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O-Nucleophilicity of Hydroxamate Ions in Reactions with Ethyl 4-Nitrophenyl Ethylphosphonate, Diethyl 4-Nitrophenyl Phosphate, and 4-Nitrophenyl 4-Toluenesulfonate

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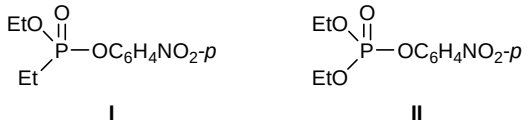
Abstract—The nucleophilicity of hydroxamate ions toward ethyl 4-nitrophenyl ethylphosphonate, diethyl 4-nitrophenyl phosphate, and 4-nitrophenyl 4-toluenesulfonate in water (μ = 1, KCl, 25°C) is described by the Brønsted equation (β_N = 0.54, 0.70, and 0.59, respectively). In these reactions, hydroxamate ions act as typical α-nucleophiles; they are more reactive than phenoxide ions with the same basicity by a factor of 300 to 800. In the series of hydroxamate ions, an anomalously high nucleophilicity was revealed for the anions possessing catalytic centers (in terms of general base catalysis), which are capable of providing anchimeric assistance in the transition state. An equation has been proposed, which relates the efficiency of such assistance in anions derived from aminohydroxamic acids to the ΔpK_a values characterizing their acidic and basic groups.

Hydroxamic acids are typical α-nucleophiles which are characterized by anomalously high reactivity with respect to electron-deficient centers of various origins, e.g., carbon [1, 2], sulfur [3], and phosphorus [4–7]. This fact attracts interest from the viewpoints of utilization of organophosphorus ecotoxicants, such as Sarin, Tabun [8], etc. [7, 9], and search for effective antidotes capable of reactivating choline esterase inhibited by organophosphorus compounds; studies on the synthesis of such antidotes are now in progress [10]. The reactivity of hydroxamate ions is roughly described by a common Brønsted equation for compounds in which the substituents exert only polar effects and for those possessing additional acid–base centers [7, 8, 11, 12]. It is believed that the main factor determining the reactivity of hydroxamate ions is their basicity [11]. However, one cannot rule out that acid–base functional groups could exert a catalytic effect in reactions with electron-deficient centers. In the framework of studies in the field of creation of new systems for decomposition of ecologically toxic substrates, the goal of the present work was to examine the nucleophilic reactivity of hydroxamate ions, especially of those possessing acidic and basic groups, toward ethyl 4-nitrophenyl ethylphosphonate (**I**), diethyl 4-nitrophenyl phosphate (**II**), and 4-nitrophenyl 4-toluenesulfonate (**III**).



I

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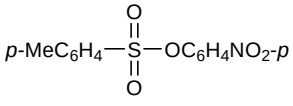


III

Decomposition of acyl-containing substrates by the action of hydroxamic acids is a stepwise process, the first step of which is attack by the anionic form of nucleophile on the electron-deficient center in the

† Deceased.

substrate to give the corresponding O-acylated nucleophile as primary intermediate product (Scheme 1).

Scheme 1.

$$RC(O)NHO^- + AcylOC_6H_4NO_2\text{-}p \xrightarrow{k_{A^-}} AcylONHC(O)R + p\text{-}O_2NC_6H_4O^-$$

Acyl = Et(EtO)P(O), $(EtO)_2P(O)$, 4-$MeC_6H_4SO_2$.

Unlike carboxylic acid derivatives [13], O-phosphorylated intermediates undergo fast Lossen rearrangement [8, 14] which makes their isolation almost impossible. Therefore, the nucleophilic substitution process was postulated on the basis of studying the Lossen rearrangement products and analysis of the rate of decomposition of Sarin by the action of benzohydroxamate ion in terms of the linear Gibbs energy relationship [8]. We did not isolate products of reactions of hydroxamate ions with substrates **I** and **II**. Nevertheless, taking into account structural similarity of compounds **I** and **II** to Sarin, it was reasonable to presume that the rate-determining stage in the reactions under study is nucleophilic substitution according to Scheme 1. This assumption is consistent with the data on deuterium isotope effect of the solvent on the rate of decomposition of phosphonate **I** in the presence of hydroxamate ions **VII** and **XXVI** in D_2O (Table 1), as well as with the thermodynamic activation parameters for the reactions of phosphonic ester **I** with hydroxamate ions **VII** and hydroxide ion (OH^-) (Table 2). These data indicate that the overall order of the above reactions is equal to 2: first order in the substrate (S) and first order in the nucleophile.

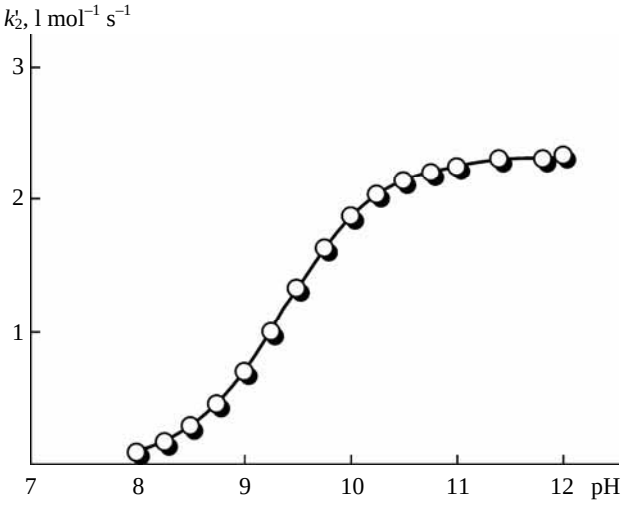


Fig. 1. Plot of the rate constants k'_2 for the reaction of acetohydroxamic acid (**IV**) with diethyl 4-nitrophenyl phosphate (**II**) versus pH; water, μ = 1.0 (KCl), 25°C.

The hydroxamate ions studied in the present work can be divided into two groups according their kinetic behavior. The first group contains anions derived from compounds **IV**–**XIX** (Table 1). The rate of the reactions with these ions is described by Eq. (1), and the pH profile (Fig. 1) is typical of processes where the reacting species are basic buffer components. With rise in pH, the rate of substrate consumption tends to a limiting value (k'_2, l mol^{-1} s^{-1}) which no longer depends on pH, and k_{A^-} can be determined at any point on that part of the pH profile (Fig. 1) since $k'_2 \to k_{A^-}$ when $\alpha_{A^-} \to 1$.

$$k'_2 = k_{A^-}\alpha_{A^-} = k_{A^-}K_a/(K_a + a_{H^+}). \quad (1)$$

Provided that pH of the medium is comparable to pK_a of hydroxamic acid, the k_{A^-} value was calculated by the modified Henderson–Hasselbalch equation:

$$k'_2 = k_{A^-} - k'_2 a_{H^+}/K_a. \quad (2)$$

In this case, apart from k_{A^-}, we can determine the acid ionization constant K_a of the corresponding hydroxamic acid (which is conjugate to the anion). In such a way, we have determined the pK_a value of hydroxamic acid **VI** in water and those of acids **VII** and **XXVI** in D_2O (Table 1). The values estimated by the kinetic and potentiometric techniques coincided within the experimental error (Table 1).

The second group includes hydroxamic acids **XX**–**XXXI** and **XXXIV**–**XXXVII** which possess two acid–base centers (Table 1); they react with substrates **I** and **III** according to Scheme 2, and the reaction rates are described by Eqs. (3) and (4):

$$k'_2 = k_{HA^-}[HA^-] + k_{A^{2-}}[A^{2-}]; \quad (3)$$

$$k'_2 = k_{HA^+}[HA^+] + k_{A^-}[A^-]. \quad (4)$$

The observed dependence of the rate of substrate consumption on the acidity of the medium unambiguously indicates that the basic buffer component contains two kinds of reactive species, HA^- and A^{2-} ($HA^\pm$ and A^-). Scheme 3 illustrates the formation of these species from bis-hydroxamic, *o*-hydroxybenzohydroxamic, and α-amino hydroxamic acids. The rate of their reaction with substrates **I**–**III** depends on their acid–base properties and pH, and it increases as the pH decreases until complete ionization of ionogenic centers in the nucleophile molecule.

