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O-Nucleophilic Features of Amidoximes In Acyl Group Transfer Reactions

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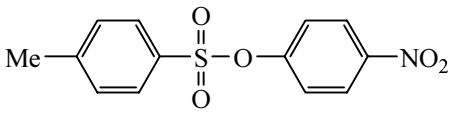
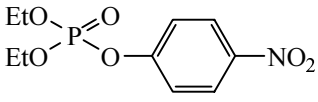
Abstract—Analysis of kinetic behavior of isomeric *Z*-amidoximes and their *Z*-ions in reactions with 4-nitrophenyl-4-toluenesulfonate, diethylphosphate, and diethylphosphonate was performed in the framework of Brønsted relationship. The reactivity of amidoximate anions with respect to the mentioned substrates is comparable to that of typical α-nucleophiles, oximate ions. The α-effect decreased with the growing basicity of amidoximate ions, and for compounds with $pK_a > 12.0$ it was totally lacking. The high nucleophilic activity of neutral amidoximes and their anionic forms was ascribed to the cyclic structure of the transition state involving two kinds of assistance: general acidic, and basic catalysis. A unique feature of amidoximes as α-nucleophiles consists in their ability to perform efficient cleavage of ecotoxic substrates in a wide pH range, from basic to acid media.

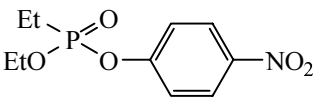
Hydroxylamine oximes, amidoximes, and hydroxamic acids [1–9] occupy a special place in the series of typical α-nucleophiles for just among them efficient reactivators of cholinesterase has been found that are still required and whose preparation is attempted up till now [2, 3, 9]. The main attention nowadays in this field of research is attracted by the nature of the factors providing the abnormally high reactivity of α-nucleophiles [2–8]. Nonetheless, the O-nucleophilic characteristics of amidoximes in acyl transfer reactions were not subjected to detailed kinetic investigation. Amidoximes are oxime derivatives, but both their neutral and anionic form operate as acyl group acceptor [10–14]. The kinetic behavior of amidoximes resembles in this respect rather that of hydroxylamine which also is capable to react with an acylating agent in neutral and anionic form [15, 16] and is a unique α-nucleophile ensuring high reaction rates in basic, neutral, and acidic media. The hydroxylamine anion is a "leader" with respect to the O-nucleophilic reactivity in the series of known classes of the α-nucleophiles [15]. Aiming at development of systems for cleavage of ecotoxic substrates [9, 17] we measured in this study the reaction rates between the neutral and anionic forms of amidoximes and 4-nitrophenyl esters of 4-toluenesulfonic (**I**), diethylphosphoric (**II**), and diethylphosphonic (**III**) acids,* estimated the α-effect value, revealed the factors controlling the O-nucleophilic features of the amidoximes, and the place these α-nucleophiles occupy among the known supernucleophiles.



I



II

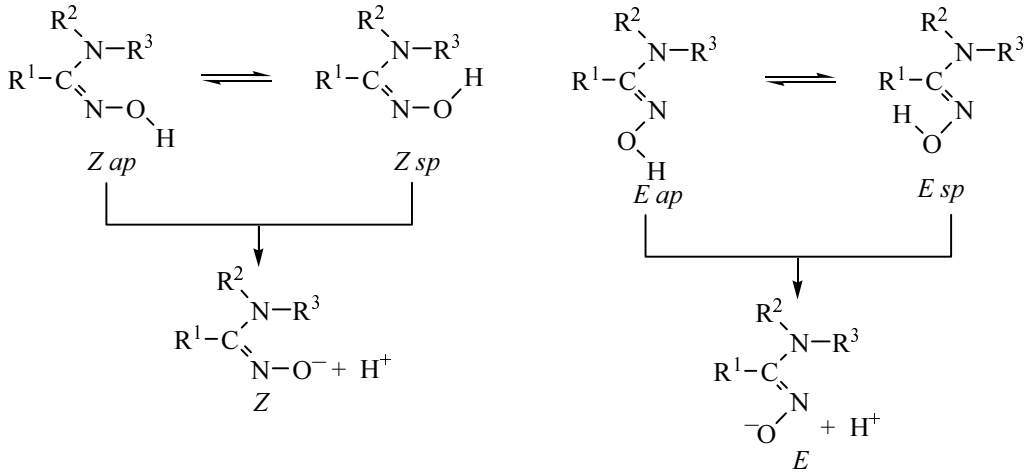


III

Isomerism and acid-base properties of amidoximes. The reactivity of typical α-nucleophiles, oximate ions, depends on the definite configuration (*Z*- or *E*-) that they take in the reaction with the acylating agents. As an example a Brønsted relationship may be cited for reactions of substituted benzaldoximate ions with 4-nitrophenyl acetate (**IV**) and thioacetate: the *E*-isomers of

* Esters **II** and **III** known under the names "paraoxone" and "armin" are typical cholinesterase inhibitors, belong to the class of stable ecotoxic substrates, and are only a little less toxic than sarin [17].

Scheme 1.

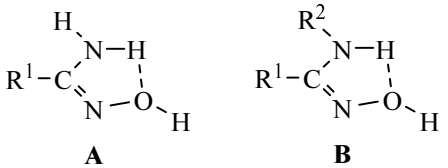


the oximate ions react with these esters 10–100 times faster than the *Z*-isomers [18]. Therefore it is interesting to establish to what extent the *Z*,*E*-isomerism of amidoximes affects their reactivity and whether this effect depends on the form (anionic or neutral) of the nucleophile.

Neutral amidoximes exist in solution and in the solid state in *Z*- and *E*-configurations, and each of them can be present in *ap*- and *sp*-conformations [19]. At ionization of the neutral form the problem of the conformational isomers is removed for here only *Z*- and *E*-configurational isomers of amidoxime ions exist. The stability of *E*- and *Z*-isomers is governed mainly by the steric effects of substituents R^2 and R^3 (Scheme 1), and also by the possibility of formation of intra- and intermolecular hydrogen bonds [20]. Usually for the N,N-dialkyl-substituted amidoximes the *E*-isomer is thermodynamically more stable whereas for the N-monosubstituted and unsubstituted amidoxime the *Z*-isomer proved to be more stable, an intramolecular hydrogen bond favoring formation of A and B complexes significantly contributing thereto (Scheme 2) [21–23].

The amidoxime group compound where R^2 and/or R^3 = H having *Z ap*-configuration is really planar and stabilized by an intramolecular hydrogen bond. This

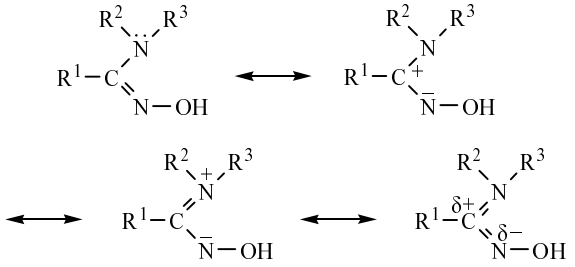
Scheme 2.



structure is proved for unsubstituted amidoximes [21–23] and is suggested for N-monoalkyl-substituted amidoximes with R^3 = Me [20].

Analysis of crystallographic data [20, 22, 24] and calculation of bond orders (*n*) for C–N, C=N bond in the amidoxime fragment (Table 1) indicated that relatively strong resonance interactions operate in the *Z*- and *E*-isomers (Scheme 3).

