Hydroxylamine Anion as a Strong Acceptor of Acyl Groups[†]

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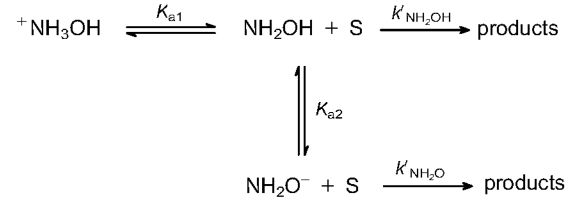
We show for the first time that the hydroxylamine anion is a strong α-nucleophile in the reactions of hydroxylamine with 4-nitrophenyl acetate, toluenesulfonate, diethylphosphate and diethylphosphonate.

Hydroxylamine occupies a special place in the series of typical α-nucleophiles. Despite the fact that hydroxylamine in aqueous solution exists in the cationic, neutral and anionic forms (Scheme 1),[‡] it is generally accepted that only the neutral form of hydroxylamine reacts with various classes of acylating agent.[1]



Scheme 1

It is difficult to agree with this interpretation of the kinetic behaviour of hydroxylamine. According to the modern concepts "structure–reactivity", hydroxylamine anion must have the properties of an α-nucleophile. This is confirmed by the results of the studies presented in this communication.

A formal kinetic analysis performed on the reactions of hydroxylamine with 4-nitrophenyl acetate **1**, 4-nitrophenyl 4′-toluenesulfonate **2**, 4-nitrophenyl diethylphosphate **3** and 4-nitrophenyl diethylphosphonate **4** indicates that the acyl group is transferred by two parallel pathways. The rate of the reaction of hydroxylamine with a substrate ($k'_2 = k_{obs}/[NH_2OH]_0$, dm^3 mol^{-1} s^{-1})[§] rapidly levels off as the pH increases, then a pH-independent transfer of the acyl group is observed and the reaction rate increases again with a decrease in the acidity of the medium starting from pH $\gtrsim$ 9 (Fig. 1). Finally, in the case of the substrates **2** and **3** at high concentrations of OH$^-$ ion, the pH-profile is distorted again reaching a constant value of $\log k'_2$ (Fig. 1). Such a pH profile for the *O*-acylation of hydroxylamine with various electrophilic substrates containing unsaturated carbon, sulfur and phosphorus atoms over a wide range of medium acidity was observed by us for the first time.

The similarity of the pH-profiles for the reactions studied (Fig. 1) irrespective of the nature of the substrate implies that hydroxylamine is the second reaction component. A neutral hydroxylamine molecule acts as a nucleophilic reagent in the region of the pH-independent transfer of the acyl group. Therefore, the k_{NH_2OH} value, dm^3 mol^{-1} s^{-1}, which characterizes the nucleophilicity of NH$_2$OH toward substrates **1–4**, can be determined from any point on the plateau of the pH-profile, because the fraction of the neutral form of hydroxylamine $\alpha_{NH_2OH} \rightarrow 1$ and

$$k'_2 = \alpha_{NH_2OH}k_{NH_2OH} = k_{NH_2OH} \qquad (1)$$

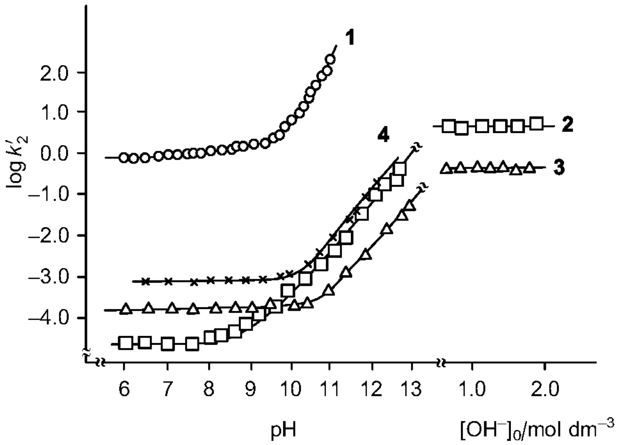


Fig. 1 pH-Profiles for the reaction of hydroxylamine with the substrates **1–4** in 5% aqueous ethanol at 25 °C and μ = 1.0 (KCl).

