KINETICS AND MECHANISM OF CYCLIZATION OF SUBSTITUTED 2-(BENZOYLAMINO)ALKANAMIDES IN STRONGLY BASIC MEDIUM

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The cyclization reaction of substituted 2-(benzoylamino)alkanamides **1a**–**1i** giving the corresponding substituted 2-phenylimidazol-4(5*H*)-ones **2a**–**2i** has been studied. The equilibrium constants of reactions of compounds **1d**–**1f** and 2-[(4-nitrobenzoyl)amino]-2,3-dimethylbutanenitrile (**3**) with methoxide have been determined in methanol–dimethyl sulfoxide media. For compound **1d** and *N*-methyl derivatives **1a**–**1c**, the cyclization rate constants have been measured in dependence on methoxide concentration in media of varying contents of dimethyl sulfoxide. The cyclization reaction mechanism involves formation of anion in a rapid pre-equilibrium and subsequent rate-limiting step: either formation of a cyclic intermediate or splitting off of OH^- ion from this intermediate. The product formed in the given medium is immediately transformed into its conjugate base. A change in reaction medium affects the reactions of all the compounds in the same way. The ratio of concentration of substrate to that of its anion at low methoxide concentrations is affected by the solvent composition (MeOH–DMSO). At higher methoxide and DMSO concentrations the reaction rate distinctly decreases, which can be interpreted by the transformation of reactive anion into non-reactive dianion. The corresponding *N*-methylbenzoylamino compounds are cyclized faster by a factor of 400 as compared with compounds having no methyl group at the benzamide group.

Key words: Reaction kinetics; Mechanism of cyclization; 2-Phenylimidazol-4(5*H*)-ones; Dissociation constants; Solvent effect.

In previous papers we discussed the synthesis as well as ^1H and ^{13}C NMR spectra of substituted 2-(benzoylamino)alkanamides[1] and 2-phenylimidazolinones[2,3].

The aim of the present work was to study the kinetics and mechanism of cyclization of substituted 2-(benzoylamino)alkanamides to the corresponding 2-phenylimidazol-4(5*H*)-ones (Scheme 1).

EXPERIMENTAL

Synthesis

The preparation of compounds **1a**–**1i** (ref.[1]) and **2a**, **2b**, **2d**–**2g** (ref.[2]), **2c**, **2h** and **2i** (ref.[3]) and **3** (ref.[4]) was described in previous communications.

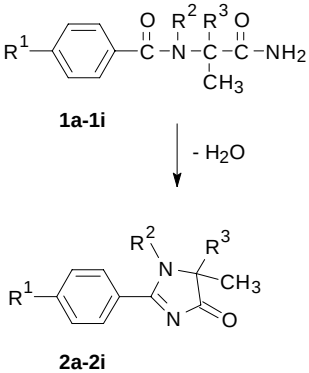
Measurement of Dissociation Constants

The spectra were measured with a Hewlett–Packard 8453 Diode Array apparatus in a 1 cm cell placed in thermostatted cell compartment of the apparatus. A saturated methanolic solution of substrate (50 μl) was injected into the respective solution of sodium methoxide (2 ml), and the spectrum was measured 5 s after mixing. The dissociation constants were measured in solutions of sodium methoxide in MeOH–DMSO mixtures at 25 °C. After inspecting the spectra of the acid form, anion, and their mixture, a suitable wavelength was chosen at which the absorbance values were read. The I values were calculated from the measured absorbances using the relationship $I = (A - A_{NH})/(A_N - A)$, where $A_{NH,}$ A_N, and A are the absorbances of the substrate, its conjugate base, and the solution measured, respectively.

Kinetic Measurements

The measurements were carried out spectrophotometrically using the above-mentioned Hewlett–Packard 8453 Diode Array apparatus and 1 cm closeable quartz cells kept at 25 °C in the cell compartment of the apparatus. Before the measurement itself, we measured the electron spectra of the substances investigated in the given medium in the wavelength range of 200–400 nm. These experiments verified the presence of isosbestic points and made it possible to select suitable wavelengths for the kinetic measurements.