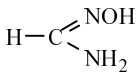
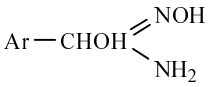
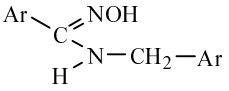
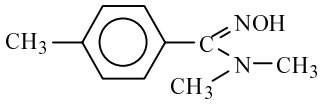
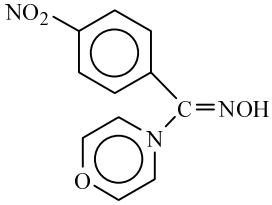
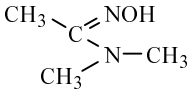
Scheme 3.



The resonance interactions in the amidoxime fragment result in a decrease in the double bond character between the nitrogen atom of the imino group and the carbon atom and in increase in the double bond character between the carbon and nitrogen of the amino group. However the electrons delocalization is more significant in the *Z*-isomer than in the *E*-form of N,N-disubstituted amidoximes; it means that the C–N bond in the unsubstituted amidoximes has a more pronounced double bond character than in the N,N-disubstituted amidoximes [20]. Similar pattern is also observed in the N-monosubstituted amidoximes (Table 1) [26].

The mentioned character of electronic interactions in the amidine fragment of amidoximes endows with

Table 1. Interatomic distances (E)[a] and bond orders (n)[b] in amidine fragment of amidoximes

Compd. no. =	Amidoxime =	C–N =	n =	C=N =	n	~~N~~–O	=
V	= 	1.334 =	1.52 =	1.288 =	1.82 =	1.415 =	
VI	= 	1.354 =	1.43 =	1.284 =	1.85 =	1.435 =	
VII	= 	1.367 =	1.37 =	1.272 =	1.94 =	1.438 =	
VIII	= 	1.382 =	1.30 =	1.287 =	1.82 =	1.424 =	
IX	= 	1.394 =	1.30 =	1.278 =	1.89 =	1.418 =	
X	= 	1.367 =	1.37 =	1.284 =	1.85 =	1.430 =	

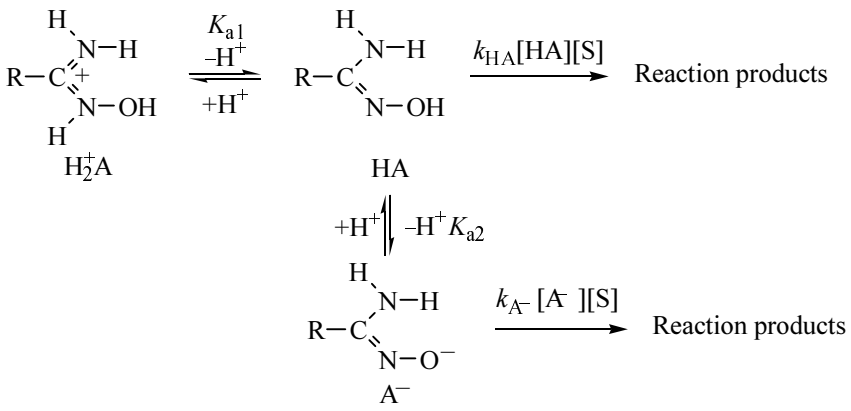
[a] Crystallographic data for amidoximes are reported in [20, 22, 24].

[b] Bond orders are calculated by Pauling equation $D_n = D_1 - [1.84(n-1)]/(0.84n + 0.16)(D_1 - D_2)$ where D_n is the experimentally measured bond length; D_1 and D_2 are the lengths of an ordinary and a double bonds; D_1 1.475 and D_2 1.265 A [25].

increased electron density the nitrogen of imino group and this in its turn facilitates the protonation of this site in the neutral amidoxime molecule. Hence the basic-acidic properties of the amidoximes are characterized by two acid ionization constants K_{a1} and K_{a2} mol l^{-1} (Scheme 4) where K_{a1} corresponds to the acidity of the cation form $H^+{}_2A$ and K_{a2} to that of the neutral molecule HA of amidoximes. This statement is supported by the character of the changes in pK_a values in the isolog series of aminomethylenenitriles and aminomethyleneamidoximes [27].

Kinetic relationships in amidoximes acylation. It is well established that in going from the solid state into solution in organic compounds of various characters and in water the amidoximes unsubstituted at the amino group retain their configuration [20]. Their thermodynamic stability is so high that they conserve the *Z*-configuration even at heating and/or photochemical treatment of the

Scheme 4.



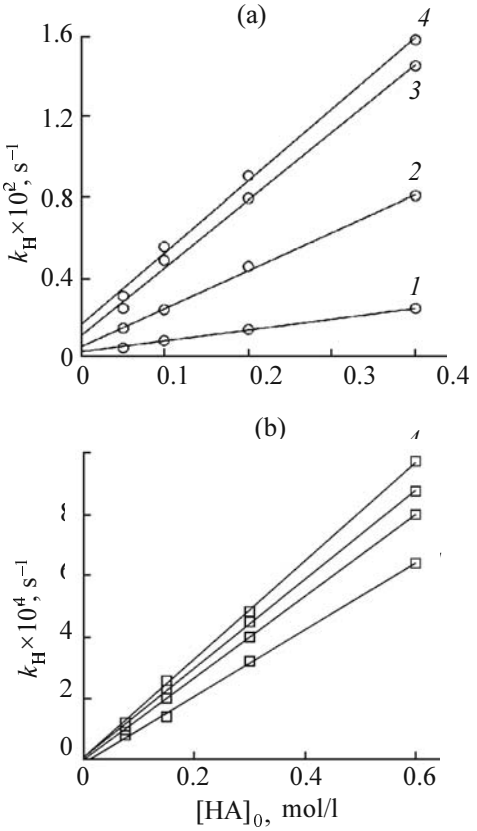


Fig. 1. Rates of reactions of 4-nitrophenyl tosylate (**I**) with an anionic form of acetamidoxime **XXIV** [(a), pH 12.3 (*1*), 12.90 (*2*), 13.15 (*3*), 13.40 (*4*)], and of 4-nitrophenyl diethylphosphonate (**III**) with a neutral form of acetamido-xime (**XII**) [b, pH 6.50 (*1*), 6.90 (*2*), 7.22 (*3*), 8.50 (*4*)] as a function of analytic concentration of amidoxime $[HA]_0$, mol l^{-1} [here and on the other figures reaction in water, 25°C, μ 1.0 (KCl)].