The situation in alkaline media is more uncertain. A considerable increase (by up to 10^3–10^5) in the transfer rate of the acyl groups (Fig. 1) is the result of: (*a*) general base catalysis by the hydroxide ion (specific base and general acid catalysis by water is an equivalent effect) of the interaction of the hydroxylamine molecule with the substrate, equation (2) or (*b*) an S$_N$2 reaction involving the hydroxylamine anion as an *O*-nucleophile occurs [equation (3), where $\alpha_{NH_2O^-}$ is the fraction of the anionic form of hydroxylamine].

$$k'_2 = \alpha_{NH_2OH}k_{NH_2OH}[OH^-]_0 = \frac{a_{H^+}}{K_{a2} + a_{H^+}}k_{NH_2OH}[OH^-]_0 \qquad (2)$$

$$k'_2 = \alpha_{NH_2O^-}k_{NH_2O^-} = \frac{K_{a2}}{K_{a2} + a_{H^+}}k_{NH_2O^-} \qquad (3)$$

A simple relation exists between these two rate laws, $k_{NH_2O^-} = k_{NH_2OH}(K_W/K_{a2})$, *i.e.*, the mechanisms (*a*) and (*b*) cannot be distinguished kinetically. It is impossible to say, based solely on the formal kinetic data, which form of hydroxylamine is responsible for the rates of transfer of the acyl group observed at pH $\geqslant$ 9. Nevertheless, we prefer equation (3) rather than (2), because the former indicates that the electron-deficient centre of the substrate undergoes an *O*-nucleophilic attack by the hydroxylamine anion. First, the fulfilment of the rate law (2) requires the existence of a stepwise mechanism for acyl group transfer,[2] implying that three sufficiently stable intermediates exist, namely, zwitterionic, neutral and anionic. This is unlikely for substrates **2–4**, because pentacoordinate intermediates with a bipyramidal structure must have short lifetimes approaching the time of the activation act.[3,4] Second, for substrates **2–4** no promotion effect due to the components of buffer systems (based on imidazole, 4-aminopyridine, tris, phosphate, *etc.*)[§] was found, although the promotion effect by buffer components is rather a rule than an exception for processes occurring *via* general acid-base catalysis. Third, the correlation relationship (4) is valid for various classes of reagents (Fig. 2),

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[†] In the subsequent discussion, the name "acyl group" is given not only to the acetyl group but also to the toluenesulfonyl, diethylphosphoryl and diethylphosphonyl groups.

[‡] In Scheme 1, S designates the substrate.

[§] The values of k'_2 for the reactions of hydroxylamine with substrates **2–4** remain unchanged at pH 11.0–12.5, both in the presence and in the absence of buffering components.

