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Inorganic Anionic Oxygen-Containing α-Nucleophiles—Effective Acyl Group Acceptors: Hydroxylamine Ranks First among the α-Nucleophile Series

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Abstract—Comparative analysis of the nucleophilicity of inorganic oxygen-containing α-nucleophiles (hydroxylamine and ClO^-, BrO^-, HOO^-, NH_2O^-, and F^- ions) covering the pK_a range from –2 to 13.81 toward 4-nitrophenyl esters (4-nitrophenyl acetate, 4-nitrophenyl *p*-toluenesulfonate, diethyl 4-nitrophenyl phosphate, ethyl 4-nitrophenyl ethylphosphonate, and 4-nitrophenyl dimethylcarbamate) in water at 25°C (ionic strength μ 1.0, KCl) was performed in terms of the extrathermodynamic Brønsted relation. It was found for the first time that hydroxylamine anion ranks first among the series of α-nucleophiles. It is more reactive than HOO^- ion with respect to 4-nitrophenyl acetate (by a factor of ~8), 4-nitrophenyl *p*-toluenesulfonate (by a factor of ~4) and 4-nitrophenyl dimethylcarbamate (by a factor of ~10). The nucleophilicities of HOO^- and NH_2O^- ions toward diethyl 4-nitrophenyl phosphate and ethyl 4-nitrophenyl ethylphosphonate are comparable. Taking into account that neutral hydroxylamine exhibits an anomalously high reactivity, as compared to not only common organic but also inorganic α-nucleophiles, it may be regarded as a unique α-nucleophile. Both neutral hydroxylamine and its anion as O-nucleophiles ensure high rates of acyl group transfer throughout a wide range of pH.

Extensive kinetic studies of the behavior of various nucleophiles toward unsaturated electron-deficient systems, such as carboxylic [1–4], sulfonic [5], phosphoric [6–9], phosphonic [10–13], and other acid esters and halides [14–16] in terms of the extra-thermodynamic Brønsted relationship led to formulation of the term "α-effect" and discovery of a group of α-nucleophiles, including inorganic HOO^-, ClO^-, N_3^-, etc. ions. Studies in the field of α-effect and design of new α-nucleophiles intensely develop, as follows from increasing number of recent publications on this topic [17–21]. In this connection, hydroxylamine anion attracts a specific interest. Hydroxylamine is a parent compound for at least three typical classes of anionic oxygen-containing α-nucleophiles: oximes, amidoximes, and hydroxamic acids, which exhibit anomalously high reactivity in processes involving acyl group transfer. Nevertheless, it is still a common opinion that just the neutral form of hydroxylamine reacts with carboxylic, phosphoric, and phosphonic esters and halides [22]; According to Bruice and Benkovic [23], hydroxylamine in the anionic form (NH_2O^-) usually does not react with esters. However, proceeding from the definition of α-effect given in [22, 24], hydroxylamine meets all requirements imposed to α-nucleophiles. First, the nucleophilic center therein is a negatively charged 2nd Row atom (oxygen). Second, there are no substituents neighboring to the nucleophilic center, which could exert steric hindrance to attack on electrophilic center of a substrate. Third, the nucleophile contains a catalytically active group (NH_2) which is capable of stabilizing transition states [25]. Finally, the electronegative nitrogen atom in the α-position with respect to the reaction center possesses an unshared electron pair which can destabilize the ground state and

I II

III IV V
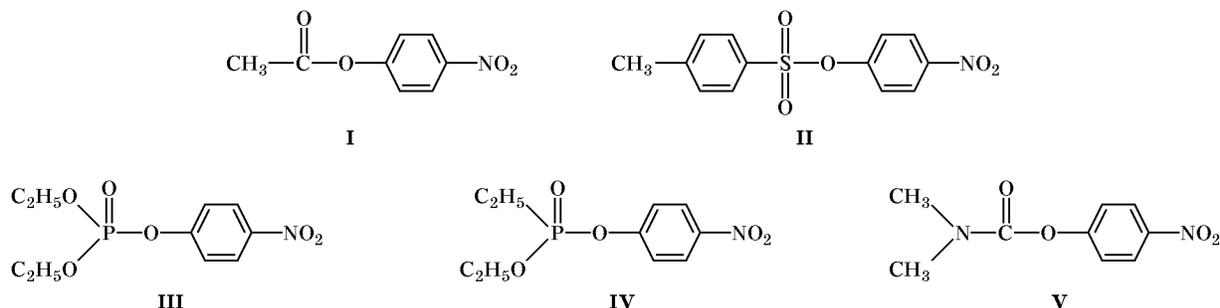
stabilize the transition state. In fact, we were the first to demonstrate [26] that the anionic form of hydroxylamine is responsible for a considerable acceleration of acyl group transfer in alkaline media.

The present article gives a detailed kinetic and thermodynamic analysis of the behavior of hydroxylamine and the most effective anionic oxygen-containing inorganic α-nucleophiles, namely HOO^-, ClO^-, BrO^-, F^- and OH^- ions, in reactions with 4-nitrophenyl acetate (**I**), 4-nitrophenyl *p*-toluenesulfonate (**II**), diethyl 4-nitrophenyl phosphate (**III**), ethyl 4-nitrophenyl ethylphosphonate (**IV**), and 4-nitrophenyl dimethylcarbamate (**V**) in water at 25°C at a ionic strength μ of 1.0, which was maintained with the aid of KCl.

The study was aimed primarily at establishing reactive forms of hydroxylamine in acyl transfer processes over a wide range of acidity of the medium, quantitatively estimating the nucleophilic reactivity of these forms in water, elucidating the reaction mechanism, and, finally, revealing factors responsible for the reactivity of hydroxylamine. It seemed to be important to estimate the α-effect for inorganic α-nucleophiles in acyl transfer processes and also to analyze their relative nucleophilities in such reactions.

Nucleophilic reactivity of fluoride ion. Attack by F^- on the four-coordinate sulfur or phosphorus atom in substrates **II**, **III**, and **IV**, as well as in **I**, leads to formation of the corresponding acyl fluorides and liberation of 4-nitrophenoxide ion. The reaction is of first order with respect to both nucleophile and substrate, and the rate of the process at pH = 8–9 (i.e., when the reagent exists only as fluoride ion) is described by the following equation:

$$k_{ap} = k_2[F^-] = k_2[NaF]_0. \qquad (1)$$

An unusual kinetic behavior of F^- toward electron-deficient centers of the above substrates (carbon, sulfur, and phosphorus atoms; see Table 1) should be noted. The point for F^- ion in the reaction with ester **I**

falls into the Brønsted plot for aroxide ions (Fig. 1a), while in the reactions with esters **II–IV**, positive deviations from standard reaction series are as follows: $\Delta^{*1} = 1.3, 4.7, 4.4$ (Fig. 1b, 1c). In the reactions with substrates **II** and **III** fluoride ion behaves like an aroxide ion with $pK_{a,calc} = 5.4$ and 11.1, whereas with ester **IV** it looks like an amine with $pK_{a,calc} = 15.3$ [36]. Analogous anomalies were also observed in reactions of F^- with equatorial phosphoric triester, 2-(2,4-dinitrophenoxy)-1,3,2λ^5-dioxaphosphinane 2-oxide^{*2} (standard series: anionic oxygen-containing nucleophiles, $\Delta = 3.9$, $pK_{a,calc} = 9.1$) [13], 4-nitrophenyl methylphosphonate ion (standard series: amines, $\Delta = 1.4$, $pK_{a,calc} = 7.7$)^{*3} [12], and 4-morpholinopyridinium phosphate dianion (standard series: anionic oxygen-containing nucleophiles, $\Delta = 1.5$, $pK_{a,calc} = 11$) [37]. Fluoride ion is also more reactive than ethoxide, phenoxide, and benzenethiolate ions with respect to diisopropyl chlorophosphate^{*4} [38, 39]. Undoubtedly, the anomalously high nucleophilicity of F^- in nucleophilic substitution at a four-coordinate phosphorus atom, regardless of the charge on the substrate and the nature of leaving group, indicates

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^{*1} $\Delta = \log k_2(\alpha\text{-Nu}) - \log k_2(\text{Nu})$, where $k_2(\alpha\text{-Nu})$ and $k_2(\text{Nu})$ are the second-order rate constants characterizing, respectively, the reactivity of α-nucleophile and a hypothetical aroxide or alkoxide ion or amine for which $pK_a(\text{Nu}) = pK_a(\alpha\text{-Nu})$.

