KINETICS AND MECHANISM OF THE FORMATION AND DECOMPOSITION OF IMIDAZOLIN-4-ONES FROM 2-(*N*-BENZOYLAMINO)ALKANAMIDES IN AQUEOUS MEDIUM

Miloš SEDLÁK[1], Jiří HANUSEK, Radim BÍNA, Jaromír KAVÁLEK[2] and Vladimír MACHÁČEK[3,*]

Department of Organic Chemistry, University of Pardubice, 532 10 Pardubice, Czech Republic; e-mail: [1] milos.sedlak@upce.cz, [2] jaromir.kavalek @upce.cz, [3] vladimir.machacek@upce.cz

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

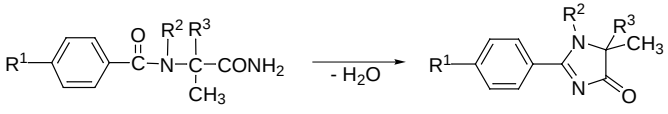
The cyclization reactions of substituted 2-(*N*-benzoyl-*N*-methyl)aminoalkanamides **1a**–**1g** have been studied in aqueous medium. The Hammett reaction constant is ρ = 1.4 for the cyclization reactions of compounds **1a**–**1e** in sodium hydroxide solutions. 2-[*N*-Methyl-*N*-(4-nitrobenzoyl)amino]-2-(4-nitrophenyl)propanamide (**1g**) is cyclized to imidazolinone **2g** in aqueous amine buffers of pH 9–11.5; the reaction is subject to specific base catalysis in these media, and the rate-limiting step is the formation of a tetrahedral intermediate. In sodium hydroxide solution, the primary cyclization product is hydrolyzed to give an intermediate **M** which is subsequently decomposed to sodium 4-nitrobenzoate and 2-methylamino-2-(4-nitrophenyl)propanamide. At low sodium hydroxide concentration, the rate-limiting step of the opening of imidazoline ring of compound **2g** is non-catalyzed decomposition of the intermediate. At higher sodium hydroxide concentrations, the other reaction path begins to make itself felt: hydroxide-ion-catalyzed decomposition of the intermediate. The dependence of observed rate constant of cyclization of compound **1f** on sodium hydroxide concentration was used to determine kinetically the value of pK_a = 13.5 ± 0.1. The kinetic deuterium isotope effect of cyclization of compounds **1f** giving **2f** (k_C^H / k_C^D = 1.7) was determined in solutions of NaOD in D_2O.

Key words: Reaction kinetics; Mechanism of cyclization; Solvent isotope effect; 2-Phenyl-5-imidazolinones; Imidazolinones; 2-Benzoylaminoalkanamides.

Imidazolinone derivatives belong among biologically active heterocyclic compounds that exhibit, depending on substituents, herbicidal, anticonvulsive[1] as well as tuberculostatic[2] activities. The most significant imidazolinones are commercially available herbicides[3] produced by American Cyanamide Company and well-known under commercial names of Arsenal, Pursuit, Imazapyr, Imazethapyr, Scepter, *etc*. These substances destroy

dicotyledonous weeds and grass, being practically harmless to mammals and fish (LD_{50} rat – 5 000 mg/kg; LD_{50} trout – 300 mg/kg) and they are not mutagenic according to the AMES test[4].

In earlier papers, we discussed synthesis and ^1H and ^{13}C NMR spectra of substituted 2-benzoylaminocarboxamides[5] and 2-phenylimidazolinones[6,7]. We also studied[8] the dependence of kinetics and mechanism of the cyclization reaction of substituted 2-benzoylaminocarboxamides on sodium methoxide concentration in methanol–dimethyl sulfoxide mixtures. The aim of the present work is to study reactions of substituted 2-benzoylaminocarboxamides in aqueous alkaline solutions and to find out whether solvolysis or cyclization takes place in these media (Scheme 1).