The cell was charged with 2 ml of sodium methoxide solution in suitable MeOH–DMSO mixture. After reaching the said temperature, 20 to 50 μl of methanolic solution of substrate was injected into the cell in such a way that the resulting substrate concentration was about $1.5 \cdot 10^{-4}$ mol l^{-1}. From the measured time change of absorbance (at 280–300 nm depending on the medium), we calculated the pseudo-first-order rate constants (k_{obs}) using the OPKIN program[5]. The solutions were prepared from analytical grade methanol (Lachema) and dimethyl sulfoxide (Fluka) dried over molecular sieve Calsit 5 type 5A.



For compounds **1** and **2**:

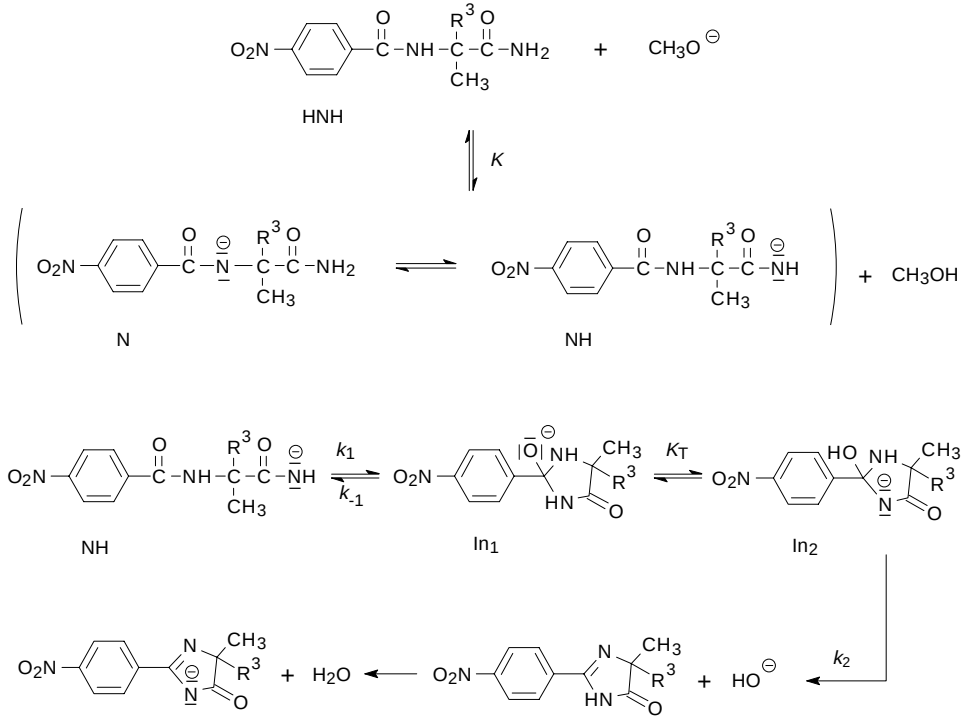
	R^1	R^2	R^3
a	H	CH_3	CH_3
b	NO_2	CH_3	CH_3
c	H	H	i-C_3H_7
d	NO_2	H	i-C_3H_7
e	NO_2	H	C_6H_5
f	NO_2	H	4-NO_2-C_6H_4
g	NO_2	CH_3	i-C_3H_7
h	CH_3O	CH_3	i-C_3H_7
i	CH_3O	H	i-C_3H_7

SCHEME 1

RESULTS AND DISCUSSION

Mechanism and Kinetics of Cyclization

The course of cyclization for compounds **1d**–**1f** can be expressed by the following mechanism (Scheme 2). The formation of anion from substrate (HNH) is a fast pre-equilibrium. The subsequent rate-limiting step can consists in the formation of cyclic intermediate (In_1) or splitting of OH^- ion from the intermediate (In_2) formed to give the product which is transformed practically completely into its conjugate base in the given medium.



