

Nucleophilic Substitution at a Four-Coordinate Sulfur Atom: VI.* Reactivity of Oximate Ions

T. M. Prokop'eva, Yu. S. Simanenko, I. P. Suprun, V. A. Savelova,
T. M. Zubareva, and E. A. Karpichev

Litvinenko Institute of Physical Organic and Coal Chemistry, Ukrainian National Academy of Sciences,
ul. R. Luxemburg 70, Donetsk, 340114 Ukraine

Received August 12, 1999

Abstract—The kinetics of the reaction of oximate ions with 2,4-dinitrophenyl *p*-toluenesulfonate, 4-nitrophenyl *p*-toluenesulfonate, diethyl 4-nitrophenyl phosphate, and ethyl 4-nitrophenyl ethylphosphonate in H₂O–DMSO mixtures (0 to 95 vol % of DMSO) cannot be described in terms of a single Brønsted equation. Regardless of the nature of the reaction center and leaving group, both in water and in 80% DMSO fast leveling of the reactivity of oximate ions is observed, the α -effect decreases at $pK_a \geq 9.0$ and disappears at $pK_a \geq 12.0$ owing to difference in the solvation of weakly ($pK_a \leq 9.0$) and strongly basic ($pK_a \geq 9.0$) oximate ions rather than to change of the transition state. Just unfavorable solvation effects are responsible for the fact that the limiting nucleophilic reactivity of oximate ions (as typical α -nucleophiles) is not higher than the reactivity of strongly basic alkoxide ions.

Nucleophilic reactivity of oximate ions (Ox[−]) has long attracted specific interest [2–5], for some representatives of this unique class of α -nucleophiles are efficient antidotes (cholinesterase reactivators [6]). Search for and design of such compounds is now in progress [5, 7, 8]. Undoubtedly, the above property of oximate ions directly originates from their anomalously high reactivity. Therefore, an important problem is to elucidate factors governing the α -effect of oximate ions.

Extrathermodynamic analysis of the behavior of “normal” anionic oxygen-containing nucleophiles in reactions involving transfer of arylsulfonyl, acetyl, phosphinoyl, and other groups [9–12] shows that solvation by water strongly affects the nucleophilic reactivity of alkoxide and aroxide ions. Just solvation effects are responsible for the extremely low sensitivity to the nature of nucleophile (alkoxide ions with $pK_a \geq 13.0$) in reactions with aryl acetates, aryl toluenesulfonates, and aryl methanesulfonates [9–12]. Terrier *et al.* [5] recently presumed that the reactivity of typical α -nucleophiles, Ox[−] ions among them, cannot be described in terms of a single Brønsted dependence and that the existence of curvilinear

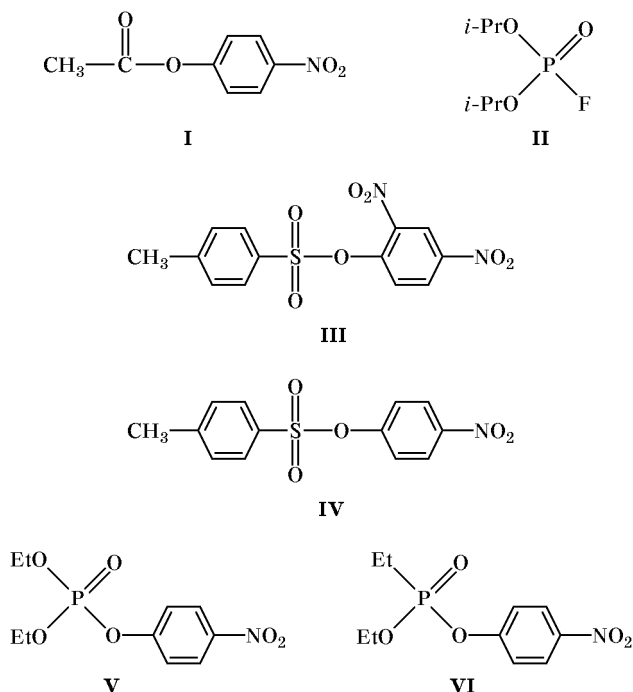
Brønsted dependences for transfer of acetyl and diisopropoxyphosphinoyl groups from compounds **I** and **II** to Ox[−] ions [$pK_a(\text{Ox}^-) \sim 7\text{--}13$] is also the result of thermodynamically unfavorable solvation effects. Presumably, curvature of Brønsted relations should also be observed in reactions of Ox[−] with other substrates provided that the above assumption is valid.

In the present work we studied nucleophilic reactivity of oximes OxH with $pK_a \sim 7\text{--}13$ toward 2,4-dinitrophenyl *p*-toluenesulfonate (**III**), 4-nitrophenyl *p*-toluenesulfonate (**IV**), diethyl 4-nitrophenyl phosphate (**V**), and ethyl 4-nitrophenyl ethylphosphonate (**VI**) in water; the reaction with substrate **IV** was also studied in 80% DMSO. The results were compared with those found for “normal” oxygen-containing nucleophiles such as aroxide and alkoxide ions. In addition, we examined the effect of DMSO concentration in H₂O–DMSO mixtures (20, 40, 60, 80, 90, and 95 vol % of DMSO) on the α -effect in the reaction of sulfonate **IV** with 4-pyridinecarbaldehyde oxime and phenol (**A**) and with isonitrosoacetylacetone and 2,4-dibromophenol (**B**). These pairs of nucleophiles (**A** and **B**) were selected since the points for 4-pyridinecarbaldehyde oxime and isonitrosoacetylacetone fit the Brønsted dependences with different β_N values (0.1 and 0.5, respectively), whereas aroxide ions fall into a single Brønsted plot with $\beta_N \approx 0.5$, the pK_a

* For communication V, see [1].

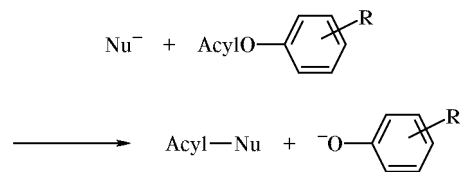
values of the normal and α -nucleophile in water being comparable.

The goal of our study was to estimate on a quantitative level the magnitude of the α -effect in H_2O –DMSO mixtures and to analyze its variations with regard to the nucleophile nature, substrate structure, and solvent composition.



The reaction of Ox^- or ArO^- ions with esters **III–VI** in H_2O –DMSO mixtures (Table 1) includes nucleophilic attack on the electron-deficient center in the substrate by the anionic nucleophile (Nu^-) to give the corresponding *O*-acyl derivatives [4] (Scheme 1; hereinafter, an acyl group is acetyl, phosphinoyl, or *p*-toluenesulfonyl).

Scheme 1.



Acyl = Ac, Ts, $(\text{EtO})_2\text{P}=\text{O}$, $\text{Et}(\text{EtO})\text{P}=\text{O}$.

