KINETICS OF CYCLIZATION OF METHYL *S*-(2,4,6-TRINITROPHENYL)-MERCAPTOACETATE TO 2-METHOXYCARBONYL-5,7-DINITRO-BENZO[*d*]THIAZOL-3-OXIDE

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The cyclization kinetics of methyl *S*-(2,4,6-trinitrophenyl)mercaptoacetate to 2-methoxycarbonyl-5,7-dinitrobenzo[*d*]thiazol-3-oxide have been studied in acetate, methoxyacetate or *N*-methylmorpholine buffers. In the acetate and methoxyacetate buffers, the cyclization obeys the rate equation $v = [SH](k'_{MeO}[CH_3O^-] + k'_{B}[B^-] + k'_{B,MeO}[B^-][CH_3O^-])$ and goes by two reaction paths differing in the order of their reaction steps, the splitting off of the proton from C–H group being the rate-limiting step in either path. In the *N*-methylmorpholine buffers, increasing concentration of the base results in gradual decrease of reaction order in the base and change in the rate-limiting step of cyclization. Methyl *S*-(2,4-dinitrophenyl)mercaptoacetate undergoes cyclization neither in the given buffers nor in methoxide solution.

Key words: Cyclization kinetics; Reaction mechanism; 2-Methoxycarbonyl-5,7-dinitrobenzo[*d*]thiazol-3-oxide.

The reactions of methyl *N*-(2,4,6-trinitrophenyl)aminoacetate[1] and methyl *N*-methyl-*N*-(2,4,6-trinitrophenyl)aminoacetate[2] with methoxide in methanol produce 2-nitroso-4,6-dinitroaniline and *N*-methyl-2-nitroso-4,6-dinitroaniline, respectively. The kinetics of these reactions were studied[1,2], and the mechanism suggested for them presumes an intramolecular attack of carbonyl group by nitrogen atom of the amino group and formation of substituted aziridinone as the key intermediate of reaction. Sulfur is more nucleophilic than nitrogen and, in addition to it, tends to form thiirane rings in reactions involving neighbouring group participation[3]. However, the base catalyzed reactions of *S*-(2-nitro-4,6-disubstituted phenyl)mercaptoacetate esters do not produce nitroso compounds but 2-alkoxycarbonyl-5,7-disubstituted benzo[*d*]thiazol-3-oxides (ref.[4]). The aim of the present work is to study the kinetics of base catalyzed cyclization of methyl *S*-(2,4,6-trinitrophenyl)mercaptoacetate leading to 2-methoxycarbonyl-5,7-dinitrobenzo[*d*]thiazol-3-oxide.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were measured on an AMX 360 Bruker apparatus at 25 °C at 360.14 and 90.57 MHz, respectively, using *ca* 5% solutions of the substances in hexadeuteriodimethyl sulfoxide. The chemical shifts are referenced to the solvent signals $\delta(^1H)$ 2.55 and $\delta(^{13}C)$ 39.60, respectively.

The mass spectra (EI) were measured on an MS 25 RFA (Kratos) spectrometer at the ionisation voltage of 70 eV and ionic current 100 μA. Temperature of ion source was 250 °C, resolution $R_{10\%} = 600$.

The electron spectra were measured on an HP 8452 A Diode Array Spectrometer at 25 °C.

Methyl *S*-(2,4,6-Trinitrophenyl)mercaptoacetate (**1**)

2,4,6-Trinitrochlorobenzene (0.5 g, 2 mmol) was dissolved in dry benzene (30 ml) in a three-necked flask with continuous stirring, whereupon methyl mercaptoacetate (0.18 ml, 0.21 g, 2 mmol) and triethylamine (0.27 ml, 0.19 g, 0.19 mmol) were added at once. The mixture was stirred under argon atmosphere at 10–20 °C for 1 h, triethylamine hydrochloride was filtered off, and the filtrate was poured in dilute hydrochloric acid (100 ml *ca* 5%), thoroughly shaken, the organic layer was separated and the aqueous layer extracted with chloroform (2 × 50 ml). Combined organic portions were dried with Na_2SO_4 and the solvent was distilled off in vacuum. According to its ^1H NMR spectrum the raw evaporation residue contained 95% product **1** beside 5% **2**. The evaporation residue was separated by column chromatography (silica gel, acetone–chloroform 1 : 5 v/v). The substance obtained from the first fraction was recrystallized from a benzene–cyclohexane mixture with addition of alumina for chromatography. Yield 0.30 g (47%), m.p. 72–73 °C. ^1H NMR spectrum: 9.14 s, 2 H (Ar); 3.91 s, 2 H (CH_2); 3.62 s, 3 H (OCH_3). ^{13}C NMR spectrum: 154.18 (C-2,6); 147.89 (C-4); 127.76 (C-1); 122.33 (C-3,5-phenyl); 168.03 (CO); 52.71 (OCH_3); 37.36 (CH_2). For $C_9H_7N_3O_8S$ (317.2) calculated: 34.08% C, 2.22% H, 13.25% N, 10.11% S; found: 34.26% C, 2.19% H, 13.34% N, 10.06% S.

2-Methoxycarbonyl-5,7-dinitrobenzo[*d*]thiazol-3-oxide (**2**)

The same procedure as above with triethylamine (0.31 ml, 2.2 mmol) and the reaction time of 2 h gave, after column chromatography (silica gel, acetone–chloroform 1 : 10 v/v) and recrystallization (toluene, alumina), product **2** (0.20 g, 33%) with m.p. 197–199 °C. ^1H NMR spectrum: 9.26 and 9.12 AB, 2 H, ^4J = 2.06 Hz (Ar); 4.02 s, 3 H (OCH_3). ^{13}C NMR spectrum: 156.88 (CO); 147.03, 146.13, 142.51, 137.38, 128.50 (5 × C_q); 121.19, 119.53 (2 × CH); 53.66 (OCH_3). EI-MS, *m/z* (%): 299 (M^+, 16); 283 ($M^+ - O$, 20); 252 ($M^+ - O - OCH_3$, 35); 225 ($M^+ - O - COOCH_3 + H$, 100). For $C_9H_5N_3O_7S$ (299.2) calculated: 36.13% C, 1.68% H, 14.04% N, 10.72% S; found: 36.44% C, 1.70% H, 14.16% N, 10.87% S.

