KINETICS OF BASE-CATALYSED HYDROLYSIS AND CYCLISATION OF SUBSTITUTED ACETAMIDE AND BENZAMIDE *O*-(PHENOXYCARBONYL)OXIMES

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Dedicated to Professor Otto Exner on the occasion of his 75th birthday.

The reaction kinetics of acetamide *O*-(4-nitrophenoxycarbonyl)oxime have been studied in aqueous buffers at pH 2–11. At pH > 9, the pH dependence of k_{obs} is linear with slope 1, the cyclisation to 3-methyl-1,2,4-oxadiazol-5(4*H*)-one and 4-nitrophenol being the only reaction. At pH < 7.5, the only reaction is the hydrolysis giving 4-nitrophenol and acetamidoxime. The dependence of k_{obs} on pH has been used to determine the rate equation and to propose the reaction mechanism. The cyclisation kinetics of substituted benzamide *O*-(phenoxycarbonyl)oximes have been studied in the pH range from 9.25 to 11. The reaction mechanism has been proposed based on the ρ constants found. In the first reaction step, the proton is split off from the NH_2 group; the subsequent, rate-limiting step involves simultaneous N–C bond formation and C–O bond splitting.

Key words: Reaction kinetics; Reaction mechanism; Oximes; Amides; Cyclisations; 1,2,4-Oxadiazol-5(4*H*)-ones.

In the last 20 years we have studied the kinetics and mechanisms of cyclisation reactions. As nucleophilic groups were the anions of ureido, thioureido, acylthioureido, amide, sulfonamide, alkoxy and aryloxy groups and as electrophiles were esters, carboxylate ions, amides, thioamides, carbamates, nitriles and ketones[1].

Recently we decided to study the cyclisation reaction of substituted benzamide *O*-(phenoxycarbonyl)- and *O*-(alkoxycarbonyl)oximes[2]. This compounds cyclised in aqueous alkali medium[3,4] and some of the cyclic products 1,2,4-oxadiazole derivatives are biology active[5–7]. Due to their low solubility in water, we studied reactions of this compounds in methanolic

solutions of sodium methanolate. To our surprise, only methanolysis occurs, rather than the expected cyclisation reaction[2].

Therefore, we decided to study these substances in aqueous media. Due to the low solubility of the pure substrates, it was only possible to measure the kinetics at pH > 9. However, derivatives of acetamidoxime enabled us to follow the reaction across the broadest pH range possible.

EXPERIMENTAL

Melting points were determined on a Kofler hot plate apparatus and are uncorrected. The electronic spectra were scanned with a Hewlett–Packard 8453 Diode Array Spectrophotometer at 25 °C. ^{1}H NMR (360 MHz) spectra were recorded on a Bruker AMX spectrometer in $(CD_3)_2SO$ (compounds **3a**–**3e**) and in $CDCl_3$ (compounds **2a**–**2d**) with tetramethylsilane as internal reference; chemical shifts are given in ppm (δ-scale). The measurements of rate constants and dissociation constants were carried out spectrophotometrically using the same apparatus. Buffer pH values were determined using an MV 870 apparatus (VEB Pröcitronic) and a combined glass and silver chloride electrode at 25 °C. The reaction products and intermediates were identified by liquid chromatography-mass spectrometry using a Waters 616 chromatograph coupled with a VG-Platform Fison-ESP-3000D mass spectrometer, and by gas chromatography using a MEGA 5160 instrument.

Kinetic Measurements

The reaction of compound **2d** was followed kinetically in 0.01 mol l^{-1} hydrochloric acid and in chloroacetate, acetate, phosphate, hydrogenphosphate, *N*-methylmorpholine, and carbonate buffers. The kinetics of other substances were measured only in carbonate and basic phosphate buffers. The ionic strength of buffers was adjusted at 1 mol l^{-1} (compounds **2a**–**2d**) or 0.5 mol l^{-1} (compounds **1a**–**1h**) by addition of 2 M potassium chloride solution.