^{*2} For the axial triester, $\Delta = 3.4$, $pK_{a,calc} = 10.3$. The values of Δ and $pK_{a,calc}$ for the axial and equatorial triesters were calculated from the data of [13].

^{*3} The values of Δ and $pK_{a,calc}$ were calculated using the Brønsted equation $\log k_2 = (-7.30 \pm 0.18) + (0.31 \pm 0.02) \times pK_a$ for 18 amines. The pK_a values of amines were measured at 25°C (for details, see [37]).

^{*4} Bunton and Shiner [40] give a pK_a^{HF} value of 4.77, while $pK_a = 3$ to 3.2 is given in [38, 39]. Insofar as in all cases the nucleophilicity of F^- was estimated in alkaline media, the difference in pK_a cannot affect the second-order rate constants. On the other hand, the positive deviations should depend on pK_a, but the qualitative pattern (Fig. 1a–1c) should remain almost unchanged.
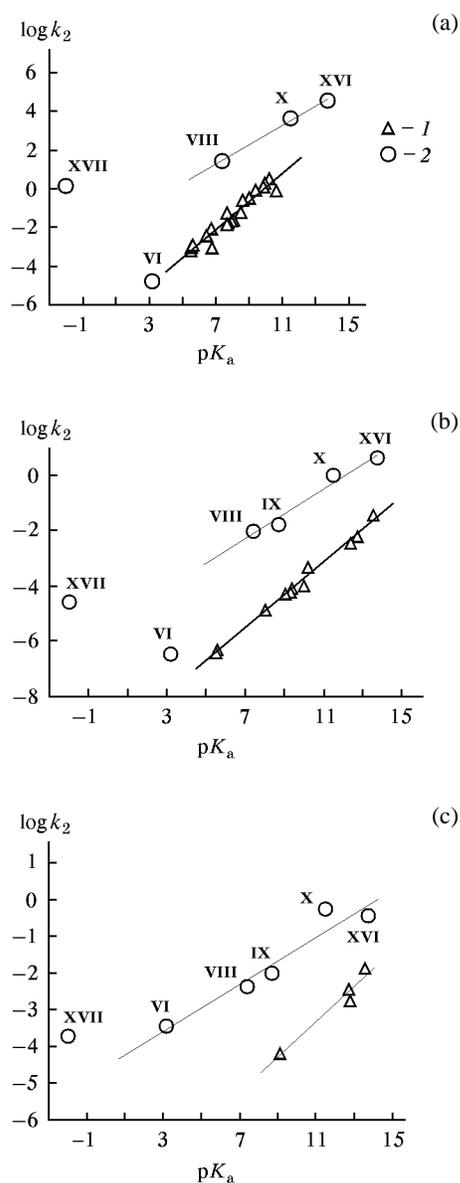
Fig. 1. (a) Brønsted dependences for the reactions of (*1*) aroxide ions and (*2*) α-nucleophiles with 4-nitrophenyl acetate (**I**); the data for aroxide ions were taken from [27]; **VI**, fluoride ion; **VIII**, hypochlorite ion; **X**, hydroperoxide ion; **XVI**, hydroxylamine anion; **XVII**, hydroxylamine (neutral). (b) Brønsted dependences for the reactions of (*1*) aroxide ions and (*2*) α-nucleophiles with 4-nitrophenyl *p*-toluenesulfonate (**II**); the data for aroxide ions were taken from [34]; **VI**, fluoride ion; **VIII**, hypochlorite ion; **IX**, hypobromite ion; **X**, hydroperoxide ion; **XVI**, hydroxylamine anion; **XVII**, hydroxylamine (neutral). (c) Brønsted dependences for the reactions of (*1*) aroxide ions and (*2*) α-nucleophiles with diethyl 4-nitrophenyl phosphate (**III**); the data for aroxide ions were taken from [35]; **VI**, fluoride ion; **VIII**, hypochlorite ion; **IX**, hypobromite ion; **X**, hydroperoxide ion; **XVI**, hydroxylamine anion; **XVII**, hydroxylamine (neutral).

a strong affinity of F^- for the phosphoryl and phosphonoyl groups. A probable reason is the high stability of fluorophosphates and fluorophosphonates [41] due to resonance interactions both in the products and in the transition states, which may be illustrated by canonical structures **A**.
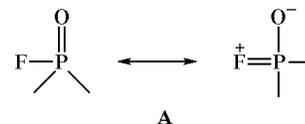
Such electronic interaction should exert a strong stabilizing effect in the transition state, thus reducing the energy barrier to the process. This assumption is supported by the following experimental data. First, fluoride ion exhibits an extremely low reactivity toward a saturated carbon atom [39]; in nucleophilic substitution at a saturated carbon atom, where no resonance interactions like **A** occur, fluoride ion reacts at a lower rate than do Cl^-, Br^-, and I^-, though its basicity is greater by 10 to 14 orders of magnitude. Second, the equilibrium constants K_{eq} for the exchange reactions of F^- with isopropyl phenyl methylphosphonates and isopropyl *m*-nitrophenyl methylphosphonate are 300 and 2000, respectively [13]; extrapolation of K_{eq} to a hypothetical phenol with $pK_a \approx pK_a^{HF}$ gives $K_{eq} = 5 \times 10^5$, i.e., the affinity of F^- for the phosphonate group is greater by a factor of 5×10^5 than the proton affinity of the hypothetical aroxide ion. Finally, the high affinity of F^- for four-coordinate phosphorus atom follows, on the one hand, from the high rate of its reaction with 2-(2,4-dinitrophenoxy)-1,3,2λ^5-dioxaphosphinane 2-oxide (the rate constant corresponds to an aroxide ion with $pK_a \approx 10$) and, on the other, from the low rate of hydrolysis of the resulting phosphorus fluoride with water (the rate of its hydrolysis is by 5 orders of magnitude lower, as compared to a hypothetical aryl ester with a leaving group whose basicity is equal to that of F^-.