2-Methoxycarbonyl-5,7-dinitrobenzo[*d*]thiazole (**3**)

A mixture of compound **2** (200 mg, 7 mmol) and PCl_3 (1.2 ml, 14 mmol) in chloroform (15 ml) was heated to boiling 1 h, whereupon the solvent was distilled off in vacuum, and the evaporation residue was submitted to column chromatography (silica gel, benzene–acetone 5 : 1 v/v) to give product **3** (100 mg, 50%) with m.p. 109–111 °C. ^1H NMR spectrum: 9.55 and 9.18 AB, 2 H, ^4J = 2.04 Hz (Ar); 4.10 s, 3 H (OCH_3). ^{13}C NMR spectrum: 162.91 (CO); 159.48, 153.64, 146.86, 142.41, 136.26 (5 × C_q); 126.22, 118.29 (2 × CH); 54.14 (OCH_3). EI-MS, *m/z* (%): 283 (M^+, 48); 252 ($M^+ - OCH_3$, 18); 225 ($M^+ - COOCH_3 + H$, 100).

Methyl *S*-(2,4-Dinitrophenyl)mercaptoacetate (**4**)

A solution of methyl mercaptoacetate (1.1 ml, 12 mmol) and triethylamine (1.4 ml, 10 mmol) in chloroform (10 ml) was added drop by drop to a solution of 2,4-dinitrofluorobenzene (1.86 g, 10 mmol) in methanol (15 ml) at room temperature during 1 h. After 3 h stirring under argon atmosphere at room temperature, the solvents were distilled off in vacuum, the evaporation residue was dissolved in chloroform, and the unreacted methyl mercaptoacetate was removed by extraction with a 5% solution of sodium carbonate. Chloroform was distilled off, and the residue was recrystallized from benzene with addition of Al_2O_3 to give compound **4** (1.6 g, 60%) with m.p. 94.5–95.5 °C (ref.[4] gives m.p. 93–94 °C). ^{1}H NMR spectrum: 9.10 d, 1 H, ^4J = 2.50 Hz (H-3); 8.40 dd, 1 H, ^3J = 9.02 Hz (H-5); 7.69 d, 1 H (H-6); 3.85 s, 2 H (CH_2); 3.79 s, 3 H (CH_3). ^{13}C NMR spectrum: 168.26 (CO); 145.07, 144.76, 144.40 (3 × C_q); 127.43, 127.14, 121.64 (3 × CH); 53.21 (OCH_3); 34.66 (CH_2).

Determination of pK_A Differences

The ΔpK_A values between acetic acid and methoxyacetic acid or *N*-methylmorpholine in methanol at the ionic strength of 0.1 mol l^{-1} at 25 °C were determined spectrophotometrically from the absorbances of 2-chloro-4-nitrophenoxide at the wavelength λ = 316 nm in the following buffers: [CH_3COONa] = [CH_3COOH] = 0.1 mol l^{-1} (a); [CH_3OCH_2COONa] = 0.1 mol l^{-1}, [CH_3OCH_2COOH] = 0.025 mol l^{-1} (b); [morpholine] = 0.1 mol l^{-1}, [morpholine . HCl] = 0.1 mol l^{-1} (c). The buffer (2 ml) was placed in a 1 cm quartz cell and after adjusting its temperature in thermostat a solution of 2-chloro-4-nitrophenol in tetrahydrofuran (30 μl, 5 . 10^{-3} mol l^{-1}) was added from a microdoser and the spectrum was measured in the wavelength range from 240 to 470 nm. The spectrum of completely dissociated 2-chloro-4-nitrophenol (A_B) was measured in methanolic 0.1 mol l^{-1} sodium acetate and that of nondissociated 2-chloro-4-nitrophenol (A_{BH}) in methanolic 0.1 mol l^{-1} acetic acid at the ionic strength I = 0.1 mol l^{-1} adjusted by addition of $NaClO_4$. For the calculation of ΔpK_A values from Eq. (*1*) for acetic (Ac) and methoxyacetic (MAc) acids we used the absorbance values A, A_B, and A_{BH} measured at 316 nm. A^{Ac} and A^{MAc} are the absorbances of 2-chloro-4-nitrophenoxide in acetate and methoxyacetate buffers, respectively.

$$\Delta pK_A = pK_A^{Ac} - pK_A^{MAc} = \log([CH_3COOH]/[CH_3COONa]) -$$
$$- \log([CH_3OCH_2COOH]/[CH_3OCH_2COONa]) + \log[(A^{Ac} - A_{BH})/(A_B - A^{Ac})] -$$
$$- \log[(A^{MAc} - A_{BH})/(A_B - A^{MAc})] = 1.16 \qquad (1)$$

For the *N*-methylmorpholine buffer we found the value $\Delta pK_A = pK_A^{Ac} - pK_A^{MPh} = 0.40$. 2-Chloro-4-nitrophenol was recrystallized from benzene, m.p. 107.5–108.5 °C, ref.[5] gives m.p. 109.5–110.5 °C.