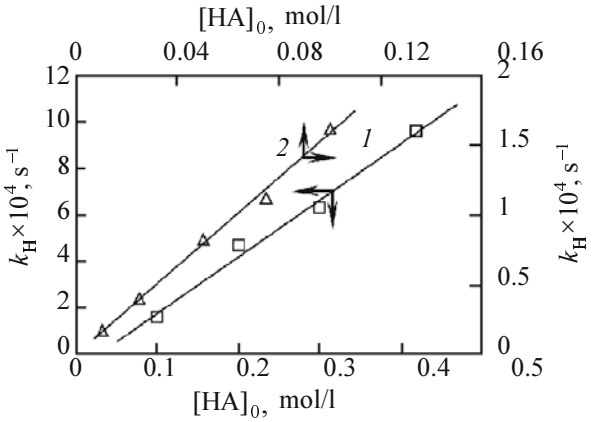


Fig. 2. Rates of reactions of 4-nitrophenyl diethylphos-phonate (**III**) with a neutral form of acetamidoxime (**XII**) (*1*, pH 8.5–10.5), and 4-nitrophenyl diethylphosphate (**II**) with an anionic form of 3-(2-amino-2-oximinomethyl)-1-methylimidazolium chloride (**XXXIII**) (*2*, pH 13.2–13.4) as a function of analytic concentration of amidoxime $[HA]_0$, mol l^{-1}.

solvents [20, 24]. In this study we investigated the chemical behavior of amidoximes with just this structure. Therefore in water with substrates **I–III** the neutral (HA) and anionic (A^-) forms of amidoximes react in the *Z*-configuration, and notwithstanding which form attacks the electrophilic site of the substrates one of the reaction products should be O-acylamidoxime (Scheme 4) [18] where the amidoximate fragment retains its *Z*-configuration.

In keeping with Scheme 4 the apparent rate constants of the pseudofirst order k_{app}, s^{-1}, are described by equation (1) including two parallel pathways: reactions of substrate S with the neutral [k_{HA}, l/(mol s)] and anionic [k_{A^-}, l/(mol s)] forms.

$$k_{app} = k_{HA}\cdot[HA] + k_{A^-}\cdot[A^-] \quad (1)$$

This equation is confirmed by the concentration profiles for amidoximes reactions with esters **I–III** presented on Fig. 1. They are typical for buffer systems where the main components of the buffer act as nucleophiles.

For further reasoning equation (1) is more conveniently presented as (2):

$$k_{app} = k_{HA}\alpha_{HA}[HA]_0 + k_{A^-}\alpha_{A^-}[HA]_0. \quad (2)$$

Here $[HA]_0$, mol l^{-1} is the analytic concentration of the amidoxime, $\alpha_{A^-} = K_{a2}/(K_{a2} + a_{H^+})$ is the anion fraction in amidoxime and $\alpha_{HA} = K_{a1}/(K_{a1} + a_{H^+})$ is the fraction of its conjugate acid. From the dependence of k_{app} on $[HA]_0$ in a narrow range of the medium acidity (where α_{HA} and α_A are practically constant) it proves to be possible to determine k_{HA} and k_A (Fig. 2). The validity of linear equation (3) when $K_{a1} \gg a_{H^+} \gg K_{a2}$ and $\alpha_{HA} \to 1$ and

$$k_{app} = k_{HA}\cdot[HA] = k_{HA}\cdot[HA]_0 \quad (3)$$

also of equation (4) when $K_{a1} \gg a_{H^+} \ll K_{a2}$ and $\alpha_{A^-} > 1$ shows that the reactions under study are of the first order with respect to nucleophile and to ester.

$$k_{app} = k_{A^-}\cdot[A^-] = k_{A^-}\cdot[HA]_0 \quad (4)$$

Another fact supporting Scheme (4) is the kinetic behavior of amidoximes in the range of $pK_{a1} - 2 < pH \ll pK_{a2} + 2$ that encompasses ~11 pH units. Within this pH range the rate of esters **I–III** cleavage is described by equation (5).

$$k_2' = \frac{k_H}{[HA]_0} = k_{HA}\frac{K_{a1}}{K_{a1} + a_{H^+}} + k_{A^-}\frac{K_{a2}}{K_{a2} + a_{H^+}} \quad (5)$$

Here k_2', l/(mol s) is the apparent rate constant of the second order.

Let us consider the dependence of log k_2' values on pH (pH-profiles) with respect to their agreement with equation (6), namely, with Scheme 4. As seen from the pH-profiles (Fig. 3) with growing pH the rate of esters **I–III** cleavage by the acetamidoxime quickly attains saturation at the neutral pH, then occurs pH-independent acyl group transfer, and in the basic media the reaction rate increases tending to the value of the constant $k_2' = k_{2\,max}$.

$$k_2' = k_{HA} \cdot (1 - \alpha_{A^-}) + k_{A^-} \frac{K_{a2}}{K_{a2} + a_{H^+}}$$

$$\frac{k_{HA} \cdot a_{H^+} + k_{A^-} \cdot K_{a2}}{K_{a2} + a_{H^+}} \qquad (6)$$

On the starting part of the pH-profile where $K_{a1} \rightarrow a_{H^+}$ and only HA form reacts with esters **I–III** the reaction rate is described by expression (5), and therefore the k_{HA} values has been calculated directly therefrom.

In the region of the pH-independent acyl group transfer to the HA form of amidoxime, when $K_{a1} \gg a_{H^+}$, the k_{HA} value can be estimated from any point on the plateau of the pH-profile for $k_2' = k_{HA}$. The average k_{HA} values for substrates **I–III** calculated for 10–20 measurements for each substrate are given in Table 2.

$$k_2' = k_{A^-} - \frac{1}{K_{a2}} (k_2' - k_{HA}) \cdot \alpha_{H^+} \qquad (7)$$

Further acceleration of cleavage observed in alkaline media originates from the acyl group transfer not only on HA form but also on the amidoxime anion [equation (6)].

And finally, when $\alpha_{A^-} > 1$, the rate of the process again reaches the limit at $K_{a2} \gg a_{H^+}$ with a constant $k_2' = k_{2,max} = k_{A^-}$.

By transformation of equation (6) into the form (7) we were able to determine both values k_A (Fig. 4), and pK_{a2} (Table 3).

The acid ionization constants of amidoximes were quantitatively evaluated not only from kinetics [equation (7)] but also by potentiometry and spectrophotometry. It seems that for highly basic amidoximes with p$K_{a2} \geq 12.0$ (Table 3) the most correct method is kinetic measurements. The validity of this method was confirmed by good agreement in the pK_{a2} values obtained by treating the pH-profiles according to equation (7) for reactions of anion **XXIV** with esters **I** and **II** that were substrates differing in the nature of the electrophilic site and

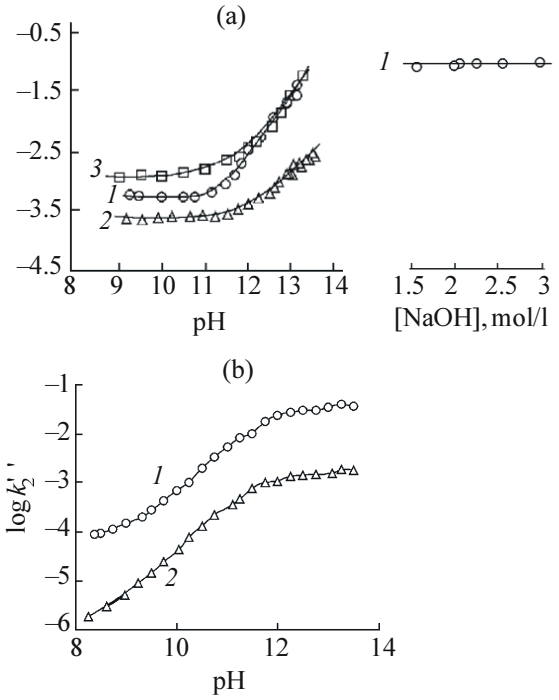


Fig. 3. pH-Profile for reactions of 4-nitrophenyl tosylate (**I**) (*1*), 4-nitrophenyl diethylphosphate (**II**) (*2*), 4-nitro-phenyl diethylphosphonate (**III**) (*3*) with acetamidoxime (**XII, XXIV**) (a); of 4-nitrophenyl tosylate (**I**) (*1*) with pyridine-4-amidoxime (**XVIII, XXXII**), and of 4-nitro-phenyldiethylphosphate (**II**) (*2*) with 3-(2-amino-2-oxi-minomethyl)-1-methylimidazolium chloride (**XXI**, **XXXIII**).