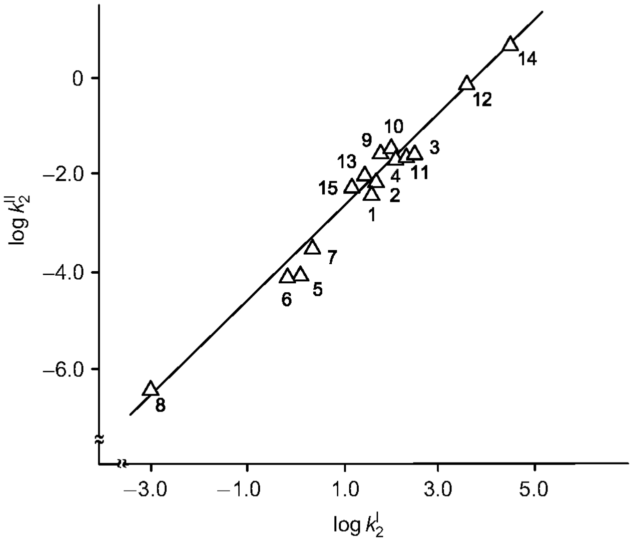

Fig. 2 Dependence of the reaction rate of substrate **2** ($\log k_2^{II}$) with various classes of *O*-nucleophilic reagents on the reaction rate of the these nucleophiles with substrate **1** ($\log k_2^{I}$) (the second-order reaction constants k_2 characterizing the *O*-nucleophilic reactivity of arylate and alcoholate ions toward substrates **1** and **2** were taken from refs. 5–9). Nucleophiles: 1 $CF_3CH_2O^-$, 2 $CHF_2CF_2CH_2O^-$, 3 $CH{\equiv}CCH_2O^-$, 4 $Me_3N^+CH_2CH_2O^-$, 5 PhO^-, 6 $4\text{-}ClC_6H_4O^-$, 7 $4\text{-}MeOC_6H_4O^-$, 8 $C_6F_5O^-$, 9 $AcNHO^-$, 10 $MeC(NH)_2{=}NO^-$, 11 $MeCH{=}NO^-$, 12 HOO^-, 13 ClO^-, 14 NH_2O^-, 15 HO^-.

which act as typical *O*-nucleophiles toward the substrates **1** and **2**. This linear relationship relates the free-energy barriers of the transfer of the toluenesulfonyl and acetyl groups to the fixed *O*-nucleophile, and the point for hydroxylamine anion falls on this line.

$$\log k_2^{II} = (-3.70 \pm 0.09) + (0.94 \pm 0.05)\log k_2^{I}, \quad r = 0.987, \ n = 15 \qquad (4)$$

Finally, the treatment of a large body of kinetic data (the interval of pH from 10 to 13, Fig. 1) for each of the substrates **2** and **3** with regard to the limiting values of $k'_{2,\max} = k_{NH_2O^-}$ according to equation (5) results in the value of $pK_a = 13.81 \pm 0.10$, which agrees well with the pK_{a2} value determined spectrophotometrically.[10] Thus, the pH-profiles of the reaction of hydroxylamine with substrates **1–4** are described adequately in terms of Scheme 1, *i.e.*, the neutral and anionic forms of hydroxylamine are responsible for the observed rates of the *O*-acylation, equation (6).

$$K_{a2} = k'_2/k'_{2,\max} \cdot a_{H^+} \qquad (5)$$

$$k_{obs} = k_{NH_2OH}[NH_2OH] + k_{NH_2O^-}[NH_2O^-] \qquad (6)$$

A comparative analysis of the k_2 values characterizing the reactivity of anionic oxygen-containing nucleophiles (Table 1, no. 2, 4–11) toward the esters **3** and **4** indicates that the hydroxylamine anion is one of the most efficient *O*-nucleophiles. When the basicities are similar, it reacts with substrates 30 times faster than the choline anion. Similar differences in the rates of transfer of the diethylphosphoryl and diethylphosphonyl groups are observed for the NH_2O^- ion and acetaldoximate, acetohydroxamate and hypohalogenite anions (see Table 1), which are α-nucleophiles. The values of $k_{NH_2O^-}$ and k_{HOO^-} become comparable only in the case of the HOO^- ion, the "leader" of α-nucleophiles. The extremely high nucleophilicity of the NH_2O^- ion can be illustrated more clearly in terms of the Brönsted extrathermodynamic approach. The maximum positive deviations $\Delta = 2.2\text{–}3.2$ from the Brönsted-type straight lines for "normal" oxygen-containing nucleophiles, namely, arylate and alcoholate ions, described by equations (7) and (8),[6,9] are observed for acetohydroxamate, hydroperoxide and hypohalogenite ions. Deviations of similar values are observed for the reaction of the NH_2O^- anion with **1** ($\Delta = 2.4$) and **2** ($\Delta = 2.0$); the hydroxylamine anion is highly competitive in reactivity with the "leader" of α-nucleophiles, the HOO^- ion, and even exceeds it: $k_{NH_2O^-}/k_{HOO^-} \approx 8$ for **1** and $k_{NH_2O^-}/k_{HOO^-} \approx 4$ for **2**. In other words, the hydroxylamine anion possesses supernucleophilic properties which are characteristic of typical α-nucleophiles only.

$$\log k_2 = \text{const}_1 + 0.68pK_a \qquad (7)$$

$$\log k_2 = \text{const}_2 + 0.59pK_a \qquad (8)$$

In conclusion, it should be emphasized that hydroxylamine is a unique α-nucleophile, and its neutral and anionic forms are strong acceptors of the acyl group, which provide extremely high reaction rates in acidic, neutral and alkaline media, unlike the other known α-nucleophiles.