Kinetic Measurements

For the kinetic measurements we used solutions of compounds **1** and **2** (5 . 10^{-3} mol l^{-1}) in dry tetrahydrofuran and solutions of the following acids and bases in preboiled p.a. methanol: acetic acid, anhydrous sodium acetate, methoxyacetic acid, *N*-methylmorpholine (1 mol l^{-1}). The methanolic solution of sodium methoxyacetate (1 mol l^{-1}) was prepared from 4.25 mol l^{-1} sodium methoxide and 2 mol l^{-1} methoxyacetic acid. The solution of *N*-methylmorpholine hydrochloride (0.5 mol l^{-1}) was prepared by dissolving the crystalline hydrochloride in methanol. The hydrochloride was prepared by saturation of *N*-methylmorpholine solution in dry ether with dry hydrogen chloride. The precipitated hydro-

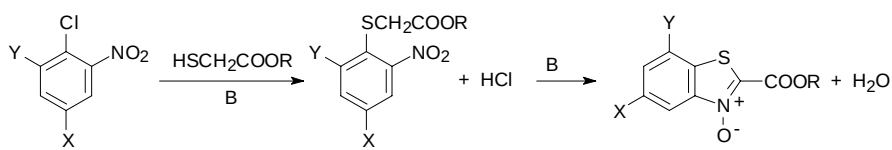
chloride was collected by suction in argon atmosphere, washed with dry ether, and dried at room temperature under argon.

Sodium perchlorate p.a. for adjusting the ionic strength was dried at 110 °C/2.6 kPa for 4 h.

The stock solutions thus prepared were then used to prepare the following buffer stock solutions with the ionic strength I = 0.1 mol l^{-1}: Acetate buffers with [CH_3COONa]/[CH_3COOH] = 8 : 1; 6 : 1; 4 : 1; 2 : 1; 1 : 1; 1 : 2; 1 : 4; methoxyacetate buffers with [CH_3OCH_2COONa]/[CH_3OCH_2COOH] = 4 : 1; 2 : 1; 1 : 1; *N*-methylmorpholine buffers with [*N*-methylmorpholine]/[*N*-methylmorpholine hydrochloride] = 4 : 1; 2 : 1; 1 : 1. The concentration of ionic component of buffer in the stock solution was always 0.1 mol l^{-1}. From these stock solutions we prepared series of buffers with various ratios of components and various concentrations. The ionic strength of these solutions was adjusted at I = 0.1 mol l^{-1} by adding methanolic 1 mol l^{-1} sodium perchlorate. For the kinetic experiments, the stock solutions prepared (2 ml) were placed in 1 cm quartz cells and kept at 25 °C in the closed cell. At the time t = 0, 20 μl stock solution of compound **1** was added and the absorbance was monitored at 292 nm. The rate constants were calculated with the help of the OPKINA programme[6].

RESULTS AND DISCUSSION

Substitued 2-alkoxycarbonylbenzo[*b*]thiazol-3-oxides are formed by base catalyzed reactions of substituted 2-nitrochlorobenzenes (which are further activated for nucleophilic substitutions) with mercaptoacetates[4]. Intermediates of these reactions – substituted alkyl *S*-phenylmercaptoacetates – were only isolated in two cases, hence the reaction described in Scheme 1 is preparatively carried out as a one-step reaction[4,7].



SCHEME 1

Methyl *S*-(2,4-dinitrophenyl)mercaptoacetate (**4**) was prepared in high yield[4] since it does not undergo a subsequent cyclization. Standing in 1 mol l^{-1} sodium methoxide does not result in cyclization but in splitting off of the side chain and formation of a mixture of products. This unwillingness to react in cyclization reaction – in contrast to 2-nitro-6-substituted sulfides of the type **4** – is obviously due to entropic effects: the conformation suitable for cyclization is energetically unfavourable in compound **4**.

Ethyl *S*-(4-cyano-2,6-dinitrophenyl)mercaptoacetate was prepared by reaction of 4-chloro-3,5-dinitrobenzonitrile and ethyl mercaptoacetate in benzene in the presence of less than equimolar amount of triethylamine[4]. The reaction of 2,4,6-trinitrochlorobenzene with methyl mercaptoacetate at similar conditions gave a mixture of methyl *S*-(2,4,6-trinitrophenyl)mercaptoacetate and 2-methoxycarbonyl-5,7-dinitrobenzo[*d*]-thiazol-3-oxide in practically quantitative yields (the ratio of the two substances was *ca* 20 : 1 after 1 h reaction). The mixture of both compounds is also formed by the reaction in benzene in the presence of $KHCO_3$, however, this reaction is slow and gives only

39% yield of compound **1** after 7 h reaction time. The anhydrous sodium acetate catalyzed reaction of 2,4,6-trinitrochlorobenzene with ethyl mercaptoacetate[4] only gave 2-ethoxycarbonyl-5,7-dinitrobenzo[*d*]thiazol-3-oxide.

Compounds **1** and **2** were identified by means of ^{1}H and ^{13}C NMR spectra, compound **2** also by means of mass spectrum as was also its deoxygenation product – 2-methoxycarbonyl-5,7-dinitrobenzo[*d*]thiazol (**3**). The mass spectrum of compound **2** shows the typical fragment $M^+ - 16$ which is absent after the deoxygenation.

The base catalyzed reaction of methyl *S*-(2,4,6-trinitrophenyl)mercaptoacetate leads to products completely different from those obtained from the base catalyzed reaction of methyl *N*-(2,4,6-trinitrophenyl)aminoacetate[1] and methyl *O*-(2,4,6-trinitrophenyl)-glycolate[8] at similar conditions. With the sulfur derivative **1** no nitroso product is formed, whereas the nitrogen derivative gives the nitroso compound as the only product. The sulfur derivative gives its product by the attack of nitrogen atom of *ortho*-standing nitro group by the carbanion $-S-CH^{(-)}-COOCH_3$ in spite of the fact that the sulfur atom in compound **1** must be much more nucleophilic than the nitrogen atom in the aminoacetates mentioned. Such an attack, on the other hand, was observed neither with nitrogen[1,2] nor oxygen[8] derivatives. The different behaviour of the sulfur derivative is obviously due to substantial increase in the acidity of $-SCH_2COOCH_3$ group as compared with $>NCH_2COOCH_3$ or $-OCH_2COOCH_3$ groups caused by the fact that sulfur atom is better able to stabilize the carbanion. The effect of sulfur on acidity of CH groups – as compared with the effect of oxygen – is obvious from the comparison of pairs of 9-X-fluorenes[9]: X (pK_A in DMSO at 25 °C) SC_6H_5 (15.4), OC_6H_5 (19.9), SC_2H_5 (18.0), OC_2H_5 (21.1).