Table 1. Basicities of hydroxamic acid anions (pK_a) and their reactivities (k_2) with respect to ethyl 4-nitrophenyl ethylphosphonate (**I**), diethyl 4-nitrophenyl phosphate (**II**), and 4-nitrophenyl 4-toluenesulfonate (**III**); water, μ = 1.0 (KCl), 25°C

Comp. no.	Hydroxamic acid	pH	Concentration of hydroxamic acid, M	N[a]	pK_a[b]	$k_2 \times 10^2$, l mol^{-1} s^{-1}
Reaction with ethyl 4-nitrophenyl ethylphosphonate (**I**)						
IV	Acetohydroxamic	7.0–8.2	0.0125–0.13	12	9.36±0.01 (P)	4.1±0.6
V	Propionohydroxamic	9.02–11.02	0.01–0.08	10	9.36±0.04 (P), 9.4±0.1 (K)	9.7±0.9
VI	Phthalohydroxamic	8.31–9.52	0.08	10	9.1±0.1 (K)	6.1±0.5
VII	Benzohydroxamic	8.01–11.24	0.04–0.08	8	8.86±0.04 (P), 8.9±0.1 (K), 9.9±0.1 (K, D_2O)	5.0±0.5 5.2±0.5 (D_2O)
VIII	4-Methoxybenzohydroxamic	8.50–11.32	0.04–0.06	7	9.12±0.06(P), 9.1±0.1(K)	5.6±0.5
IX	2-Methoxybenzohydroxamic	8.00–8.74	0.03–0.06	6	8.5±0.1(K)	3.6±0.4
X	Chloroacetohydroxamic	7.82–10.64	0.05–0.1	8	8.4±0.1(K)	2.5±0.1
XI	3-Chlorobenzohydroxamic	10.00–10.52	0.01–0.03	6	8.3 [22]	2.8±0.1
XII	*N*-Hydroxyphthalimide	8.00–9.03	0.05–0.1	8	5.95±0.04 (P)	0.11±0.05[c]
XIII	2-Pyridinecarbohydroxamic	9.43–10.02	0.07–0.1	6	8.39±0.05 (P)	2.8±0.2
XIV	3-Pyridinecarbohydroxamic	8.41–11.01	0.1–0.15	10	8.09±0.04 (P)	1.7±0.1
XV	4-Pyridinecarbohydroxamic	8.82–11.03	0.1–0.15	6	7.67±0.04 (P)	0.94±0.06
XVI	1-Methylpyridine-2-carbohydroxamic	–	–	–	5.73±0.02 (P)	0.86[d]
XVII	1-Methylpyridine-3-carbohydroxamic	–	–	–	6.62±0.03 (P)	2.8[d]
XVIII	1-Methylpyridine-4-carbohydroxamic	–	–	–	6.14±0.02 (P)	1.5[d]
XIX	1-Methyl-3-(2-hydroxyamino-2-oxoethyl)imidazolium chloride	7.5–9.95	0.015–0.06	8	7.88±0.04 (P)	1.40±0.05
XX	3-Aminopropionohydroxamic	7.90–11.60	0.05–0.08	15	9.88±0.05 (P)	8.8±0.8[e]
XXI	3-Aminopropionohydroxamic	7.90–11.60	0.05–0.08	15	8.43±0.06 (P)	3.2±0.2[f]
XXII	Aminoacetohydroxamic	7.82–11.20	0.075–0.1	17	9.32±0.03 (P)	7.6±0.7[e]
XXIII	Aminoacetohydroxamic	7.82–11.20	0.075–0.1	17	7.52±0.06 (P)	0.8±0.09[f]
XXIV	2-Amino-3-hydroxypropionohydroxamic	6.38–12.18	0.05–0.1	19	8.99±0.01 (P)	5.5±0.5[e]
XXV	2-Amino-3-hydroxypropionohydroxamic	6.38–12.18	0.05–0.1	19	6.75±0.05 (P)	0.16±0.01[f]
XXVI	*o*-Hydroxybenzohydroxamic	7.25–11.49	0.025–0.19	15	9.57±0.06 (P), 10.6± 0.1 (K, D_2O)	41±5,[e] 42±4 (D_2O)
XXVII	*o*-Hydroxybenzohydroxamic	7.25–11.49	0.025–0.19	15	7.52±0.02 (P)	0.75±0.08
XXVIII	Malonodihydroxamic	11.29–11.80	0.05	7	9.63±0.06 (P)	22±2[g]
XXIX	Malonodihydroxamic	7.50–8.51	0.05–0.08	7	8.14±0.04 (P), 8.3±0.1 (K)	4.82±0.4[e]
XXX	Oxalodihydroxamic	8.00–10.25	0.007	8	8.50±0.03 (P)	8.4±0.5[g]

Table 1. (Contd.)

Comp. no.	Hydroxamic acid	pH	Concentration of hydroxamic acid, M	N[a]	pK_a[b]	$k_2\times10^2$, l mol^{-1} s^{-1}
XXXI	Oxalodihydroxamic	6.51–7.02	0.005	8	6.70±0.04 (P), 6.8±0.1 (K)	0.26±0.04[e]
XXXII	Imidazole-4,5-dicarbo-hydroxamic	9.41–12.6	0.008–0.03	15	10.8±0.1 (P)	20±2[h]
XXXIII	Imidazole-4,5-dicarbo-hydroxamic	9.41–12.6	0.008–0.03	15	8.8±0.1 (P)	10±1[g]
	Reaction with diethyl 4-nitrophenyl phosphate (**II**)					
IV	Acetohydroxamic	8.4–11.5	0.05–0.4	12	9.36±0.03 (P)	2.3±0.3
VII	Benzohydroxamic	–	–	–	8.75 (P) [7]	1.67 [7]
XV	4-Pyridinecarbohydroxamic	8.82–11.03	0.1–0.15	6	7.67±0.04 (P)	0.26±0.03
XIX	1-Methyl-3-(2-hydroxyamino-2-oxoethyl)imidazolium chloride	9.0–10.0	0.01–0.10	8	7.88±0.04 (P)	0.17±0.02
XXVII	*o*-Hydroxybenzohydroxamic	7.25–11.49	0.025–0.19	15	7.43 (P) [7]	0.12 [7]
	Reaction with 4-nitrophenyl 4-toluenesulfonate (**III**)					
IV	Acetohydroxamic	8.4–10.85	0.05–0.4	15	9.36±0.03 (P)	2.3±0.3
V	Propionohydroxamic	9.02–10.82	0.025–0.2	10	9.36±0.04 (P), 9.4±0.1 (K)	9.7±0.9
VI	Benzohydroxamic	8.01–10.91	0.0125–0.5	8	8.86±0.04 (P), 8.9±0.1 (K)	5.0±0.5
XIII	3-Pyridinecarbohydroxamic	8.41–9.86	0.025–0.2	10	8.09±0.04 (P)	1.7±0.1
XIV	4-Pyridinecarbohydroxamic	8.82–11.03	0.025–0.2	8	7.67±0.04 (P)	0.94±0.06
XIX	1-Methyl-3-(2-hydroxyamino-2-oxoethyl)imidazolium chloride	9.0–10.0	0.01–0.10	8	7.88±0.04 (P)	0.17±0.02
XX	3-Aminopropionohydroxamic	7.90–10.60	0.05–0.08	10	9.88±0.05 (P)	7.0±0.7[e]
XXI	3-Aminopropionohydroxamic	7.90–10.60	0.05–0.08	10	8.43±0.06 (P)	2.7±0.2[f]
XXII	Aminoacetohydroxamic	7.02–11.00	0.075–0.1	16	9.32±0.03 (P)	2.3±0.7[e]
XXIII	Aminoacetohydroxamic	7.02–11.00	0.075–0.1	16	7.52±0.06 (P)	0.14±0.02[f]
XXIV	2-Amino-3-hydroxypropiono-hydroxamic	6.38–10.98	0.05–0.1	12	8.99±0.01 (P)	1.0±0.5[e]
XXV	2-Amino-3-hydroxypropiono-hydroxamic	6.38–10.98	0.05–0.1	12	6.75±0.05 (P)	0.022±0.001[f]
XXXIV	2-Aminopropionohydroxamic	7.90–11.60	0.05–0.08	15	9.35±0.05 (P)	7.12±0.60[e]
XXXV	2-Aminopropionohydroxamic	7.90–11.60	0.05–0.08	15	7.05±0.06 (P)	3.16±0.10[f]
XXXVI	2-Aminopentanohydroxamic	7.95–11.50	0.05–0.08	10	9.53±0.05 (P)	5.0±0.5[e]
XXXVII	2-Aminopentanohydroxamic	7.90–11.50	0.05–0.08	10	7.31±0.04 (P)	3.5±0.3[f]

[a] N is the number of kinetic experiments

[b] Letters in parentheses denote potentiometric (P) and kinetic (K) methods.