Nucleophilic reactivity of hydroperoxide ion. The rate of disappearance (k_{ap}, s^{-1}) of substrates **II–V** ([S] = 1 M) in buffer solutions of hydrogen peroxide linearly increases with rise in the analytical concentration of H_2O_2 and pH. However, the dependence of $k_2' = k_{ap}/[HOOH]_0$ (as well as of k_{ap}, s^{-1}, at a constant $[HOOH]_0$) versus acidity of the medium is curvilinear, indicating that the reactive species is hydroperoxide ion. The rate of the process is described by Eq. (2), where $\alpha_{HOO^-} = K_a/(K_a + a_{H^+})$ is the fraction of HOO^- ion.

$$k_{ap} = k_2'[HOOH]_0 = k_2 \alpha_{HOO^-}[HOOH]_0. \qquad (2)$$

Table 1. Experimental conditions, basicities of nucleophiles (pK_a), and their reactivities (k_2, $l\,mol^{-1}\,s^{-1}$) toward substrates **I–V**; water, 25°C, $\mu = 1.0$ (KCl)

No.	Nucleophile	pK_a[a]	I		II[b]	
			pH	k_2	pH	k_2
VI	F⁻	3.18 [28]	–	1.05×10^{-5} [2]	8.00	$(3.4 \pm 0.6) \times 10^{-7}$
VII	HO⁻ [c]	15.7 [28]	–	14.4 [2]	12.0–13.5	$(8.0 \pm 0.3) \times 10^{-3}$
VIII	ClO⁻	7.4 ± 0.1 (k) 7.5 (p) [28]	–	26.8 [2]	11.75	$(9.1 \pm 0.5) \times 10^{-3}$
IX	BrO⁻	8.7 [28]	–	–	8.99–12.29	$(1.7 \pm 0.1) \times 10^{-2}$
X	HOO⁻	11.5 ± 0.1 (k) 11.6 [29]	–	4560 [2]	11.00–12.69	0.99 ± 0.01
XI	$CHF_2CF_2CH_2O^-$ [d]	12.74 [30]	–	61 [33]	12.45–13.65	$(5.8 \pm 0.1) \times 10^{-3}$
XII	$(Me)_3N^+CH_2CH_2O^-$ [d]	12.8 [31]	–	133 [33]	12.9–13.65	$(4.00 \pm 0.05) \times 10^{-3}$
XIII	$CH_3CH{=}NO^-$ [d]	11.8 ± 0.1 (k)	7.82–9.00	470 ± 40	10.3–12.8	$(2.5 \pm 0.1) \times 10^{-2}$
XIV	CH_3CONHO^- [d]	9.36 ± 0.03 (p)	7.00–8.20	95 ± 10	8.4–11.5	$(3.06 \pm 0.09) \times 10^{-2}$
XV	$CH_3C(NH_2)NO^-$ [d]	12.9 [9]		35 ± 5	10.0–13.19	$(3.5 \pm 0.1) \times 10^{-2}$
XVI	NH_2O^-	13.8 ± 0.1[e] 13.74 [32]	9.50–10.66	36490 ± 1960[f]	9.90–12.80	4.0 ± 0.4
XVII	NH_2OH	6.09 ± 0.05 (p)	6.0–10.66	1.41 ± 0.21[f]	6.0–9.30	$(2.50 \pm 0.25) \times 10^{-5}$

No.	III		IV		V	
	pH	k_2	pH	k_2	pH	k_2
VI	8.0–9.0	$(3.2 \pm 0.5) \times 10^{-4}$	8.00–11.0	$(9.2 \pm 0.4) \times 10^{-3}$	–	–
VII	12.5–13.4	$(9.6 \pm 0.6) \times 10^{-3}$	10.0–13.0	0.15 ± 0.01	11.5–12.8	$(5.6 \pm 0.1) \times 10^{-4}$
VIII	10.0–11.79	$(4.2 \pm 0.6) \times 10^{-3}$	10.68–12.01 9.00–10.06	$(6.8 \pm 0.4) \times 10^{-2}$ $(7.2 \pm 0.9) \times 10^{-2}$ [g]	12.5–13.10	$(1.8 \pm 0.4) \times 10^{-4}$
IX	11.0–12.0	$(1.0 \pm 0.3) \times 10^{-2}$	11.20–11.50	0.15 ± 0.04	–	–
X	10.8–12.5	0.55 ± 0.02	11.05–12.50	7.3 ± 0.8	10.5–12.8	$(1.6 \pm 0.4) \times 10^{-2}$
XI	12.5–13.0	$(5.7 \pm 0.1) \times 10^{-2}$	11.98–13.00	$(2.4 \pm 0.2) \times 10^{-2}$	–	–
XII	12.9–13.3	$(1.75 \pm 0.15) \times 10^{-3}$	11.50–12.65	$(2.5 \pm 0.2) \times 10^{-2}$	11.70–13.30	$(3.2 \pm 0.1) \times 10^{-4}$
XIII	10.8–12.8	$(1.1 \pm 0.1) \times 10^{-2}$	9.0–10.5	0.10 ± 0.01	10.8–12.8	$(2.4 \pm 0.2) \times 10^{-4}$
XIV	8.4–11.5	$(2.3 \pm 0.3) \times 10^{-2}$	7.00–8.20	$(4.1 \pm 0.6) \times 10^{-2}$	8.40–10.95	$(4.9 \pm 0.4) \times 10^{-4}$
XV	12.0–13.1	$(2.9 \pm 0.1) \times 10^{-3}$	10.96–13.09	$(4.1 \pm 0.6) \times 10^{-2}$	11.90–13.30	$(1.9 \pm 0.1) \times 10^{-4}$
XVI	10.91–12.89	0.36 ± 0.02	10.47–12.00	4.10 ± 0.07	10.5–12.7	0.15 ± 0.02
XVII	6.0–9.3	$(1.90 \pm 0.15) \times 10^{-4}$	7.00–9.22	$(1.1 \pm 0.1) \times 10^{-3}$	8.00	$(7.5 \pm 0.7) \times 10^{-7}$

[a] The acid ionization constants were determined by potentiometric (p) or kinetic (k) method.

[b] The reactions of nucleophiles with ester **III** were studied in 5% aqueous ethanol.

[c] The activity of hydroxide ion was estimated by the equation $K_w = a_{H^+}\,a_{OH^-} = 10^{-14}$.

[d] For determination of $k_2^{NH_2OH}$ and $k_2^{NH_2O^-}$, quantitative treatment of the experimental data was performed using the equation $k_2'/\alpha_{NH_2OH} = k_2^{NH_2OH} + k_2^{NH_2O^-}\,\alpha_{NH_2O^-}/\alpha_{NH_2OH}$.

[e] Average pK_a value; see text.

[f] The reactivity of anions derived from 2,2,3,3-tetrafluoropropanol, choline, acetaldehyde oxime, acetohydroxamic acid, and acetamide oxime was determined using the equation $k_{ap} = k_2[Nu^-]$.

[g] The reactivity of hypochlorite ion was estimated from the disappearance of ester **IV** (λ 280 nm).

Transformation of Eq. (2) into (3) allows us to calculate k_2, which characterizes the nucleophilicity of HOO⁻ ion, and acid ionization constant of the conjugate acid (K_a).

$$k_2' = k_2 - k_2' \, a_{H^+} K_a^{-1}. \qquad (3)$$

The calculated values of k_2 and pK_a*5 are given in Table 1. A good agreement between the calculated values and those reported in [28] indicates that only nucleophilic attack by HOO⁻ ion on substrates **II–V** occurs, resulting in formation of the corresponding peroxy acids.

Hydroperoxide ion as a typical α-nucleophile exhibits a high reactivity toward any electron-deficient center, regardless of its nature (carbon, sulfur, or phosphorus atom) [22]. Its behavior in reactions with substrates **I–V** is not an exception. The α-effect in the transfer of acetyl (**I**), *p*-toluenesulfonyl (**II**), and phosphoryl (**III**) groups ($k_2^{HOO^-}/k_2^{ArO^-}$) is 22, 7.0×10^2, and 9.1×10^2, respectively; in other words, HOO⁻ reacts like aroxide ions with $pK_{a,calc}$ = 14.6, 16.4, and 22.0, respectively. In the reaction with **IV**, hydroperoxide ion behaves like an amine with $pK_{a,clac}$ = 22.3, and the α-effect is equal to 1.3×10^4. Even larger $pK_{a,calc}$ value (~28.0) was found for the reaction of HOO⁻ with 4-morpholinopyridinium phosphate dianion; here, the α-effect was estimated at 6×10^2 [37]. Naturally, the absolute value of α-effect for HOO⁻ ion, as well as for any other α-nucleophile, depends on the selected standard series. Nevertheless, it is quite obvious that hydroperoxide ion is one of the most powerful acyl group acceptors.