SCHEME 2

The basicity of the medium at a given methoxide concentration increases with the DMSO content in the mixture whereby the equilibrium is shifted in favour of the anions of the starting amide. The ratio of "reactive", cyclizable anion (NH) to that of the other anion (N) cannot be determined from spectral or kinetic measurements. In a previous communication[4], we compared a series of pK_a values of structurally similar 2-(benzoylamino)alkanamides and found that a combination of sufficiently bulky substituents R^3

(isopropyl, phenyl) with methyl group has a significant steric effect on the values of dissociation constants and, hence, on the cyclization rate. A very low concentration of N-anion derived from acetamide moiety (NH) is sufficient for the cyclization to proceed in sodium methoxide solutions at room temperature.

In the case of derivatives with R^3 = H, this steric effect is small and the dissociation only takes place in the benzamide moiety, and the cyclization does not proceed at all.

The effect of medium on the cyclization (both on the formation of intermediate and on its decomposition into the starting compound or product) is substantially smaller than that on the pre-equilibrium because both the anion (NH) and the two transition states are of considerably similar structures, and it cannot at all be *a priori* estimated if the cyclization rate will be lowered or increased by addition of DMSO.

In the case of the cyclization followed as a pseudo-first-order reaction, it is possible to express the overall rate equation by Eq. (*1*) on the basis of Scheme 2,

$$v = k_{obs}\, c_s = k_c[\mathrm{NH}] = k_c'([\mathrm{N}] + [\mathrm{NH}])\,, \qquad (1)$$

where c_s is total concentration of substrate, [NH] is concentration of reactive anion, and k_c is overall rate constant of cyclization of the reactive anion (*2*).

$$k_c = k_1 K_T k_2 / k_{-1} \qquad (2)$$

In the methoxide concentration range in the given medium where the ratio I (Eq. (*3*)) is about 0.1 to 10, it is possible to express the concentration of both anions by Eq. (*4*), so that the observed rate constant can be described by the relationship (*5*).

$$I = ([\mathrm{N}] + [\mathrm{NH}])/[\mathrm{HNH}] \qquad (3)$$

$$c_s = [\mathrm{HNH}] + [\mathrm{N}] + [\mathrm{NH}] = [\mathrm{HNH}](I/(I + 1)) \qquad (4)$$

$$k_{obs} = k_c'(I/(I + 1)) = k_c' \left(\frac{1}{K[CH_3O^-]} + 1 \right)^{-1} \qquad (5)$$

K is the equilibrium constant of the acid-base reaction (Scheme 2) valid for the given medium (methanol, MeOH–DMSO).

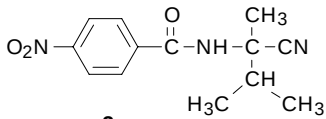
At low methoxide concentrations, relation (*5*) is simplified to Eq. (*6*).

$$k_{obs} = k_c' I = k_c' K[CH_3O^-] \qquad (6)$$

In the region of high methoxide concentrations, k_c' need not have a constant value and can change with the change of medium. In order to be able to determine k_c' at such DMSO concentrations when $I < 0.1$ (where I cannot be determined spectrophotometrically), it was necessary to construct an acidity function for amides in the range from 0 to 85% (v/v) DMSO and, on the basis of the acidity function, to determine the I ratio at low DMSO concentrations or even in methanol alone[4].

Effect of DMSO and Methoxide Concentrations on Basicity of Medium and Equilibrium Constants

For compounds **1d**–**1f**, we measured the equilibrium and rate constants of cyclization at various DMSO concentrations in methanol. Because of the low acidity, it was impossible to determine their equilibrium constants in pure methanol, and thus we prepared 2-[(4-nitrobenzoyl)amino]-2,3-dimethylbutanenitrile (**3**). This nitrile has a structure similar to compounds **1**, in spite of the terminal amide group being replaced by a nitrile group. This substitution increases the acidity of the NH group, which made it possible to measure the acidity of compound **3** in neat methanol and at low DMSO



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concentrations. The dependences of log I on logarithm of methoxide concentration at DMSO concentrations of 75 and 50% are given in Figs 1 and 2 for compounds **1d** and **1e**, respectively. The dependence of log I on logarithm of methoxide concentration for methoxide concentrations below 0.1 mol l^{-1} should be linear[6] with a slope of unity.