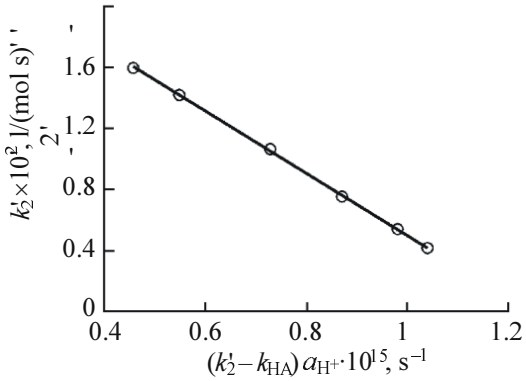
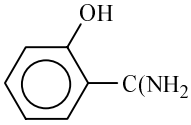
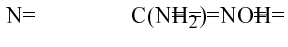
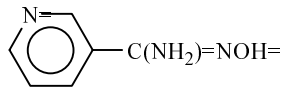
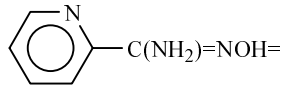
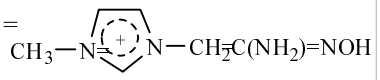


Fig. 4. Dependence of k_2', l/(mol s), values on $(k_2' - k_{HA})a_{H^+}$, s^{-1}, for reaction between 4-nitrophenyl tosylate (**I**) with an anionic form of acetamidoxime (**XXIV**).

reactivity. Besides the pK_{a2} value estimated by potentiometry agreed within the experimental error with the same value obtained from kinetic measurements for

$$pK_{a2} = pH + \log \frac{1 - \alpha_{A^-}}{\alpha_{A^-}} \qquad (8)$$

Table 2. Experimental conditions, pK_{a1} values of neutral forms of amidoximes and hydroxylamine, and their reactivity k_{HA}, l/(mol s), with respect to 4-nitrophenyl tosylate (**I**), 4-nitrophenyl diethylphosphate (**II**), and 4-nitrophenyl diethylphosphonate (**III**) [water, 25°C, μ 1.0 (KCl)]

Compd. no. =	Nucleophile =	Substrate =	pK_{a1} (P)[a] =	$[HA]_0$, mol/l =	pH =	$k_{HA}\times 10^4$, = l/(mol·s) =
XI	$HON{=}C(NH_2)–(CH_2)_4–C(NH_2){=}NOH$ =	**I**	6.20 =	0.025–0.2 =	7.5–9.0 =	7.2±0.7 =
XII	$CH_3–C(NH_2){=}NOH$ =	**I**	6.10 =	0.3–0.6 =	8.5–10. =	5.9±0.6 =
		III		0.3–0.6 =	06.5–10.0 =	16.0±0.1 =
XIII	$C_2H_5–C(NH_2){=}NOH$ =	**I**	5.96 =	0.3–0.5 =	7.0–9.0 =	5.7±0.5 =
XIV	$(CH_3)_2CHC(NH_2){=}NOH$ =	**III**	6.20 =	0.1 =	8.00–8.22 =	17.0±0.1 =
XIV	$HON{=}C(NH_2)CH_2C(NH_2){=}NOH$ =	**I**	4.98 =	0.05–0.1 =	7.5–9.0 =	3.16±0.03 =
XVI	= 	**I**	4.98 =	0.05–0.1 =	6.5–7.0 =	3.0±0.1 =
		II		0.05–0.1 =	6.5–7.0 =	~0.5 =
		III		0.05–0.1 =	6.5–7.0 =	8.2±0.7 =
XVII	$HON{=}C(NH_2)CH_2C(O)NHOH$ =	**I**	4.55 =	0.05–0.1 =	6.5–7.0 =	1.99±0.01 =
		II		0.05–0.1 =	6.5–7.0 =	1.2±0.1 =
		III		0.05–0.1 =	6.5–7.0 =	7.5±0.5 =
XVIII	= 	**I**	2.79 =	0.05–0.1 =	7.5–9.0 =	~0.88 =
XIX	= 	**I**	2.20 =	0.05–0.1 =	7.5–9.0 =	~0.89 =
XX	= 	**I**	2.40 =	0.05–0.1 =	7.5–9.0 =	~0.9 =
XXI	= 	**I**	2.70 =	0.05–0.1 =	7.5–9.0 =	~0.90 =
		II				0.10±0.01 =
		III				1.5±0.2 =
XXII	NH_2OH =	**I**	6.09 =	1.0 =	6.0–9.3 =	0.25±0.03 =
		II		1.0 =	6.0–9.3 =	1.90±0.14
		III		0.2–0.8 =	7.0–9.2 =	11±1 =

[a] Experimental error in determination of pK_{a1} value by potentiometric method (P) does not exceed ±0.06 pK_a units.

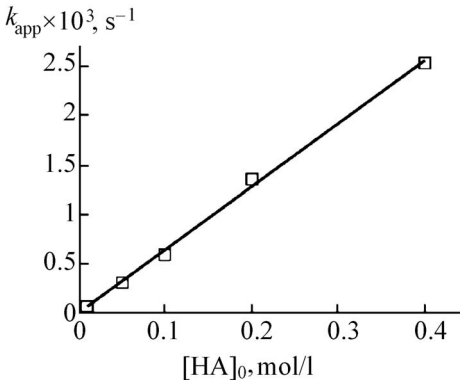


Fig. 5. Dependence of k_{app}, s^{-1}, values on analytic concentration of acetamidoxime $[HA]_0$, mol l^{-1}, for reaction of 4-nitrophenyl tosylate (**I**) with an anionic form of compound **XXIV** ($[NaOH]_0$ = 1.5–3 mol/l).

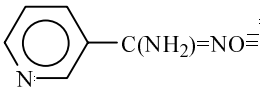
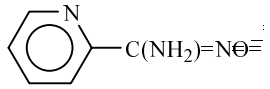
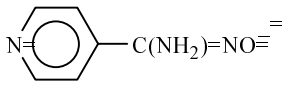
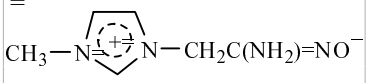
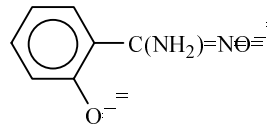
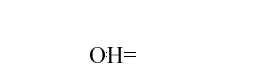
the reaction of anion **XXXII** and ester **II**. Therewith the k_{A^-} values calculated by equation (6) and (7) are also well consistent (Fig. 5). Finally, the treatment of a large number of kinetic data for the reaction of anion **XXIV** with ester **I** (~20 values of k_2', pH 12.5–13.8), amidoximate ions **XXXI** and **XXXII** with ester **I** (~20 values of k_2', pH 10.9–13.5) and ester **II** (~20 values of k_2', pH 11.0–13.6) accounting for the limiting values of $k_{2\,max}$ by equation (8)* furnished the values pK_{a2} = 13.3 ± 0.1 (**XXIV**), 11.75±0.06 (**XXXI**), and 11.58±0.06 (**XXXIII**).