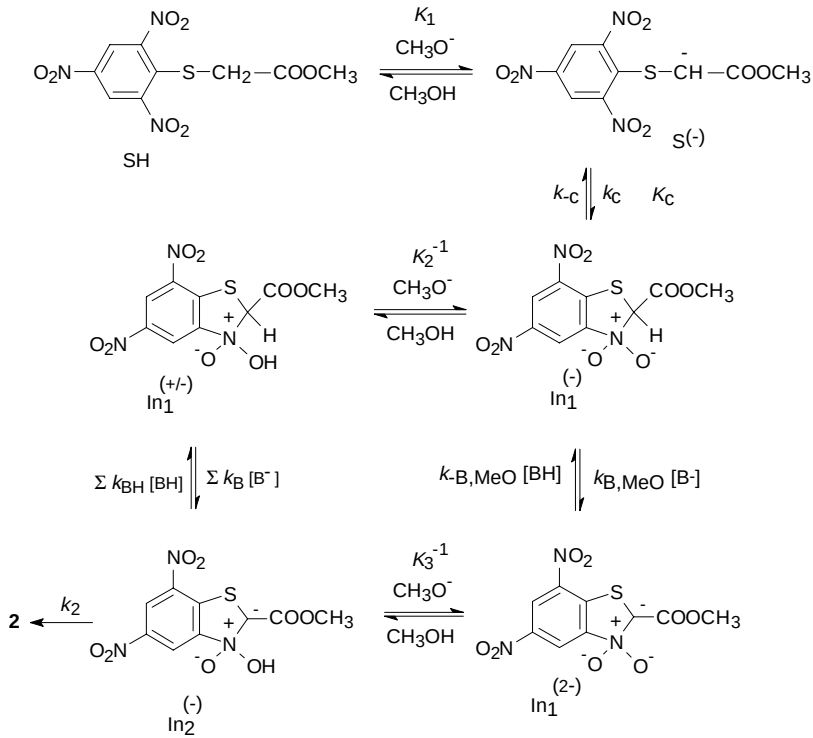
The reaction of compound **1** with bases in methanol was studied spectrophotometrically at 25 °C. The reaction with methanolic sodium methoxide of concentrations above $5 \cdot 10^{-3}$ mol l^{-1} is very fast: the reaction course is complicated by formation of Meisenheimer adducts and the character of absorbance–time dependences at various wavelengths indicates that there occur consecutive reactions. Compound **2** is not the final product of the reaction. Further decrease in methoxide concentration can be achieved by application of buffers. In acetate, methoxyacetate and *N*-methylmorpholine buffers the cyclization of compound **1** obeyed the 1st order rate equation, no intermediates accumulated in the reaction course, and the reaction product showed the electronic spectrum identical with that of compound **2** in the same buffer at the same concentration. The half-lives of cyclization of compound **1** to compound **2** ranged from about 30 to 7 200 s.

The mechanism of cyclization of compound **1** to compound **2** can be expressed by Scheme 2. The cyclization can take two paths differing by the order of events: intermediate $In_2^{(-)}$ can be formed from intermediate $In_1^{(-)}$ either *via* intermediate $In_1^{(2-)}$ after primary deprotonation of CH group and subsequent protonation of oxygen, or on the other hand, the protonation of oxygen can come first and be followed by deprotonation

of CH group in intermediate $In_1^{(+/-)}$. The resulting intermediate $In_2^{(-)}$ splits off hydroxyl ion to give product **2**. The rate-limiting step can be deprotonation of CH group in compound **1** or in some of the intermediates $In_1^{(-)}$ or $In_1^{(+/-)}$ or hydroxide ion splitting off from the intermediate $In_2^{(-)}$. The steps involving the protonation of oxygen in Scheme 2 must be fast equilibria. On the basis of kinetic studies it is possible to decide which path is really adopted by the cyclization.

Acetate and methoxyacetate buffers. Tables I and II summarize the values of observed rate constants k_{obs} (s^{-1}) of cyclization of compound **1** for buffers with various ratios of components and various concentrations. In the acetate and methoxyacetate buffers we found linear dependences of k_{obs} *vs* buffer concentration in series of buffers with constant ratios of components (Figs 1 and 2). The increasing ratio $[B^-]/[BH]$ of the buffer components increases both the intercepts obtained by extrapolation to zero buffer concentration and the slopes of dependences. Such behaviour is compatible with rate equation (*2*):

$$k_{obs} = k^0 + k'_{MeO}[CH_3O^-] + k'_B[B^-] + k'_{B,MeO}[B^-][CH_3O^-] \ . \qquad (2)$$



SCHEME 2

TABLE I

Observed (k_{obs}) and calculated (k_{cal}, from Eq. (*2*)) values (s^{-1}) of rate constants of cyclization of compound **1** to **2** in methanolic acetate buffers at 25 °C and I = 0.1 mol l^{-1}

$[B^-]/[BH]$	[B], mol l^{-1}	$k_{obs} . 10^3$, s^{-1}	$k_{cal} . 10^3$, s^{-1}
8 : 1	0.10	13.41	13.51
	0.05	11.91	11.86
	0.01	10.51	10.55
6 : 1	0.10	10.36	10.36
	0.05	9.02	9.02
	0.01	7.78	7.95
4 : 1	0.10	7.22	7.21
	0.07	6.71	6.59
	0.05	6.27	6.18
	0.01	5.55	5.36
2 : 1	0.10	4.11	4.06
	0.05	3.35	3.34
	0.01	2.79	2.76
1 : 1	0.10	2.53	2.49
	0.07	2.14	2.14
	0.05	1.92	1.92
	0.01	1.48	1.46
1 : 2	0.10	1.62	1.70
	0.07	1.34	1.40
	0.05	1.15	1.21
	0.02	0.86	0.91
	0.01	0.75	0.81
1 : 4	0.10	1.04	–
	0.085	0.97	–
	0.07	0.90	–
	0.05	0.75	–
	0.035	0.66	–
	0.02	0.52	
	0.01	0.42	–