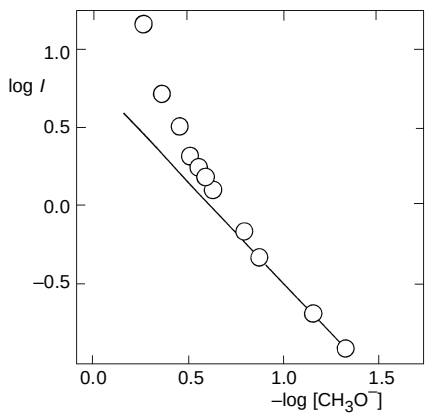

FIG. 1
Dependence of log I *vs* –log [CH_3O^-] in 75% (v/v) DMSO at 25 °C for compound **1d**

From Figs 1 through 5, it follows that:

1. Deviations from the slope of unity appear at methoxide concentrations above 0.2 mol l^{-1} (Fig. 1) and above 0.6 mol l^{-1} (Fig. 2).

2. The difference between the log *I* values (Δ log *I*) for any pair of compounds is constant (within experimental error) in a given medium, even at methoxide concentrations above 0.1 mol l^{-1}, *i.e.*, the change in methoxide concentration has a similar effect on *I* for all the compounds investigated (Δ log *I* is constant for a given pair of compounds in solutions of the same DMSO concentration).

3. The difference in log *I* at the same methoxide concentration but different DMSO concentrations is the same in the given media for all the compounds studied, *i.e.*, the change in DMSO concentration has the same effect on log *I* for all the compounds, and Δ log *I* is the same at the same change in DMSO concentration for all the compounds.

Figure 3 presents the dependence of log *K* on the molar fraction of DMSO in MeOH (x_{DMSO}) for the individual substances. In the cases of 50% dissociation of the substrate at a methoxide concentration below 0.1 mol l^{-1}, the K_1 values were calculated directly from Eq. (*7*).

$$\log I = \log K_1 + \log [CH_3O^-] \qquad (7)$$

In the cases of 50% dissociation of the substrate at methoxide concentrations above 0.1 mol l^{-1} (the slope of dependence of log *I* upon $-\log [CH_3O^-]$ gradually increasing), we made use of the fact that Δ log *I* for any pair of compounds is constant even at higher

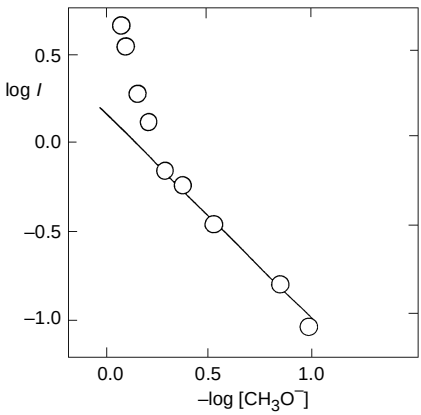

FIG. 2
Dependence of log *I* *vs* $-\log [CH_3O^-]$ in 50% (v/v) DMSO at 25 °C for compound **1e**

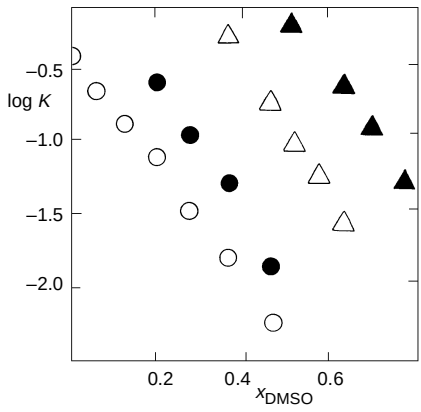

FIG. 3
Dependence of log *K* on molar fraction of DMSO (x_{DMSO}) at 25 °C for compounds **3** (❍), **1f** (●), **1e** (Δ), and **1d** (▲)

methoxide concentrations. Therefore, it was possible to calculate the equilibrium constant from Eq. (*8*).