In this case, decomposition of ester **I**–**III** follows Scheme 5.

The pK_{a2} values presented in Table 3 were determined by various methods: kinetic [equation (7)], "kinetic

* In equation (8) $\alpha_{A^-} = k_2'/k_{2\,max}$.

Table 3. Experimental conditions, pK_{a2} values for vamidoximate ions, and their reactivity k_A-, l/(mol s), with respect to 4-nitrophenyl tosylate (**I**), 4-nitrophenyl diethylphosphate (**II**), and 4-nitrophenyl diethylphosphonate (**III**) [water, 25°C, μ 1.0 (KCl)]

Compd. no.	Nucleophile	Substrate	pK_{a2}[a]	$[HA]_0$, mol/l	pH	k_A-×10^2, l/(mol s)
XXIII	$C_2H_5C(NH_2)=NO^-$	**I**	13.3 (K)	0.05–0.2	12.0–13.5	12±1
XXIV	$CH_3C(NH_2)=NO^-$	**I**	12.9 [11]	0.05–0.4	12.30–13.5	6.1±0.4
		II	13.3 (K)	0.05–.4	12.30–13.5	0.29±0.01
		III	13.3 (K.t.)[b]	0.05–0.1	11.0–13.0	4.1±0.6
XXV	$C_6H_5CH_2C(NH_2)=NO^-$	**I**	12.9 (K)	0.05–0.12	11.9–13.5	11±0.5
XXVI	$(CH_3)_2NCH_2C(NH_2)=NO^-$	**I**	12.9 (K)	0.05–0.18	8.25–13.4	8.7±0.3
XXVII	$(CH_3)_2CHC(NH_2)=NO^-$	**I**	12.9 (K)	0.1	12.3–13.0	5.10±0.07
XXVIII	$^-ON=C(NH_2)CH_2C(O)–NHO^-$	**I**	12.0 (P)	0.01	11.0–13.0	7.3±0.2
		II		0.01	11.0–13.0	0.52±0.01
		III		0.01	11.2–11.98	20±1
XXIX	$HON=C(NH_2)CH_2C(O)–NHO^-$	**I**	8.55 (P)	0.01–0.1	8.10–10.40	2.6±0.02
		II		0.01–0.1	8.20–10.60	0.18±0.01
		III		0.01–0.1	8.18–10.50	6.1±0.1
XXX		**I**	11.98 (S)	0.01–0.1	9.0–13.0	6.2±0.3
XXXI		**I**	11.92 (S)	0.01–0.2	9.0–13.0	2.9±0.2
XXXII		**I**	11.78 (S), 11.75 (K.t.)[b]	0.01–0.2	9.0–13.0	3.7±0.3
XXXIII		**I**	11.55 (P), 11.6 (K)	0.01–0.1	9.0–12.8	4.8±0.3[c] 4.8±0.05[d]
		II	11.58 (K.t.)[b]	0.1	9.0–12.5	0.16±0.01[c]
		III		0.01–0.1	9.0–12.0	5.5±0.3
XXXIV		**I**	12.43 (K)	0.15	10.80–12.85	1.60±0.05
		II		0.15	10.95–12.90	0.57±0.01
		III		0.05–0.15	10.7–12.79	6.2±0.2
XXXV		**I**	8.85 (P), 8.7 (K)	0.15	8.0–10.55	1.55±0.10
		II		0.15	7.9–10.82	0.50±0.03
		III		0.15	7.72–10.72	6.0±0.6

[a] Experimental error in determination of pK_a value by potentiometric (P) and spectrophotometric (S) methods does not exceed ±0.06 pK_a units, by kinetic (K) method ±0.1pK_a units.

[b] Estimated by "kinetic titration" (K.t.) [equation (8), see text].

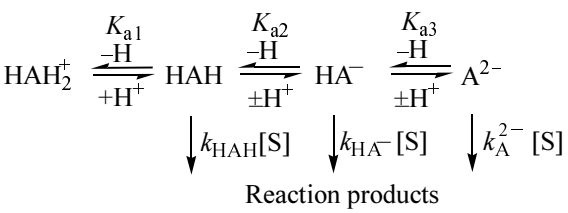
[c] Estimated from equation (7).

[d] Calculated by equation (5).

titration" [equation (8)], potentiometric, and spectrophotometric, and their agreement served a good proof of the validity of the kinetic approach to the quantitative estimation of these constants.

Hence the analysis of pH-profiles of reactions involving amidoximes (**XI–XXI, XXIII–XXVIII, XXX–XXXIII**) in Tables 2 and 3 according to expression (5) not only

Scheme 5.



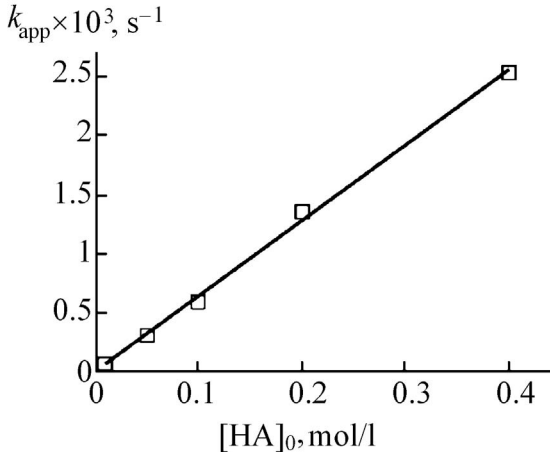


Fig. 6. pH-Profile for reaction of 4-nitrophenyl diethylphosphonate (**III**) with salicyl-amidoxime (**XVI, XXXIV, XXXV**).

allowed an adequate description of their kinetic behavior in the cleavage of esters **I–III** but permitted evaluation of the reactivity of neutral and anionic forms of amidoximes and the basicity of the amidoximate ions (Tables 2 and 3) thus actually proving the Scheme 4.

Compounds containing three proton-active centers capable of providing three types of reactive forms HAH, HA^-, and A^{2-}, e.g., salicylamidoxime (Scheme 6) and methyleneamidoxime of acetylhydroxamic acid, behave differently (Scheme 7).

The dependence of the rate of acyl group transfer on pH is described by equation (9).

$$k_2' = k_{HAH}\,\alpha_{HAH} + k_{HA^-}\,\alpha_{HA^-} + k_{A^{2-}}\,\alpha_{A^{2-}} \qquad (9)$$

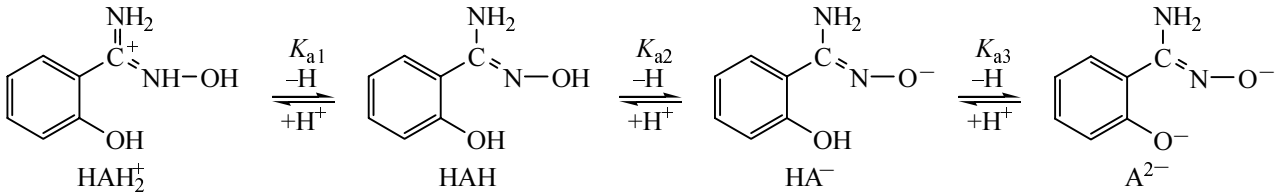
Here $\alpha_{HAH} = K_{a1}/(K_{a1} + a_{H^+})$, $\alpha_{HA^-} = K_{a2}/(K_{a2} + a_{H^+})$, $\alpha_{A^{2-}} = K_{a3}/(K_{a3} + a_{H^+})$ are fractions of the corresponding forms of salicylamidoxime and methyleneamidoxime of acetylhydroxamic acid, and k_{HAH}, k_{HA^-}, $k_{A^{2-}}$ are second order rate constants corresponding to their reactivity.

