1}) were determined as the average value for some (3—5) ratios between the concentrations of the initial components; the error of estimation was less than ±10%. The accuracy of determination of the coefficients in Eqs. (1)—(4) was 6—14%, and in Eqs. (5)—(9) it was 35—40%. NR were purified according to standard procedures.

Deuterated HA (HA-D) were prepared as follows. Taking into account the small solubility of water in hexane (0.43%),[9] after the nondeuterated HA (HA-H) was obtained according to the procedure mentioned, D_2O ($8.7 \cdot 10^{-4}$ g, $1.09 \cdot 10^{-2}$ mol L^{-1}) was added to 4 mL of a solution of HA-H. The solution was thoroughly stirred. Taking into account the 100-fold molar excess of D_2O with respect to HA-H and the rapid exchange,[10] we assumed that hydrogen in the N—OH group is completely replaced by deuterium. The deuterium entering into the (OH)C group of HA (**4**) during exchange with D_2O should not significantly affect the rate of the exchange reaction (1). We assumed also that any other rapid H—D exchange during the preparation of HA-D is absent, except for the participation of the N—OH and possibly C—OH groups of HA (**4**).

Results and Discussion

The interaction of sterically-hindered HA with NR obeys the regularities of reversible second-order reactions which are of first order with respect to each component and the persistence of the rate constants of the direct and reverse reactions, independent of the concentrations of the reagents. In all the systems studied, the equilibrium was achieved in 50—200 ms after the onset of the reaction (Fig. 1). The side reaction of HA with O_2, which is present in small amounts after purging the system with argon, does not affect reaction (1), since the rate constants of reaction (1) (see Table 1) are several orders higher than the rate constant k_0 for the reaction of HA with oxygen, which is equal, for example for HA **4**, to $1 \cdot 10^{-3}$ mol^{-1} L s^{-1}.

As can be seen in Table 1, the HA studied exhibit high reductive properties. It was of interest to compare the reductive properties of these HA with those of hydrazobenzene (HB) studied previously[11] with the use of reaction (2) with the same NR under similar conditions (22 °C, hexane as solvent; k_{HB} is the constant of the rate-determining stage of reaction (2)). Using the values of constants k_1 (see Table 1) and k_{HB} (Table 2) for HA (**1**—**4**), we obtained the following dependences:

$$\log k_1(\mathbf{1}) = 3.76 + 0.98 \cdot \log k_{HB}, \qquad (1)$$

$$\log k_1(\mathbf{2}) = 4.3 + 0.97 \cdot \log k_{HB}, \qquad (2)$$

$$\log k_1(\mathbf{3}) = 3.959 + 1.03 \cdot \log k_{HB}, \qquad (3)$$

$$\log k_1(\mathbf{4}) = 3.71 + 0.96 \cdot \log k_{HB}. \qquad (4)$$

Figure 2 shows the dependence in logarithmic coordinates of the rate constants k_1 for the reaction of HA (**4**) with NR (**5**, **6**, **7**, **8**, **13**, **14**) on the rate constants k_{HB} for the same NR with HB.

As seen in Eqs. (1)—(4), the reductive abilities of HA (**1**—**4**) are nearly 10^4 times higher than that of HB. This is due to the higher pre-exponentinal factor and lower activation energy of the reaction of HA with NR. Thus, for the reaction of the same nitroxyl radical (**7**) with HA (**4**), $k_1 = 1.9 \cdot 10^8 \cdot \exp(-3160/RT)$ with E_1 = 3160 cal mol^{-1}, whereas for the reaction with HB, $k_{HB} = 8 \cdot 10^4 \cdot \exp(-6300/RT)$ mol^{-1} L s^{-1} and E_{HB} = 6300 cal mol^{-1}.