[c] Large error in the determination of k_2 results from hydrolysis of *N*-hydroxyphthalimide in alkaline medium with a second-order rate constant k_{OH}- of 1.5±0.1 l mol^{-1} s^{-1}.

[d] Estimated by the Brønsted equation (Table 3).

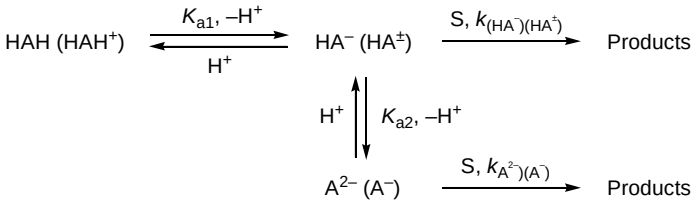
[e] Monoanion.

[f] Zwitterion.

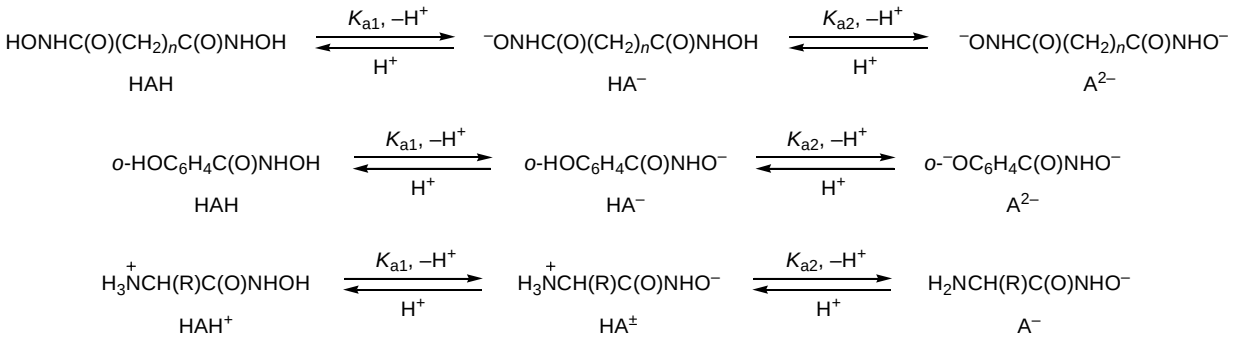
[g] Dianion.

[h] Trianion.

Scheme 2.



Scheme 3.



In order to estimate k_{HA^-} and $k_{A^{2-}}$, as well as k_{HA^+} and k_{A^-}, which characterize the reactivity of each of the above species, we initially determined by potentiometric titration the pK_{a1} and pK_{a2} values. Using Eqs. (5) and (6), we then calculated the corresponding second-order rate constants for compounds **XX**–**XXXI** and **XXXIV**–**XXXVII** (Table 1).

$$k_2'/\alpha_{HA^-} = k_{HA^-} + k_{A^{2-}}\alpha_{A^{2-}}/\alpha_{HA^-}; \quad (5)$$

$$k_2'/\alpha_{HA^+} = k_{HA^+} + k_{A^-}\alpha_{A^-}/\alpha_{HA^+}. \quad (6)$$

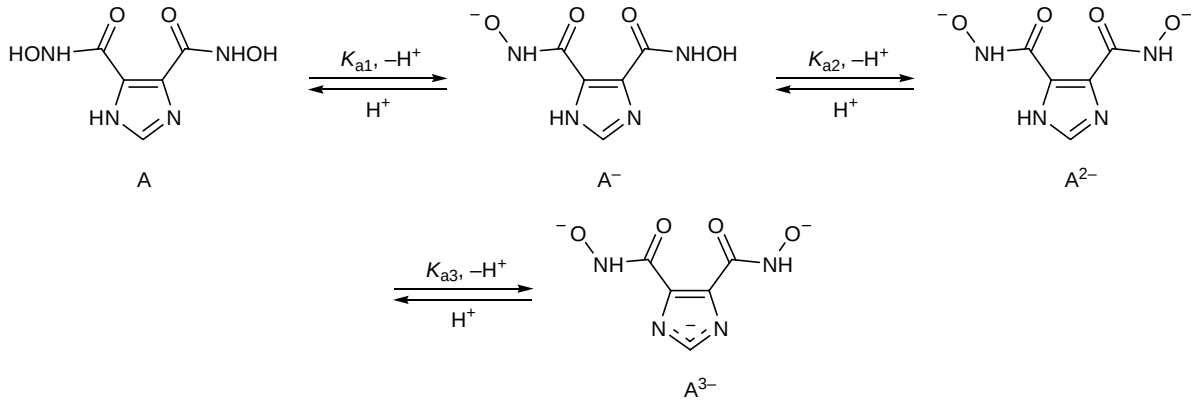
For this purpose, by varying the acidity of the medium we selected such reaction conditions that the contribution of the flux $k_{HA^-}\alpha_{HA^-}$ or $k_{A^{2-}}\alpha_{A^{2-}}$ ($k_{HA^\pm}\alpha_{HA^\pm}$ or $k_{A^-}\alpha_{A^-}$) was no less than 20–50% of the apparent k_2' value.

Imidazole-4,5-dicarbohydroxamic acid differs from the other examined nucleophiles in the kinetic behavior. Ionization of this trihydric acid gives rise to three anionic species: A^-, A^{2-}, and A^{3-} (Scheme 4). Therefore, the apparent rate of substrate consumption should fit kinetic equation (7) which takes into account three parallel pathways:

$$k_H = k_{A^-}\alpha_{A^-}[A]_0 + k_{A^{2-}}\alpha_{A^{2-}}[A]_0 + k_{A^{3-}}\alpha_{A^{3-}}[A]_0. \quad (7)$$

Here, α_{A^-}, $\alpha_{A^{2-}}$, and $\alpha_{A^{3-}}$ are the fractions of anions A^-, A^{2-}, and A^{3-}, respectively. The observed pH dependence of $k_2' = k_H/[A]_0$ for the reaction of imidazole-4,5-dicarbohydroxamic acid with ethyl 4-nitrophenyl ethylphosphonate (**I**) is very consistent with Eq. (7). At pH > 11.67, the rate of disappearance of ester **I** does not depend on the acidity of the medium;

Scheme 4.