A 1 cm quartz cell with lid was charged with 2 ml of aqueous buffer solution and placed in the thermostat block of the spectrophotometer cell compartment at 25 °C. After attaining the temperature required, 20–50 μl of a solution of the substrate **1a**–**1h** and **2a**–**2d** in dioxane ($c = 5 \cdot 10^{-3}$ mol l^{-1}) was added, the content of cell was mixed and the absorbance change was recorded. The observed rate constant was calculated by the program installed in the computer of spectrometer. Experiments with reaction half-lives below 5 s were carried out using a Durrum D-150 stopped-flow spectrophotometer.

Identification of Reaction Products

In the case of compound **1e** we used direct LC MS analysis of the reaction mixture obtained under kinetic conditions. Reaction in carbonate buffer (pH 10.4) yielded equivalent amounts of the cyclic product **3e** and 4-nitrophenol. Not even trace amounts of benzamidoxime were detected. A partly reacted sample in acetate buffer contained *ca* 80% unreacted substrate **1e** and equal proportions of 4-nitrophenol and benzamidoxime. The presence of cyclic product **3e** could not be found. In the case of compound **2d** we dissolved 100 mg sample in 10 ml (i) carbonate buffer (pH *ca* 10.4); (ii) phosphate buffer (pH *ca* 6.0); or (iii) 0.01 M hydrochloric acid. At the end of reaction, each of the three samples was evaporated, the residue ex-

tracted with acetone and the acetone extracts analysed by GC. In carbonate buffer we could unambiguously prove the presence of 4-nitrophenol and the cyclic product **5** in quantitative amounts, the hydrolysis product of acetamidoxime was not detected at all. In the reactions carried out in phosphate buffer and hydrochloric acid 4-nitrophenol and acetamidoxime were formed in quantitative amounts; the cyclic product **5** was absent.

Chemicals

The substituted X-benzamide *O*-(Y-phenoxycarbonyl)oximes (**1a**–**1h**; Scheme 1) were synthesised from the appropriate substituted benzamidoximes and aryl chloroformates as described elsewhere[2].

Substituted Acetamide *O*-(Y-Phenoxycarbonyl)oximes (**2a**–**2d**; Scheme 2); General Procedure

Acetamidoxime. A solution of hydroxylamine[8] (18 g, 0.54 mol) in dry butan-1-ol (100 ml) was stirred and treated with acetonitrile (25 ml, 0.48 mol), added at once, and the reaction mixture was stirred at 50–55 °C for 55 h. After distilling off 60 ml butanol, the remaining solution was filtered with charcoal. The product that separated on cooling (18 g, 50%) (m.p. 135–137 °C in accordance with ref.[9]) was pure enough to be used for the subsequent step.

Oximes **2a**–**2d**. A 100 ml flask was charged with acetamidoxime (0.74 g, 0.01 mol), dry dichloromethane (20–50 ml) and triethylamine (1.45 ml, 0.01 mol). The mixture was cooled to 0–5 °C and treated dropwise with a solution of the respective aryl chloroformate in 10–20 ml dichloromethane. After distilling off the solvent, the residue was suspended in 75 ml dry acetone. The insoluble triethylamine hydrochloride was filtered off and the acetone filtrate evaporated. The oily residue crystallised on standing, and was recrystallised from chloroform or a benzene–hexane mixture.

Acetamide O-(phenoxycarbonyl)oxime (**2a**). Yield: 67%, m.p. 109–111 °C. For $C_6H_{10}N_2O_3$ (194.2) calculated: 55.67% C, 5.19% H, 14.43% N; found: 55.61% C, 5.21% H, 14.54% N. ^{1}H NMR ($CDCl_3$): 7.17–7.21 m, 2 H (H-2, H-6); 7.35–7.40 m, 2 H (H-3, H-5); 7.23–7.25 d, 1 H (H-4); 4.93 brs, 2 H (NH_2); 1.95 s, 3 H (CH_3).

Acetamide O-(4-chlorophenoxycarbonyl)oxime (**2b**). Yield: 27%, m.p. 84–86 °C. For $C_9H_9ClN_2O_3$ (228.2) calculated: 47.28% C, 3.97% H, 15.51% Cl, 12.25% N; found: 47.52% C, 4.03% H, 51.28% Cl, 12.32% N. ^{1}H NMR ($CDCl_3$): 7.13–7.15 d, 2 H (H-2, H-6); 7.32–7.35 d, 2 H (H-3, H-5); 4.96 brs, 2 H (NH_2); 1.97 s, 3 H (CH_3).