The dependence of the apparent pseudofirst-order rate constants k_{ap} (s^{-1}) on the overall nucleophile concentration $[\text{NuH}]_0$ (M) is typical of processes where the reactive species is the major buffer component ($\text{Nu}^- = \text{Ox}^-$ or ArO^-). The rate of the reaction increases both as pH rises and as nucleophile concentration increases (Fig. 1) and is described by Eq. (1):

$$k_{\text{ap}} = K_{\text{OH}^-} a_{\text{OH}^-} + k'_2 [\text{NuH}]_0 \quad (1)$$

When $[\text{NuH}]_0 = 0$, the intercept on the y axis coincides within the experimental error with the $k_{\text{OH}^-} a_{\text{OH}^-}$ value determined by special experiments, which reflects the contribution of alkaline hydrolysis to the apparent reaction rate. The slope of the corresponding plot is the apparent second-order rate constant at a given pH value, i.e., $k'_2 = (k_{\text{ap}} - k_{\text{OH}^-} a_{\text{OH}^-}) / [\text{NuH}]_0$, $\text{l mol}^{-1} \text{s}^{-1}$. The second-order rate constants k_2 , $\text{l mol}^{-1} \text{s}^{-1}$, which characterize nucleophilic reactivity of anionic oxygen-containing nucleophiles, were determined from the linear relation between k'_2 and α_{Nu^-} . The latter quantity is the fraction of Ox^- , ArO^- , or RO^- ion provided that the $\text{p}K_{\text{a}}$ value of nucleophile is known (Fig. 2).

$$k'_2 = k_2 \alpha_{\text{Nu}^-} = k_2 \frac{K_{\text{a}}}{K_{\text{a}} + a_{\text{H}^+}} \quad (2)$$

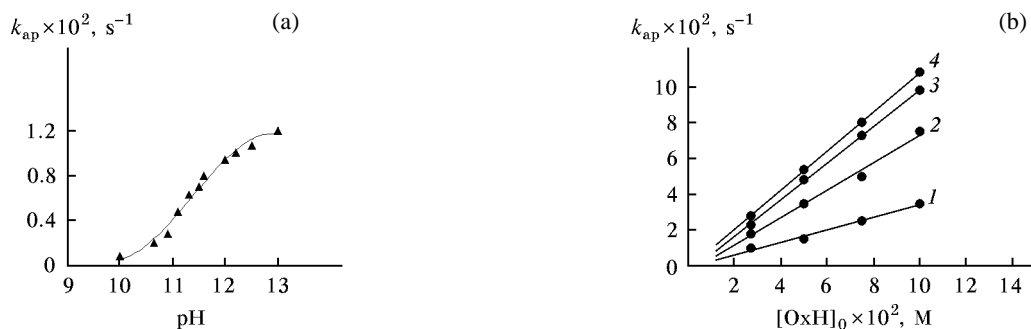


Fig. 1. Plots of the rate constants for the reaction of ethyl 4-nitrophenyl ethylphosphonate (**VI**) with imidazole-4-carbaldehyde oxime (**XXIV**) in water (25°C , $\mu = 1.0$) versus (a) pH ($[\text{OxH}]_0 = 0.1 \text{ M}$) and (b) oxime concentration $[\text{OxH}]_0$ at (1) pH 10.81, (2) 11.52, (3) 11.88, and (4) 12.05.

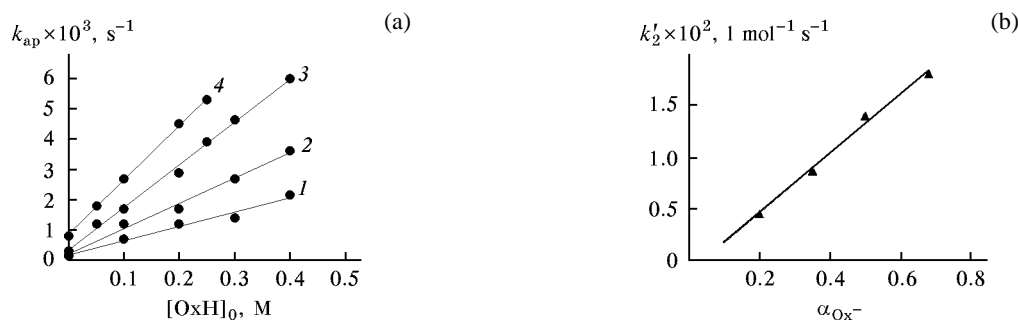


Fig. 2. (a) Plots of the rate constants for the reaction of 4-nitrophenyl *p*-toluenesulfonate (**IV**) with acetone oxime (**XXVIII**) in water (25°C, $\mu = 1.0$) versus oxime concentration $[OxH]_0$ at (1) pH 12.00, (2) 12.30, (3) 12.60, and (4) 12.80 and (b) processing of the results by Eq. (2).

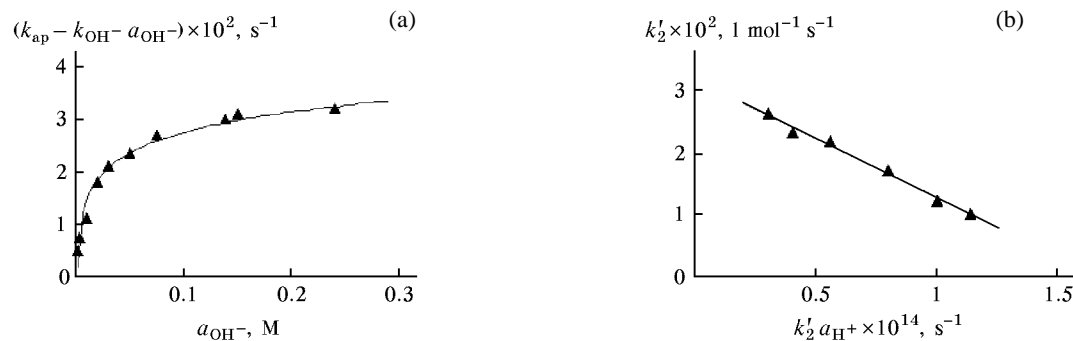


Fig. 3. (a) Plot of the rate constant for the reaction of 4-nitrophenyl *p*-toluenesulfonate (**IV**) with cyclohexanone oxime (**XXVI**) in water (25°C, $\mu = 1.0$) versus activity of hydroxide ions, $[OxH]_0 = 0.1 M$, and (b) processing of the results by Eq. (3).