1a-1g **2a-2g**

1,2	R^1	R^2	R^3
a	H	CH_3	*i*-C_3H_7
b	NO_2	CH_3	*i*-C_3H_7
c	OCH_3	CH_3	*i*-C_3H_7
d	CN	CH_3	*i*-C_3H_7
e	Cl	CH_3	*i*-C_3H_7
f	NO_2	H	4-$O_2NC_6H_4$
g	NO_2	CH3	4-$O_2NC_6H_4$

SCHEME 1

EXPERIMENTAL

Preparation of the following compounds has been described previously: 2-(*N*-benzoyl-*N*-methyl)amino-2,3-dimethylbutanamide (**1a**)[5], 2-(*N*-(4-nitrobenzoyl)-N-methyl)amino-2,3-dimethylbutanamide (**1b**)[5], 2-(*N*-(4-methoxybenzoyl)-*N*-methyl)amino-2,3-dimethylbutanamide (**1c**)[5], 2-(*N*-(4-cyanobenzoyl)-*N*-methyl)amino-2,3-dimethylbutanamide (**1d**)[5], 2-(*N*-(4-chlorobenzoyl)-*N*-methyl)amino-2,3-dimethylbutanamide (**1e**)[5], 2-(4-nitrobenzoyl)-amino-2-(4-nitrophenyl)propanamide (**1f**)[5], 2-(*N*-methyl-*N*-(4-nitrobenzoyl)amino)-2-(4-nitrophenyl)propanamide (**1g**)[5]; 2-phenyl-5-isopropyl-1,5-dimethylimidazolinone (**2a**)[6], 2-(4-nitrophenyl)-5-isopropyl-1,5-dimethylimidazolinone (**2b**)[6], 2-(4-methoxyphenyl)-5-isopropyl-1,5-dimethylimidazolinone (**2c**)[7], 2-(4-cyanophenyl)-5-isopropyl-1,5-dimethylimidazolinone (**2d**)[7], 2-(4-chlorophenyl)-5-isopropyl-1,5-dimethylimidazolinone (**2e**)[7], 5-methyl-2,5-bis(4-nitrophenyl)imidazolinone (**2f**)[6], 1,5-dimethyl-2,5-bis(4-nitrophenyl)-imidazolinone (**2g**)[6].

Hydrolysis of the 1,5-dimethyl-2,5-bis(4-nitrophenyl)imidazolinone (**2g**): 354 mg (1 mmol) of the compound (**2g**) was mixed in 50 ml 0.5 mol l^{-1} NaOH solution at 25 °C for one week. The final decomposition products were identified by means of thin-layer chromatography and UV/VIS spectrophotometry (2-methylamino-2-(4-nitrophenyl)propanamide[5]: R_F 0.65;

Silufol, $CHCl_3$–CH_3OH (1 : 2); sodium 4-nitrobenzoate: λ_{max} = 275 nm; 4-nitrobenzoic acid: λ_{max} = 265 nm).

Measurement of Dissociation Constants

The dissociation constants of protonated imidazolinones **2f** and **2g** were determined spectrophotometrically using a Hewlett–Packard UV/VIS 8453 Diode Array apparatus. The measurements were carried out at 25 °C in a 1 cm cell using series of aqueous HCl solutions of various concentrations and constant ionic strength I = 1 mol l^{-1} adjusted by addition of KCl solution (2 mol l^{-1}). The respective solution of acid was placed in the cell and 50 µl of methanolic solution of substrate **2f** or **2g** ($2 \cdot 10^{-4}$ mol l^{-1}) was injected thereto. The spectra of the acid form (HCl, 2 mol l^{-1}), neutral form (methanol), and their mixtures were recorded and the absorbance values (A_{NH}, A_N, and A) were read at the suitable wavelength chosen. The pK_a values were calculated from equation pK_a = pH + I, where I was obtained from the absorbances measured according to relationship $I = (A - A_{NH})/(A_N - A)$, where A_{NH}, A_N, and A are absorbances of the protonated substrate, unprotonated substrate, and the measured solution, respectively.

Kinetic Measurements

The measurements were carried out spectrophotometrically in 1 cm closeable quartz cells using the above-mentioned HP apparatus. Before the measurement proper, the electronic spectra of compounds **1a**–**1g** and **2g** were measured in the given medium within the wavelength range of 200–800 nm. These experiments served for selection of analytical wavelength suitable for the kinetic measurements. The cell was charged with 2 ml NaOH or NaOD solution (99.8% D_2O; determined by means of NMR), or 2 ml of the respective buffer solution. After attaining 25 °C, 20 to 50 µl of a methanolic solution of the substrate (**1a**–**1g** and **2g**) was injected into the cell to make the resulting substrate concentration equal to $1.5 \cdot 10^{-5}$ mol l^{-1}. The absorbance–time dependence was recorded, and the pseudo-first-order rate constants (k_{obs}) were calculated from it using the OPKIN program[9].