The anomalously high reactivity of hydroperoxide ion in acyl group transfer processes is interpreted in terms of general acid catalysis, i.e., assistance to elimination of leaving group. Stabilization of transition states **B** and **C** via hydrogen bonding with equatorial oxygen atom of the acyl group should favor fast elimination of 4-nitrophenoxide ion in reactions with esters **I–V**.

B   **C**
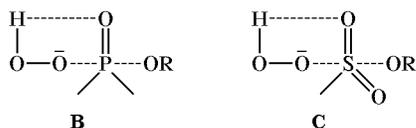
The stronger nucleophilicity of HOO⁻ relative to CH₃OO⁻ in reactions with 4-nitrophenyl sulfate

*5 The value of K_a for hydrogen peroxide was determined as an average of four K_a values obtained by treatment of the kinetic data for all the substrates by Eq. (3).

($k^{HOO^-}/k^{CH_3OO^-} \approx 30$) [37] and 4-nitrophenyl methylphosphonate monoanions ($k^{HOO^-}/k^{CH_3OO^-} \approx 50$) [12], as well as with triacetylenediamine ($k^{HOO^-}/k^{CH_3OO^-} \approx 20$) [42], is consistent with hydrogen bond formation in transition states like **B** and **C**. However, the effect of such assistance in reactions with aryl carboxylates is likely to be insignificant, for the nucleophilicities of HOO⁻ and CH₃OO⁻ differ by a factor of only ~3. Therefore, it is improbable that general acid catalysis (or the absence of it) is the only factor responsible for supernucleophilic properties of hydroperoxide ion. In fact, reactions of HOO⁻ with alkyl halides occur at an anomalously high rate [22], though this kind of catalysis does not play a significant role in alkyl group transfer reactions. It is also unlikely that high rates of acid-catalyzed addition of HOO⁻ ion to aldehydes originate from formation of intramolecular hydrogen bond in these processes [43].

It should be emphasized that the positive deviations of F⁻ and HOO⁻ from standard reaction series for processes involving transfer of phosphoryl (**III**) and phosphonoyl groups (**IV**) are similar, though fluoride ion is not an α-nucleophile. Analogous Brønsted analysis of the kinetic behavior of "normal" anionic oxygen-containing nucleophiles and F⁻ and HOO⁻ ions gives comparable deviations for F⁻ and HOO⁻ in reactions with 4-morpholinopyridinium phosphate dianion (**XVIII**) [37]. On the other hand, comparative analysis of the degree of bond dissociation (β_{lg}) in the transition state and the stability of transition states ($\log k_{Nu}^{XVIII}$) in reactions of the above nucleophiles with substrate **XVIII** shows that the dependence β_{lg}—k_{Nu}^{XVIII} is linear. Therefore, an important role in the reactivity of HOO⁻ (as well as of F⁻, see above) is played by the stability of reaction products and transition states; i.e., the nucleophilicity of hydroperoxide ion is essentially controlled by thermodynamic factor. Presumably, just intramolecular acid catalysis and relatively high thermodynamic stability of transition states **B** and **C** are responsible for the observed α-effect of HOO⁻ ion in acyl group transfer processes.

Nucleophilic reactivity of hypohalite ions. While estimating the reactivity of ClO⁻ and BrO⁻ ions on a quantitative level, it should be kept in mind that these ions are efficient nucleophilic catalysts [2, 44] and that their conjugate acids exhibit pronounced oxidizing ability with respect to 4-nitrophenoxide ion. The kinetic curves plotted in Fig. 2a illustrate variation of the absorption of 4-nitrophenoxide ion with time at different pH in the reaction of ClO⁻ with ester **II**. The ascending branches of the curves correspond to accumulation of 4-nitrophenoxide ion in the system

as a result of substrate dissociation, and the descending branches correspond to its oxidation. Displacement of the maxima, reduction of the time necessary to reach the maximum, and decrease of D_{max} with rise in the acidity of the medium suggest a complex mechanism of oxidation of 4-nitrophenoxide ion (Fig. 2a). Study of oxidation of 4-nitrophenoxide ion in buffer solutions at various pH values (Table 2) led us to the following equation for the reaction rate:

$$k'_{ap} = k_{ox}[\text{HHlgO}]\, a_{\text{H}^+}, \qquad (4)$$

where [HHlgO] is the equilibrium concentration of the corresponding hypohalic acid. Treatment of the experimental data (Table 2) according to Eq. (5):

$$k_{ap}/[\text{HHlgO}]_0 = k_{ox}\, \alpha_{\text{HHlgO}}\, a_{\text{H}^+}, \qquad (5)$$

where α_{HHlgO} is the fraction of the conjugate acid, gives the following third-order rate constants k_{ox}: $k_{ox}^{\text{HClO}} = (9.15 \pm 0.35) \times 10^7 \ \text{l}^2\ \text{mol}^{-2}\ \text{s}^{-1}$ and $k_{ox}^{\text{HBrO}} = (5.20 \pm 0.09) \times 10^{10}\ \text{l}^2\ \text{mol}^{-2}\ \text{s}^{-1}$ (Fig. 2b). The obtained experimental data convincingly indicate that the reaction with ClO⁻ and BrO⁻ ions is a stepwise process which is characterized by change of the rate-determining stage on variation of the acidity of the medium.
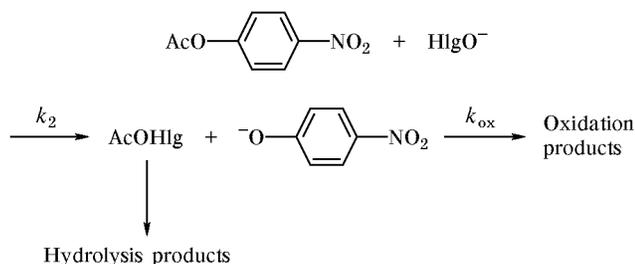
In the first stage, attack by HlgO⁻ ion on the electron-deficient center of the substrate yields 4-nitrophenoxide ion and acyl hypohalite. The latter undergoes fast hydrolysis with regeneration of HlgO⁻. In the second stage, 4-nitrophenoxide ion is oxidized with hypohalic acid. If the oxidation of 4-nitrophenoxide ion is slow, it is possible to determine the nucleophilic reactivity of ClO⁻ ($9.4 \leq$ pH ≤ 11.5) and BrO⁻ ions (11.0 pH ≤ 12.0) in a usual way (Table 1).