The rate constants k_2 can also be calculated by Eq. (3) which allows simultaneous determination of both k_2 and the acid ionization constant of the reagent (Fig. 3).

$$\frac{k'_2}{a_{H^+}} = k_2 - \frac{1}{K_a} \frac{k'_2}{a_{H^+}^2}. \quad (3)$$

2,3-Butanedione dioxime reacts with substrates **III–VI** according to Scheme 2, and the reaction rate is given by Eq. (4):

$$k_{ap} = k_{OH^-} a_{OH^-} + k_{HOx^-} [HOx^-] + k_{Ox^{2-}} [Ox^{2-}]. \quad (4)$$

The rate constants k_{HOx^-} and $k_{Ox^{2-}}$, $l mol^{-1} s^{-1}$, which characterize the reactivities of the anion and dianion, respectively, were determined as follows. First, the acid ionization constants K_{a1} and K_{a2} were found by potentiometric titration, and the desired

$$\frac{k'_2}{a_{HOx^-}} = k_{HOx^-} + k_{Ox^{2-}} \frac{\alpha_{Ox^{2-}}}{\alpha_{HOx^-}}. \quad (5)$$

values of k_{HOx^-} and $k_{Ox^{2-}}$ were then calculated using linear relation (5) (Fig. 4). Table 1 contains the second-order rate constants and pK_a values of the examined nucleophiles in water and 80% DMSO.

The effect of the basicity of the leaving group $[pK_a(ArO^-)]$ in the substrate on the rate of sulfonyl group transfer to the nucleophile was examined using three reactions: (1) the reaction of anion **VIII** with

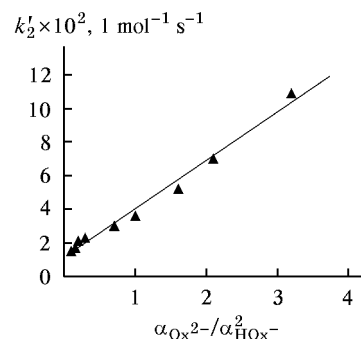
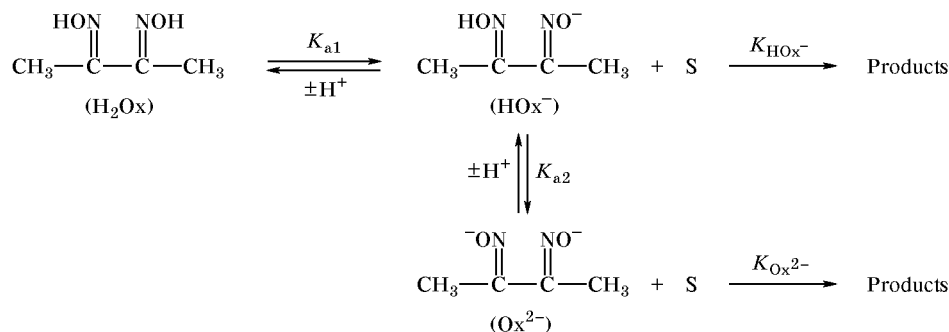


Fig. 4. Plot of the rate constant for the reaction of 4-nitrophenyl *p*-toluenesulfonate (**IV**) with 2,3-butanedione dioxime in 80% DMSO (25°C, $\mu = 1.0$), according to treatment by Eq. (5); pH 15.03–16.73.

Scheme 2.



2,4-dinitro- and 4-nitrophenyl *p*-toluenesulfonates in 30% ethanol* [Eq. (6)]; (2) the reaction of anion **XXV** with 2,4-, 2,6-, 2,5-dinitro-, 4-nitro-, and 4-phenylazophenyl *p*-toluenesulfonates in 30% ethanol [Eq. (7), Table 2]; and (3) the reaction of anion **XV** with 3-nitro-, 4-nitro-, 2,5-dinitro-, and 4-phenylazophenyl *p*-toluenesulfonates in 80% DMSO [Eq. (8), Table 2].

$$\log k_2 = 3.20 - 0.83 \text{p}K_a; \quad n = 2; \quad (6)$$

$$\log k_2 = (3.96 \pm 0.55) - (0.78 \pm 0.09) \text{p}K_a; \quad (7)$$

$$n = 5, \quad r = 0.981, \quad s = 0.40;$$

$$\log k_2 = (6.62 \pm 0.55) - (0.73 \pm 0.02) \text{p}K_a; \quad (8)$$

$$n = 4, \quad r = 0.993, \quad s = 0.005.$$

Brønsted equations (6)–(8) indicate that the rate of nucleophilic attack on the four-coordinate sulfur atom of the substrate increases in parallel with the basicity of the leaving group ($\beta_X < 0$) and that the sensitivity to the nucleofuge basicity remains constant regardless of the reactivity of Ox^- ions and solvent nature. Figures 5 and 6 show the Brønsted plots describing the reactivity of Ox^- ions with respect to substrates **III**–**VI** in water and 80% DMSO; for comparison, the kinetic data for normal oxygen-containing nucleophiles, aroxide and alkoxide ions, are also given. The linear parts of the above plots are characterized by the Brønsted slopes β_N which are collected in Table 3. The Brønsted dependences for substrates **III** and **VI** in water are clearly curvilinear with a bend located at $\text{p}K_a \sim 9.0$; At $\text{p}K_a < 9$, the Brønsted sensitivities are close to $\beta_N \sim 0.5$ – 0.6 (reaction series *a* and *e*), and then β_N decreases to ~ 0.1 (reaction series *b* and *f*; Table 3). An analogous variation of the Brøn-

sted slopes was found for the reactions of Ox^- ions with substrates **I** and **II** (Fig. 5a, 5b) [5, 7, 8]. Presumably, the same is the case of esters **IV** and **V** for which it was impossible to vary the structure of oximes with $\text{p}K_a < 9.0$ because of experimental difficulties (oximate ions strongly absorb in the region of working wavelengths, and the initial rate technique cannot be applied because of the poor solubility of the substrates in 5–15% ethanol). Estimation of k_2 for the reaction of substrates **IV** and **V** with isonitrosoacetylacetone and salicylaldehyde oxime in 30% dioxane gave β_N values of about 0.5–0.6.

Analysis of the Brønsted dependences obtained for the reactions of oximate, aroxide, and alkoxide ions with the above substrates, as well as with compounds **I** and **II** [5, 7–9, 11] and sarin [3], allowed us to reveal a series of general relations in the variation of k_2 and α -effect with regard to the oxime structure. First, in acyl group transfer reactions Ox^- ions act as typical α -nucleophiles, but the magnitude of the α -effect which is defined as $\Delta = k_2(\text{Ox}^-)/k_2[\text{Ar}(\text{R})\text{O}^-]$ at $\text{p}K_a(\text{Ox}^-) \approx \text{p}K_a[\text{Ar}(\text{R})\text{O}^-]$ strongly depends on the oxime structure. As the acidity of oxime decreases [$\text{p}K_a(\text{Ox}^-) \leq 9.0$], the α -effect remains constant within a single reaction series and is about 200, 1000, 300, 1500, and 800 for substrates **I**, **III**, **IV**, **V**, and **VI**, respectively. Although further increase of the oxime basicity [$\text{p}K_a(\text{Ox}^-) \geq 9.0$] leads to a slight increase in k_2 , the α -effect starts to decrease (Fig. 5). Finally, the reactivity of oximate ions with $\text{p}K_a \geq 12.0$ is not higher than that of strongly basic alkoxide ions ($\Delta \sim 1$), i.e., α -effect disappears. Moreover, Ox^- ions and strongly basic alkoxide ions form a single Brønsted dependence. This means that for all substrates, regardless of the nature of electron-deficient center, the limiting reactivity of Ox^- ions is comparable with the limiting reactivity of alkoxide ions. It should be emphasized that at $\text{p}K \geq 9.0$ the nucleophilic reactivity of Ox^- ions becomes leveled, whereas “complete” leveling with normal anions is observed at $\text{p}K_a > 12$.