The dependence of k_{obs} *vs* $[B^-]$ is not quite linear but slightly curved for the most acidic acetate buffer (4 : 1), which resembles – even though to a much less extent – the dependences of k_{obs} *vs* [B] in the *N*-methylmorpholine buffers (Fig. 7) and could indicate the same kinetic behaviour. As, however, in the still more acidic methoxyacetate buffers the dependences of k_{obs} *vs* $[B^-]$ are linear, the curvature in the acidic acetate buffer is obviously due to a change in character of medium at the highest concentrations of acetic acid. The term $k'_{MeO}\,[CH_3O^-]$ corresponds to the cyclization catalyzed by methoxide and its value was determined by extrapolation of linear dependences to the zero buffer concentration. The k'_{MeO} values found in the series of acetate buffers are constant and equal to $(1.268 \pm 0.012) \cdot 10^{-3}\ s^{-1}$ (for acetate buffer with ratios of components 1 : 1). Identical or very close values of k'_{MeO} were found in methoxyacetate and morpholine buffers after recalculation to pH values of the acetate buffers with the help of the ΔpK_A values found: $k'_{MeO} = 1.268 \cdot 10^{-3}\ s^{-1}$ (for methoxyacetate buffers) and $k'_{MeO} = 1.304 \cdot 10^{-3}\ s^{-1}$ (for morpholine buffers).

TABLE II
Observed (k_{obs}) and calculated (k_{cal}, from Eq. (*2*)) values (s^{-1}) of rate constants of cyclization of compound **1** to **2** in methanolic methoxyacetate buffers at 25 °C and I = 0.1 mol l^{-1}

$[B^-]/[BH]$	[B], mol l^{-1}	$k_{obs} \cdot 10^4$, s^{-1}	$k_{cal} \cdot 10^4$, s^{-1}
4 : 1	0.100	5.20	5.12
	0.085	4.82	4.86
	0.070	4.52	4.60
	0.050	4.22	4.25
	0.020	3.77	3.73
	0.010	3.60	3.56
2 : 1	0.100	3.07	2.99
	0.070	2.58	2.58
	0.050	2.31	2.31
	0.030	2.01	2.04
	0.010	1.73	1.77
1 : 1	0.100	1.92	1.93
	0.070	1.54	1.58
	0.050	1.34	1.34
	0.030	1.05	1.11
	0.010	0.97	0.87

As the dissociation constant K_A of acid buffer component in methanol at the ionic strength I = 0.1 mol l^{-1} is not known, the concentration of methoxide in Eq. (*2*) was expressed by means of the concentration ratio $[B^-]/[BH]$ of the buffer components. The methoxide concentration and the ratio of buffer components are interrelated by Eq. (*3*) where K_{MeOH} is the ion product of methanol ($K_{MeOH} = 10^{-16.92}$, ref.[10]). By introducing the relation for methoxide concentration from Eq. (*3*) into Eq. (*2*) we get Eq. (*4*).

$$[CH_3O^-] = K_{MeOH}[B^-]/K_A[BH] \qquad (3)$$

$$k_{obs} = k^0 + k'_{MeO} K_{MeOH}[B^-]/K_A[BH] + k'_B[B^-] + k'_{B,MeO}(K_{MeOH}[B^-]/K_A[BH])[B^-] \qquad (4)$$

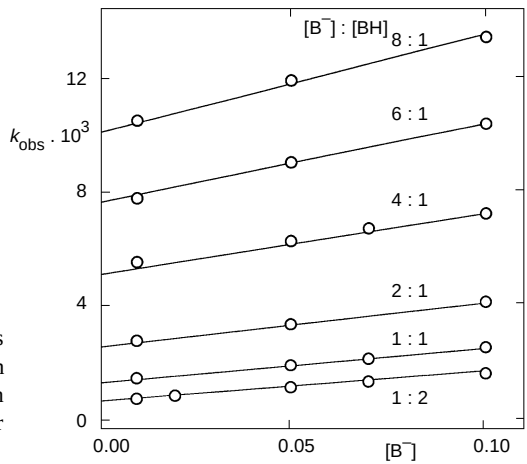


FIG. 1
Dependence of observed rate constants k_{obs} (s^{-1}) of transformation of **1** into **2** upon concentration of acetate ion $[B^-]$ (mol l^{-1}) in acetate buffers with varying ratio of buffer components at I = 0.1 mol l^{-1} at 25 °C

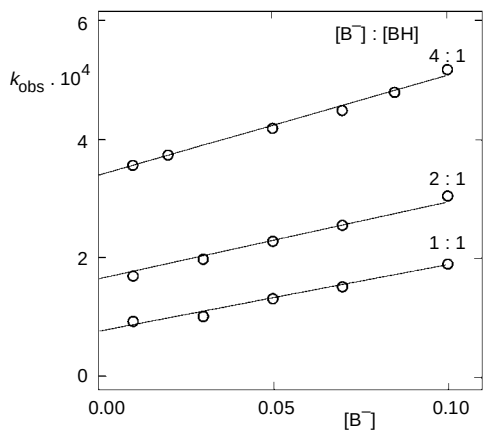


FIG. 2
Dependence of observed rate constants k_{obs} (s^{-1}) of transformation of **1** into **2** upon concentration of methoxyacetate ion $[B^-]$ (mol l^{-1}) in methoxyacetate buffers with varying ratio of buffer components at I = 0.1 mol l^{-1} at 25 °C

The dependences of k_{obs} on concentration [B⁻] of the basic buffer component are linear. The intercepts D_i for a given ratio of buffer components are expressed as the sum $D_i = k^0 + k'_{MeO}(K_{MeOH}/K_A)([B^-]/[BH])$ and correspond to the cyclization catalyzed by methoxide. The slopes A_i of these dependences are expressed as the sum $k'_B + k'_{B,MeO}(K_{MeOH}/K_A)([B^-]/[BH])$. The values of intercepts and slopes are presented in Table III.