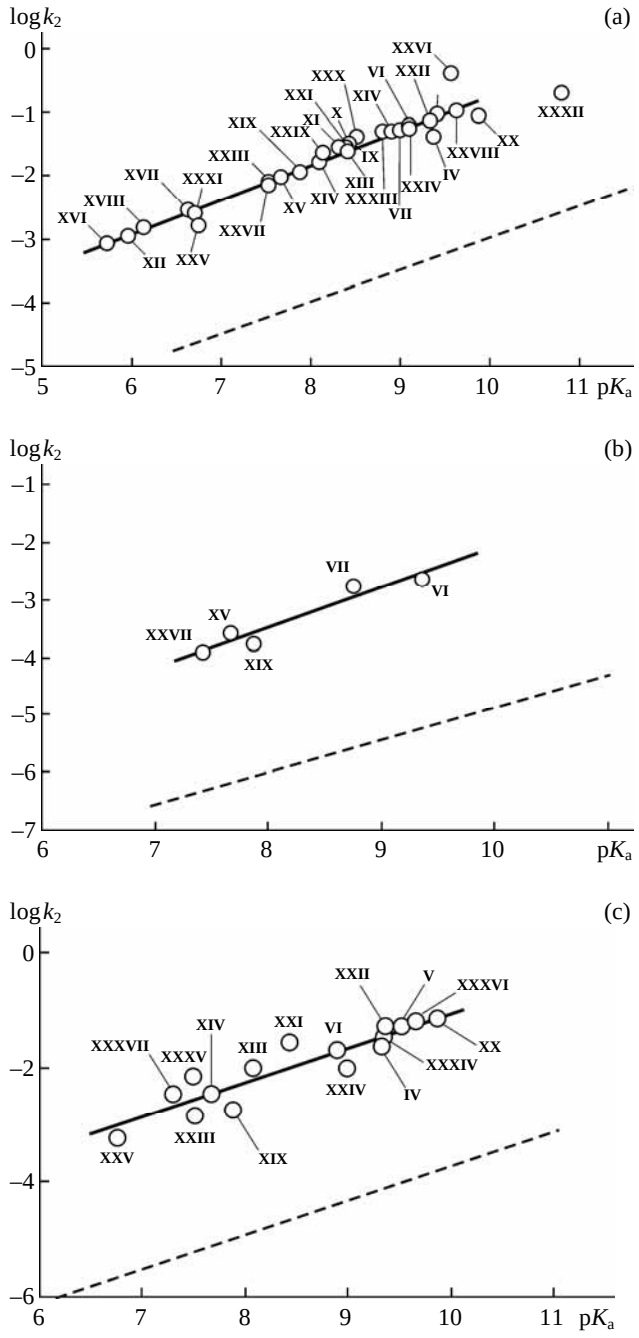


Fig. 2. Brønsted correlations for the reactions of hydroxamate ions (solid lines; for numbering, see Table 1) and aroxide ions (dashed lines) [16] with (a) ethyl 4-nitrophenyl ethylphosphonate (**I**), (b) diethyl 4-nitrophenyl phosphate (**II**), and (c) 4-nitrophenyl 4-toluenesulfonate (**III**); water, μ = 1.0 (KCl), 25°C.

the fraction $\alpha_{A^{3-}}$ tends to unity, and $k_2' = k_H/[A]_0 = k_{A^{3-}} \approx 0.2$ l mol^{-1} s^{-1}. Rise in the acidity to pH 9.41 leads to decrease in k_2' by a factor of 2, while the concentration of trianione A^{3-} (**XXXII**) decreases by more than two orders of magnitude (Table 1). Under these conditions, the rate of the process cannot be maintained by the reactivity of trianion A^{3-} since the contribution of the flux $k_{A^{3-}}\alpha_{A^{3-}}$ to k_2' is less than 10%. On the other hand, there are no grounds to believe that monoanion A^- exhibits an anomalous reactivity toward substrate **I**. Therefore, at pH 9.86, when the fraction of dianion **XXXIII** $\alpha_{A^{2-}}$ tends to unity, $k_2' \approx k_{A^{2-}} \approx 0.1$ l mol^{-1} s^{-1}. We failed to estimate the reactivity of monoanion A^- because of very poor solubility of imidazole-4,5-dihydroxamic acid in neutral and weakly basic media.

Comparison of the Brønsted plots (Fig. 2) for hydroxamate and aroxide ions shows that the former are more reactive than the latter with the same basicity by a factor of 300 to 800. This means that hydroxamate ions are typical α-nucleophiles and that they are comparable in the α-effect with oximate ions [15]. The rate of substrate consumption is linearly related to the basicity of hydroxamate ion, and the straight lines plotted in Figs. 2a and 2c, include points for mono- and dihydroxamic acids and amino hydroxamic acids. Exceptions are the points for dianion **XXVI** and trianion **XXXII**, which deviate by 0.46 and –0.86 log units, respectively, from the straight line. It should be noted that the Brønsted plots (Figs. 2a, 2c) include both zwitterionic species and monoanions of amino hydroxamic acids provided that the basicity constant of the amino group therein is taken as pK_a. However, the reaction center in both zwitterion and monoanion is the hydroxamate oxygen atom rather than nitrogen atom of the amino group [7, 11]. The difference in the reactivity of the zwitterionic species and monoanions of amino hydroxamic acids **XX**–**XXV** and **XXXIV**–**XXXVII** (Table 1), as well as of monoanion **XXVI** and dianion **XXVII**, is so strong that it cannot be interpreted in terms of the presence of an additional nucleophilic center in their molecules: neither glycine nor phenoxide ion was shown to exhibit enhanced reactivity [16]. Taking into account the above stated and a relatively high sensitivity of the reaction rate to the basicity of hydroxamate ions (Table 3), we can conclude that the basicities of the reactive anionic species derived from amino hydroxamic acids are different. The reason is the difference in polar effects of the protonated and nonprotonated amino group in the corresponding ions. As a result, monoanion turns out to be more reactive than the zwitterion. It is impossible to determine how much does the basicity of hydroxamate ion increase upon deprotonation of the zwitterionic species and could it become comparable with the basicity of the amino group. However, we succeeded in solving an analogous problem for

Table 2. Activation parameters of the reactions of benzohydroxamate ion (**VII**) and hydroxide ion (OH^-) with ethyl 4-nitrophenyl ethylphosphonate (**I**); water, μ = 1 (KCl)

Nucleophile	$\Delta G^{\neq}$, kJ/mol			$\Delta H^{\neq}$, kJ/mol	$\Delta S^{\neq}$, e.u.	n[b]
	298 K	308 K	328 K			
VII	80.4 0.050±0.005[a]	81.8 0.090±0.008[a]	84.7 0.22±0.02[a]	38.0±3.8	–34±5	2.0
OH^-	77.9 0.15±0.01[a]	79.5 0.22±0.02[a]	82.6 0.48±0.04[a]	30.5±3.3	–38±5	2.3

[a] k_{A^-}, l mol^{-1} s^{-1}.
[b] Overall reaction order [11].

Table 3. Parameters of the Brønsted equation $\log k_2 = \beta_N pK_a + C$[a] for the reactions of hydroxamate and aroxide (alkoxide) ions with ethyl 4-nitrophenyl ethylphos-phonate (**I**), diethyl 4-nitrophenyl phosphate (**II**), 4-nitrophenyl 4-toluenesulfonate (**III**), and 4-nitrophenyl acetate (**XXXVIII**)

Substrate	Nucleophile	β_N	$-C$	R[b]
I	Hydroxamate ions	0.54±0.02	6.2±0.15	0.968
I	Aroxide (alkoxide) ions	0.50±0.01 [16]	8.00±0.12	0.999
II	Hydroxamate ions	0.70±0.10	8.1±0.9	0.926
II	Aroxide (alkoxide) ions	0.57±0.16 [16]	9.6±2.0	0.853
III	Hydroxamate ions	0.60±0.08	7.2±0.7	0.801
III	Aroxide (alkoxide) ions	0.59±0.02 [16]	9.8±0.2	0.991
XXXVIII	Hydroxamate ions	0.72±0.03 [1]	4.8±0.3	0.982
XXXVIII	Aroxide ions	0.69±0.02 [17]	6.7±0.2	0.989