* 30% Ethanol was taken instead of water because of poor solubility of aryl *p*-toluenesulfonates.

Table 1. Basicities of oximate ions and some *O*-nucleophiles (pK_a) and their reactivities toward 2,4-dinitrophenyl *p*-toluenesulfonate (**III**), 4-nitrophenyl *p*-toluenesulfonate (**IV**), diethyl 4-nitrophenyl phosphate (**V**), and ethyl 4-nitrophenyl ethylphosphonate (**VI**) in water and *p*-toluenesulfonate **IV** in 80% DMSO at 25°C

Comp. no.	Nucleophile (neutral form)	pK_a^a	$k_2, \text{ l mol}^{-1} \text{ s}^{-1}$			
			III ^b	IV ^c	V ^c	VI ^d
VII	Ethyl isonitrosoacetylacetate	6.92 ± 0.06 (P) 9.45 ± 0.03 (P) ^e	0.45 ± 0.02	– (2.9 ± 0.2) × 10 ⁻² ^e	–	(4.7 ± 0.2) × 10 ⁻³
VIII	Isonitrosoacetylacetone	7.39 ± 0.04 (P) 9.85 ± 0.09 (P) ^e	1.16 ± 0.25	(1.4 ± 0.8) × 10 ⁻³ ^f (5.0 ± 0.4) × 10 ⁻² ^e	(1.1 ± 0.1) × 10 ⁻⁴ ^f	(1.2 ± 0.2) × 10 ⁻²
IX	2-Hydroxyimino-1-methylpyridinium iodide	8.04 ± 0.05 (P) 9.96 ± 0.06 (P) ^e	2.06 ± 0.23	– (3.4 ± 0.3) × 10 ⁻² ^e	–	–
X	4-Hydroxyimino-1-methylpyridinium iodide	8.61 ± 0.04 (P) 10.78 ± 0.05 (P) ^e	3.84 ± 0.35	– (1.52 ± 0.07) × 10 ⁻¹ ^e	–	(5.6 ± 0.1) × 10 ⁻²
XI	Salicylaldehyde oxime	9.3 ± 0.1 (K) 12.14 ± 0.10 (P) ^e	7.80 ± 0.7	(1.5 ± 0.1) × 10 ⁻² (4.7 ± 0.3) × 10 ⁻¹ ^e	(8.2 ± 0.7) × 10 ⁻³	(7.1 ± 0.6) × 10 ⁻²
XII	3-Hydroxyimino-1-methylpyridinium iodide	9.51 ± 0.06 (P) 12.67 ± 0.08 (P) ^e	5.5 ± 0.4	– 1.24 ± 0.03 ^e	–	–
XIII	4-Pyridinecarbaldehyde oxime	9.82 ± 0.04 (P) 13.33 ± 0.05 (P) ^e	8.00 ± 0.7	(1.5 ± 0.1) × 10 ⁻² 1.44 ± 0.06 ^e	(9.1 ± 0.9) × 10 ⁻³	(6.7 ± 0.5) × 10 ⁻²
XIV	2-Pyridinecarbaldehyde oxime	10.00 ± 0.06 (P) 13.70 ± 0.06 (P) ^e	8.0 ± 0.8	– 1.16 ± 0.06 ^e	–	–
XV	Benzimidazole-2-carbaldehyde oxime	9.90 ± 0.06 (S) 12.45 ± 0.2 (P) ^e	–	(1.5 ± 0.1) × 10 ⁻² (6.6 ± 0.06) × 10 ⁻¹ ^e	–	(5.9 ± 0.7) × 10 ⁻²
XVI	3-Pyridinecarbaldehyde oxime	10.21 ± 0.05 (P) 13.95 ± 0.04 (P) ^e	7.9 ± 0.6	(1.3 ± 0.05) × 10 ⁻² 1.87 ± 0.14 ^e	(7.3 ± 0.6) × 10 ⁻³	–
XVII	3-Bromobenzaldehyde oxime	10.28 ± 0.05 (S)				
XVIII	4-Bromobenzaldehyde oxime	10.33 ± 0.05 (S) 14.22 ± 0.05 (P) ^e	8.00 ± 0.6	(1.8 ± 0.1) × 10 ⁻² 2.07 ± 0.15 ^e	(9.4 ± 0.9) × 10 ⁻³	(3.4 ± 0.5) × 10 ⁻²
XIX	3-(2-Hydroxyimino-propyl)-1-methylimidazolium chloride	10.70 ± 0.10 (K)	8.0 ± 0.7	(1.5 ± 0.2) × 10 ⁻²		(9.0 ± 0.9) × 10 ⁻²
XX	2,3-Butanedione dioxime	10.54 [13] 14.68 ± 0.07 (P) ^e		(1 ± 0.1) × 10 ⁻² 1.20 ± 0.1 ^d		
XXI	4-Methoxybenzaldehyde oxime	10.78 ± 0.03 (K)				(4.7 ± 0.4) × 10 ⁻²
XXII	(2-Hydroxyimino-propyl)trimethylammonium bromide	10.97 ± 0.10 (K)	14.4 ± 0.9	(2.5 ± 0.1) × 10 ⁻²		
XXIII	Furfurol oxime	10.8 ± 0.1 (K) 14.82 ± 0.10 (P) ^e		(2.7 ± 0.2) × 10 ⁻² 4.37 ± 0.20 ^e	(8.0 ± 0.6) × 10 ⁻³	(7.7 ± 0.9) × 10 ⁻²

Table 1. (Contd.)