Interestingly, in reaction of salicylamidoxime with acyl-containing substrates the reaction rate virtually ceased to depend on pH (at pH > 9.6) although the α_{HA^-} and $\alpha_{A^{2-}}$ changed with growing pH, and the fraction of the dianionc form of amidoxime increased (Fig. 6). To put it differently, the decrease in the rate of esters **I–III** cleavage due to diminishing concentration of HA form is practically recompensed by the grough in the rate caused by increasing concentration of A^{2-} form of salicylamidoxime; i.e., the lack of dependence of $\log k_2'$ values on pH (Fig. 6) is an apparent phenomenon. Actually, the process rate is controlled by the acidity of the medium up to pH = pK_{a3} + 1, a $k_{HA^-} = k_{A^{2-}}$.

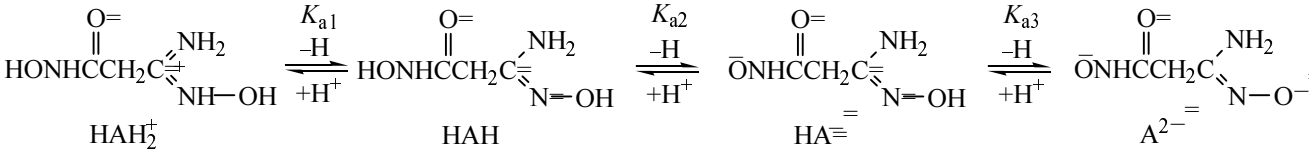
$$\frac{k_2'}{\alpha_{HA^-}} \quad k_{HA^-} = + k_{A^-}^{2-} = \frac{\alpha_A^{2-}}{\alpha_{HA^-}} = \qquad (10)$$

The kinetic rate law (9) is valid at any acidity of the medium; however it is always possible to apply such reaction conditions where one of the pathways of substrates **I–III** cleavage may be neglected. For instance, at pH > 7 the contribution to reaction with esters **I–III** from the neutral forms of salicylamidoxime and methyleneamidoxime of acetylhydroxamic acid amounted to less than 1% from apparent k_2' values . Therefore the

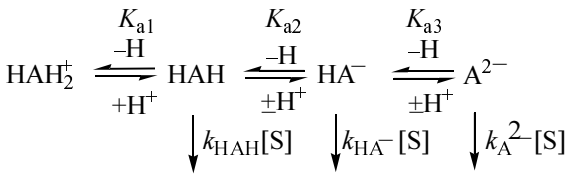
Scheme 6.



Scheme 7.



Scheme 8.



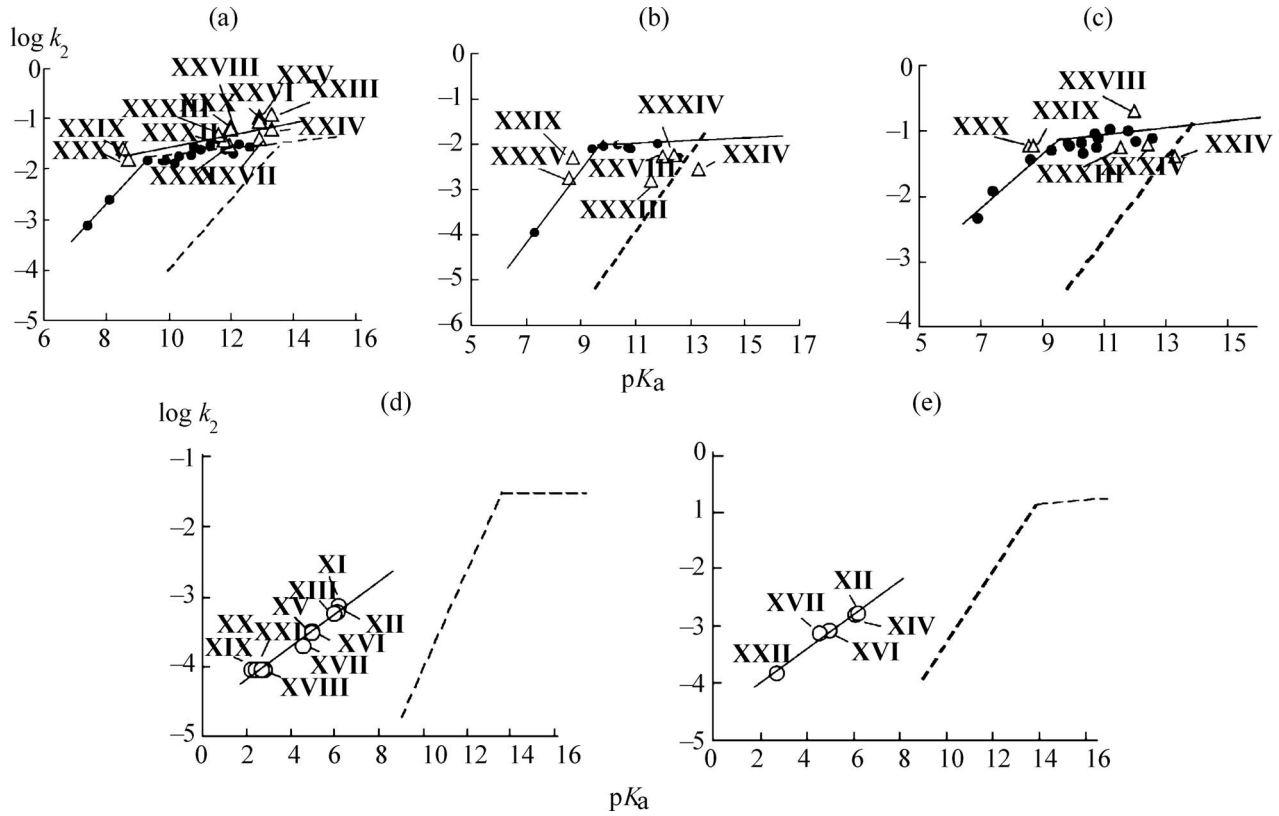


Fig. 8. Bro\nsted relationship for reactions of amidoximate (Δ), oximate (●), and arylate ions (dashed lines) with 4-nitrophenyl tosylate (**I**) (a), 4-nitrophenyl diethylphosphate (**II**) (b), 4-nitro-phenyl diethylphosphonate (**III**) (c), and neutral forms of amidoximes with esters **I** (d) and **III** (e). Data concerning amidoximes are presented in Tables 2 and 3, for oximate ions are taken from [8, 15, 31]. Brønsted parameters for all relations are given in Table 4.

transformation of equation (9) into (10) permitted the quantitative evaluation of the reactivity of mono- and dianions of these amidoximes (Fig. 7).