Table 2. The rate constants (k_{HB}/mol^{-1} L s^{-1}) for the reaction of NR with HB[11] (22 °C)

NR	k_{HB}	NR	k_{HB}
5	0.37	**11**	13.9
6	1.37	**12**	$5 \cdot 10^3$
7	2.17	**13**	1.5
8	8.7	**14**	6.6
9	420.0	**15**	$3.1 \cdot 10^3$
10	366.0		

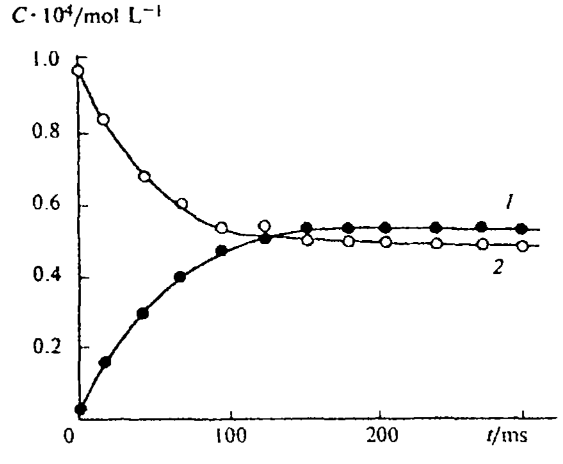


Fig. 1. Kinetic curves for the accumulation of NR (**15**) (*1*) and consumption of HA (**4**) (*2*) (calculated) for the hydrogen exchange reaction in the system NR (**7**)—HA (**4**). Initial concentrations (C/mol L^{-1}): NR (**7**), $1.0 \cdot 10^{-3}$, HA (**4**), $9.55 \cdot 10^{-4}$; hexane as solvent, 18.8 °C.

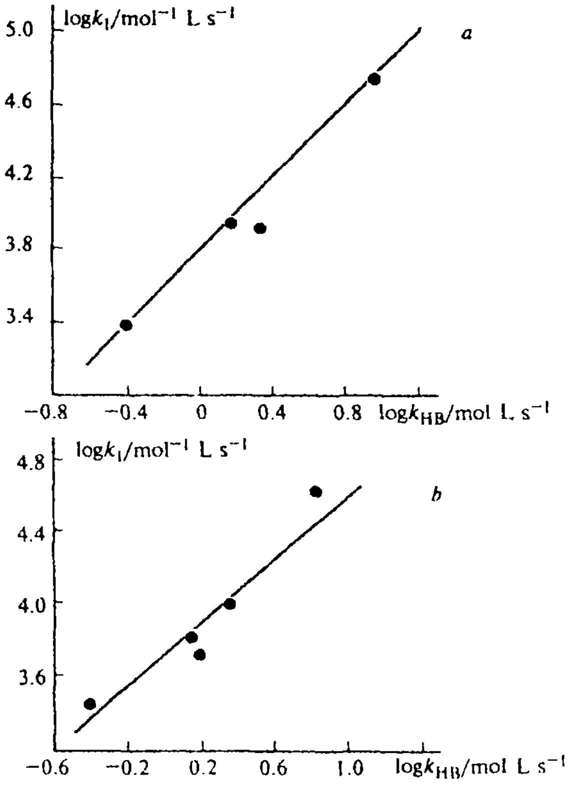


Fig. 2. Dependence of the rate constants (k_1) for the hydrogen exchange reaction in the systems HA—NR on the rate constants (k_{HB}) for the reaction of NR with HB; hexane as solvent, 18.8 °C. *a*, HA (**1**), NR (**5**, **6**, **7**, **8**); *b*, HA (**4**), NR (**5**, **6**, **7**, **13**, **14**).

Table 3. The isotope effect in the hydrogen exchange reaction for the system sterically-hindered hydroxylamine—nitroxyl radical (–20 °C, hexane as solvent, $[HA]_0$ = (0.76—0.96) · 10^{-4} mol L^{-1}, $[NR]_0$ = (1—10) · 10^{-4} mol L^{-1}