$$k_{ap} = k_2[\text{HlgO}^-]. \qquad (6)$$

The reactivity of ClO⁻ ion can also be estimated quantitatively using Eq. (7) at such pH values when the rate of oxidation of 4-nitrophenoxide ion is much higher than the rate of the reaction of ClO⁻ with ester **IV**, provided that the reaction course is monitored
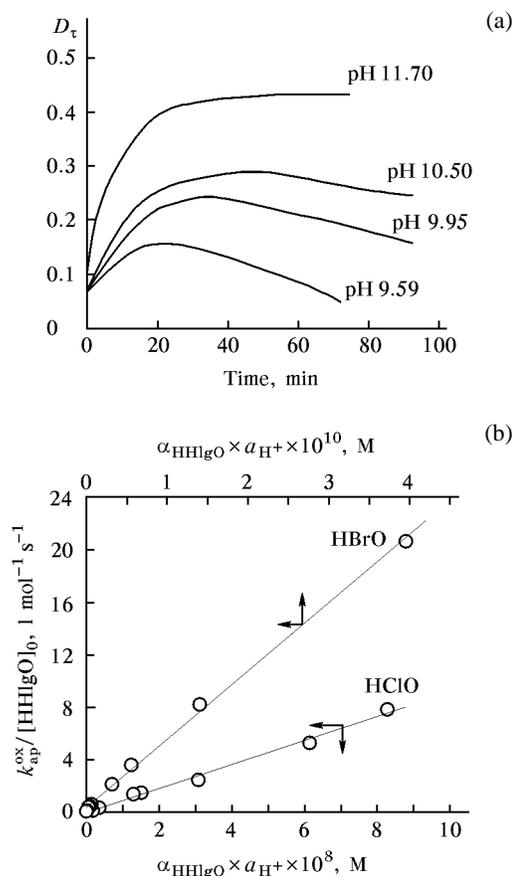
Fig. 2. (a) Change of the optical density (λ 440 nm) with time in the reaction of hypochlorite ion with 4-nitrophenyl *p*-toluenesulfonate (**II**); water, 25°C, μ = 1.0 (KCl), $[\text{HClO}]_0 = 0.034$ M, $[\textbf{II}]_0 = 4 \times 10^{-5}$ M. (b) Plots of the apparent second-order rate constants $k_{ap}^{ox}/[\text{HHlgO}]_0$, l mol⁻¹ s, versus $\alpha_{\text{HHlgO}}\, a_{\text{H}^+}$, M, for the oxidation of 4-nitrophenoxide ion with hypohalic acids.

following the disappearance of ester **IV**. The fact that k_2 values determined under different conditions (Table 1) are similar indicates validity of the above scheme.

Hypohalite ions (ClO⁻- and BrO⁻) react with all the examined substrates at an anomalously high rate. The positive deviations of points from the Brønsted dependences for standard reaction series (Fig. 1a–1c) are Δ(ClO⁻) = 3.2–3.6 and Δ(BrO⁻) = 2.7–3.5, and their nucleophilicities are comparable with the reactivity of hypothetical nucleophiles with $\text{p}K_{\text{a,calc}} = 11.6$–18.8. It should be noted that the positive deviations are very similar and are almost independent on the substrate nature, i.e., BrO⁻ and ClO⁻ ions exhibit properties typical of α-nucleophiles. Probably, the α-effect for hypohalite ions originates from formation of such rate-determining transition state in which the

Table 2. Experimental conditions and apparent pseudo-first-order rate constants for the oxidation of 4-nitrophenoxide ion with hypohalic acids at 25°C, $\mu = 1.0$ (KCl)

HClO			HBrO		
pH[a]	k_{ap}, s^{-1}	[HClO]$_0$, M	pH[a]	k_{ap}, s^{-1}	[HBrO]$_0$, M
6.95	0.041	0.005	8.99	0.154	0.00747
7.07	0.027	0.005	9.22	0.0617	0.00747
7.27	0.013	0.005	9.44	0.0272	0.00747
7.48	0.015	0.01	9.57	0.0163	0.00747
7.42	0.014	0.01	9.95	0.0106	0.016
7.86	0.0037	0.01	10.02	0.0078	0.016
8.08	0.0015	0.01	10.2	0.0066	0.016
			10.4	0.0024	0.016
			10.55	0.0016	0.016

[a] The required pH values were maintained using a solution of sodium carbonate ([Na$_2$CO$_3$]$_0$ = 0.02 M) in the case of hypobromous acid and a solution of sodium phosphate ([Na$_3$PO$_4$]$_0$ = 0.02 M) in the case of hypochlorous acid.

acyl oxygen atom interacts with vacant *d*-orbitals of hypohalite ion. In essence, hypohalite ions as Lewis acids are capable of assisting acyl transfer in the same manner as do Brønsted acids.

Nucleophilic reactivity of hydroxylamine. Reactions of hydroxylamine with the esters under study are

Fig. 3. Semilog plots of the rate constants ($\log k_2'$) for the reaction of hydroxylamine with 4-nitrophenyl *p*-toluenesulfonate (**II**) versus buffer concentration: (*1*) imidazole buffer, pH = 12.75; (*2*) phosphate buffer, pH = 12.20; (*3*) piperidine buffer, pH = 11.00; (*4*) carbonate buffer, pH = 9.50; (*5*) 4-aminopyridine buffer, pH = 9.45; (*6*) TRIS buffer, pH = 9.00; water, 25°C, $\mu = 1.0$ (KCl).

weakly sensitive to the ionic strength, and the acid–base components of TRIS, acetate, phosphate, carbonate, 4-aminopyridine, and imidazole buffers almost do not affect the apparent second-order rate constants $k_2' = (k_{ap} - k_{OH^-} a_{OH^-})/[NH_2OH]_0$, l mol^{-1} s^{-1}, of these processes (Fig. 3). The reactions are of an overall second order: first in hydroxylamine and first in the substrate; these orders do not change throughout the examined pH range (Fig. 4a).

On the other hand, the pH profiles obtained for the above processes differ considerably from those observed for substrate **I** [2], 4-nitrophenyl methylphosphonate [12], etc. [45]. As pH increases, the rate of the reaction of hydroxylamine with the examined substrates ($\log k_2'$) rapidly comes to a plateau (even at pH 7.0); pH-independent acyl group transfer then occurs; and, beginning with pH $\geq$ 9.0, the reaction rate again increases as the acidity of the medium falls down (Fig. 4b). In the pH range from 10.4 to 12.9, the rate of transfer of *p*-tolylsulfonyl, diethoxyphosphinoyl, ethoxy(ethyl)phosphinoyl, and dimethylcarbamoyl groups is linearly related to pH [Eq. (7)].

$$\log k_2'(\mathbf{II}) = -(13.08 \pm 0.16) + (0.99 \pm 0.01)\,\text{pH}; \quad (7)$$
$$n = 10, \quad s = 0.035, \quad r = 0.99.$$

The same tendency in the character of pH effect on the reaction rate is observed in the reaction of hydroxylamine with ester **I** at pH = 9.6–10.8. Finally, the pH profiles for the reactions with compounds **II**, **III**, and **V** show one more bend at relatively high concentrations of hydroxide ion, and $\log k_2'$ attains its maximal value ($\log k_{2,\,max}'$) at [OH$^-$] $\geq$ 2 M (Fig. 4b). We were the first to reveal such an unusual behavior of hydroxylamine toward substrates having different electrophilic centers (unsaturated carbon, sulfur, and phosphorus atoms) on variation of the acidity of the medium over a wide range.

The similarity of the pH profiles for the examined esters suggests that the observed pattern should be interpreted in terms of hydroxylamine properties. The latter in aqueous solution can exist in the following forms: cationic ($\overset{+}{N}H_3OH$), neutral (NH$_2$OH), and anionic (NH$_2$O$^-$) (see scheme below); two of these, NH$_2$OH and NH$_2$O$^-$, can act as O-nucleophile.