RESULTS AND DISCUSSION

First we studied the reaction of substituted 2-(*N*-benzoyl-*N*-methyl)-amino-2,3-dimethylbutanamides **1a**–**1e** in aqueous solutions of sodium hydroxide. Comparison of electronic spectra of final reaction mixtures with those of the corresponding cyclization products (of the same concentration) showed that the respective imidazolinone derivative is the only reaction product, *i.e.* the cyclization in aqueous medium follows Scheme 1. For the cyclization studied under pseudo-first-order reaction conditions the rate constant of overall reaction defined in Scheme 2 is expressed by Eq. (*1*) where c_S is total concentration of substrate, [NH^-] the concentration of acetamide anion, and k_C the overall rate constant of cyclization (Eq. (*2*)).

$$v = k_{obs} c_S = k_C \left[NH^- \right] \qquad (1)$$

$$k_C = \frac{k_1 K_T k_2}{k_{-1}} \qquad (2)$$

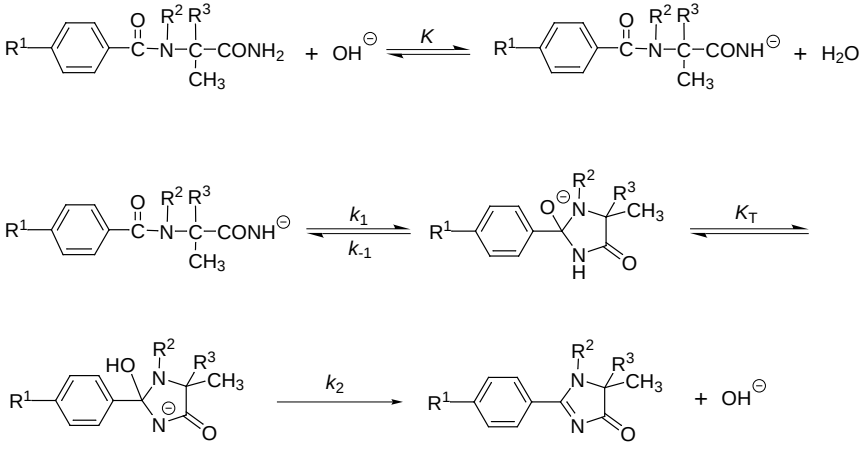
The measured dependences of observed rate constant, k_{obs} (s^{-1}), on sodium hydroxide concentration (mol l^{-1}) are linear for derivatives **1a**–**1e** (Fig. 1) and the observed rate constant is given by Eq. (*3*).

$$k_{obs} = k_C K [OH^-] \qquad (3)$$

The Hammett correlation for the cyclization reaction represented in Scheme 2 makes it possible to express logarithm of the ratio of k_{obs} (for derivatives **1b**–**1e**) to k^0_{obs} (for the nonsubstituted derivative **1a**) by Eq. (*4*).

$$\log \frac{k_{obs}}{k^0_{obs}} = \log \frac{K}{K^0} + \log \frac{k_C}{k^0_C} = \rho_1 \sigma^0_P + \rho_2 \sigma^0_P \qquad (4)$$

As the dissociation takes place at the terminal amide nitrogen atom, which is considerably distant from the reaction centre, the value ρ_1 would be expected to be very small or even negligible, and the overall ρ value will mainly be given by the magnitude of ρ_2. The value found for constant ρ is positive and greater than 1 ($\log (k_C / k^0_C) = -(2.30 \pm 0.06) + (1.4 \pm 0.1)\sigma$; correlation coefficient $r^2 = 0.9976$), which is in accordance with the presumption that the rate-limiting step of reaction consists in nucleophilic attack at the benzamide carbonyl group (Scheme 2).