Acetamide O-(3-nitrophenoxycarbonyl)oxime (**2c**). Yield: 61%, m.p. 107–110 °C. For $C_9H_9N_3O_5$ (239.2) calculated: 45.19% C, 3.79% H, 17.57% N; found: 45.43% C, 3.75% H, 17.76% N. ^{1}H NMR ($CDCl_3$): 8.09–8.18 m, 2 H (H-2, H-4); 7.55–7.61 m, 2 H (H-5, H-6); 4.96 brs, 2 H (NH_2); 2.00 s, 3 H (CH_3).

Acetamide O-(4-nitrophenoxycarbonyl)oxime (**2d**). Yield: 77%, m.p. 118–120 °C. For $C_9H_9N_3O_5$ (239.2) calculated: 45.19% C, 3.79% H, 17.57% N; found: 45.39% C, 3.67% H, 17.32% N. ^{1}H NMR ($CDCl_3$): 7.39–7.42 d, 2 H (H-2, H-6); 8.26–8.29 d, 2 H (H-3, H-5); 4.89 brs, 2 H (NH_2); 2.01 s, 3 H (CH_3).

Substituted 3-Phenyl-(4*H*)-1,2,4-oxadiazol-5-ones (**3a**–**3e**; Scheme 2) – General Procedure

Oxime **1** (0.02 mol) was dissolved in aqueous solution of sodium hydroxide (50 ml, 2 mol l^{-1}) at 30–40 °C. After 10 min stirring, the reaction mixture was cooled and acidified with hy-

drochloric acid to pH 3–4. The separated oxadiazolone **3** was isolated by filtration, washed with ice water, and recrystallised from ethanol. The compound **3e** can be purified by sublimation under reduced pressure.

3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5(4H)-one (**3a**). Yield: 65%, m.p. 210–212 °C. For $C_9H_8N_2O_3$ (192.2) calculated: 56.25% C, 4.20% H, 14.58% N; found: 56.09% C, 4.22% H, 14.56% N. ^{1}H NMR $(CD_3)_2SO$: 7.80–7.81 m, 2 H (H-2, H-6); 7.16–7.19 d, 2 H (H-3, H-5); 3.41 brs, 1 H (NH); 3.88 s, 3 H (CH_3).

3-(4-Methylphenyl)-1,2,4-oxadiazol-5(4H)-one (**3b**). Yield: 61%, m.p. 222–224 °C. For $C_9H_8N_2O_2$ (176.2) calculated: 61.36% C, 4.58% H, 15.90% N; found: 61.26% C, 4.66% H, 15.66% N. ^{1}H NMR $(CD_3)_2SO$: 7.74–7.76 m, 2 H (H-2, H-6); 7.42–7.44 d, 2 H (H-3, H-5); 3.58 brs, 1 H (NH); 2.43 m, 3 H (CH_3).

3-(4-Chlorophenyl)-1,2,4-oxadiazol-5(4H)-one (**3c**). Yield: 57%, m.p. 281–283 °C. For $C_8H_5ClN_2O_2$ (196.6) calculated: 48.88% C, 2.56% H, 18.03% Cl, 14.25% N; found: 48.92% C, 2.59% H, 18.36% Cl, 14.21% N. ^{1}H NMR $(CD_3)_2SO$: 7.71–7.74 m, 2 H (H-2, H-6); 7.86–7.88 d, 2 H (H-3, H-5); 3.40 brs, 1 H (NH).

3-(4-Nitrophenyl)-1,2,4-oxadiazol-5(4H)-one (**3d**). Yield: 54%, m.p. 313–315 °C. For $C_8H_5N_3O_4$ (207.2) calculated: 46.39% C, 2.43% H, 20.29% N; found: 46.40% C, 2.38% H, 20.38% N. ^{1}H NMR $(CD_3)_2SO$: 7.10–7.13 m, 2 H (H-2, H-6); 8.45–8.48 d, 2 H (H-3, H-5); 3.41 brs, 1 H (NH).