In the region of pH-independent acyl group transfer, where only the neutral form of hydroxylamine reacts with the substrate and its fraction α_{NH_2OH} tends to unity, the value of $k_2^{NH_2OH}$ may be determined from any point lying on the plateau of the pH-profile, since $k_2' = k_2^{NH_2OH}$. In the acidity range corresponding to $0.9 > \alpha_{NH_2OH} > 0.1$, the kinetic data were treated according to the formula $k_2' = k_2^{NH_2OH}\,\alpha_{NH_2OH}$. Table 1 contains the average values for esters **I–V** derived from 12–16 measurements for each substrate.

The situation in alkaline media is less clear. A considerable increase (by 3 to 5 orders of magnitude) of the rate of acyl group group transfer may result from (1) general base catalysis by hydroxide ion (a kinetic equivalent is specific base catalysis and general acid catalysis with water) of the reaction of hydroxylamine with the substrates under study [Eq. (8)] and (2) S_N2 reaction involving nucleophilic attack on the substrate by the oxygen atom of NH_2O^- [Eq. (9)].

$$k_2' = k_3^{NH_2OH}\,\alpha_{NH_2OH}\,[OH]_0 = \frac{a_{H^+}}{K_{a2} + a_{H^+}}\,k_3^{NH_2OH}\,[OH]_0;$$
(8)

$$k_2' = k_2^{NH_2O^-}\,\alpha_{NH_2O^-} = \frac{K_{a2}}{K_{a2} + a_{H^+}}\,k_2^{NH_2O^-}.$$
(9)

There is a simple relation between the above kinetic expressions:

$$k_2^{NH_2O^-} = k_3^{NH_2OH}(K_w/K_{a2});$$

therefore, the two mechanisms are kinetically indistinguishable. On the basis of formal kinetic analysis it is impossible to determine which form of hydroxylamine is responsible for acyl group transfer at pH $\geq$ 10. Nevertheless, we prefer Eq. (9) rather than (8), i.e., O-nucleophilic attack by NH_2O^- on the electron-deficient center of the substrate (S_N2 reaction). Kinetic expression (8) implies a stepwise mechanism of acyl group transfer [38] with formation of a fairly stable intermediate, zwitterionic, neutral, or anionic. It is hardly probable for substrates **II–IV** since the corresponding five-coordinate intermediates having a bipyramidal structure should be characterized by a lifetime approaching the duration of the activation act [46]. Furthermore, for none of the examined substrates we observed promoting effect of acid–base buffer components (Fig. 3), though such an effect is rather a rule than an exception for systems involving acid–base catalysis [47]. Reactions of substrates **I** and **II**, **III** and **IV** with common nucleophiles, such as
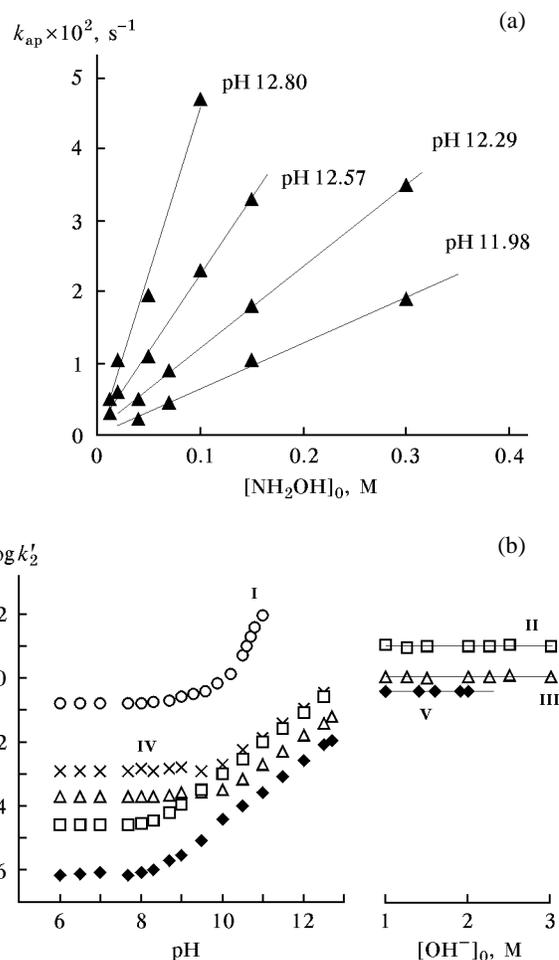
Fig. 4. (a) Dependences of the appearent pseudofirst-order rate constants k_{ap}, s^{-1}, for the reaction of hydroxylamine with 4-nitrophenyl *p*-toluenesulfonate (**II**) versus initial hydroxylamine concentration $[NH_2OH]_0$ at different pH; 5% aqueous ethanol, 25°C, $\mu = 1.0$ (KCl). (b) pH-Profiles for the reactions of hydroxylamine with 4-nitrophenyl acetate (**I**), 4-nitrophenyl *p*-toluenesulfonate (**II**), diethyl 4-nitrophenyl phosphate (**III**), ethyl 4-nitrophenyl ethylphosphonate (**IV**), and 4-nitrophenyl dimethylcarbamate (**V**); water, 25°C, $\mu = 1.0$ (KCl).

aroxide, alkoxide, and hydroxide ions, and with a number of typical α-nucleophiles, such as anions derived from acetamide oxime, acetaldehyde oxime, acetohydroxamic acid, hydrogen peroxide, and hypohalic acids, fit linear correlations (10)[*6] and (11) which interrelate activation barriers to transfer of *p*-tolylsulfonyl and acetyl, diethoxyphosphinoyl and ethoxy(ethyl)phosphinoyl groups to a fixed anionic oxygen-containing nucleophile (Fig. 5). These correla-

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[*6] While building up correlation (10), the data for fluoride ion were not taken into account.
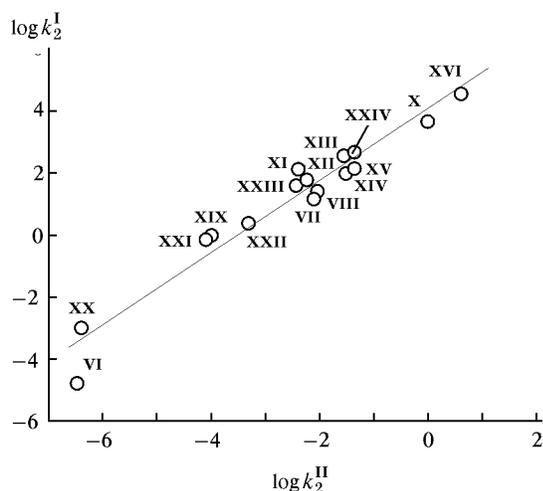
Fig. 5. Correlation between the rate constants of the reactions of various O-nucleophiles with 4-nitrophenyl acetate (**I**) and 4-nitrophenyl *p*-toluenesulfonate (**II**). Nucleophiles: **VI**, fluoride ion; **VII**, hydroxide ion; **VIII**, hypochlorite ion; **X**, hydroperoxide ion; **XI**, 2,2,3,3-tetrafluoropropanol; **XII**, choline; **XIII**, acetaldehyde oxime ion; **XIV**, aceto-hydroxamate ion; **XV**, acetamide oxime ion; **XVI**, hydroxylamine anion; **XIX**, phenol; **XX**, pentafluorophenol; **XXI**, 4-chlorophenol; **XXII**, 4-methoxyphenol; **XXIII**, 2,2,2-trifluoroethanol; **XXIV**, 2-propynyl alcohol. The data for compounds **XIX**–**XXIV** were taken from [2, 33, 34].

tions cover the range of nucleophilic substitution rates of about 7 orders of magnitude for the pair **II**–**I** [Eq. (10)] and 4 orders of magnitude for the pair **III**–**IV** [Eq. (11)]. The data for hydroxylamine anion are also included.