SCHEME 2

Next we studied the cyclization reaction of derivative **1g**, in which the isopropyl group of derivative **1b** had been replaced by 4-nitrophenyl group. The aim of this structural variation was to prepare a derivative with more acidic terminal amide group. In its kinetic dependence of observed rate constant (k_{obs}) on NaOH concentration, such a derivative should have exhibited a region of k_{obs} independence of sodium hydroxide concentration (where all the substrate is transformed into its anion). From this dependence it would be possible to determine kinetically the pK_a value of compound **1g** and obtain the cyclization rate constant k_C. On the basis of kinetic experiments, however, we found a quite different behaviour of compound **1g** as compared with the previous cases of **1a**–**1e**. It was found that 2-(*N*-methyl-*N*-(4-nitrobenzoyl)amino)-2-(4-nitrophenyl)propanamide (**1g**) is cyclized very rapidly in sodium hydroxide solution to give 1,5-dimethyl-2,5-bis(4-nitrophenyl)imidazolinone (**2g**) with a half life of several milliseconds, whereupon there takes place a ring opening which produces intermediate **M** with a half life of several minutes (Scheme 3). On acidification, intermediate **M** is cyclized again to 1,5-dimethyl-2,5-bis(4-nitrophenyl)-imidazolinone (**2g**). In the presence of sodium hydroxide, the intermediate is slowly decomposed to sodium 4-nitrobenzoate and 2-methylamino-2-(4-nitrophenyl)propanamide (Scheme 3).

An attempt at determining the structure of intermediate **M** by means of ^{1}H NMR spectroscopy failed. Therefore, the structure of intermediate **M** was suggested on the basis of the following facts:

– In the given medium of 0.05–5 mol l^{-1} NaOH, the cyclization product does not form any Meisenheimer complexes[10] (coloured intermediates), which indicates that the reaction does not go by S_NAr mechanism.

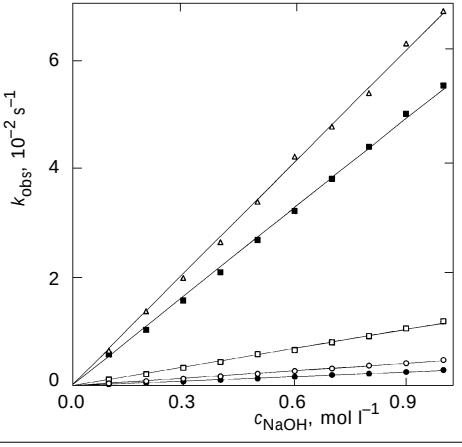
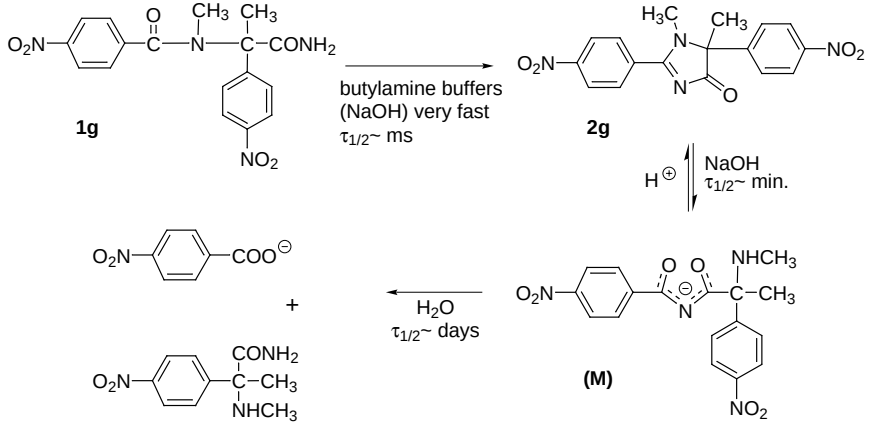


FIG. 1
Dependence of observed rate constant k_{obs} *vs* c_{NaOH} for cyclization of compounds **1a**–**1e** to **2a**–**2e** (○ **1a**, H; △ **1b**, NO_2; ● **1c** CH_3O; ■ **1d** CN; ❒ **1e** Cl)

– On acidification, intermediate **M** cyclizes back to compound **2g**.