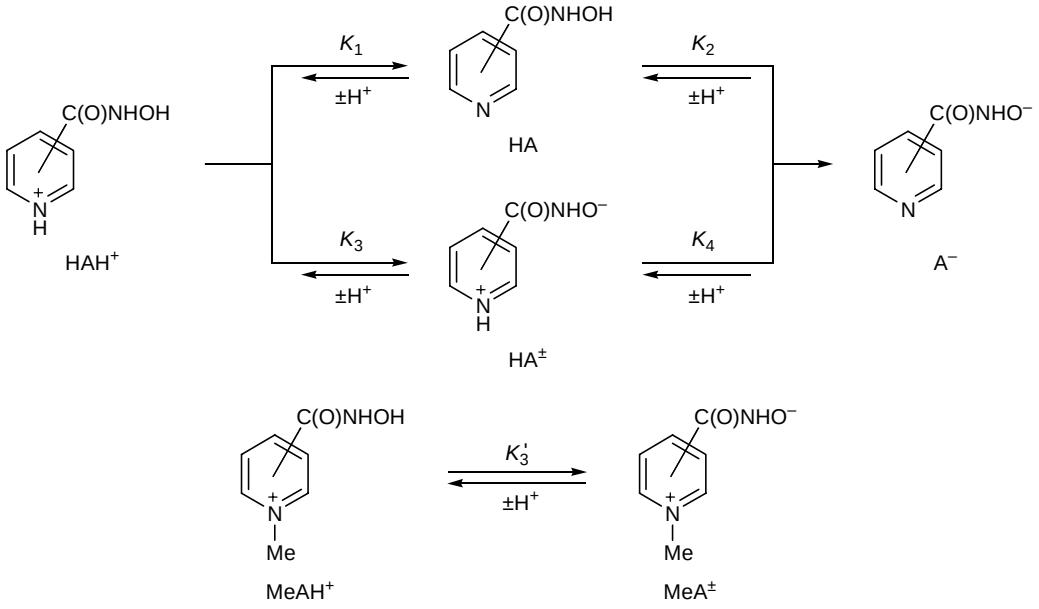
[a] K_a is the acid ionization constant of the nucleophile.
[b] Correlation coefficient.

pyridinecarbohydroxamic acids. Here, anion A^- is formed from protonated species HAH^+ (Scheme 5) through either neutral form AH ($K_1 K_2$) or zwitterion $HA^{\pm}$ (path $K_3 K_4$).

Insofar as the change in the standard Gibbs energy of the system does not depend on the transformation pathway ($HAH^+ \rightarrow A^-$; $pK_1 + pK_2 = pK_3 + pK_4$), and K_3 may be assumed equal to K'_3 due to structural similarity of HAH^+ and $MeAH^+$, we believe that $K_4 = K_1 K_2/K'_3$. Table 4 contains the values of K_4, which were determined from the experimental values of K_1, K_2, and K'_3, and $k_{HA^{\pm}}$ values (l mol^{-1} s^{-1}) estimated by the Brønsted equation. Comparison of the second-order rate constants for A^- and $HA^{\pm}$ with pK_2 and pK_3 shows that the reactivity does increase upon deprotonation of $HA^{\pm}$ and that the reason is the greater basicity of A^- as compared to $HA^{\pm}$.

However, a much more important problem is not to compare the reactivity and basicity of reactive species A^- and $HA^{\pm}$, but to elucidate whether the basicity of the hydroxamate moiety in going from A^- to $HA^{\pm}$ can change so strongly that it will become comparable to the basicity of the pyridinium nitrogen atom in the anion. Taking into account mutual effect of functional groups in pyridinecarbohydroxamic acid molecules, this problem is in fact the reverse to that which should be solved for amino hydroxamic acids. Although protonation of the nitrogen atom in pyridine does not reduce the basicity of the hydroxamate group, in no case pK_3 is equal to pK_4. Usually, pK_3 is gerater than pK_4, and the difference is approximately equal to a pK_a unit. Therefore, the basicity of the hydroxamate group cannot be compared with the basicity of the amino group in the monoanion derived from amino hydroxamic acid. Insofar as the efficiency of transmission of electronic effects in aliphatic amino hydroxamic acids is lower than in pyridinecarbohydroxamic acids, it becomes perfectly clear that the basicity of hydroxamate ion will always be lesser than the basicity of the amino group in amino hydroxamic acid monoanion. In other words, the reactivity of monoanions does not conform to the corresponding pK_{a1} values, and the use of the latter for such purpose is hardly justified.

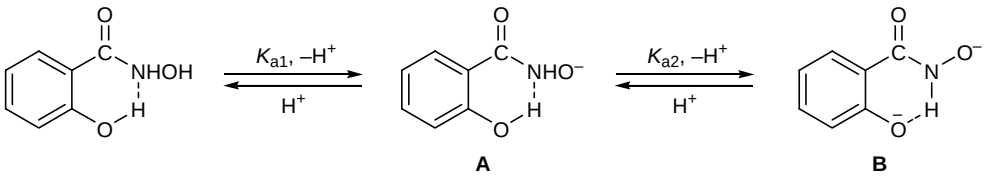
Scheme 5.



An additional support to the above stated is given by the data for the dianion derived from *o*-hydroxybenzohydroxamic acid (**XXVI**). Dianion **XXVI** would react with substrate **I** according to the Brønsted equation (Table 3) if the basicity of the hydroxamate moiety were characterized by a pK_{a2} value of 10.4, which is greater by almost an order of magnitude than the observed value (pK_{a2} 9.57). Therefore, the points for amino hydroxamic acid monoanions, as well as the point for dianion **XXVI**, should deviate considerably from the Brønsted plot (toward more positive values), and their higher reactivity (relative to the zwitterions) should be attributed to the catalytic or anchimeric assistance by the amino group to attack by hydroxamate ion on the electron-deficient centers in substrates **I** and **III**. Presumably, an analogous assistance is observed for phenoxide ion in the reaction of dianion **XXVI** with ethyl 4-nitrophenyl ethylphosphonate (**I**).

An unusual behavior of dianion **XXVI** in the reaction with substrate **I** led us to postulate a specific role of the *ortho*-hydroxy group in the nucleophile. A reasonable explanation of the experimental data is based on the assumption that *o*-hydroxybenzohydroxamic acid in aqueous solution gives rise to intramolecular H-complexes **A** and **B** (Scheme 6) where the unionized hydroxy group acts as proton donor (complex **A**) and the deprotonated hydroxy group acts as proton acceptor (**B**). The formation of complex **A** should increase the acidity of the neutral species due to stabilization of the corresponding monoanion via intramolecular hydrogen bonding. In fact, in going from 2-methoxybenzohydroxamic acid (pK_a 11.09 [18]) to *o*-hydroxybenzohydroxamic acid, the acidity of the hydroxamate moiety increases by more than an order of magnitude, though the methoxy and hydroxy groups are characterized by similar polar effects. On the other hand, the pK_a values of 4-hydroxy- and 4-methoxybenzohydroxamic acids are similar (as might be expected; pK_a ≈ 9.1 [8, 18], Table 1). Even 2-nitrobenzohydroxamic acid (pK_a 8.87 [18]) is weaker than *o*-hydroxybenzohydroxamic acid [8]. Therefore, *o*-hydroxybenzohydroxamic acid shows an anomalously high acidity, whereas its conjugate base is characterized by an anomalously low basicity. Taking into account that the point for monoanion **XXVII** conforms to the Brønsted relation (Fig. 2a), the intramolecular

Scheme 6.



hydrogen bond equally stabilizes both initial and transition state of the reaction.

The formation of H-complex **A** not only affects the K_{a1} value but also reduces the acidity of the phenolic hydroxy group in the monoanion. Moreover, energetically unfavorable Coulomb interactions between similarly charged centers in dianion **B** could give rise to anomalous variations in K_{a2}, which are actually observed for *ortho*-substituted phenols (the pK_{a2} values for 4-hydroxybenzoic acid, 2-hydroxybenzoic acid, hydroquinone, and pyrocatechol are 9.46, 13.82, 9.96, and 12.8, respectively [19]). Regardless of the substituent nature, the acidity of the phenolic hydroxy group decreases by 2–3 orders of magnitude, as compared to phenol. On the other hand, an appreciable increase of the acidity of the hydroxy group in monoanion **XXVII** is possible only when some interactions in dianion **XXVI** compensate mostly unfavorable electrostatic effects. In particular, such interactions include the intramolecular hydrogen bond in complex **B** (unlike complex **A**, the ionized hydroxy group in **B** acts as proton acceptor rather than donor).