Comp. no.	Nucleophile (neutral form)	pK_a^a	$k_2, \text{ l mol}^{-1} \text{ s}^{-1}$			
			III ^b	IV ^c	V ^c	VI ^d
XXIV	4-Imidazolecarbaldehyde oxime	11.19 ± 0.06 (P)	11.4 ± 0.3	$(3.0 \pm 0.3) \times 10^{-2}$		0.11 ± 0.01
XXV	Acetaldehyde oxime	11.8 ± 0.1 (K) 15.57 ± 0.1 (P) ^e	16.8 ± 0.6	$(2.5 \pm 0.1) \times 10^{-2}$ 1.33 ± 0.05^d		0.10 ± 0.01
XXVI	Cyclohexanone oxime	12.23 ± 0.1 (K) 16.2 ± 0.2 (P) ^e	14.1 ± 0.5	$(3.1 \pm 0.3) \times 10^{-2}$ 3.3 ± 0.15^e		
XXVII	2,3-Butanedione dioxime monoanion	12.05 [13] 16.2 ± 0.1 (P) ^e		$(2.0 \pm 0.2) \times 10^{-2}$ 2.80 ± 0.07^e		$(6 \pm 0.3) \times 10^{-2}$
XXVIII	Acetone oxime	12.6 ± 0.1 (K) 16.3 ± 0.3 (P) ^e		$(2.7 \pm 0.2) \times 10^{-2}$ 1.47 ± 0.05^e	$(8.0 \pm 0.8) \times 10^{-3}$	$(6.5 \pm 0.5) \times 10^{-2}$
XXIX	1,1,2,2-Tetrafluoropropanol	12.74	0.83 ± 0.8	$(5.8 \pm 0.1) \times 10^{-3}$	$(3.7 \pm 0.4) \times 10^{-3}$	$(2.4 \pm 0.3) \times 10^{-2}$
XXX	2-Propynyl alcohol	13.55	9.1 ± 0.5	$(3.5 \pm 0.1) \times 10^{-2}$	$(1.3 \pm 0.1) \times 10^{-2}$	
XXXI	Choline	13.90	16.9 ± 0.9	$(2.7 \pm 0.2) \times 10^{-2}$	$(1.5 \pm 0.1) \times 10^{-2}$	0.17 ± 0.003
XXXII	Glycerol	14.1	16.4 ± 1.2	$(7 \pm 2) \times 10^{-3}$	$(2 \pm 0.15) \times 10^{-2}$	
XXXIII	Phenol	9.98 ± 0.03 (S) 13.52 ± 0.05 (P) ^e	$(5.6 \pm 0.5) \times 10^{-2}$	$(9.9 \pm 0.5) \times 10^{-5}$ $(1.22 \pm 0.07) \times 10^{-2e}$	$(1.6 \pm 0.1) \times 10^{-5}$	$(5.0 \pm 0.1) \times 10^{-4}$
XXXIV	Water	15.74 [14] 20.44 [15] ^e	1.6 ± 0.01	$(8.0 \pm 0.3) \times 10^{-3}$ 0.62 ± 0.06^d	$(9.6 \pm 0.6) \times 10^{-3}$	0.15 ± 0.02

^a The ionization constants were determined by potentiometry (P), spectrophotometry (S), or kinetic method (K).

^b Solvent 10% ethanol.

^c Solvent 5% ethanol.

^d Solvent water.

^e Solvent 80% DMSO.

^f Solvent 30% dioxane.

Second, processes with participation of Ox^- ions are characterized by extremely early bend of the Brønsted plot, which is observed at $pK_a \sim 8.0\text{--}9.0$. An analogous bend on the Brønsted plots for aroxide and alkoxide ions is located at $pK_a \sim 12.5\text{--}13.5$ [9, 11, 12], and for neutral and anionic nitrogen-containing nucleophiles, at $pK_a 10.0\text{--}11.0$ [17]. This is the reason that the α -effect rapidly drops down. In the reaction of acetone oxime (XXVIII, $pK_a 12.6$) with substrates IV, VI, and V the α -effect falls down 60-, 300-, and 800-fold, respectively, as compared with the values expected from the Brønsted relation with $\beta_N 0.5\text{--}0.6$.

Curvature of the Brønsted dependences for the reactions of anionic nucleophiles (aroxide, alkoxide, and oximate ions, etc.) with substrates containing electron-deficient carbon, sulfur, or phosphorus center may be explained by both change of the transition state structure and unfavorable solvation effects whose contribution increases as the basicity of nucleophile rises [9, 11, 12, 17]. As concerns the reaction series under study, it seems improbable that increase in the basicity of Ox^- ions is accompanied by sharp change of the transition state structure. For all series, regardless of the nature of the electron-deficient center in the substrate and the nature of the leaving group (cf.

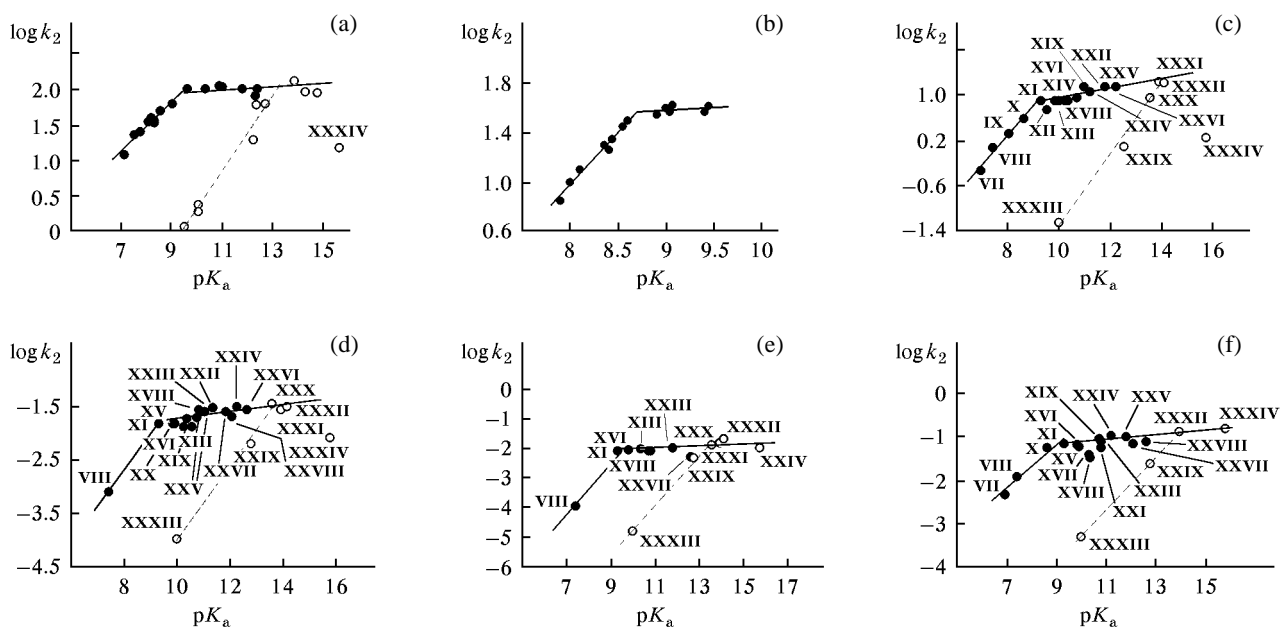
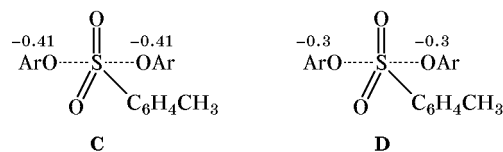