3-Phenyl-1,2,4-oxadiazol-5(4H)-one (**3e**). Yield: 65%, m.p. 203–204 °C. For $C_8H_6N_2O_2$ (162.2) calculated: 59.26% C, 3.73% H, 17.28% N; found: 59.24% C, 3.73% H, 17.34% N. ^{1}H NMR $(CD_3)_2SO$: 7.60–7.68 m, 2 H (H-2, H-6); 7.85–7.87 m, 3 H (H-3, H-4, H-5); 3.41 brs, 1 H (NH).

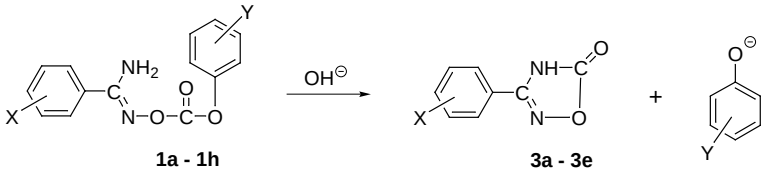
Acetamide O-(methoxycarbonyl)oxime (**4**; Scheme 3) was prepared in the same way from acetamidoxime and methyl chloroformate in 30% yield, m.p. 86–88 °C. For $C_4H_8N_2O_3$ (132.1) calculated: 36.36% C, 6.10% H, 21.20% N; found: 36.11% C, 6.16% H, 21.43% N.

3-Methyl-1,2,4-oxadiazol-5(4H)-one (**5**; Scheme 3). Oxime **4** (2.1 g, 28 mmol) was dissolved in water (25 ml) and sodium hydroxide solution (2–3 drops, 1 mol l^{-1}) added. After 12 h, the solution was acidified with hydrochloric acid to pH 2–3. The water was distilled off, and the oily residue was left to crystallise (several days). Repeated recrystallisation from a benzene–cyclohexane mixture (2 : 3) gave 1.6 g (75%) white crystals, m.p. 63–64 °C in accordance with ref.[10]. For $C_3H_4N_2O_2$ (100.1) calculated: 36.01% C, 4.03% H, 28.00% N; found: 35.98% C, 40.10% H, 27.62% N.

RESULTS

The preparation of starting compounds **1**, **2**, and **4** was achieved by standard procedure[2]. Cyclisation of these compounds in alkaline aqueous solutions afforded the corresponding 1,2,4-oxazol-5(4*H*)-ones **3** and **5** in good yields (Schemes 1–3). Detailed kinetic studies of these reactions have been performed.

The kinetics of the reaction of compound **2d** accompanied by splitting off of 4-nitrophenoxide ion was followed in 0.01 M hydrochloric acid and in aqueous buffer solutions in the pH range from 2 to 11.86. The kinetics of the reaction of compounds **2a**–**2c** was measured in carbonate and two

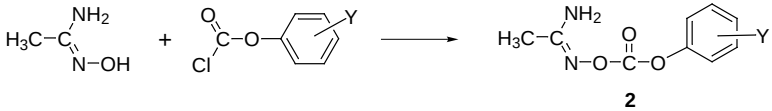


1a - 1h **3a - 3e**

1	X	Y	**1**	X	Y
a	4-CH_3O	4-NO_2	**e**	H	4-NO_2
b	4-CH_3	4-NO_2	**f**	H	3-Cl
c	4-Cl	4-NO_2	**g**	H	4-Cl
d	4-NO_2	4-NO_2	**h**	H	H