All reagents (except for commercial-grade reagents) were synthesized and purified according to known procedures. The consumption of the substrate during the reaction of nucleophiles (NuH – an acid form coupled with the Nu^- base) with **1–4** was monitored spectrophotometrically by measuring the absorption of the 4-nitrophenolate ion evolved ($4\text{-}NO_2C_6H_4O^-$) at λ = 400–410 nm. The yield of the

Table 1 Basicity of nucleophiles (pK_a) and their reactivity (k_2) toward substrates **1**–**4**.[a]

No.	Nucleophile	pK_a	$k_2/dm^3\ mol^{-1}\ s^{-1}$			
			1	**2**	**3**	**4**
1	NH_2OH	6.09 ± 0.05(P)	1.42 ± 0.21	$(2.52 \pm 0.25) \times 10^{-5}$	$(1.91 \pm 0.14) \times 10^{-4}$	0.011 ± 0.001
2	NH_2O^-	13.74[10]	36500 ± 2000	4.00 ± 0.4	0.36 ± 0.02	4.10 ± 0.07
3	$MeC(NH_2){=}NOH$	6.10 ± 0.03(P)	0.63 ± 0.04	$(5.85 \pm 0.28) \times 10^{-4}$	$(2.75 \pm 0.09) \times 10^{-4}$	0.0016 ± 0.0001
4	$MeC(NH_2){=}NO^-$	12.9[11]	102 ± 13	0.0348 ± 0.0042	$(2.91 \pm 0.09) \times 10^{-3}$	0.041 ± 0.006
5	$AcNHO^-$	9.36 ± 0.03	95 ± 10	0.0306 ± 0.0004	0.0228 ± 0.0003	0.092 ± 0.001
6	$MeCH{=}NO^-$	11.8 ± 0.1(K)	470 ± 40	0.0254 ± 0.0008	0.0110 ± 0.0008	0.10 ± 0.01
7	$Me_3N^+CH_2CH_2O^-$	13.9[7]	133[7]	0.027 ± 0.001	0.0119 ± 0.0009	0.17 ± 0.01
8	HOO^-	11.5 ± 0.1(K)	4560[8]	0.99 ± 0.01	0.55 ± 0.02	7.3 ± 0.8
9	HO^-	15.7[12]	14.4[8]	0.0080 ± 0.0003	0.0096 ± 0.0006	0.150 ± 0.002
10	ClO^-	7.5[12]	26.8[8]	0.091 ± 0.0005	–	0.072 ± 0.003
11	BrO^-	8.7[12]	–	0.017 ± 0.001	–	0.15 ± 0.04

[a] All reactions were studied in 5% aqueous ethanol at 25 °C and an ionic strength μ = 1.0 (KCl). [b] pK_a values were determined by the potentiometric (P) and kinetic (K) methods.

$4\text{-}NO_2C_6H_4O^-$ ion was always quantitative; when the reaction was completed, it gave $[4\text{-}NO_2C_6H_4O^-] = [S]_0 = 5\times10^{-5}$ mol dm^{-3}. The rate of substrate consumption was described by the equation $k_{obs} = k_{OH}a_{OH} + k_2[NuH]_0$. The pseudo-first order rate constants were always corrected for the contribution from alkaline hydrolysis, *i.e.* $k_{obs} = k'_{obs} - k_{OH}a_{OH}$, s^{-1}. The methods of kinetic measurements have been reported elsewhere.[5,6]

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