Fig. 5. Brønsted plots for the reactions of oximate (dark circles), alkoxide, and aroxide ions with (a) 4-nitrophenyl acetate (**I**) [5, 7, 9, 11], (b) diisopropyl fluorophosphate (**II**) [5, 7, 9, 11], (c) 2,4-dinitrophenyl *p*-toluenesulfonate (**III**), (d) 4-nitrophenyl *p*-toluenesulfonate (**IV**), (e) diethyl 4-nitrophenyl phosphate (**V**), and (f) ethyl 4-nitrophenyl ethylphosphonate (**VI**); dashed lines correspond to the Brønsted plots for the reactions of aroxide and alkoxide ions with esters **I** and **III–VI**. The point numbering is the same as compound numbering in Table 1.

compounds **I–VI**, the β_N values change from 0.5–0.6 [$pK_a(\text{Ox}^-) \leq 9.0$] to 0.1–0.2 [$pK_a(\text{Ox}^-) \geq 9.0$] despite the fact that the greatest difference in the reactivity in going from ester **I** to **V** is about 5 orders of magnitude. Moreover, the correlation plots are bent at a nucleophile basicity corresponding to $pK_a \sim 8.5$, and the position of the bend does not depend on the substrate structure and its reactivity. Most probably, nonlinear Brønsted dependences for the reactions with Ox^- ions should reflect differences in solvation of weakly and strongly basic Ox^- ions by water, as is assumed for reactions involving acyl group transfer to aroxide and alkoxide ions [11, 12] and also neutral and anionic nitrogen-containing reagents [17].

In going from water to H_2O –DMSO mixtures containing 0 to 95 vol % of DMSO, the nucleophilicity of oximate ion increases together with the DMSO concentration, the maximal effect being ~ 150 times. It is unlikely that this is the result of variation of the transition state structure. An analogous increase in nucleophilicity was also observed for anionic oxygen-containing nucleophiles, namely aroxide ions, in 80% DMSO [16]. Taking into account that sulfonyl group transfer to ArO^- ions is a permanent process, the effective charge distribution over the reacting centers and the Leffler–Grunwald parameters for the bonds being formed (α_N) and broken (α_X) may be

estimated on a quantitative level. The calculated parameters suggest that the transition states for the reactions under study in water and 80% DMSO are characterized by high degree of symmetry and similar charge distributions over the reaction centers (**C** and **D**) [12, 16].



$$\alpha_N = 0.45, \alpha_X = 0.55 \quad \alpha_N = 0.43, \alpha_X = 0.57$$

It is difficult to obtain quantitative estimates of δ , α_N , and α_X for Ox^- ions; however, the similarity of the Brønsted sensitivities to the nucleophile and nucleofuge basicities (reaction series *c*, *g*, and *h*; Table 3) indicates formation of similar transition states in water and 80% DMSO. Most probably, the reduced energy barrier to tosyl group transfer to ArO^- and Ox^- ions in H_2O –DMSO mixtures results from destabilization of the initial state due to partial desolvation of anionic nucleophile or weakening of hydrogen bonds between the nucleophile and water in the solvate complex [18].

Table 2. pK_a values of nucleofuges and rate constants k_2 ($l \text{ mol}^{-1} \text{ s}^{-1}$) for the reaction of aryl *p*-toluenesulfonates with anions derived from 2-benzimidazolecarbaldehyde oxime (**XV**) ($\mu = 0.1$, KCl) and acetaldehyde oxime (**XXV**) ($\mu = 1.0$, KCl); temperature 25°C

Comp. no.	XV (80% DMSO)		XXV (30% EtOH)	
	pK_a^a	k_2	pK_a^b	k_2
III	–	–	3.88	16.77 ± 0.29
IV	9.42	0.660 ± 0.045	7.51	0.0144 ± 0.001
XXXV	–	–	3.54	16.43 ± 0.47
XXXVI	6.27	114 ± 20	5.26	1.90 ± 0.03
XXXVII	10.65	0.077 ± 0.004	8.66	7.57×10^{-4}
XXXVIII	10.81	0.060 ± 0.003	–	–

^a Data of [16].

^b Data of [12].

The Brønsted dependences for ArO^- and Ox^- ions in 80% DMSO remain essentially the same as in water (cf. Figs. 5 and 6). The Brønsted dependence for ArO^- ions is linear, and that for oximate ions is curvilinear with a bend at $pK_a \geq 12.0$; the linear parts of the latter are characterized by β_N values of 0.46 and 0.007 (reaction series *g* and *h*; Table 3). Presumably, similar Brønsted dependences should be observed for Ox^- ions in H_2O –DMSO mixtures containing both greater and smaller than 80% of DMSO. It should be noted that the linear parts of the Brønsted plots obtained for reaction series *a*–*h* (Table 3) with $\beta_N \sim 0.5$ and $\beta_N \sim 0$ – 0.1 are formed by the same Ox^- anions. The first group of these includes oximes possessing powerful electron-acceptor substituents which are capable of reducing the effective charge on the reac-

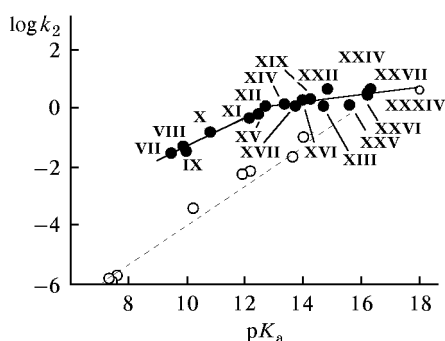
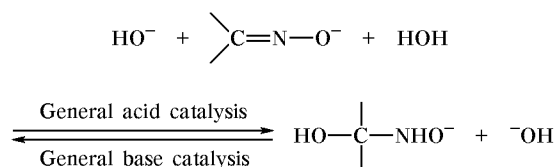


Fig. 6. Brønsted plots for the reactions of oximate (dark circles) and aroxide ions [16] (light circles) with 4-nitrophenyl *p*-toluenesulfonate (**IV**) in 80% DMSO (25°C , $\mu = 0.1$). For point numbering, see compound numbering in Table 1.

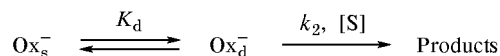
tion center of α -nucleophile (Figs. 5, 6). In this case oximate ions act as typical α -nucleophiles but the magnitude of the α -effect essentially depends on the oxime structure. The α -effect decreases as the basicity of oxime increases: it is ~ 140 for isonitrosoacetylacetone (**VII**) anion (pK_a 9.85) and ~ 1.0 for acetaldehyde oxime (**XXV**) anion (pK_a 15.57), i.e., the α -effect disappears (Fig. 6). Starting from $pK_a(\text{Ox}^-) \geq 12.0$ the reactivities of oximate ions become leveled. It should be emphasized that the points located in the vicinity of the bend on the Brønsted plot in 80% DMSO belong to the same compounds as in water. Like in water, it is hardly probable that the reason for curvature of the Brønsted plots and disappearance of the α -effect is sharp change of the transition state structure. The main reason is most likely to be different solvation of weakly and strongly basic oximes.

Equilibrium hydration of oximes in aqueous solution gives rise to reversible formation of α -hydroxy *N*-hydroxyamines [19] (Scheme 3).