The dependence of slopes A_i on the ratio [B⁻]/[BH] of the buffer components is linear with the intercept corresponding to k'_B and the slope corresponding to $k'_{B,MeO} K_{MeOH}/K_A$. These dependences for acetate and methoxyacetate buffers are represented graphically in Figs 3 and 4. The slope values are loaded with large error in the case of the methoxyacetate buffers and the justification for the presumption of linear dependence in this case (Fig. 4) is supported by the results of the multiple linear regression carried out. The intercepts at the *y*-axis have the values $k'_B = (80.1 \pm 8.6) \cdot 10^{-4}$

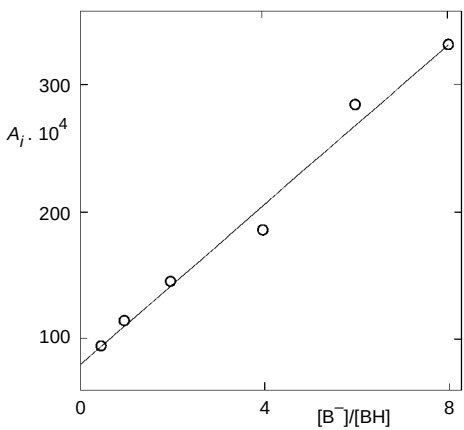


FIG. 3
Dependence of slopes $A_i = \Delta k_{exp}/\Delta[B^-]$ (l mol^{-1} s^{-1}) upon ratio [B⁻]/[BH] of buffer components in acetate buffers at I = 0.1 mol l^{-1} at 25 °C

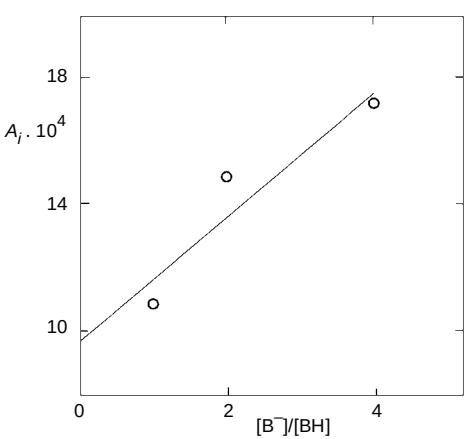


FIG. 4
Dependence of slopes $A_i = \Delta k_{exp}/\Delta[B^-]$ (l mol^{-1} s^{-1}) upon ratio [B⁻]/[BH] of buffer components in methoxyacetate buffers at I = 0.1 mol l^{-1} at 25 °C

and (9.7 ± 1.9) . 10^{-4} l mol^{-1} s^{-1} for the acetate and methoxyacetate buffers, respectively. The respective slopes $k'_{B,MeO} = k_{B,MeO}K_cK_1K_A/K_{MeOH}$ have the values (31.8 ± 1.9) . 10^{-4} and (1.97 ± 0.71) . 10^{-4} l^2 mol^{-2} s^{-1}.

On the basis of the Bodenstein steady state approximation it is possible to formulate the rate equations (*5*) or (*6*) for the system of consecutive reactions described by Scheme 2 and going from starting compound **1** to product **2** *via* the intermediate $In_1^{(2-)}$ or $In_1^{(+/-)}$, respectively.

$$v_{(2-)} = k_{obs}^{(2-)}[SH] = k_cK_1k_{B,MeO}[CH_3O^-][B^-][SH]/(k_{-c} + k_{B,MeO}[B^-]) \quad (5)$$

$$v_{(+/-)} = k_{obs}^{(+/-)}[SH] = K_cK_1k_2k_B[B^-][SH]/K_2(k_{BH}[BH] + k_2) \quad (6)$$

The key intermediates for deriving the approximation are $In_1^{(-)}$ and $In_2^{(-)}$ for the paths *via* $In_1^{(2-)}$ and $In_1^{(+/-)}$, respectively.

The cyclization of compound **1** in acetate and methoxyacetate buffers follows fully neither of the rate equations given because linear dependences were found experimentally between k_{obs} and concentrations of bases (Eq. (*2*)). If $k_{-c} >> k_{B,MeO}[B^-]$, then Eq. (*5*) is reduced to Eq. (*7*). If $k_2 >> k_{BH}[BH]$, then Eq. (*6*) is reduced to Eq. (*8*).

$$v_{(2-)} = k_{obs}[SH] = K_cK_1k_{B,MeO}[CH_3O^-][B^-][SH] \quad (7)$$

$$v_{(+/-)} = k_{obs}[SH] = K_cK_1k_B[B^-][SH]/K_2 \quad (8)$$

TABLE III
Values of intercepts D_i (s^{-1}) = ($k'_{MeO}(K_{MeOH}/K_A)([B^-]/[BH])$) and slopes A_i (l mol^{-1} s^{-1}) = $k'_B + k'_{B,MeO}(K_{MeOH}/K_A)([B^-]/[BH])$ of dependences of k_{obs} *vs* base concentration in acetate (Ac) and methoxyacetate (MAc) buffers determined by linear regression

$[B^-]/[BH]$	Ac		MAc	
	D_i . 10^4	A_i . 10^4	D_i . 10^4	A_i . 10^4
1 : 2	6.63 ± 0.06	96.30 ± 1.05	–	–
1 : 1	13.51 ± 0.24	116.00 ± 3.71	0.80 ± 0.05	10.93 ± 0.87
2 : 1	26.33 ± 0.22	146.90 ± 3.41	1.57 ± 0.02	14.82 ± 0.29
4 : 1	53.60 ± 0.35	187.30 ± 5.29	3.34 ± 0.05	17.07 ± 0.84
6 : 1	75.29 ± 0.77	285.90 ± 11.90	–	–
8 : 1	102.30 ± 0.92	321.30 ± 14.20	–	–