HA	NR	$H_2O \cdot 10^2$	$D_2O \cdot 10^2$	$k_1 \cdot 10^{-4}$	$k_{-1} \cdot 10^{-4}$	k_1^H/k_1^D	k_{-1}^H/k_{-1}^D
		mol L^{-1}		mol^{-1} L s^{-1}			
4	**13**	—	—	0.45	13.2		
		1.1	—	0.51	13.3		
		—	1.1	0.29	7.7	1.78	1.72
4	**14**	—	—	3.96	3.11		
		—	—	3.66	2.99		
		1.1	—	4.1	2.89		
		—	1.1	2.52	1.92	1.63	1.51
4	**7**	—	—	0.97	15.2		
		—	—	0.78	13.7		
		1.39	—	0.86	13.7		
		—	1.09	0.57	9.9	1.52	1.38
2	**13**	—	—	1.39	6.34		
		1.1	—	1.37	6.16		
		—	1.1	0.73	3.0	1.88	2.06

Using Eqs. (1)—(4) and the values of the rate constants for the reaction of HB with NR of various classes obtained in Ref. 11 (more than 70), one can evaluate ~300 rate constants k_1 for reaction (1), including those for the systems HA—NR in which the reaction rates exceed the temporal limit of registration for the setup used under the conditions of experiment.

Using the values of the rate constants k_{-1} for reaction (1) of NR (**9**, **10**, **12**, **15**) with HA (see Table 1) and of the rate constants k_{HB} for reactions of the same NR with HB (see Table 2), equations similar to Eqs. (1)—(4) were obtained for evaluation of the reductive abilities of the HA series:

$$\log k_{-1}(\mathbf{16}) = 1 \cdot \log k_{HB}, \quad (5)$$

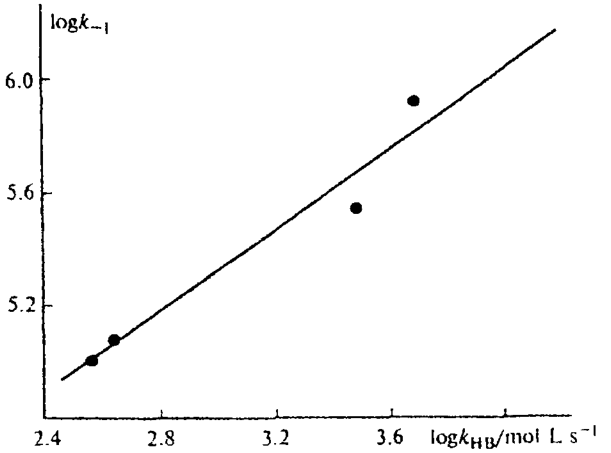


Fig. 3. Dependence of the rate constants (k_{-1}) for the hydrogen exchange reaction in the systems HA (**18**)—NR (**9**, **10**, **12**, **15**) on the rate constants (k_{HB}) for the reaction of NR (**9**, **10**, **12**, **15**) with HB; hexane as solvent, 18.8 °C.

$$\log k_{-1}(\mathbf{17}) = 3.2 \cdot \log k_{HB}, \quad (6)$$

$$\log k_{-1}(\mathbf{18}) = 3.23 + 0.7 \cdot \log k_{HB}, \quad (7)$$

$$\log k_{-1}(\mathbf{19}) = 2.65 + 0.78 \cdot \log k_{HB}, \quad (8)$$

$$\log k_{-1}(\mathbf{20}) = 2.88 + 0.69 \cdot \log k_{HB}. \quad (9)$$

Figure 3 presents the dependence in logarithmic coordinates of the rate constant k_{-1} for reaction (1) of NR (**9**, **10**, **12**, **13**) with HA (**18**) on the rate constant k_{HB} for the reaction of the same NR with HB.

Based on Eqs. (5)—(9), the rate constants for hydrogen exchange between HA (**18**, **19**, **20**) and "own" NR were estimated to be equal to: **18**, 845; **19**, 571; **20**, 1296 mol^{-1} L s^{-1}.

From the data of Table 1 and Eqs. (1)—(9), the scale of the reductive abilities of hydroxylamines of various classes can be represented as follows:

2 > **3** > **1** > **4** > **20** > **18** > **19** > **16** > **17**.