Scheme 3.



Scheme 4.



Both hydration of oximes and dehydration of hydroxyamines conform to the general acid–base catalysis mechanism, and the concentration of the hydrated product strongly depends on the initial oxime structure. Probably, the degree of hydration of oximes with $pK_a(\text{Ox}^-) < pK_a(\text{bend})$ in H_2O and H_2O –DMSO mixtures is very small, while oximes with $pK_a(\text{Ox}^-) > pK_a(\text{bend})$ are hydrated to a considerable extent. The resulting differences in solvation of weakly and strongly basic oximes are responsible for the observed Brønsted plots in the reactions of Ox^- ions with diethyl 4-nitrophenyl phosphate, ethyl 4-nitrophenyl ethylphosphonate, 4-nitrophenyl *p*-toluenesulfonate, 4-nitrophenyl acetate, and other substrates [5]. Taking into account the above and the fact that nucleophilic attack is preceded by dehydration of α -nucleophile (Scheme 4), the Brønsted relation for oximate ions in water and 80% DMSO can be written as follows:

$$\log k_2 = \beta_{\text{exp}} \text{p}K_a + C, \quad (9)$$

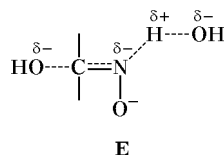
where

$$\beta_{\text{exp}} = (\beta + \beta^d)/(1 + \beta^d), \quad (10)$$

and β^d characterizes the sensitivity of desolvation to the basicity of dehydrated Ox^- ion: $\log K_d = \beta^d \text{p}K_a^d + C_1$. Using correlation (9) we can describe the kinetic behavior of oximes in water and H_2O –DMSO mixtures. Equation (9) for oximate ions with $\text{p}K_a(\text{Ox}^-) \leq \text{p}K_a(\text{bend})$ and $|\beta_d \rightarrow 0|$ can be transformed into the common Brønsted equation $\log k_2 = \beta \text{p}K_a + C$; $\beta_{\text{exp}} = \beta$. This is confirmed by the constancy of the α -effect for pair **B** (Fig. 7a). In the case of oximate ions with $\text{p}K_a(\text{Ox}^-) > \text{p}K_a(\text{bend})$ and β^d ranging from -0.42 to -0.50 , when the concentration of the active form of α -nucleophile is considerably reduced due to hydration, the Brønsted dependence becomes nonlinear, and the experimental sensitivity β_{exp} conforms to Eq. (10). The same follows from decrease in the α -effect for pair **A** with rise in DMSO concentration in the binary mixture (Fig. 7b). Then negative deviations of points for strongly basic oximes from the Brønsted dependence (9) should fit Eq. (11):

$$\Delta \log k_2 = (1 - \beta_{\text{exp}}) \log K_d. \quad (11)$$

According to Eq. (11), energetically unfavorable dehydration of Ox^- ions increases negative deviations from the Brønsted plot. A similar conclusion can be drawn by considering the reduced concentration of the active form of Ox^- ions to be the result of formation of solvate complex like **E** rather than of tetrahedral intermediate adduct [19]:



Finally, let us consider a new approach proposed by Buncl *et al.* [8, 20, 21], which ensures quantitative estimation of the effect of nucleophile basicity on its reactivity upon variation of $\text{p}K_a(\text{Nu}^-)$ via alteration of solvent composition rather than substituent nature. According to the authors, the proposed concept considerably simplifies the procedure. While conventional Brønsted dependences for ArO^- and Ox^- ions are curvilinear [5, 7, 9, 11, 12], the new approach deals with either a set of linear correlations, as in the

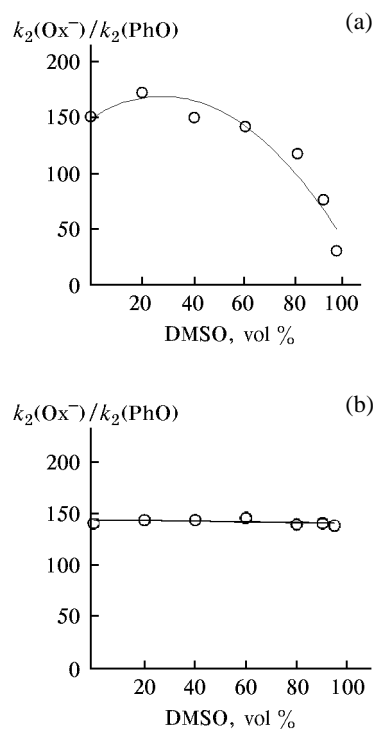


Fig. 7. Plots of the α -effect $[k_2(\text{Ox}^-)/k_2(\text{Ar}^-)]$ versus solvent composition for the reactions of 4-nitrophenyl *p*-toluenesulfonate (**IV**) with (a) 4-pyridinecarbaldehyde oxime and phenol (pair **A**) and (b) isonitrosoacetylacetone and 2,4-dibromophenol (pair **B**).

case of the reactions of ArO^- ions with *p*-nitrophenyl benzenesulfonate (**XXXIX**) and *p*-nitrophenyl diphenylphosphinate (**XL**) [8] (β_N decreases as the nucleophile basicity rises), or nonlinear dependences, as in the reaction of Ox^- ions with esters **I** and **XXXVI** for which a bend is observed at a DMSO concentration of ~ 80 vol % [8]. Such sensitivity ratio for the pair of nucleophiles ArO^-/Ox^- gives rise to a bell-like mode of variation of the α -effect for Ox^- [8]. It should be noted (the same was pointed out in [8, 20, 21]) that the differences in the slopes are so small that the confidence intervals of the corresponding dependences overlap. We made an attempt to apply the above approach to analysis of the behavior of two pairs of nucleophiles, **A** and **B**: $\text{p}K_a(\text{Ox}^-) > \text{p}K_a(\text{bend})$ (**A**) and $\text{p}K_a(\text{Ox}^-) < \text{p}K_a(\text{bend})$ (**B**). We found that both ArO^- and Ox^- ions conform to linear correlations (12) and (13) with similar β_N^* values on variation of the DMSO concentration from 0 to 90%.

* Treatment of the kinetic data for each oxime and phenol in pairs **A** and **B** in terms of the relation $\log k_2 - \text{p}K_a$ leads to β_N values coinciding with those in Eqs. (12) and (13) within the experimental error.