One more evidence in favor of formation of complexes like **B** is the different reactivities of monoanion **XXVII** and dianion **XXVI**. The latter reacts with substrate **I** at a rate which exceeds the rate of the reaction with monoanion **XXVII** by a factor of ~50; presumably, the reason is that the reactive species is just complex **B**. The degree of proton transfer in complex **B** is not obvious. Therefore, such complexes can act as true nucleophilic reagents (path *a*) or their nucleophilic attack on a substrate is catalyzed by phenoxide ion (general base catalysis; path *b*). In the first case (*a*), proton transfer in complex **B** is complete in the initial state. In the second case (*b*), only partial proton transfer in complex **B** occurs in the initial state (or it does not occur at all), while it is complete only in the transition state. Both these mechanisms are kinetically indistinguishable. Nevertheless, we give preference to path *a* since it is more consistent with the deuterium isotope effect of the solvent, which is equal to unity [the $k_{A^-}(H_2O)/k_{A^-}(D_2O)$ values for nucleophiles **VII** and **XXVI** and ion OD^- are 0.96, 1.03, and 1.04, respectively], and with the effect of complex formation on the acid–base properties of the dianion. In keeping with path *b*, the deuterium isotope effect should be considerably greater than unity [20], and partial proton transfer in complex **B** in the initial state is unlikely to ensure sufficient stabilization of dianion **XXVI**.

Presumably, the kinetic behavior of amino hydroxamic acids, in particular the higher reactivity of their

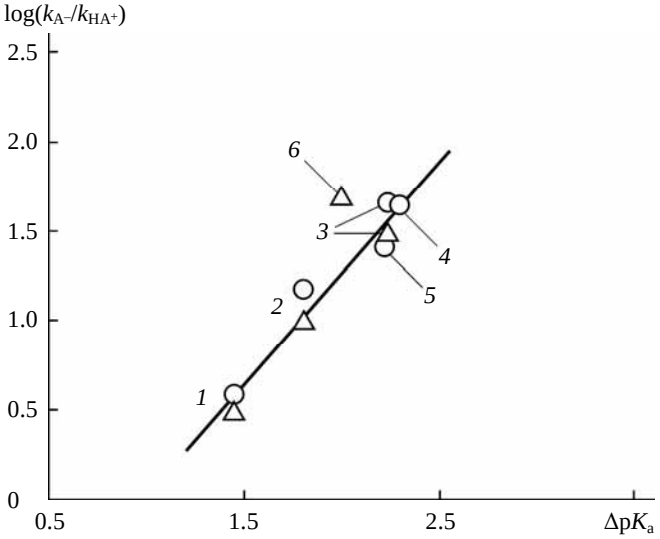


Fig. 3. Plot of $\log(k_{A^-}/k_{HA^+})$ versus ΔpK_a for the reactions of (*1*) 3-aminopropionohydroxamic acid (**XX**, **XXI**), (*2*) aminoacetohydroxamic acid (**XXII**, **XXIII**), (*3*) 2-amino-hydroxypropionohydroxamic acid (**XXIV**, **XXV**), (*4*) 2-aminopropionohydroxamic acid (**XXXIV**, **XXXV**), (*5*) 2-aminopentanohydroxamic acid (**XXXVI**, **XXXVII**), and (*6*) *o*-hydroxybenzohydroxamic acid [**XXVI**, **XXVII**; $\log(k_{A^{2-}}/k_{HA^-})$] with ethyl 4-nitrophenyl ethylphosphonate (**I**) (light triangles) and 4-nitrophenyl 4-toluenesulfonate (**III**) (light circles); water, μ = 1.0 (KCl), 25°C.

monoanions as compared to zwitterionic species, is also determined by the fact that the monoanion reacts with substrates **I** and **III** according to path *a*. Furthermore, relatively basic O^- and NH_2 groups (which are Brønsted bases) act as general base catalysts and exert an additional stabilizing effect on the transition state, thus favoring increase in the rate of substrate consumption in going from zwitterion to monoanion of amino hydroxamic acid and from monoanion to dianion of *o*-hydroxybenzohydroxamic acid. The catalytic effect of these groups is described by the ratio k_{A^-}/k_{HA^+} ($k_{A^{2-}}/k_{HA^-}$ for *o*-hydroxybenzohydroxamic acid), and it depends on a number of factors [20]. However, the main factor is that originating from acid–base properties of the conjugate acid–base couple, i.e., from its ability to form complexes like **B**. For example, the increase in the reaction rate with phosphonate **I** is maximal for nucleophiles **XXIV** and **XXV** (ΔpK_a = 2.24) and minimal for compounds **XX** and **XXI** (ΔpK_a = 1.45), i.e., the catalytic effect actually depends on the ability of the acid–base couple to afford H-complexes. When ΔpK_a tends to unity, $\log(k_{A^-}/k_{HA^+})$ tends to zero; in other words, the reactivities of these species approach each other so that they cannot be distinguished by kinetic methods. The catalytic effect

of the amino group is linearly related to $\Delta pK_a = pK_{a2} - pK_{a1}$:

$$\log(k_{A^-}/k_{HA^+}) = (-1.23 \pm 0.26) + (1.24 \pm 0.13)\Delta pK_a. \quad (8)$$

Undoubtedly, the relation between $\log(k_i/k_j)$ and ΔpK_a as a measure of the efficiency of catalytic assistance by additional acid–base centers in hydroxamic acid molecules is empirical and is a particular case of the widely known linear Gibbs energy relationship [21]. Therefore, such correlations for structurally dissimilar nucleophilic reagents should be characterized by different slopes and different ΔpK_a values at which $\log(k_i/k_j) > 0$. Probably, this is the reason why the point for *o*-hydroxybenzohydroxamic acid does not fit the general correlation for amino hydroxamic acids shown in Fig. 3. Nevertheless, the significance of such correlations is obvious. They make it possible not only to estimate the limits of the catalytic effect of general base (or general acid) centers in the α-nucleophile molecule but also to select the most efficient nucleophile by relating the catalytic effect to ΔpK_a.

An additional information on the effect of the *ortho*-hydroxy group in *o*-hydroxybenzohydroxamic acid can be obtained by studying the formation of the corresponding boric acid esters and their reactivity. It is known that borates effectively catalyze both intramolecular acyl group transfer processes and analogous intermolecular processes where substrate and reagent should approach each other, e.g., as in the hydroxymethylation of phenol [20, 22]. We believed that these data will allow us to make a more reasonable choice between possible mechanisms (*a* and *b*) for the reaction of ethyl 4-nitrophenyl ethylphosphonate **(I)** with *o*-hydroxybenzohydroxamic acid.