At pH < 7 and $a_{H^+} \approx K_{a1}$ over 99% of contribution into the apparent k_2' values belong to the pathways involving HAH forms of amidoximes. Therefore the nucleophilic properties of the HAH forms were evaluated basing on equation (11).

$$k_2' = k_{HAH} \frac{K_{a1}}{K_{a1} + a_{H^+}} \qquad (11)$$

The determined rate constants k_{HA}, k_{HAH}, k_{A^-}, k_{HA^-}, and $k_{A}2-$, and also values of pK_{a1}, pK_{a2}, pK_{a3} for the amidoximes under study are compiled in Tables 2 and 3.

Relation structure – reactivity for amidoximes. Anionic forms of amidoximes may be regarded as the corresponding oximate ions where the hydrogen atom of CH=N moiety is replaced by NH_2 group. Therefore no wonder that the kinetic behavior of these two α-nucleophiles classes (amidoximate and oximate anions) is similar in reactions of acyl group transfer. Analysis of Brønsted relationships "log k_2 – pK_a" for reactions of amidoximate, oximate ions with pK_a 8.8–13.3, and of "normal" anionic oxygen-containing nucleophiles (standard reaction series) with esters **I–III** (Fig. 8, Table 4) revealed some general trends in the kinetic behavior of these O-nucleophiles. Firstly, amidoximate anions in reactions of acyl group

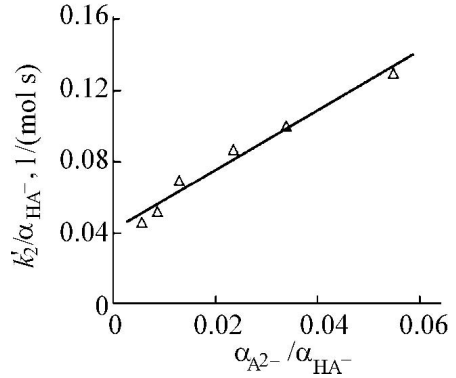
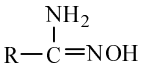
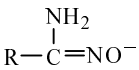
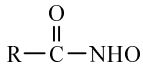
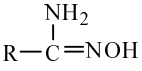
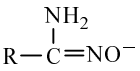
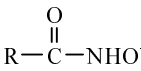
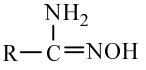
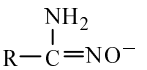
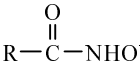


Fig. 7. Dependence of k_2'/α_{HA^-}, l/(mol s), values on $\alpha_A 2-/\alpha_{HA^-}$ for reaction of 4-nitrophenyl diethylphosphonate (**III**) with methyleneamidoxime of acetylhydroxamic acid (**XXVIII, XXIX**).

Table 4. Brønsted parameters[a] for reactions of various classes of α-nucleophiles (amidoximes, amidoximate, oximate, hydroxamate ions) and of "normal" nucleophiles (arylate and alcoholate ions) with 4-nitrophenyl tosylate (**I**), 4-nitrophenyl diethylphosphate (**II**), and 4-nitrophenyl diethylphosphonate (**III**)

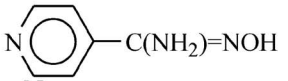
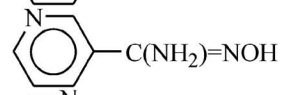
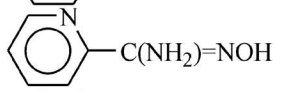
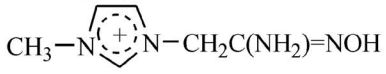
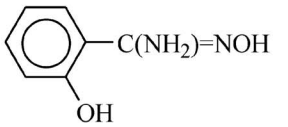
Substrate =	Nucleophile =	β_N =	–C =	*n* =
I	= 	0.23 ± 0.01 =	–4.64 ± 0.06 =	10 =
	= 	0.13 ± 0.03 =	2.90 ± 0.40 =	12 =
	Ox^- ($pK_a \geq 9.0$) =	0.10 ± 0.01 =	2.8 ± 0.3 =	14 =
	= 	0.60 ± 0.08 =	7.20 ± 0.70 =	16 =
	ArO^- (RO^-): $pK_a \leq 13.0$ =	0.59 ± 0.02 =	9.8 ± 0.2 =	11 =
	$pK_a \geq 13.0$ =	~0.08 =	– =	3 =
II	= 	–	–	– =
	= 	~0.02 =	2.7 ± 0.6 =	6 =
	Ox^- ($pK_a \geq 9.0$) =	0.014 ± 0.009 =	2.2 ± 0.1 =	7 =
	= 	0.70 ± 0.10 =	8.1 ± 0.9 =	5 =
	ArO^- (RO^-): $pK_a \leq 13.0$ =	0.57 ± 0.16 =	9.6 ± 2.0 =	4 =
	$pK_a \geq 13.0$ =	~0.08 =	– =	3 =
III	= 	0.30 ± 0.02 =	–4.60 ± 0.15 =	5 =
=	= 	~0 =	~1.0 =	5 =
	Ox^- ($pK_a \leq 9.0$) =	0.62 ± 0.06 =	6.53 ± 0.05 =	9 =
	Ox^- ($pK_a \geq 9.0$) =	0.10 ± 0.07 =	2.3 ± 0.8 =	10 =
=	= 	0.54 ± 0.02 =	6.20 ± 0.15 =	28 =
=	ArO^- (RO^-): $pK_a \leq 13.0$ =	0.50 ± 0.01 =	8.00 ± 0.12 =	5 =

[a] Brønsted parameters are calculated by equation $\log k_2 = \beta_N pK_a + C$; *n* is number of points.

transfer behave like typical α-nucleophiles, but the α-effect value determined as $\Delta = k_2/k_2$ at $pK_{a2} = pK_a$ (ArO^- is arylate ion, RO^- is alcoholate ion) depends essentially on the amidoxime structure. Inasmuch as the nucleophilic power of amidoximate ions very weakly depends on their basicity (Table 4), the α-effect value steeply decreses with growing pK_a. Amidoximate ions with $pK_a > 12.0$ virtually already do not surpass in reactivity or are close to that of the highly basic alcoholate ions, namely, the α-effect is lacking. This conclusion is also valid for the other acyl-containing substrates, in particular, for 4-nitrophenyl acetate (**IV**) [13, 14], 4-nitrophenyl diphenylphosphate [10] etc. [3, 8]. Secondly, Brønsted relationships for oximate and amidoximate ions virtually coincide (Fig. 8), and the α-effect value for the amidoximate with the lowest basicity among those studied, salicylamidoxime (pK_{a2} 8.85) is ~400 (**I**), ~10 (**II**), ~200 (**III**) times, and for salicylaldoximate anion (pK_a 9.30) it is ~220 (**I**), ~25 (**II**), and ~140 (**III**) times [8]. Finally, the similarity in kinetic behavior of amidoximate and oximate ions evidences that the introduction of an amino group practically does not affect the reactivity of the anionic forms of amidoximes.