$$\log K = \log K_R - \Delta \log I \,, \qquad (8)$$

where K_R is the equilibrium constant of the "reference substance" measured at methoxide concentrations below 0.1 mol l^{-1}. The equilibrium constant of compound **3** measured in methanol was taken as the basis, and from the found equilibrium constants of the substances at various DMSO concentrations we calculated the equilibrium constants of these substances in methanol using Eq. (*9*).

$$\log K_i = \log K_i^0 + \Sigma \Delta \log I \qquad (9)$$

The quantity K_i^0 means the equilibrium constant of the *i*-th compound in methanol, and $\Sigma \Delta \log I$ is the sum of averaged values of $\Delta \log I$ (at the same methoxide concentration) between the individual DMSO concentrations for the compounds measured in these solutions. In an analogous way, we also calculated the K_i values in such DMSO concentration regions where it was impossible to determine them experimentally. The values of $\Delta \log I$ are a quantitative measure of the increase in basicity with increasing DMSO concentration (referenced to compounds of similar structural type, which were measured, *i.e.* amides). The log K_i values are presented in Table I and the dependence of log *I* upon $-\log [CH_3O^-]$ is depicted in Fig. 4. The log *I* values needed for determination of cyclization rate constants at methoxide concentrations below 0.1 mol l^{-1} were calculated from Eq. (*7*).

The equilibrium constant in the individual solutions can be defined by Eq. (*10*).

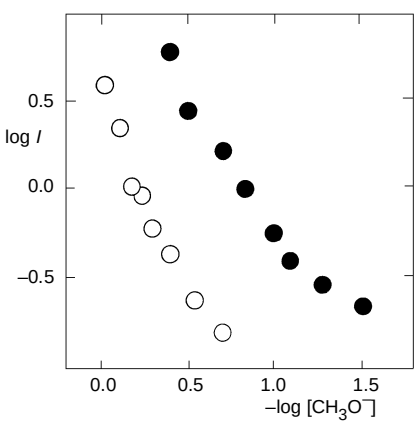

FIG. 4
Dependence of log *I* *vs* $-\log [CH_3O^-]$ in 60% (v/v) DMSO at 25 °C for compounds **1d** (○) and **1e** (●)

$$K_i = \frac{I}{[CH_3O^-]} \frac{\gamma_{NH}}{\gamma_{HNH}\,\gamma_{CH_3O^-}} \qquad (10)$$

At methoxide concentrations below 0.1 mol l^{-1}, the activity coefficient of methoxide ion is practically equal to unity (Eq. (*3*)). At higher methoxide concentrations, it is necessary to adopt the extended Debye–Hückel equation[7] in the form (*11*).

TABLE I
Equilibrium constants log *K* of compounds **3** and **1d–1f** (and their standard deviations *s*) in methanolic solutions of DMSO

%(v/v)DMSO (x_{DMSO})	log *K* (*s*)			
	3	**1d**	**1e**	**1f**
0	–0.55	–	–	–
(0)	(0.01)			
10	–0.70	–	–	–
(0.06)	(0.05)			
20	–0.96	–	–	–
(0.125)	(0.01)			
30	–1.15	–	–	–0.66
(0.197)	(0.03)			(0.03)
40	–1.50	–	–	–1.00
(0.276)	(0.05)			(0.04)
50	–1.85	–	–0.36	–1.35
(0.364)	(0.02)		(0.04)	(0.02)
60	–2.30	–0.17	–0.82	–1.92
(0.462)	(0.02)	(0.02)	(0.04)	(0.04)
65	–	–0.40	–1.00	–
(0.515)		(0.05)	(0.02)	
70	–	–	–1.30	–
(0.572)			(0.04)	
75	–	–0.75	–1.65	–
(0.632)		(0.05)	(0.03)	
80	–	–1.00	–	–
(0.695)		(0.04)		
85	–	–1.40	–	–
(0.764)		(0.04)		

$$\log \frac{\gamma_{NH}}{\gamma_{HNH}\,\gamma_{CH_3O^-}} = A\sqrt{m}\left[\frac{1}{1+a_{NH}\sqrt{m}} - \frac{1}{1+a_{CH_3O}\sqrt{m}}\right] + b[CH_3O^-] \qquad (11)$$