The right-hand sides of Eqs (*7*) and (*8*) are terms of Eq. (*2*). This means that the cyclization of compound **1** in acetate and methoxyacetate buffers goes by both paths in Scheme 2, *i.e. via* both the intermediates $In_1^{(2-)}$ and $In_1^{(+/-)}$. The third term in Eq. (*2*), $k'_{MeO}[CH_3O^-]$, corresponds to specific base catalyzed reaction. It cannot be decided which reaction path is adopted by the cyclization. The cyclizations obeying the rate equations (*7*) and (*8*) can be described by the sequences of steps in (*A*) and (*B*). In both paths the deprotonation of CH group of the intermediates is rate limiting. The Gibbs energy changes along the reaction coordinate in the cyclizations going *via* the intermediates $In_1^{(2-)}$ and $In_1^{(+/-)}$ are represented qualitatively in Figs 5 and 6 (graph a), respectively.

$$\mathrm{SH} \overset{K_1}{\rightleftharpoons} \mathrm{S^{(-)}} \overset{K_c}{\rightleftharpoons} \mathrm{In_1^{(-)}} \xrightarrow[\mathrm{RLS}]{k_B} \mathrm{In_1^{(2-)}} \rightleftharpoons \mathrm{In_2^{(-)}} \longrightarrow \mathrm{P} \qquad (A)$$

$$\mathrm{SH} \overset{K_1}{\rightleftharpoons} \mathrm{S^{(-)}} \overset{K_c}{\rightleftharpoons} \mathrm{In_1^{(-)}} \overset{K_2}{\rightleftharpoons} \mathrm{In_1^{(+/-)}} \xrightarrow[\mathrm{RLS}]{k_B} \mathrm{In_2^{(-)}} \longrightarrow \mathrm{P} \qquad (B)$$

Experimentally accessible are only the values of stoichiometric rate constants $k'_{B,MeO} = k_{B,MeO}K_cK_1K_A/K_{MeOH}$ and $k'_B = k_BK_cK_1/K_2$ because the values of corresponding equilibrium constants are not known.

The parameters of rate equation (*4*) were also evaluated by multiple linear regression. k_{obs} was chosen for the dependent variable, and the interpreting variables involved $[B^-]$, $[B^-]/[BH]$ and $[B^-][B^-]/[BH]$. The values of rate constants thus obtained for acetate and methoxyacetate buffers are summarized in Table IV. Tables I and II give beside the k_{obs} values also the k_{cal} values recalculated from the rate constant values for each buffer and each base concentration. We also tested the statistical significance

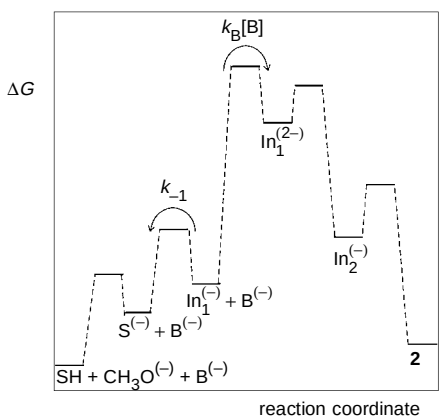


FIG. 5
Gibbs energy profile of cyclization of **1** to **2** with the rate-limiting formation of $In_1^{(2-)}$ intermediate

of the k^0 constant, *i.e.* of the possibility of the cyclization catalyzed by methanol. The value of test criterion is $t = 1.470$, $t_{0.975}(18) = 2.101$ in the acetate buffers and $t = 1.990$, $t_{0.975}(12) = 2.179$ in the methoxyacetate buffers. The k^0 value is statistically insignificant wherefrom it follows that the solvent-catalyzed cyclization takes place neither in acetate nor in methoxyacetate buffers.

N-Methylmorpholine buffers. In contrast to the acetate and methoxyacetate buffers, the dependences of k_{obs} *vs* [B] are not linear (Fig. 7, Table V), the slopes being decreased with increasing base concentration. This indicates a decreasing reaction order in base with its increasing concentration and a change in the rate-limiting step. The dependences of k_{obs} *vs* [B] extrapolated to zero buffer concentration form intersects at *y*-axis whose magnitude is proportional to the methoxide concentration in the buffers. This indicates the existence of the $k'_{MeO}[CH_3O^-]$ term in the rate equation for the cyclization. As long as the cyclization in the *N*-methylmorpholine buffers follows the same

TABLE IV
Rate constants k_i, their standard deviations, residual standard deviation *s*, and correlation coefficient *R* of multiple correlation

Parameter	Ac	MAc
$k^0 \cdot 10^5$, s^{-1}	7.742 ± 5.256	1.228 ± 0.615
$k'_{MeO} \cdot 10^4$, s^{-1}	12.680 ± 0.122	0.877 ± 0.023
$k'_B \cdot 10^4$, l mol^{-1} s^{-1}	83.540 ± 8.340	9.858 ± 1.004
$k'_{B,MeO} \cdot 10^4$, l^2 mol^{-2} s^{-1}	30.610 ± 1.918	1.878 ± 0.358
$s \cdot 10^5$	8.446	0.585
R	0.9998	0.9993

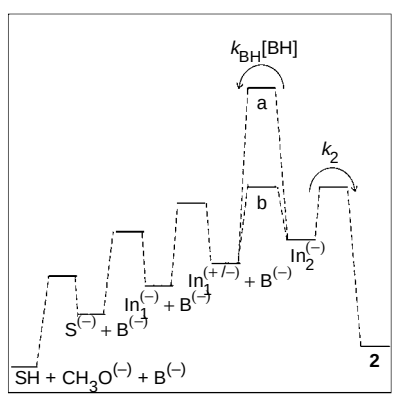


FIG. 6
Gibbs energy profile of cyclization of **1** to **2** with the rate-limiting formation of $In_2^{(-)}$ intermediate (a) or with comparable velocities of decomposition of $In_2^{(-)}$ intermediate into $In_1^{(+/-)}$ and transformation of $In_2^{(-)}$ to **2** (b)

mechanism as that in the acetate and methoxyacetate buffers, it should obey the rate equation (*9*) or (*10*).