3	**a**	**b**	**c**	**d**	**e**
X	4-OCH_3	4-CH_3	4-Cl	4-NO_2	H

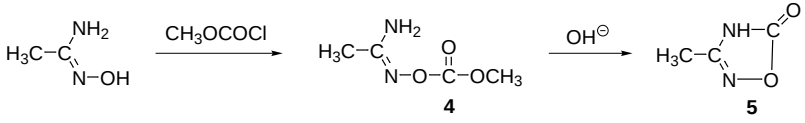
SCHEME 1



2

2	**a**	**b**	**c**	**d**
Y	H	4-Cl	3-NO_2	4-NO_2

SCHEME 2



4 **5**

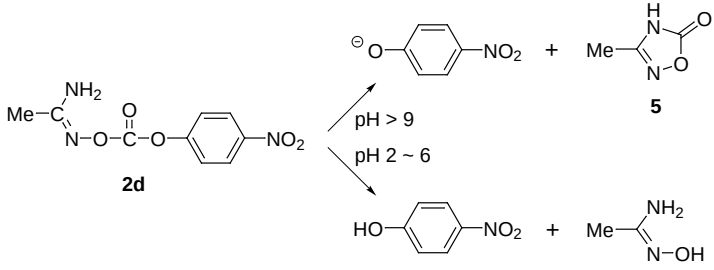
SCHEME 3

phosphate buffers (pH 10.35–11.59) and of **1a**–**1h** in carbonate buffer (pH 10.35). The reactions followed pseudo-first-order kinetics in all solutions. In the case of compounds **2a**–**2d** the k_{obs} values increased linearly with the buffer concentration and were extrapolated to the zero buffer component. In the case of compounds **1a**–**1h** the k_{obs} values were independent of the buffer concentration or showed only mild increase. The rate constants k_{OH} related to the activity of hydroxyl ion are given in Tables I and II.

TABLE I
Rate constants k_{OH} (l mol^{-1} s^{-1}) of cyclisation reaction **2**→**5**. The respective Hammett constant is $\rho = 0.96 \pm 0.03$

Compound	**2a**	**2b**	**2c**	**2d**
k_{OH}	2.5 ± 0.08	4.0 ± 0.4	11.5 ± 0.6	17.5 ± 0.5

The dependence of buffer independent log *k* values on pH of **2d** is presented in Fig. 1. At pH > 9, where the dependence is linear with slope 1, the only reaction products are 4-nitrophenoxide and **5**. At pH < 7.5, hydrolysis is the only reaction (Scheme 4).



SCHEME 4

The rate of formation of 4-nitrophenoxide ion was also measured with compound **1d** in four carbonate and two basic phosphate buffers (pH 9.25–10.90). The reaction kinetics was pseudo-first order; again the dependence of buffer independent log *k* values on pH was linear with slope 1 (Fig. 1). At lower pH values is the reaction slower and the measurement is complicated by association of the substrate: the spectral lines did not cross the isosbestic points, and the absorbance–time dependence was no longer exponential. The results of these measurements were not used in the calculations of k_{obs}. At still lower pH values, the solution began to become turbid due to separation of the substrate.

DISCUSSION

From the dependence of log *k* on pH of compound **2d** (Fig. 1) and the reaction products identified it follows that in the region of the dependence of *k vs* pH with slope 1 the reaction product is cyclisate **5**. In the region of the

TABLE II
Rate constants k_{OH} (l mol^{-1} s^{-1}) of cyclisation reaction **1**→**3**. The Hammett constants for compounds **1a**–**1e** and **1e**–**1h** are ρ = 0.52 ± 0.02 and 1.04 ± 0.03, respectively

Compound	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**
k_{OH}	114 ± 3	121 ± 2	184 ± 3	370 ± 5	143 ± 4	56 ± 2	39.0 ± 0.5	23.1 ± 0.4

dependence of log *k* *vs* pH with slope 0 or –1, the substrate is only hydrolysed. Both these regions can be discussed separately.

The rate of the cyclisation reaction in which substrate **2d** reacts with OH^- ion is expressed by Eq. (*1*).

$$v = k_{OH}[\mathbf{2d}]a_{OH} = k_{OH}[\mathbf{2d}]K_w/a_H \qquad (1)$$

The same is also true for the cyclisation reactions of the other substances **1** and **2**. The values of the respective k_{OH} constants are given in Tables I and II.

At pH below 7.5, the relationship between the observed rate constant and proton activity is of the form given by Eq. (*2*).

$$k_{obs} = (a + ba_H)/(c + da_H) \qquad (2)$$

At pH < 6, the reaction obviously involves the protonated substrate SH^+ and water, and the reaction rate increases with increasing proton activity as the concentration of the protonated substrate increases simultaneously, too.