– In NaOH–H_2O medium, intermediate **M** decomposes (attacked by OH^- ion) into 2-methylamino-2-(4-nitrophenyl)propanamide and sodium 4-nitrobenzoate, analogously to hydrolysis products of *N*-benzoylbenzamides[11] structurally similar to intermediate **M**.



SCHEME 3

Moreover, it was found that compound **1g** only undergoes cyclization to compound **2g** (without any further change) in the system of CH_3ONa–CH_3OH and in aqueous ethanolamine and butylamine buffers.

The cyclization reaction was studied in more detail by using butylamine and ethanolamine buffers of various concentrations and varying ratios of acidic/basic buffer components with ionic strength equal to 1 mol l^{-1} and constant pH in each series.

The kinetic dependences obtained are presented in Fig. 2 wherefrom it is obvious that the reaction is not subject to buffers catalysis but is subject to specific base catalysis in these media. The rate-limiting step consists in formation of tetrahedral intermediate, so proton-transfer is not involved in the rate-limiting step of reaction (k_2 is greater than k_{-1}; Scheme 2; R^3 = 4-nitrophenyl). Extrapolation of linear dependences of the observed rate constant k_{obs} (s^{-1}) to zero concentration of the basic buffer component (Fig. 2) gave the values of $k_{extrapol}$ constants (s^{-1}) whose logarithms were then plotted against pH values of the individual buffers (Fig. 3). The dependence thus obtained is linear with the slope equal to 1 in the range measured. It is impossible to separately determine the values of equilibrium constant K and cyclization constant k_C for the cyclization of **1g** to **2g**.

The reopening of cyclization product **2g** (formation of intermediate **M**) in solutions of sodium hydroxide can be expressed by Scheme 4.

The found dependence of observed rate constant (k_{obs}) on sodium hydroxide concentration (c_{NaOH}) showed that increasing sodium hydroxide concentration causes a nonlinear increase in the reaction rate of formation of intermediate **M** (Fig. 4).

From Fig. 4 it follows that at low NaOH concentrations the rate-limiting step consists in the non-catalyzed decomposition of tetrahedral intermediate into intermediate **M** (the first reaction path in Scheme 5).

Since in the NaOH concentration interval of 0.05–0.3 mol l^{-1} the k_{obs} value increases linearly, the observed rate constant can be expressed by Eq. (*5*).

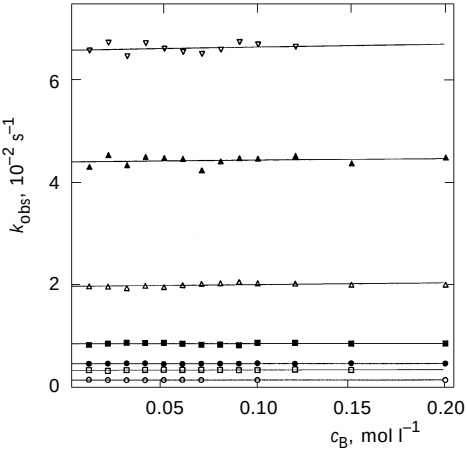


FIG. 2
Dependence of observed rate constant k_{obs} on the concentration of basic component of buffer c_B for cyclization of **1g** to **2g** (❍ ETA 1 : 1, pH 9.77; ❒ $BuNH_2$ 1 : 4 acidic, pH 10.07; ● ETA 1 : 3 basic, pH 10.26; ■ $BuNH_2$ 1 : 2 acidic, pH 10.45; Δ $BuNH_2$ 1 : 1, pH 10.83; Δ $BuNH_2$ 1 : 2 basic, pH 11.24; ∇ $BuNH_2$ 1 : 4 basic, pH 11.4)