The origin of the isotope effect in the hydrogen exchange reaction for several HA—NR systems can provide additional data on the mechanism of the process. With this purpose, the kinetics of the reactions of HA-H (**4**-H), (**2**-H), and HA-D (**4**-D), (**2**-D) with NR (**7**, **13**, and **14**) were studied. HA-D were obtained by rapid exchange, when D_2O was introduced into the solution containing nondeuterated HA-H, according to the reaction

$$2\ NO\text{—}H + D_2O \rightleftharpoons 2\ NO\text{—}D + H_2O,$$

whose equilibrium is quite completely shifted to the right at a 100-fold molar excess of D_2O over H_2O. The rate constants k_1 and k_{-1} for the chosen systems without additives and with D_2O and H_2O introduced (in the latter case, in comparable concentrations with D_2O used for preparation of HA-D) were compared. The rate constants k_1 and k_{-1} for the systems without additives and with H_2O introduced were in fact indistinguishable (see Table 3). When D_2O is introduced into the systems instead H_2O (the experimental conditions are comparable, Table 3), the rate constants for the reaction in the HA—NR systems differ from each other. The ratios of both $k_1{}^H/k_1{}^D$ and $k_{-1}{}^H/k_{-1}{}^D$ for all the systems studied were close to 1.7 (±10%). The low value of the isotope effect can be explained by the fact that the processes of scission of the original bond and formation of the new bond are synchronous. In this case, the transition state is most likely close to symmetrical and linear.[12]

The authors are grateful to A. B. Shapiro for providing nitroxyl radicals.

References

1. P. G. Komarov, O. N. Toskaev, and R. I. Zhdanov, *Dokl. Akad. Nauk SSSR,* 1987, **297**, 734 [*Dokl. Chem.*, 1987, **297** (Engl. Transl.)].
2. R I. Zhdanov and E. G. Rozantsev, *Khim.-Pharm. Zh.*, 1988, 147 [*Chem. Pharm. Bull.*, 1988 (Engl. Transl.)].
3. Yu. E. Rashba, V. A. Chernikov, L. M. Baider, and L. S. Vartanyan, *Biologicheskie membrany* [*Biological Membranes*], 1986, **3**, 838 (in Russian).
4. Z. S. Kartashova, Ph. D. (Chem.) Thesis, Institute of Chemical Physics, Akad. Nauk of SSSR, Moscow, 1989 (in Russian).
5. M. A. Schwartz, J. M. Pazce, and H. M. McConnell, *J. Am. Chem. Soc.*, 1979, **101**, 3592.
6. T. Toda, E. Morly, and K. Murayama, *Bull. Chem. Soc. Japan*, 1872, **45**, № 6, 1904.
7. S. A. Dikanov, I. A. Grigor'ev, L. B. Volodarskii, and Yu. D. Tsvetkov, *Zh. Fiz. Khim.*, 1982, **50**, № 11, [*Russ. J. Phys. Chem.*, 1982 **50**, (Engl. Transl.)].
8. L. B. Volodarskii, I. A. Grigor'ev, S. A. Dikanov, V. A. Reznikov, and G. I. Shchukin, *Imidazolinovye nitroksil'nye radikaly* [*Imidazoline Nitroxyl Radicals*], Nauka, Sib. Otd., Novosibirsk, 1988, 215 (in Russian).
9. A. Ya. Berlin, *Tekhnika laboratornykh rabot v organicheskoi khimii* [*Technique of Laboratory Experiments in Organic Chemistry*], Khimiya, Moscow, 1973 (in Russian).
10. G. P. Miklukhin, *Izotopy v organicheskoi khimii* [*Isotopes in Organic Chemistry*], Izd. Akad. Nauk UkrSSR, Kiev, 1961, 731 (in Russian).
11. A. D. Malievskii, S. B. Korotaev, A. B. Shapiro, and L. B. Volodarskii, *Izv. Akad. Nauk SSSP, Ser. Khim.*, 1990, 2575 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 2331 (Engl. Transl.)].
12. L. Melander and W. H. Saunders, *Reaction Rates of Isotopic Molecules*, Wiley-Interscience Publ., New-York, 1980.

Received April 3, 1995
in revised form September 2, 1997