The ratio of activity coefficients at concentrations lower than 0.1 mol l^{-1} is equal to unity (hence the value of the expression in brackets is practically zero). This means that at higher concentrations of methoxide anion, log *I* is expressed by Eq. (*12*).

$$\log I = \log K_i + \log [CH_3O^-] + b[CH_3O^-] \qquad (12)$$

The dependence of difference $Y = \log I - \log [CH_3O^-]$ on the methoxide concentration in 60% DMSO is given in Fig. 5 for compounds **1d** and **1e**.

Kinetics of Cyclization of Compounds **1d**–**1f**

The cyclization kinetics of compound **1d** was measured in solutions of sodium methoxide alone and in solutions of DMSO (20, 40, 50, 60, and 75% (v/v) DMSO) in the sodium methoxide concentration range from 0.1 to 1.6 mol l^{-1}. The dependence of k_{obs} on $[CH_3O^-]$ in the individual mixtures is presented in Figs 6 and 7.

In the solutions in neat methanol and at low concentrations of DMSO, the slope of dependence k_{obs} *vs* $[CH_3O^-]$ increases with increasing methoxide concentration at first (the concentration of anion is much lower than that of the neutral form of substrate).

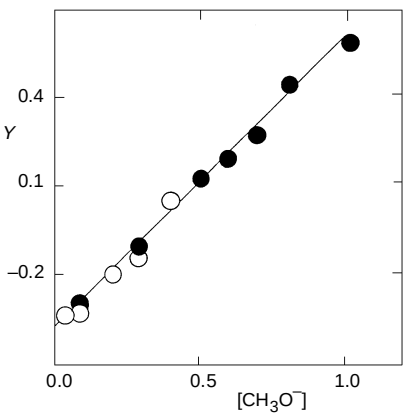

FIG. 5
Dependence of $Y = \log I - \log [CH_3O^-]$ *vs* $[CH_3O^-]$, mol l^{-1}, in 60% (v/v) DMSO at 25 °C for compounds **1e** (❍) and **1d** (●)

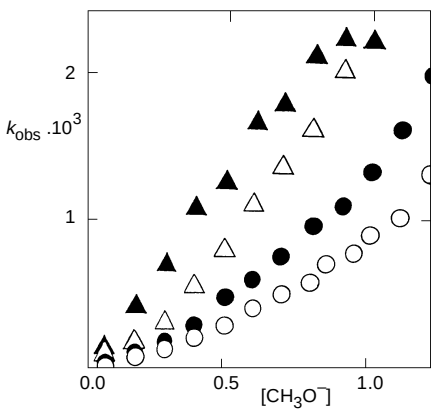

FIG. 6
Dependence of observed rate constant (k_{obs}, s^{-1}) *vs* $[CH_3O^-]$, mol l^{-1}, measured for compound **1d** in methanol (❍), 20% (v/v) DMSO (●), 40% (v/v) DMSO (Δ), and 60% (v/v) DMSO (▲) at 25 °C

The reaction rate is defined by the relationship (*13*).

$$v = k_{obs}\, c_s = k_c'\, I c_s \qquad (13)$$

The increase in the observed rate constant with increasing methoxide concentration is similar to the increase in *I* with methoxide concentration.

Besides the effect on *I*, an effect of methoxide concentration upon the rate constant k_c' can also be seen. Therefore, the dependence of *I* on methoxide concentration was plotted for compound **3** (which does not cyclize) in neat methanol (Table I). The *I* values thus obtained were then plotted against k_{obs} in the same medium for compound **1d**. The dependence is linear within the limits of experimental error and is presented in Fig. 8; obviously the k_c' constant changes but slightly in the given range.