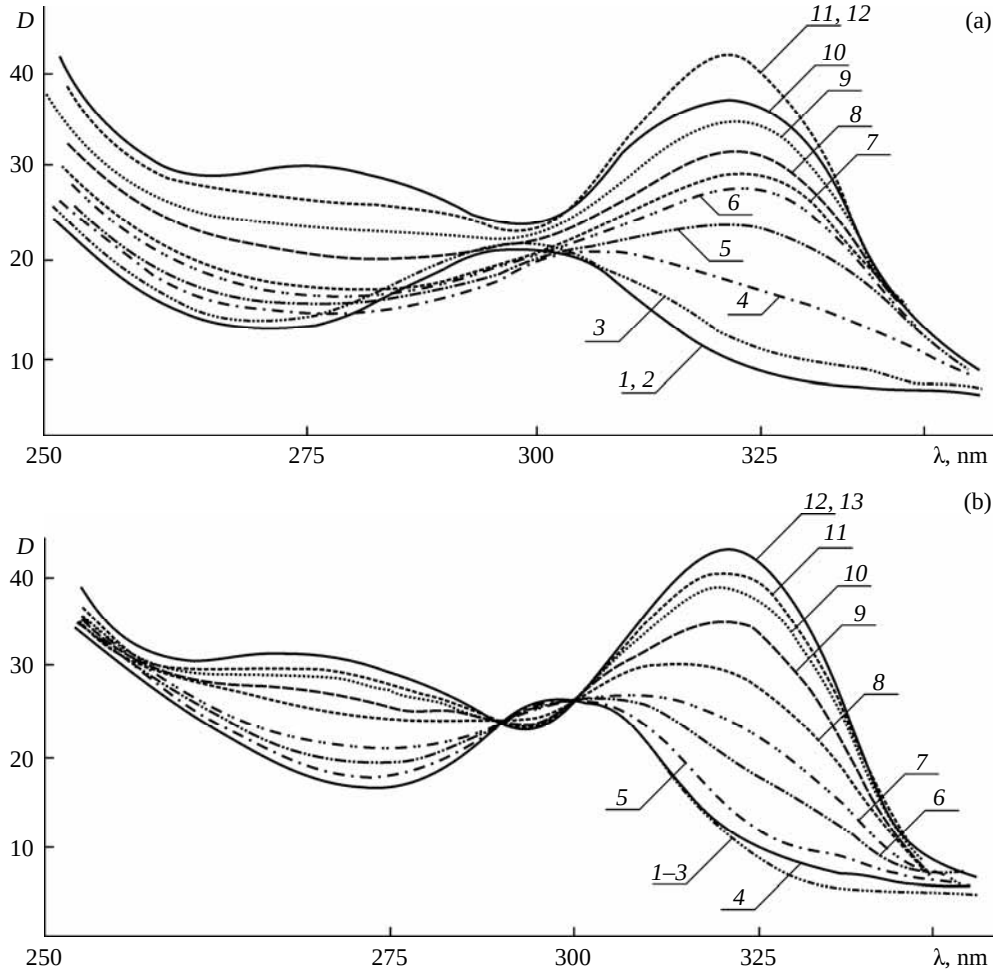


Fig. 4. UV spectra of *o*-hydroxybenzohydroxamic acid, $[HAH]_0 = 4\times10^{-5}$ M; water, μ = 1.0 (KCl), 25°C: (a) in the absence of H_3BO_3: (*1*) pH 5.00, (*2*) 6.00, (*3*) 7.00, (*4*) 7.45, (*5*) 8.05, (*6*) 8.60, (*7*) 9.00, (*8*) 9.30, (*9*) 9.60, (*10*) 10.00, (*11*) 11.00, (*12*) 12.00; (b) in the presence of H_3BO_3, $[H_3BO_3]_0$ = 0.2 M: (*1*) pH 6.00, (*2*) 7.20, (*3*) 8.50, (*4*) 10.00, (*5*) 10.25, (*6*) 10.55, (*7*) 10.75, (*8*) 11.00, (*9*) 11.30, (*10*) 11.55, (*11*) 11.75, (*12*) 12.00, (*13*) 12.50.

Figure 4 shows the UV spectra of *o*-hydroxybenzohydroxamic acid at different acidities of the medium in the presence of H_3BO_3 and in the absence of it. These data indicate that *o*-hydroxybenzohydroxamic acid with boric acid forms esters whose stability depends on the acidity of the medium. These esters are not hydrolyzed with water up to pH ~10.0, and their UV spectra coincide with the spectrum of monoanion **XXVII**, although at that pH value in the absence of H_3BO_3 the monoanion is almost completely converted into dianion **XXVI**. At greater pH values, the esters undergo hydrolysis, and absorption bands belonging to phenoxide ion appear in the spectrum. However, even at pH ~11.0, the system contains boric acid esters together with the dianion.

The formation of esters from boric and *o*-hydroxybenzohydroxamic acids affects quantitative kinetic parameters of the reaction with substrate **I**. The rate of substrate disappearance increases as $[H_3BO_3]_0$ rises, and it tends to some limiting k_2' value, which no longer depends on $[H_3BO_3]_0$. This is the result of transformation of *o*-hydroxybenzohydroxamic acids into the corresponding boric acid esters (Fig. 5). At $[H_3BO_3]_0$ = 0.1 M, the rate of substrate consumption decreases by a factor of ~50 relative to the rate of the process in the absence of H_3BO_3. Here, only anionic forms of the boric acid esters react with phosphonate **I**. An analogous conclusion follows from analysis of the kinetic data given in Table 5, which illustrate the effect of pH on the rate of the reaction of substrate **I** with *o*-hydroxybenzohydroxamic acid in buffer solution with $[H_3BO_3]_0$ = 0.1 M. At pH = 9.20, the reactive species are esters derived from *o*-hydroxybenzohydroxamic and boric acids (the inhibition is characterized by a factor of 50), while at pH > 11.0 only *o*-hydroxybenzohydroxamic acid dianion reacts with phosphonate **I**. These data are fully consistent with the results of UV spectroscopic study.

o-(Hydroxycarbamoyl)phenyl borates in aqueous solution can exist as monoanions **XXXIX** and dianions **XL** (Scheme 7). We have no precise acid ionization

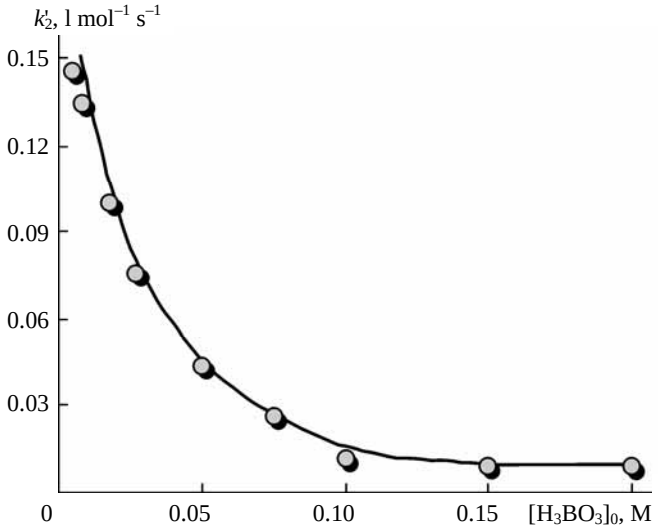
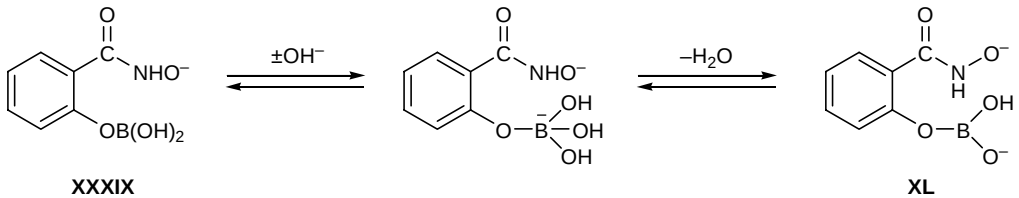


Fig. 5. Plot of the rate constants k_2' for the reaction of *o*-hydroxybenzohydroxamic acid ($[HAH]_0$ = 0.05 M) with ethyl 4-nitrophenyl ethylphosphonate (**I**) versus concentration of boric acid; pH 9.43, water, μ = 1.0 (KCl), 25°C.

constants which could allow us to estimate the concentration of each of the above species. However, from the data of [22] it follows that both the corresponding monoanion and dianion should exist in solution at pH ~9–10. Therefore, the reactivities of the monoanion and dianion derived from *o*-(hydroxycarbamoyl)phenyl borates are similar. Presumably, the lack of anomalous kinetic behavior of dianion **XL** indicates that the formation of intramolecular hydrogen bond like in complex **B** requires strict spatial compatibility of the functional groups involved therein, e.g., as in the dianion derived from *o*-hydroxybenzohydroxamic acid or monoanions derived from aliphatic amino hydroxamic acids. On the other hand, steric requirements imposed on the proton donor and proton acceptor in general base catalysis are not so rigorous [20], and the reactions between the examined electron-deficient substrates with *o*-hydroxybenzohydroxamic acid dianion and amino hydroxamic acid monoanions may be presumed to follow path *a* where the reactive species are complexes of type **B** in which proton transfer occurs in the initial state.