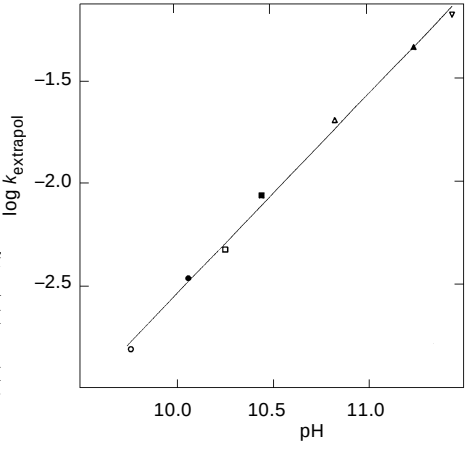
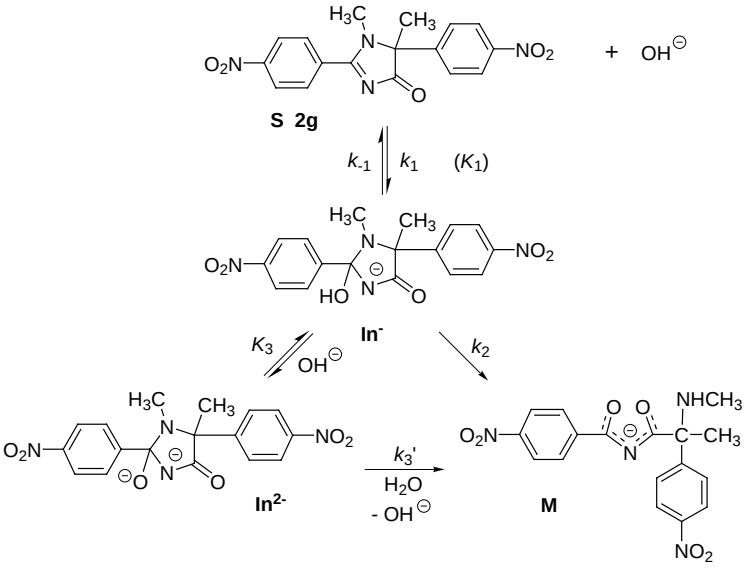
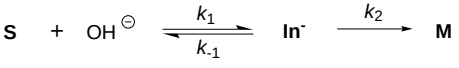


FIG. 3
Dependence of log $k_{extrapol}$ on pH of ethanolamine and butylamine buffers (❍ ETA 1 : 1, pH 9.77; ● $BuNH_2$ 1 : 4 acidic, pH 10.07; ❒ ETA 1 : 3 basic, pH 10.26; ■ $BuNH_2$ 1 : 2 acidic, pH 10.45; Δ $BuNH_2$ 1 : 1, pH 10.83; Δ $BuNH_2$ 1 : 2 basic, pH 11.24; ∇ $BuNH_2$ 1 : 4 basic, pH 11.44)



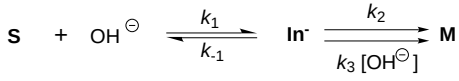
SCHEME 4



SCHEME 5

$$k_{obs} = \frac{k_1 k_2}{k_{-1} + k_2}\left[OH^-\right] \qquad (5)$$

In the NaOH concentration region of 0.3 mol l^{-1}, a nonlinear increase in the observed rate constant takes place, which means that the second reaction path (*i.e.* OH^- ion-catalyzed decomposition of intermediate **In**$^-$ (Scheme 6)) starts to make itself felt.



SCHEME 6

On the basis of experimental values and with application of multiple nonlinear regression[9], we found that the observed rate constant obeys the following rate equation (Eq. (*6*)).

$$k_{obs} = a[OH^-] + b[OH^-]^2 \qquad (6)$$

From Scheme 4 and/or Scheme 6 it follows that the regression parameters a and b correspond to the following products: $a = K_1k_2$ and $b = K_1k_3$, where the value of k_3 can be expressed as $k_3 = K_3k_3'$. The calculated values of the products are $K_1k_2 = (2.17 \pm 0.05) \cdot 10^{-3}$ l mol^{-1} s^{-1}; $K_1k_3 = (1.06 \pm 0.03) \cdot 10^{-3}$ l^2 mol^{-2} s^{-1}. In order to support the suggested mechanism of opening of imidazolinone cycle in compound **2g**, we studied the reaction kinetics also in NaOD–D_2O systems. The observed kinetic deuterium isotope effect of solvent can involve the contribution of primary isotope effect as well as that of secondary isotope effect[12,13] as shown in Eq. (*7*).

$$\left(\frac{k_{H_2O}}{k_{D_2O}}\right)_{obs} = \left(\frac{k_H}{k_D}\right)_{prim}\left(\frac{k_H}{k_D}\right)_{sec} \qquad (7)$$