At higher concentrations of DMSO and methoxide, where *I* ranges from about 0.1 to 10.0, we used Eq. (*5*). In this case it was found for compound **1d** that at values $I > 10$, the constant decreases more and more rapidly. This decrease is in accordance with that in the observed rate constant (Fig. 7). From the dependences given it is obvious that at various DMSO concentrations the decrease in the observed rate constant occurs at various methoxide concentrations (from 1.3 mol l^{-1} in 50% DMSO down to 0.4 mol l^{-1} in 75% DMSO).

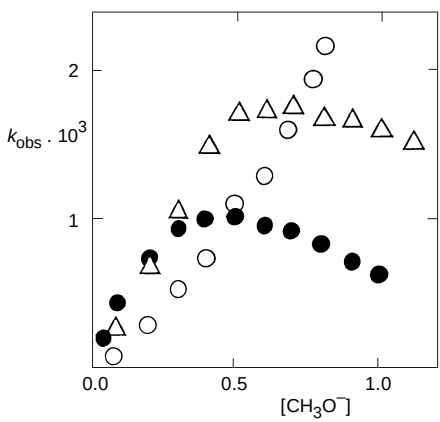

FIG. 7
Dependence of observed rate constant (k_{obs}, s^{-1}) *vs* $[CH_3O^-]$, mol l^{-1}, measured for compound **1d** in 50% (v/v) DMSO (○), 65% (v/v) DMSO (●), and 75% (v/v) DMSO (Δ) at 25 °C

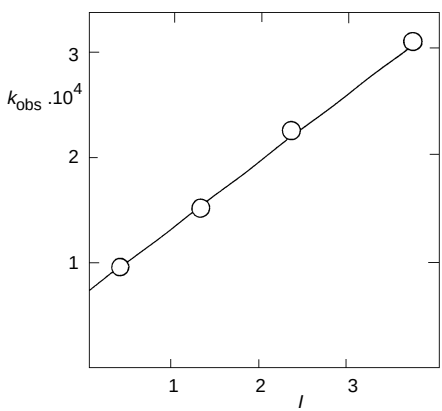

FIG. 8
Dependence of observed rate constant (k_{obs}, s^{-1}) measured for compound **1d** in methanol *vs* *I* ratio determined in methanol (in dependence on $[CH_3O^-]$, mol l^{-1}) for compound **3** at 25 °C

This behaviour is entirely different from what has been found from the dependence of logarithm of ratio of activity coefficients upon methoxide concentration (Fig. 5, Eq. (*10*)). This dependence was linear in the whole range studied although the structure of anion of compound **1d** differs very much from that of solvated methoxide anion, the former being considerably similar to the structure of negatively charged activated complex. Therefrom it follows that the considerable and rapidly developing decrease in the region of predominant occurrence of the starting substance in anionic form has another reason (Fig. 7). When measuring the equilibrium constants in media with DMSO concentrations above 50%, we observed formation of another isosbestic point (the second degree of dissociation). The second equilibrium constant (dissociation of the acetamide moiety), however, could not be determined experimentally. The drop in the reaction rate can be interpreted by the formation of an unreactive dianion.

We also studied the cyclization kinetics of compounds **1e** and **1f**, where the steric effect should be comparable with that of isopropyl group; hence the difference in the polar effects of the phenyl and 4-nitrophenyl groups should be sensible. This is most distinct in the difference of log K values (Table I) for compounds **1d** and **1e** ($\Delta \log I = 0.65$) and for compounds **1d** and **1f** ($\Delta \log K = 1.85$). Both substituents also influence the acidity of benzamide group, which was manifested when the k_{obs} values were determined at the same DMSO concentrations and low concentrations of methoxide anion.

The k_{obs} values were practically the same with all the substances in a given medium. On the other hand, a large difference was observed in the maximum rates reached. The maximum cyclization rates of compounds **1e** and **1f** were lower by the factors of 7 and 15, respectively, than that of compound **1d**. This is probably due to the fact that the formation of dianion starts to be more significant with compounds **1f** and **1e** then with **1d**.