At pH < 3.5, almost all the substrate is present in its protonated form, and the reaction rate becomes pH-independent. The change in slope of the dependence log *k* *vs* pH from 1 to 0 gives rise to a value of $pK_A = 4.6$ for the protonated substrate. This part of the dependence in Fig. 1 is defined by the Eq. (*3*).

$$k_{extr} = k_0^{SH} a_H/(a_H + K_A) \qquad (3)$$

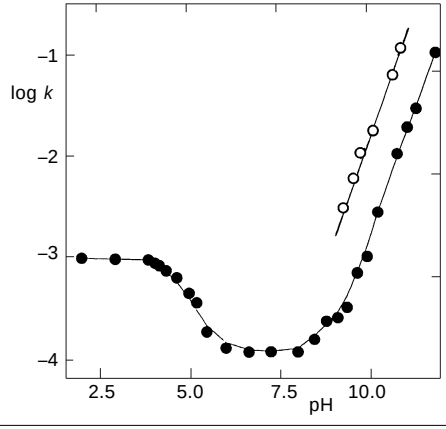


FIG. 1
Logarithmic dependence of rate constants *k* (s^{-1}) on pH of the reactions of amidoxime carbonates **1e** (○) and **2d** (●) measured at 25 °C in aqueous solutions of 0.01 M hydrochloric acid and buffers with constant ionic strength (I = 1.0 mol l^{-1} for compound **2d** and I = 0.5 mol l^{-1} for compound **1e**). The solid line is the theoretical dependence calculated from Eq. (*6*) and the constants given in Discussion

In the pH range of 6–8, the non-protonated substrate can react with water. Then the reaction rate can be defined by Eq. (*4*).

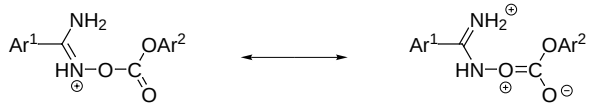
$$v = k_0^S[S] \tag{4}$$

A kinetically equivalent, more probable, alternative ist the reaction of the protonated substrate with hydroxyl ion. In such a case the reaction rate is given by Eq. (*5*).

$$v = k_{OH}^{SH^+}[SH^+]a_{OH} = k_{OH}^{SH^+}(K_w/(a_H + K_A))[S] \tag{5}$$

This alternative can be preferred for the following reasons.

1. The difference between the rate constants k_0^S and $k_0^{SH^+}$ is one order of magnitude only. The protonation of substrate increases the rate of reaction with water by at least two orders due to the electrostatic effect of the positive charge. At the same time delocalisation of the electron pair at the oxygen of N–O group is eliminated, which substantially increases the reactivity of the carbonyl carbon atom (Scheme 5).



SCHEME 5

2. Esters with good leaving groups[11] show a break in the log *k vs* pH dependence due to the change of reaction pathway from [substrate + hydroxyl ion] to [substrate + water] at pH 6–7. With amidoxime carbonate **2d**, this change takes place at about pH 9; however, at this pH, there is no hydrolysis but cyclisation to product **5**, which means that the hydroxyl ion-catalysed hydrolysis takes place at pH ≥ 10.

3. If a neutral substrate of RCOOAr type reacts with water, then this reaction is subject to general base catalysis or nucleophilic catalysis[12]. The hydrolysis of amidoxime carbonate **2d** exhibits independence of k_{obs} on the concentration of acid phosphate buffer. The resulting equation (*6*) for the values *k* has the form:

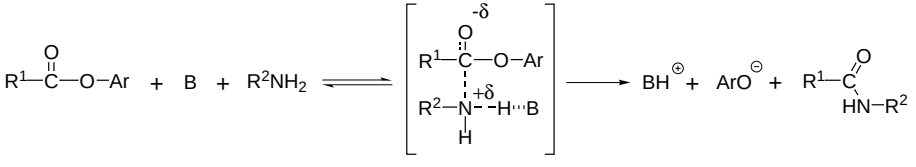
$$k = \frac{k_0^{SH^+} + k_{OH}^{SH^+}\frac{K_w}{a_{H^+}} + k_{OH}^{S}K_A\frac{K_w}{a_H^2}}{1 + \frac{K_A}{a_{H^+}}}, \tag{6}$$