Table 3. Brønsted parameters of the reactions of oximate ions with 2,4-dinitrophenyl *p*-toluenesulfonate (**III**), 4-nitrophenyl *p*-toluenesulfonate (**IV**), diethyl 4-nitrophenyl phosphate (**V**), and ethyl 4-nitrophenyl ethylphosphonate (**VI**)^a

Reaction series	Substrate	p <i>K</i> _a (OxH)	Solvent	β _N	- <i>S</i>	<i>n</i>	<i>r</i>	<i>s</i>
<i>a</i>	III	≤9.0	10% Ethanol	0.50±0.04	3.70±0.30	5	0.990	0.006
<i>b</i>	III	≥9.0	10% Ethanol	0.12±0.002	0.29±0.003	6	0.871	0.08
<i>c</i>	IV	≥9.0	5% Ethanol	0.10±0.01	2.8±0.27	14	0.761	0.09
<i>d</i>	V	≥9.0	5% Ethanol	0.014±0.009	2.2±0.10	7	0.590	0.05
<i>e</i>	VI	≤9.0	H ₂ O	0.62±0.06	6.53±0.05	3	0.994	0.005
<i>f</i>	VI	≥9.0	H ₂ O	0.10±0.07	2.3±0.83	10	0.42	0.03
<i>g</i>	IV	≤12.0	80% DMSO	0.46±0.03	5.96±0.31	8	0.989	0.012
<i>h</i>	IV	≥12.0	80% DMSO	0.007±0.005	0.87±0.85	9	0.50	0.23

^a The Brønsted parameters were determined from the equation $\log k_2 = \beta_N pK_a + C$.

This result contradicts the data obtained by plotting a conventional Brønsted correlation in 80% DMSO, for at $pK_a(\text{Ox}^-) \geq 12.0$ correlation (12) should be bent and the α -effect should change. On the other hand, in keeping with Eqs. (12) and (13), the α -effect remains almost constant on variation of $pK_a(\text{Ox}^-)$ by about 8 orders of magnitude. Plotting of the log dependence hides more than twofold decrease of the α -effect for pair **A**, when it is estimated in a usual manner using the parameter Δ (Fig. 7). Even in this case, the values of Δ are somewhat distorted since it is almost impossible to select such Ox^-/ArO^- pairs for which $pK_a(\text{Ox}^-) = pK_a(\text{ArO}^-)$. The corresponding difference for H₂O–DMSO mixtures with any DMSO concentration (both for pair **A** and for pair **B**) attains $\Delta pK_a = pK_a(\text{ArO}^-) - pK_a(\text{Ox}^-) \approx 0.3$ at β_N 0.54 [Eq. (13)].

$$\text{Ox}^-: \log k_2 = (0.50 \pm 0.03)pK_a + (-6.6 \pm 0.34); \quad (12)$$

$$n = 12, r = 0.980, s = 0.06;$$

$$\text{Ar}^-: \log k_2 = (0.54 \pm 0.04)pK_a + (-9.23 \pm 0.43); \quad (13)$$

$$n = 12, r = 0.970, s = 0.055.$$

This difference in pK_a leads to overestimation of $k_2(\text{ArO}^-)$ in $\Delta = k_2(\text{Ox}^-)/k_2(\text{ArO}^-)$ by a factor of about 1.5, i.e., the data given in Fig. 7 reflect mainly a qualitative pattern of variation of the α -effect. One more uncertainty resulting from the application of the Buncl approach [8, 20, 21] is that it does not take into account change of the nucleofuge basicity. Provided that the correlation of $k_2(\text{Ox}^-)$ and $k_2(\text{ArO}^-)$ is valid for each H₂O–DMSO mixture, the nature of

the leaving group should necessarily be taken into account while constructing nontrivial Brønsted-like dependences [Eqs. (12) and (13)]. For example, the basicity of 4-nitrophenoxide ion (the leaving group in substrates **III–VI**) increases by 3.26 log units in going from water to 90% DMSO, which undoubtedly affects the k_2 value. Moreover, analysis of the data obtained in H₂O–DMSO mixtures for oximes with similar pK_a values (20% DMSO, 4-pyridinecarbaldehyde oxime, pK_a 10.11, $\log k_2$ -1.85; 80% DMSO, isonitrosoacetylacetone, pK_a 9.85, $\log k_2$ -1.3) leads to a surprising result: the reactivity of Ox^- ions increases as the nucleofuge basicity rises [pK_a (20% DMSO) 7.20, pK_a (80% DMSO) 9.42]. An analogous pattern is observed for aroxide ions (20% DMSO, phenol, pK_a 10.48, $\log k_2$ -4.1; 80% DMSO, 2,4-dibromophenol, pK_a 10.21, $\log k_2$ -3.44). The above data indicate that application of the approach developed in [8, 20, 21] to analysis of structure–reactivity relations requires special care and should be supplemented by (1) detailed analysis of the effect of the nucleophile and nucleofuge nature on the rate of the process and (2) proper choice of appropriate reactant pairs and pairs α -nucleophile–normal nucleophile. We believe that the conventional procedure involving variation of the structure of nucleophile and leaving group at a fixed solvent composition (as is postulated for the Brønsted approach) is preferred.

EXPERIMENTAL

Acetone oxime, acetaldehyde oxime, furfural oxime, cyclohexanone oxime, 2,3-butanedione di-oxime, salicylaldehyde oxime, phenol, 2,4-dibromo-

phenol, 1,1,2,2-tetrafluoroethanol, 2-propynyl alcohol, choline, glycerol, diethyl 4-nitrophenyl phosphate, and ethyl 4-nitrophenyl ethylphosphonate were commercial products which were purified by repeated distillation or recrystallization from appropriate solvents. Ethyl isonitrosoacetoacetate was synthesized as described in [22], and isonitrosoacetylacetone was obtained by the Wolff reaction [23]. The other oximes were synthesized by standard general procedure, by reaction of the corresponding aldehyde with hydroxylamine. 2-, 3-, and 4-Hydroxyimino-1-methylpyridinium iodides were synthesized from the corresponding oximes and methyl iodide. Aryl *p*-toluenesulfonates were obtained by acylation of phenols with *p*-toluenesulfonyl chloride in the presence of triethylamine [24].

Substituted phenol and benzimidazole sodium salts (as buffer components in H₂O–DMSO mixtures) were prepared in anhydrous ethanol by adding an equimolar amount of sodium ethoxide to the corresponding phenol or benzimidazole. In some experiments, sodium phenoxides and sodium benzimidazoles were prepared *in situ*.

Dimethyl sulfoxide of pure grade was kept for 24 h over sodium hydroxide, distilled twice over solid NaOH (bp 50°C/2–3 mm), and stored over 4-Å molecular sieves. Inorganic reagents of ultrapure or chemically pure grade were used without additional purification.

Solutions of nucleophilic reagents were prepared just before each series of kinetic experiments using double distilled water and freshly distilled DMSO. The solutions were adjusted to a required pH value by adding a concentrated solution of KOH, HCl, or tetraethylammonium hydroxide (for H₂O–DMSO mixtures). The ionic strength was maintained at 1 M (water) or 0.1 M (H₂O–DMSO) with the aid of KCl. The progress of reactions was monitored by UV spectroscopy following accumulation of the corresponding aroxide ions (for analytical wavelength, see [24]). The procedures for kinetic measurements and determination of apparent pseudofirst-order rate constants (k_{app} , s⁻¹) were described in detail in [12, 16, 17, 24]. The acid ionization constants of oximes and phenols were determined by potentiometric titration or kinetic methods [12, 24].

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