The addition of lyate ion LO^- (HO^-, DO^-) to the substrate is connected[13] with the isotope effect of 0.5 (DO^- is twice as strong a base as HO^-). From experimental values (Fig. 4) we obtained the following values of product by multiple nonlinear regression: $K_1^Dk_2^D = (3.15 \pm 0.10) \cdot 10^{-3}$ l mol^{-1} s^{-1}; $K_1^Dk_3^D = (1.40 \pm 0.08) \cdot 10^{-3}$ l^2 mol^{-2} s^{-1}. If we divide the ratios $K_1^Hk_2^H/K_1^D\ k_2^D$ and $K_1^Hk_3^H/K_1^Dk_3^D$ by the coefficient 0.5 (the value of isotope effect K^H/K^D for addition of the lyate ion), we obtain the values of primary kinetic isotope effect: $k_2^H/k_2^D = 1.4$ and $k_3^H/k_3^D = 1.5$. The primary kinetic isotope effect of OH^- ion-catalyzed hydrolysis of substituted amides[14] reaches the maximum value of about 4.5. The relatively low values of primary kinetic isotope effect found by us indicate that the atoms N···H···O do not lie on a straight line[13] in the transition state of solvolysis of compound **2g**.

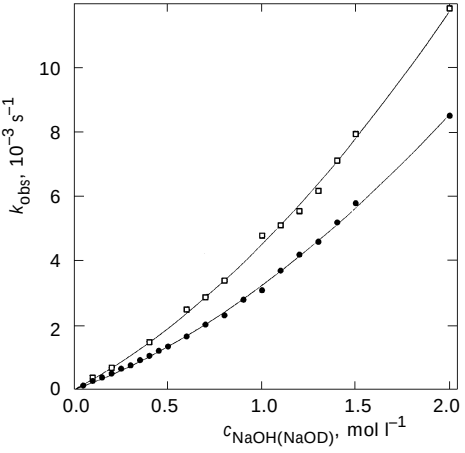


FIG. 4
Dependence of observed rate constant k_{obs} of the formation of the intermediate **M** *vs* c_{NaOH} or c_{NaOD} for starting compound **1g** or **2g** (● NaOH–H_2O, ❒ NaOD–D_2O)

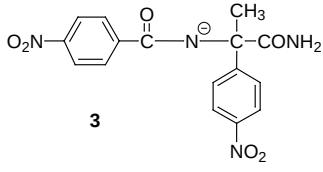
In order to compare the effect of methyl substituent on benzamide nitrogen upon the course of reaction of compound **1g**, we prepared 2-(4-nitrobenzoyl)amino-2-(4-nitrophenyl)propanamide (**1f**), which, in contrast to compound **1g**, has no methyl group on benzamide centre. Again the kinetic measurements were carried out under the conditions of pseudo-first-order reaction in aqueous solutions of sodium hydroxide or in NaOD–D_2O systems at the same conditions as those used in the cyclization and subsequent solvolysis of compound **1g** (25 °C and I = 1 mol l^{-1}).

According to expectation it was found that in these media (NaOH–H_2O and NaOD–D_2O) in concentration range of 0.05–1.4 mol l^{-1}, compound **1f** is only cyclized to anion of 5-methyl-2,5-bis(4-nitrophenyl)imidazolinone (**2f**) which does not change any more. This was confirmed by comparing the electronic spectrum of reaction product obtained from compound **1f** with that of compound **2f** in the same medium.

It was possible only to determine spectrophotometrically the values of pK_{a1} = 1.21 ± 0.03 and 1.67 ± 0.04 (the first deprotonation; H_2O, 25 °C, I = 1 mol l^{-1}) for the protonated forms of **2f** and **2g**, respectively. It was impossible to find the value of pK_{a2} of compound **2f** (*i.e.* for formation of anion as the cyclization product): the substance was not soluble enough for a titration determination to be carried out, and the spectrophotometric determination was prevented by the fact that the buffers used have similar absorption as the substrate. Comparison of electronic spectra of compound **2f** in solutions of 0.01 M HCl, in acetate buffer (1 : 1; 0.1 mol l^{-1}), and in 0.05, 1.0, and 1.4 mol l^{-1} NaOH showed that **2f** is present in the anionic form in solutions of 0.05–1.4 mol l^{-1} NaOH.