$$\log k_2^{\mathbf{I}} = (3.87 \pm 0.13) + (1.02 \pm 0.06) \log k_2^{\mathbf{II}}; \quad (10)$$

$$n = 15, \ r = 0.96;$$

$$\log k_2^{\mathbf{IV}} = (1.00 \pm 0.14) + (0.98 \pm 0.06) \log k_2^{\mathbf{III}}; \quad (11)$$

$$n = 12, \ r = 0.97.$$

Finally, the following should be noted: treatment of a large array of kinetic data (~20 values of k_2', pH range 10–13.5) for each substrate **II**, **III**, and **V** by Eq. (12) with account taken of the limiting values of $k_2' = k_{2,\max}'$ gave pK_{a2} values for hydroxylamine equal to 13.83 ± 0.11, 13.79 ± 0.09, and 13.81 ± 0.08, respectively.

$$pK_{a2} = pH + \log[(1 - \alpha_{NH_2O^-})/\alpha_{NH_2O^-}]. \quad (12)$$

Here, α_{A^-} values were calculated by the formula

$$\alpha_{A^-} = k_2'/k_{2,\max}'.$$

A good agreement between the acid ionization constants determined by the "kinetic titration" technique and $pK_{a2} = 13.74$ found by spectrophotometry [32] is unlikely to be accidental. Most probably, the above data directly indicate the absence of general acid–base catalysis by the Brønsted pair OH$^-$–H$_2$O of hydroxylamine reactions at pH > 10. Another conclusion is that the limiting values of apparent second-order rate constants at [OH$^-$]$_0$ > 1 M for substrates **II**, **III**, and **V** characterize just the nucleophilicity of NH$_2$O$^-$ ion, i.e., $k_{2,\max}' = k_2^{NH_2O^-}$. Thus the pH-profiles for the reactions of hydroxylamine with substrates **II**, **III**, and **V** are correctly interpreted in terms of the proposed reaction scheme (see above) and the rate of acyl group transfer to the neutral and anionic forms of hydroxylamine is described by Eq. (13):

$$k_{ap} = k_2^{NH_2OH} [NH_2OH] + k_2^{NH_2O^-} [NH_2O^-]. \quad (13)$$

Comparative analysis of the reactivity of inorganic α-nucleophiles. Hydroxylamine occupies a specific place among inorganic oxygen-containing anionic α-nucleophiles, for it is the only compound which in aqueous solution gives rise to two reactive O-nucleophilic species, NH$_2$OH and NH$_2$O$^-$. The basicities of these forms differ very strongly, by about 16 orders of magnitude (Table 1). This difference may be compared only with the difference in the basicities of oxygen in a neutral water molecule and hydroxide ion. The differences in the kinetic behavior of NH$_2$OH and NH$_2$O$^-$ are also surprising.

The positive deviations for NH$_2$O$^-$ ion from standard reaction series are as follows: $\Delta = 1.5$ (**I**), 2.1 (**II**), 1.5 (**III**), and 1.0 (**IV**). However, it is much more important that the reactivity of hydroxylamine anion toward esters **I**, **II**, and **V** exceeds the reactivity of one of the most powerful α-nucleophiles, hydroperoxide ion, by a factor ($k_2^{NH_2O^-}/k_2^{HOO^-}$) of ~8, ~4, and ~10, respectively (Table 1). In the reactions with **III** and **IV**, the nucleophilicities of HOO$^-$- and NH$_2$O$^-$ are comparable. Undoubtedly, NH$_2$O$^-$ is the most powerful acyl group acceptor, so that there are all grounds to rank it first in the series of α-nucleophiles.

Brønsted dependences (14)–(16) are fulfilled for the reactions of inorganic α-nucleophiles with esters **I**, **II**, and **V**:

$$\log k_2^{\mathbf{I}} = (-2.2 \pm 0.4) + (0.50 \pm 0.04) pK_a; \quad (14)$$

$$n = 3, \ r = 0.99;$$

$$\log k_2^{\mathbf{II}} = (-5.5 \pm 0.6) + (0.45 \pm 0.06) pK_a; \quad (15)$$

$$n = 4, \ r = 0.97;$$

$$\log k_2^{\mathbf{V}} = (-7.2 \pm 0.1) + (0.46 \pm 0.01)\,pK_a; \qquad (16)$$

$$n = 3, \ r = 0.99.$$

Hence the basicity is among factors determining the nucleophilicity of inorganic anionic α-nucleophiles. The basicity of esters **III** and **IV** also controls the rate of transfer of diethoxyphosphinoyl and ethoxy(ethyl)phosphinoyl groups [Eqs. (17), (18)], but the points for HOO⁻ are characterized by positive deviations: $\Delta(\mathbf{III}) = 0.94$, $\Delta(\mathbf{IV}) = 0.93$. A probable reason is that their reactions involve intramolecular general acid catalysis (see structure **B** above). Probably, here we observe enhanced reactivity of HOO⁻ rather than reduced reactivity of NH₂O⁻.

$$\log k_2^{\mathbf{III}} = (-4.4 \pm 0.1) + (0.28 \pm 0.01)\,pK_a; \qquad (17)$$

$$n = 4, \ r = 0.99;$$

$$\log k_2^{\mathbf{IV}} = (-2.9 \pm 0.2) + (0.25 \pm 0.02)\,pK_a; \qquad (18)$$

$$n = 4, \ r = 0.99.$$

An additional support to the above stated is given by the fact that HOO⁻ and NH₂O⁻ ions fit linear dependences (10) and (11) which interrelate stabilities of transition states in the reactions of common nucleophiles and α-nucleophiles with substrates **I/II** and **III/IV** (Fig. 5). An important role of the thermodynamic factor in the reactivity of nucleophiles is also indicated by the following. The Brønsted dependences for α-nucleophiles reacting with esters **III** and **IV** (Fig. 1c) include the point for fluoride ion, though the latter is not an α-nucleophile; in the case of esters **I** and **II** (Fig. 1a, 1b), the points for fluoride ion show appreciable negative deviations: $\Delta(\mathbf{I}) = -4.2$ and $\Delta(\mathbf{II}) = -2.4$. Presumably, the existence of correlations (10) and (11) provides an additional support to the assumption that thermodynamical stability of transition states is an important factor responsible for the reactivity of not only common nucleophiles but also α-nucleophiles.

The kinetic behavior of neutral hydroxylamine species in acyl group transfer processes seems to be even more surprising. The points for NH₂OH show considerable positive deviations not only from standard reaction series [$\Delta(\mathbf{I}) \approx 9.0$, $\Delta(\mathbf{II}) \approx 6.0$, $\Delta(\mathbf{III}) \approx 6.0$, $\Delta(\mathbf{IV}) \approx 6.1$] but also from Brønsted relations (14)–(18) for α-nucleophiles [$\Delta(\mathbf{I}) \approx 3.4$, $\Delta(\mathbf{II}) \approx 1.8$, $\Delta(\mathbf{III}) \approx 1.6$, $\Delta(\mathbf{IV}) \approx 0.5$, $\Delta(\mathbf{V}) \approx 2.0$] (Fig. 1a–1c). Obviously, the neutral form of hydroxylamine exhibits an anomalously high reactivity even among the series of inorganic α-nucleophiles; with the substrates under

study it reacts like hypothetical α-nucleophiles with $pK_a \approx 1$–5 (Fig. 1a–1c). In fact, these data suggest that the mechanism of acyl group transfer to NH₂OH radically differs from the mechanism typical of inorganic α-nucleophiles. On the basis of kinetic isotope effects, Hess *et al.* [3] recently proposed the following mechanism for the reaction of hydroxylamine with 4-nitrophenyl acetate (**I**). In the first reversible stage (which involves general base assistance by the amino group of hydroxylamine), zwitterionic tetrahedral addition product **D** is formed. Two hydrogen atoms of the amino group in **D** form intramolecular hydrogen bond with the carbonyl oxygen atom:

D
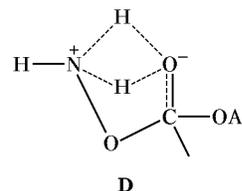
In the rate-determining stage (under conditions of general acid catalysis), intermediate **D** slowly decomposes to give *O*-acetylhydroxylamine. Naturally, the occurrence of general acid–base assistance is crucial for understanding a number of aspects of the kinetic behavior of such weakly basic O-nucleophile as hydroxylamine. Nevertheless, the proposed O-acylation mechanism remains questionable, for it can explain neither the behavior of *N,N*-dialkylhydroxylamines in the same reaction nor the existence of a single Brønsted dependence for the reactions of hydroxylamine and its *N*-alkyl- and *N,N*-dialkyl derivatives with substrate **I** [48]. Presumably, unlike the mechanism including formation of zwitterionic intermediate **D**, the acylation of hydroxylamine involves cyclic transition states like **E**–**G**. A necessary and sufficient condition is that only the hydroxy

E   **F**

G
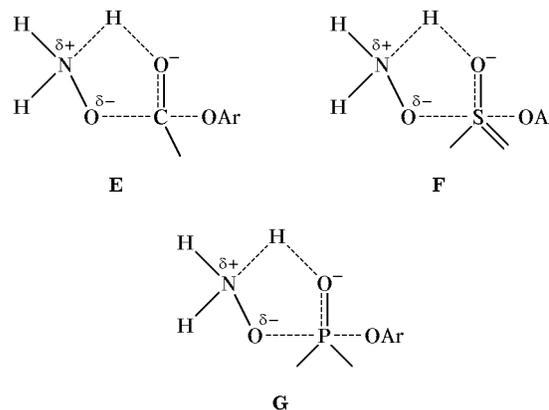
hydrogen atom of hydroxylamine should participate in hydrogen bonding. The presence of an amine-like form of hydroxylamine in transition states **E**–**G**, as well as general acid–base assistance, should reduce the energy barrier and hence should favor high rates of acyl group transfer to both hydroxylamine and its *N*-alkyl and *N,N*-dialkyl derivatives.

To conclude, let us emphasize once more that hydroxylamine is a unique α-nucleophile whose neutral and anionic forms ensure high rates of acyl group transfer throughout a wide pH range. None of the known α-nucleophiles can compete with hydroxylamine in this respect.

EXPERIMENTAL

Substrates **I**–**V** were synthesized by acylation of 4-nitrophenol with acetic anhydride, *p*-toluenesulfonyl chloride, diethyl chlorophosphate, ethyl ethylchlorophosphonate, and dimethylcarbamoyl chloride, respectively, in dry dioxane in the presence of triethylamine. After isolation, ester **I** was purified by double recrystallization from hexane, and esters **II** and **V** were recrystallized thrice from anhydrous ethanol. Esters **III** and **IV** were doubly distilled under reduced pressure (0.05 mm). The physical constants of compounds **I**–**V** (melting points and n_D^{20} values) and their UV spectra were in full agreement with published data.

Hydroxylamine hydrochloride was thrice recrystallized from ethanol, mp 159°C (decomp.); the purity of $NH_2OH \cdot HCl$ was checked by titration with potassium bromate [49]. Acetohydroxamic acid was synthesized by the procedure reported in [50] and was purified by triple recrystallization from anhydrous ethanol, mp 92°C. Acetamide oxime was prepared as described in [51]; it was repeatedly crystallized from butanol until constant melting point, mp 135°C. Acetaldehyde oxime and 2,2,3,3-tetrafluoropropanol were purified by standard procedures. Choline chloride (Sigma) was used without additional purification. Hypochlorous acid containing no Cl_2 and Cl^- was synthesized according to the following scheme:

$$2Cl_2 + HgO \longrightarrow HgCl_2 + Cl_2O \longrightarrow 2HClO$$

Hypobromous acid was prepared by adding bromine to water in a dropwise manner [52]. Inorganic reagents of ultrapure or chemically pure grade were not subjected to additional purification.

The procedure for kinetic measurements was described in detail in [5, 34]. The progress of reactions was monitored following the absorption of liberated 4-nitrophenoxide ion (λ 400–440 nm). Solutions of

reactants were prepared just before each series of kinetic experiments, and their concentrations were selected in such a way that they also act as buffer components. If the initial nucleophile concentration was less than 0.02 M, the acidity of the medium was maintained with the aid of potassium phosphate (pH 6.0–7.5), tris(hydroxymethyl)aminomethane (TRIS, pH 7.5–9.0), and sodium carbonate (pH 9.0–11.5) at a concentration of 0.1–0.05 M. Buffer solutions were adjusted to a required pH value by adding a concentrated solution of KOH or HCl. The acidity of the medium was checked both before and after each kinetic experiments; if the difference in the initial and final pH values was greater than 0.05, the data were rejected. The ionic strength (μ = 1.0) was maintained with potassium chloride. The concentration of hydrogen peroxide, hypochlorous acid, and hypobromous acid was determined by permanganatometric and iodometric titration, and ionic strength was then fixed at μ = 1.0. In alkaline medium hydroxylamine can be oxidized by oxygen dissolved in water [32]. Prior to kinetic studies, by special experiments we showed that hydroxylamine solutions (pH 10–13) prepared both in air and under argon showed the same reactivity.

All experiments were performed in water or 5% aqueous ethanol (for substrate **II**) at 25°C. Doubly distilled water and anhydrous ethanol were used. In the kinetic experiments, the initial substrate concentration ($[S]_0 \approx 5 \times 10^{-5}$ M) was much less than the initial nucleophile concentration, and the apparent pseudo-first-order rate constants (k'_{ap}, s^{-1}) remained constant up to six half-conversion periods of the sustrate. The values of k'_{ap}, s^{-1}, were determined from the change in the optical density using the equation

$$\ln(D_\infty - D_\tau) = \ln(D_\infty - D_0) - k'_{ap}\tau,$$

where D_0, D_τ, and D_∞ are the optical densities at $\tau = 0$ (reaction start), $\tau = \tau_1$, and after reaction completion. As a rule, the apparent rate constants k'_{ap}, s^{-1}, were corrected for the contribution of alkaline hydrolysis provided that it was more than 5% of k'_{ap}; i.e., $k_{ap} = k'_{ap} - k_{OH} a_{OH}$. The rate constants of alkaline hydrolysis k_{OH}, $l\,mol^{-1}\,s^{-1}$, for the substrates under study were determined independently on the basis of the activity of hydroxide ion in water at 25°C (μ = 1.0); their values are given in Table 1.

The acid ionization constants of hydroxylamine, acetamide oxime, and acetohydroxamic acid in 5% aqueous ethanol (μ = 1.0) at 25°C were determined by potentiometric titration (Table 1) with 0.1 M KOH or HCl. The pK_a values were calculated by the

Henderson–Hasselbach equation [28]. The pK_a values for ClO$^-$ and HOO$^-$ were determined from the kinetic measurements.

The errors in determination of pK_a were estimated by small sample statistics; linear correlations were treated by the least-squares procedure.

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