Scheme 7.



XXXIX **XL**

Table 4. Reactivities of zwitterionic forms of pyridinecarbohydroxamic acids ($k_{HA^{\pm}}$, l mol^{-1} s^{-1}) toward ethyl 4-nitrophenyl ethylphosphonate (**I**) and pK_1, pK_2, pK_3, and pK_4 values characterizing the acidity of monocations (HAH^+), neutral species (HA), and zwitterionic forms ($HA^{\pm}$) of pyridinecarbohydroxamic acids; water, μ = 1.0 (KCl), 25°C

Nucleophile	$k_{HA^{\pm}} \times 10^3$ [a]	pK_1	pK_2	pK_3	pK_4
XIII	0.86	2.40 ± 0.06 (P)	8.39 ± 0.05 (P)	5.73 ± 0.02 (P)	5.06
XIV	1.5	3.41 ± 0.04 (P)	8.09 ± 0.04 (P)	6.62 ± 0.03 (P)	4.88
XV	2.8	3.61 ± 0.04 (P)	7.67 ± 0.04 (P)	6.14 ± 0.02 (P)	5.14

[a] Estimated by the Brønsted equation (Table 3).

EXPERIMENTAL

Ethyl 4-nitrophenyl ethylphosphonate (**I**), diethyl 4-nitrophenyl phosphate (**II**), and 4-nitrophenyl 4-toluenesulfonate (**III**) were prepared by acylation of *p*-nitrophenol according to the procedure described in [16]. Hydroxamic acids were synthesized (except for *o*-hydroxybenzohydroxamic acid which was a commercial product) and purified by known methods [7–9, 12]. Solutions of phthalohydroxamic acid were obtained by hydrolysis of *N*-hydroxyphthalimide and were immediately used in the kinetic measurements.

The inorganic reagents of chemically pure or ultrapure grade, as well as heavy water (D_2O) and solutions of DCl in D_2O containing 99.8% of the deuterated substance, were used without additional purification; sodium and potassium deuteroxides were prepared as described in [23]. Benzohydroxamic and *o*-hydroxybenzohydroxamic acids used in the study of the kinetic isotope effect of solvent were recrystallized 2–3 times from D_2O and dried over P_2O_5 under nitrogen.

Table 5. Dependence of the kinetic parameters on pH for the reaction of *o*-hydroxybenzohydroxamic acid (**XXVI**) ($[HAH]_0$ = 0.05 M) with ethyl 4-nitrophenyl ethylphosphonate (**I**) in the presence of 0.1 mol/l of H_3BO_3; water, μ = 1.0 (KCl), 25°C

pH	k'_{ap}, s^{-1}	k'_2, l mol^{-1} s^{-1}	$(k'_{HA^-} + k'_{A^{2-}})/k'_2$ [a]
11.00	1.33×10^{-2}	2.63×10^{-1}	1.5
10.73	9.83×10^{-3}	1.95×10^{-1}	1.97
10.49	6.42×10^{-3}	1.27×10^{-1}	2.89
10.29	3.73×10^{-3}	7.40×10^{-2}	4.68
9.97	1.20×10^{-3}	2.37×10^{-2}	12.5
9.74	5.17×10^{-4}	1.02×10^{-2}	24.3
9.43	1.98×10^{-4}	3.88×10^{-3}	45.5
9.20	1.25×10^{-4}	2.45×10^{-3}	52.4

[a] Inhibition as a result of addition of boric acid, $[H_3BO_3]_0$ = 0.1 M; in the absence of H_3BO_3, the values of k'_{HA^-} and $k'_{A^{2-}}$ at specified pH values were calculated from the data in Table 1.

Kinetic measurements. All solutions were prepared from doubly distilled water just before each series of kinetic measurments. The analytical concentrations of hydroxamic acids (HA) were selected in such a way that reactant solutions be simultaneously buffer solutions; the required ionic strength (μ = 1.0) was maintained by addition of KCl (1 M).

The reactions of nucleophiles with substrates **I**–**III** in water at different pH values resulted in formation of *p*-nitrophenoxide ion (or *p*-nitrophenol) as one of the products. Therefore, depending on the acidity of the medium, the progress of reactions was monitored by the accumulation of *p*-nitrophenoxide ion (λ_{max} = 400–410 nm) or *p*-nitrophenol (λ_{max} = 320 nm). In all cases, the analytical substrate concentration was much lower than the analytical nucleophile concentration.

A typical kinetic experiment was performed as follows. A quartz cell containing 2.5–3 ml of a solution of hydroxamic acid with a specified pH value was adjusted to a required temperature. A 0.02–0.04-ml portion of a substrate solution (c = 0.01 M) in dioxane or ethanol was quickly added, and the mixture was quickly stirred. The moment of reactant mixing was taken as the reaction start. The acidity of the medium was determined before and after each kinetic experiment. If the difference in the initial and final pH values exceeded 0.05 pH unit, the data were discarded. The apparent pseudofirst-order rate constants k'_{ap} were determined from the change in the absorption A with time:

$$\ln(A_\infty - A_\tau) = \ln (A_\infty - A_0) - k'_{ap}\tau. \quad (9)$$

Here, A_0, A_τ, and A_∞ are, respectively, the absorptions at $\tau = 0$, $\tau = \tau_i$, and by the end of the process. The calculated pseudofirst-order rate constants for consumption of substrates **I**–**III** were corrected for the contribution of alkaline hydrolysis $k_{ap} = k'_{ap} - k_{OH^-} a_{OH^-}$ (where k_{OH^-}, l mol^{-1} s^{-1}, characterizes the nucleophilicity of OH^- ion), and the reactivity of hydroxamate ions was estimated from the k_{ap} values (s^{-1}).

In the determination of the solvent kinetic isotope effect, pD values were calculated from the experimental pH values and temperature (T, °C) [23].

Determination of ionization constants of hydroxamic acids. The ionization constants of hydroxamic acids were determined at a ionic strength μ of 1.0 using potentiometric [19] and kinetic techniques [20, 24]. The mixed ionization constants were calculated by the Henderson–Hasselbalch equation [19]. The titration was performed with 0.1 M solutions of HCl (DCl) and KOH (KOD). Some of the examined compounds (Table 1) possess two groups capable of being ionized. Compounds **XXVI**–**XXXI** in which both ionogenic groups are acidic were titrated in succession with 2 equiv of KOH. In all cases, while determining pK_a values of ionogenic groups in polyelectrolytes, the validity of the results was checked by reverse titration. The kinetic technique is based on the relation between the reaction rate and pH. Here, it is assumed that the error in the determination of mixed ionization constants does not exceed 0.1 log unit.

Determination of thermodynamic activation parameters. The activation parameters for the reactions of hydroxide and benzhydroxamate ions with phosphonate **I** were calculated in two steps. Initially, the Gibbs activation energies $\Delta G^{\neq}$ (kJ/mol), were estimated from the k_{A^-} values (l mol^{-1} s^{-1}) measured at 298, 308, and 328 K using the formula $\Delta G^{\neq} = R\,T \times \ln[(k_B\,T)/(k_{A^-}\,h)]$, where k_B (kJ/K) is the Boltzmann constant, h (kJ s) is the Planck constant, R (kJ × mol^{-1}K^{-1}) is the universal gas constant, and T (K) is the temperature. In the second step, assuming that k_{A^-} values characterize the reaction rate at a unit concentration (1 M) of hydroxide and benzohydroxamate ion, substrate, and the corresponding transition state, we calculated the enthalpy of activation $\Delta H^{\neq}$ (kJ/mol) and the entropy of activation $\Delta S^{\neq}$ (entropy units) by the formula $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$.

The accuracy in the determination of pK_a values and rate constants was estimated by the microstatistics technique. Linear relations were processed by the least-squares procedure.

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