Figure 5 presents the dependence of observed rate constant, k_{obs} (s^{-1}), on concentration of NaOH or NaOD for the cyclization of compound **1f** to imidazolinone **2f**.

From the dependence found it follows that increasing concentration of lyate ion (HO^-, DO^-) brings about a decrease in the slope of cyclization rate which can be interpreted by formation of the nonreactive benzamide anion **3**.



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In the limiting case, when all the substrate is present in the form of these anions, the reaction rate becomes independent of the lyate ion concentration.

The dependence mentioned (Fig. 5) is expressed by Eq. (*8*) of the given form[8] where k'_C involves cyclization of the equilibrium mixture of reactive acetamide and nonreactive benzamide anions, whose proportions in the equilibrium mixture cannot be determined.

$$k_{obs} = \frac{k'_C K[OH^-]}{1 + K[OH^-]} = \frac{k'_C[OH^-]}{1/K + [OH^-]} \qquad (8)$$

From the experimental values and Eq. (*8*) and using a known optimization program[9], we found the values of constants K and k'_C for the reactions in both NaOH and NaOD. The experimental points were fitted by a function corresponding to Eq. (*8*) after introducing the found values of the two constants (Fig. 5).

For the cyclization catalyzed by OH^- ion in water, we found the value of equilibrium constant K^H = 2.85 l mol^{-1} (pK_a = 13.5 ± 0.1) and the value of cyclization constant k_C^H = 1.77 · 10^{-3} s^{-1}. The corresponding values for the cyclization catalyzed by OD^- ion in deuterium oxide are K^D = 5.89 l mol^{-1} and k_C^D = 1.05 · 10^{-3} s^{-1}. From the values of K^H and K^D constants it is then possible to calculate the kinetic isotope effect of the equilibrium (Scheme 2), namely K^H/K^D = 0.48.

This value corresponds to that found earlier[13] for the equilibrium addition of the lyate ion to the substrate (Eq. (*7*)). Moreover, from the cyclization constants ($k_{C'}$) it is possible to calculate the kinetic isotope effect for cyclization reaction of aminoamide **1f**: k'^H_C/k'^D_C = 1.7.

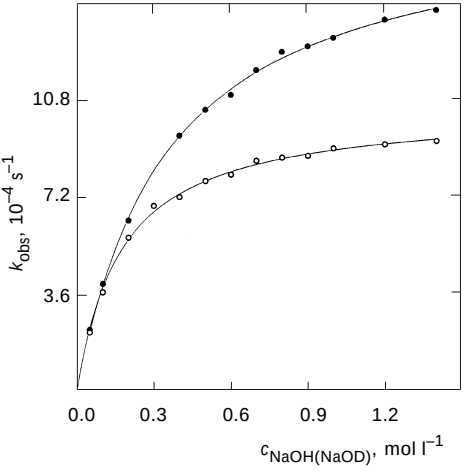

FIG. 5
Dependence of observed rate constant k_{obs} *vs* c_{NaOH} or c_{NaOD} for cyclization of compound **1f** to **2f** (● NaOH–H_2O; ❍ NaOD–D_2O)

CONCLUSION

From the results given it follows that in aqueous solution substituted 2-(benzoylamino)alkanamides **1a**–**1f** do not undergo hydrolysis but are cyclized to the corresponding substituted imidazolinones **2a**–**2f**. This means that the syntheses carried out earlier in non-aqueous media[3,6,7] can be realized in aqueous medium, which can have both economic and ecological impacts on mass production of these substances. Also the evaluation of stability of the imidazolinones formed in solution of sodium hydroxide is important. The imidazolinones having an acidic proton of amide group can form stable anions in sodium hydroxide solutions which does not undergo any subsequent nucleophilic attack by hydroxyl ions. The hydrolysis (imidazolinone ring opening) is only observed after introduction of methyl group on amide nitrogen atom (when the anion formation is no longer possible), and even then it needs the presence of electron-acceptor substituents facilitating the nucleophilic attack. Under such conditions, but with low concentration of hydroxide ion, the hydrolysis of the ring formed is relatively slow, which means that such imidazolinones can also be synthesized in aqueous buffers, too.

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