In the case of compound **1e**, the observed rate constant measured in the whole range of methoxide concentrations in 50% DMSO (Fig. 9) was recalculated on the basis of Eq. (*5*) to give the k_c' constant. As it follows from Table II, the k_c' value is practically constant up to $I = 8$, showing a linear decrease for I values higher than 10.

Kinetics of Cyclization of N-Methylamides **1a**–**1c**

Another part of our work dealt with investigation of cyclization kinetics of *N*-methylamides **1a**–**1c**. These substrates can undergo dissociation in the acetamide group only, which means that the cyclization rate constant found should not decrease with increasing basicity of medium. A comparison of rate constants of cyclization of two compounds differing only in the presence of methyl group or hydrogen on the benzamide nitrogen atom made it possible to determine the effect of the methyl group on the cyclization rate. The cyclization rate constant of 2,3-dimethyl-2-[*N*-methyl-*N*-(4-nitrobenzoyl)amino]butanamide (**1g**) was immeasurably high, even at low methoxide concentrations. Therefore, several other derivatives were prepared in which the nitro group was replaced by hydrogen (compound **1c**) or the isopropyl group by methyl group (com-

pound **1b**). At methoxide and DMSO concentrations allowing spectral determination of the ratio of anion to starting substance, the cyclization rate of all those compounds was high but still measurable. Therefore, we tried to determine the equilibrium constant of the starting substrate from the kinetic dependence of the observed rate constant on methoxide concentration.

However, when following the cyclization kinetics of compounds **1a**, **1b**, and **1g** in 50% DMSO at methoxide concentrations above 1 mol l^{-1}, we found that the rates of formation and decomposition of the intermediate were comparable, so that kinetically the reaction proceeded as a consecutive reaction with two relaxation times τ_1 and τ_2, which were functions of all the rate constants (k_1, k_{-1}, k_2); hence no conclusions could be made from these experiments. In order to obtain information about the influence of *N*-methyl group on the cyclization rate, we measured the cyclization rates of methoxy derivatives **1h** and **1i** (differing in methyl group in benzamide moiety) in 50% DMSO at the methoxide concentration of 1.5 mol l^{-1}. For compounds **1h** and **1i**, we found the

TABLE II
Dependence of *I* values for compound **3** on methoxide concentration [CH_3O^-], mol l^{-1}, and k_c', s^{-1}, for compound **1e**

[CH_3O^-]	*I*	$k_c' . 10^4$	[CH_3O^-]	*I*	$k_c' . 10^4$
0.05	0.09	5.1	0.6	2.8	6.4
0.2	0.4	7.2	0.7	7.58	5.5
0.3	0.78	5.5	0.8	9.33	5.16
0.4	1.25	5.6	0.9	20.4	4.5
0.5	1.95	5.6	1.1	39.8	3.88

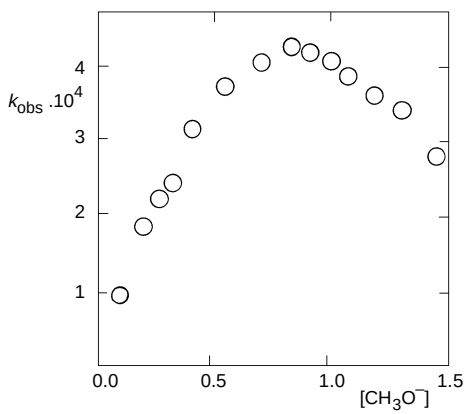

FIG. 9
Dependence of observed rate constant (k_{obs}, s^{-1}) *vs* [CH_3O^-], mol l^{-1}, measured for compound **1e** in 50% (v/v) DMSO at 25 °C

rate constant values k_{obs} = 2.7 . 10^{-1} and 6.8 . 10^{-4} s^{-1}, respectively. From the ratio of the cyclization rate constants of compounds **1h** and **1i**, we deduced that the introduction of methyl group instead of hydrogen resulted in the cyclization rate increase by a factor of 400.

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