where $k_0^{SH^+}$ = (1.01 ± 0.02) · 10^{-3} is the rate constant of reaction of the protonated substrate with water, k_0^S = (1.18 ± 0.01) · 10^{-4} is the rate constant of neutral substrate with water calculated from Eq. (*4*); k_{OH}^S = 17.5 ± 0.9 l mol^{-1} s^{-1} is the rate constant of reaction of the neutral substrate with hydroxyl ion, $k_{OH}^{SH^+}$ = (2.82 ± 0.02) · 10^5 l mol^{-1} s^{-1} is the rate constant of reaction of the protonated substrate with hydroxyl ion, K_A = (2.4 ± 0.4) · 10^{-5} mol l^{-1} is the dissociation constant of the substrate.

The rate constants k_{OH} of cyclisation of compounds **1a**–**1e** (substituent X in benzamidoxime) and **2a**–**2d**, **1e**–**1h** (substituent Y in phenoxy group) were correlated with σ^0 constants.

The constant ρ for compounds **1a**–**1e** (substituent X in benzamidoxime) is 0.52 ± 0.02, for splitting off the substituted phenols (not including 4-nitro derivatives **1a** and **2d**), 0.96 ± 0.03 for compounds **2** and 1.04 ± 0.03 for compounds **1**. The experimentally found values of σ constants for 4-nitro group in compound **1e** was 0.81 (the same as in its methanolysis[2]) and 0.9 for compound **2d**. This is due to the imbalance between the change in the charge at the phenoxy group oxygen in the transition state and the degree of delocalisation of the π electrons because delocalisation of π electrons lags behind the charge transfer in the transition state and does not occur to a sufficient extent until the C–O bond is broken to a large extent[13–16].

For determination of mechanism of cyclisation of amidoxime carbonates **1** and **2**, the decisive effect is that of substituents in the benzene ring of compounds **1a**–**1e**. With very weak nucleophiles such as weakly-basic amines, it is possible to presume two mechanisms for the base-catalysed reaction. The first involves general base-catalysed removal of the proton from amino group in the transition state and with formation of a tetrahedral intermediate[12] (Scheme 6).

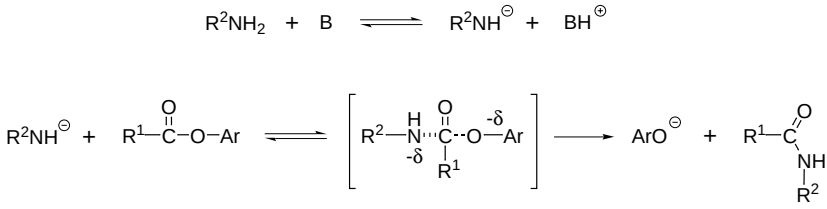


SCHEME 6

The amino group carries a partial positive charge in the transition state, hence an electron-withdrawing substituent in the R^2 group will slow down the reaction, and the ρ constant has negative sign.

The second mechanism presumes that the proton is split off from the amino group in a pre-equilibrium step, and the activated complex of the

subsequent rate-limiting step has a partial negative charge at the nitrogen atom (Scheme 7).



SCHEME 7

The first step of this mechanism will be enhanced by electron-withdrawing R^2 groups and the ρ constant will have positive sign. The second step will be retarded by electron-withdrawing groups (negative ρ). However, the experimentally determined ρ value of 0.52 is only consistent with this mechanism and indicates that the pre-equilibrium has the larger ρ value.

In carbonate and basic phosphate buffers, the k_{obs} constants of reactions of compounds **2a**–**2d** increased linearly with increasing concentration of the basic buffer component, which could indicate a general base catalysis by CO_3^{2-} and PO_4^{3-} ions, *i.e.* manifestation of the first mechanism mentioned (or simultaneous operation of both the mechanisms) for these bases. The small or no increase of k_{obs} with carbonate and phosphate buffers for compounds **1a**–**1h** may be due to their greater reactivity with HO^- ions.