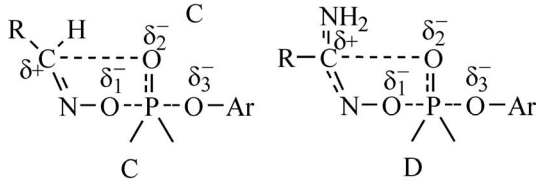
Notwithstanding the nature of the electron-deficient center of oximes their Brønsted relationships posses an early break of the curve at pK_a ~8–9.0 [8]. We like to focus attention on the fact that the linear parts of these relationships having β_N ~0.5 and ~0 correspond to the same oximes, and the second group constitute the oximes

Table 5. Solvents for recrystallization of amidoximes and melting points of hte compounds

Compounds	Solvent for recrystallization	mp, °C	mp, °C [ref.]
HON=C(NH_2)–(CH_2)$_4$–C(NH_2)=NOH	1- Butanol	226–227	226 [29]
CH_3–C(NH_2)=NOH	1- Butanol	134–135	135 [29]
C_2H_5–C(NH_2)=NOH	1- Butanol	143–145	144−145 [30]
(CH_3)$_2$CHC(NH_2)=NOH	Benzene	57	55–58 [29]
HON=C(NH_2)CH_2C(NH_2)=NOH	Ethanol water	165–167	163–167 [29]
	Benzene	197–198	199 [29]
	Benzene	133–134	134 [29]
	Water	117	116−117 [29]
	Ethanol	214–215[a]	
$C_6H_5CH_2$C(NH_2)=NOH	Ethanol water	80	79–80 [29]
(CH_3)$_2$NCH_2C(NH_2)=NOH	Ethanol		
HON=C(NH_2)CH_2C(O)–NHOH	Water	149–150	150 [29]
	Water	97	98 [29]

[a] Synthesized by alkylation of 1-methylimidazole with chloroacetonitrile followed by treatment with hydroxylamine.

lacking powerful electron-withdrawing substituents capable of reducing effective charges on the reacting centers of the α-nucleophile. The unfavorable solvation effect of the solvent whose contribution increases with the growing basicity of the oximate ion [8] causes apparently the break on the Brønsted relation curve. The amidoximate ions with pK_a > 8.5 reported in this study also fit to a single relationship "log k_2–pK_a" (Fig. 8) with β_N ~0 (Table 4). However we failed to vary the basicity of the amidoximate ions in a wider range (pK_a < 8.5), therefore it is difficult to state whether the reactivity of oximate and amidoximate ions was controlled by factors of the same type. Nonetheless, the similar β_N values for

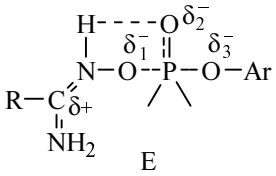


these classes of α-nucleophiles testify to the analogy in the transition states of the reactions: Stoichiometric composition is 1:1, and the charge distribution is of the same type (C, D).

Both in case of oximate ions (C) and amidoximate ions (D) occurs a general acid-base catalysis, and the anionic forms of these α-nucleophiles function as Lewis acids.

In contrast to oximate ions the amidoximes behave as efficient acyl group acceptors not only in the anionic but also in the neutral form (Fig. 8), and the α-effect value for the acetamidoxime ($\Delta = k_{HA}/k_2^{ArO-}$ at pK_{a1} = pK_a^{ArO-}) amounts to ~650 (**I**), ~30 (**II**), and ~130 (**III**). Inasmuch as the reaction center in the neutral amidoxime molecule is the oxygen of the amidoximate fragment, and the difference in basicity of two O-nucleophilic forms, RC(NH_2)=N–OH and RC(NH_2)=N–O^-, most likely reaches 14 orders of magnitude or more [cf. basicity difference of HOH (–1.74) and of ion HO^- (15.74)] [28],

the α-effect value for acetamidoxime may attain ≥10^5 times. The high reactivity of the neutral forms of amidoximes (as also of hydroxylamine) and their N-alkyl-, N,N-sialkyl derivatives toward esters **II, IV**, and others is commonly ascribed to the effect of the general acid-base catalysis [10–14]. The resonance stabilization in the amidoximate fragment (Scheme 3) decreases the double-bond character of the bond between the imine nitrogen and carbon and increases the double-bond character of the bond between the amino group and carbon atom. The leveling of the electron density in the amidine fragment of the amidoximes is the cause of electron density increase on the nitrogen of the imino group resulting in its protonation (Scheme 3) [20]. This is also the reason of the possibility of bipolar ions formation. Thus for reactions of the neutral forms of amidoximes the existence of two types of promotion assistance in the transition state, general basic and acid catalysis (E), cannot be excluded.



E

It should be pointed out in conclusion that although neither amidoximes or oximes can compete in the alkaline medium with the most powerful inorganic α-nucleophile, hydroxylamine anion [15], the unique feature of amidoximes as α-nucleophiles consists in their ability to ensure relatively high rate of cleavage of substrates stable in water in a wide pH range (in alkaline, neutral, and acid media.

EXPERIMENTAL

Substrates were prepared by acylation of 4-nitrophenol with 4-toluenesulfonyl chloride, diethyl chlorophosphate, and diethyl chlorophosphonate respectively. After isolation substrate **I** was twice recrystallized from anhydrous ethanol, and esters **II** and **III** were twice distilled in a vacuum at the pressure of 0.05 mm Hg. The physicochemical characteristics (mp, n_D^{20}), and UV spectra of esters obtained were in full agreement with the published data. Amidoximes were prepared along standard procedures and purified by crystallization from appropriate solvents till constant melting point (Table 5). Inorganic reagents of grades "special purity" and "chemically pure" were used as received.

Kinetic measurements. The reaction progress was monitored by the absorption of the accumulating 4-nitrophenolate ion (λ 400–440 nm). The solutions of reagents were prepared just before each series of kinetic runs, and their concentration was sufficient for playing also the role of buffer. The required pH values were adjusted with concn. KOH or HCl solutions. The acidity of the medium was controlled before and after each kinetic run; when the pH after the end of the run differed from that at the beginning by more than 0.05 pH units, the result of the run was rejected. Ionic force of solution (μ 1.0) was kept constant by KCl addition. All reactions were carried out in water (**II** and **III**) or in 5% ethanol solution in water (**I**) at 25 ± 0.1°C. As solvents double-distilled water and anhydrous ethanol were used. In all kinetic runs the analytic substrate concentration {$[S]_0$ ~5×10^{-5} mol/l)} was far less than the initial nucleophile concentration, and the experimentally measured apparent constants of the pseudofirst order (k'_{app}, s^{-1}) remained constant within six periods of the half-time of substrate consumption. The values k'_{app}, s^{-1}, were determined from the optical density variation with time by equation (13).

$$\ln (D_\infty - D_\tau) = \ln (D_\infty - D_0) - k'_{app} \cdot \tau \qquad (13)$$

Here D_0, D_τ, and D_∞ are optical densities at the moments $\tau = 0$, $\tau = \tau_i$ and at the completion of the reaction. In estimation of nucleophiles reactivity the observed k'_{app}, s^{-1}, values were corrected for the contribution of the alkaline hydrolysis of substrate if the latter was more than 5% of the k'_{app} value, i.e., $k_{app}= k'_{app} - k_{OH^-}a_{OH^-}$. The rate constants of the alkaline hydrolysis [k_{OH^-}, l/(mol s)] for substrates under study were determined independently and based on the activity of the hydroxyl ion in water, μ 1.0 (KCl) at 25°C [31].

Measurement of pK_a values. The acid ionization constants were measured by potentiometric, spectrophotometric, and kinetic procedures in 5% aqueous ethanol (μ 1.0, 25°C). As titrants served 0.1 M solutions of KOH or HCl. The calculation of pK_a values at potentiometric and spectrophotometric measurements were performed using Henderson–Hasselbalch equation.

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