Beside the determination of reaction mechanism of cyclisation, the study of substituent effects also enables an estimate of the extent of formation of a new bond to nucleophile and splitting of the bond to the leaving group in the transition state. Suitable pieces of information[17] can be obtained from the β_{nuc} and β_{lg} values of the rate-limiting step (Eqs (*7*) and (*8*)).

$$\beta_{nuc} = \mathrm{d} \log k_{nuc} / \mathrm{d}pK_{A,nuc} \qquad (7)$$

$$\beta_{lg} = \mathrm{d} \log k_{lg} / \mathrm{d}pK_{A,lg} \qquad (8)$$

In the case of amidoxime carbonates, the nucleophilic group forms a part of the substrate with the substituted benzene ring (the reaction is intramolecular), and the leaving group is a substituted phenol.

In the cyclisation reaction, the k_{OH}^{S} value is a product of the dissociation constant K_A^S of the neutral substrate and the rate constant k_{nuc} of the rate-limiting step (Eq. (*9*)).

$$k_{OH}^{S} = k_{nuc} K_A^S / K_w \qquad (9)$$

and $\rho = \rho_{nuc} + \rho_{K_A}$.

As the dissociation of neutral substrates is very similar to that of substituted benzoic acids, its ρ constant will be similar identical with the value ρ = 1 of benzoic acids.

Therefrom it follows that the ρ constant of the rate-limiting step is $\rho_{nuc} \approx 0.52 - 1 \approx -0.48$, and $\beta_{nuc} = -\rho_{nuc} \approx 0.48$.

The constant for splitting off of the substituted phenols was determined in compounds **1e**–**1h** (ρ = 1.04). This constant can be transformed into β_{lg} by division by –2.23, which is the negative value of ρ constant for dissociation of substituted phenols[18], $\beta_{lg} = -0.47$.

The values found for β_{nuc} (0.48) and β_{lg} (–0.47) express the extent of change of charge in the reaction centre in the activated complex of the rate-limiting step of reaction involving an attack of the neutral substrate by negatively charged nucleophile with formation of a neutral reaction product and a negatively charged nucleofuge. Comparison of β_{nuc} and β_{lg} shows that in the transition state, the change in charge at both the reacting atoms (N and O) is approximately the same.

In methanolic solution[2], methoxide reacts as a nucleophile with the carbonyl group of substrate **1**. On the other hand, in aqueous solution, where the dependence of log *k* on pH has the slope 1, the reaction involves an acid-base reaction of hydroxyl ion with the substrate and subsequent intramolecular attack at the carbonyl group by the NH anion formed to give the cyclic product. This difference in mechanism lies in the far higher nucleophilicity of methoxide ion as compared with that of hydroxyl ion. For example, methoxide reacts with aryl acetates in aqueous solution almost two orders faster than hydroxyl ion[19] although the pK_A value of methanol in water is almost the same as the pK_A of water[20].

The decisive reason lies in the substantially lower energy needed for partial desolvation of methoxide ion in water as compared with hydroxyl ion in water. Since the solvation energy of methoxide ion in methanol is much lower than that in water (its value is not known at present but the difference of solvation energies will be the same as, or larger than, that of chlo-

ride and acetate ions, *i.e.*, 13.2 and 16.0 kJ mol^{-1}, respectively[21]), the increase in its nucleophilicity as compared with its basicity will be even more distinct than that in water.

CONCLUSION

In contrast to the reaction of compound **1** with methoxide in methanol, where methanolysis is the only process[2], the products of reaction of non-protonated compounds **1** and **2** with hydroxyl ion in aqueous media are the cyclic compounds **3** and **5**, respectively. This appears due to the much higher energy needed for partial desolvation of hydroxyl ion in its attack on carbonyl group, hence the cyclisation reaction becomes more advantageous energetically. The cyclisation reaction proceeds *via* two steps: the first, reversible, step involves loss of a proton from the amino group, and the second, concerted, step involves N–C bond formation and C–O bond cleawage (Scheme 7). Compound **2d** at pH < 7.5 exclusively undergoes hydrolysis of the protonated substrate with hydroxyl ion, and in moderately acid media, it reacts with water.

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