$$k_{obs} = k'_{MeO}[CH_3O^-] + (K_c K_1/K_2)(k_2 k_B[B]/(k_{BH}[BH^+] + k_2)) \qquad (9)$$

$$k_{obs} = k'_{MeO}[CH_3O^-] + k_c k_{B,MeO} K_1 [CH_3O^-][B]/(k_{-c} + k_{B,MeO}[B]) \qquad (10)$$

Both equations express straight lines in the coordinates $1/(k_{obs} - k'_{MeO}[CH_3O^-])$ and $1/[B]$ (Eqs (*11*) and (*12*)). Parameters a_1, a_2, a_3, a_4 are combinations of rate and equilibrium constants. For a series of buffers with various concentrations and various ratios of components the solution of Eq. (*11*) represents a series of parallel straight lines with the slope of $1/a_1 = K_2/K_c K_1 k_B$.

$$(k_{obs} - k'_{MeO}[CH_3O^-])^{-1} = (a_1[B])^{-1} + (a_2[CH_3O^-])^{-1} \qquad (11)$$

$$(k_{obs} - k'_{MeO}[CH_3O^-])^{-1} = (a_3[CH_3O^-][B])^{-1} + (a_4[CH_3O^-])^{-1} \qquad (12)$$

In the case of Eq. (*12*) the slopes depend on the methoxide concentration in *N*-methylmorpholine buffer (the slope $(a_3[CH_3O^-])^{-1}$). The cyclization of compound **1** in *N*-methylmorpholine buffers obeys rate equation (*9*) (Fig. 8), hence it goes through the $In_1^{(+/-)}$ intermediate. Again it is impossible to decide about the reaction path taken by the

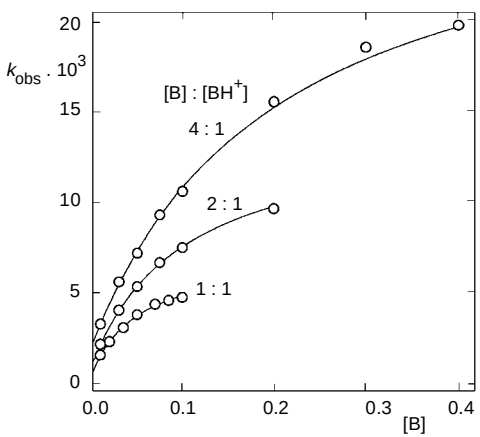


FIG. 7
Dependence of observed rate constants k_{obs} (s^{-1}) of transformation of **1** into **2** upon concentration of *N*-methylmorpholine [B] (mol l^{-1}) in *N*-methylmorpholine–*N*-methylmorpholinium chloride buffers with varying ratio of buffer components at $I = 0.1$ mol l^{-1} at 25 °C

specific base catalyzed reaction. The graph in Fig. 6 depicts qualitatively the Gibbs energy changes along the reaction coordinate. At low concentrations of *N*-methylmorpholine buffer the reaction is 1st order in base and the rate-limiting step is the formation of the $In_2^{(-)}$ intermediate. Both the formation and the reverse decomposition of intermediate $In_2^{(-)}$ are accelerated by increasing buffer concentration, and the reaction order in *N*-methylmorpholine is decreased. The above-mentioned changes in the rate-limiting step are reflected in the difference between graphs a and b in Fig. 6.

TABLE V
Observed (k_{obs}) and calculated (k_{cal}) values (s^{-1}) of rate constants of cyclization of compound **1** to **2** in methanolic *N*-methylmorpholine–*N*-methylmorpholinium chloride buffers at 25 °C at I = 0.1 mol l^{-1}

[B]/[BH^+]	[B], mol l^{-1}	$k_{obs} . 10^3$, s^{-1}	$k_{cal} . 10^{3,a}$, s^{-1}	$k_{cal} . 10^{3,b}$, s^{-1}
4 : 1	0.400	19.72	19.42	19.54
	0.300	18.52	17.75	17.77
	0.200	15.55	15.22	15.13
	0.100	10.60	10.92	10.75
	0.075	9.32	9.33	9.16
	0.050	7.21	7.40	7.26
	0.030	5.62	5.54	5.46
	0.010	3.30	3.30	3.31
2 : 1	0.200	9.64	9.73	9.77
	0.100	7.51	7.55	7.57
	0.075	6.68	6.61	6.62
	0.050	5.36	5.36	5.37
	0.030	4.05	4.02	4.03
	0.010	2.19	2.19	2.21
1 : 1	0.100	4.76	4.81	4.89
	0.085	4.59	4.57	4.64
	0.070	4.38	4.27	4.34
	0.050	3.80	3.74	3.78
	0.035	3.10	3.17	3.20
	0.020	2.33	2.36	2.37
	0.010	1.59	1.58	1.60

[a] Calculated on the basis of the results obtained by linearization. [b] Calculated on the basis of the results obtained by multiple nonlinear regression.

The rate constants were obtained from both the linearized form (Eq. (*11*)) and nonlinear regression. Equation (*9*) was modified to Eq. (*13*).

$$k_{obs} = k'_{MeO}([B]/[BH^+]) + ((K_c K_1/K_2)k_B[B])/((k_{BH}/k_2)[BH^+] + 1) \qquad (13)$$

With regard to the broad range of the dependent variable, the ln k_{obs} values were used in the optimization. The following values of rate constants and their combinations were obtained from the calculation:

$$k'_{MeO} = (5.19 \pm 0.20) \,.\, 10^{-4}\ s^{-1},\ K_C K_1 k_B/K_2 = 0.129 \pm 0.004\ l\ mol^{-1}\ s^{-1},$$

$$k_{BH}/k_2 = 19.56 \pm 0.89\ l\ mol^{-1}.$$

The residual standard deviation determined for the ln k_{obs} values was $s = 1.946 \,.\, 10^{-2}$, which indicates a very good fit.

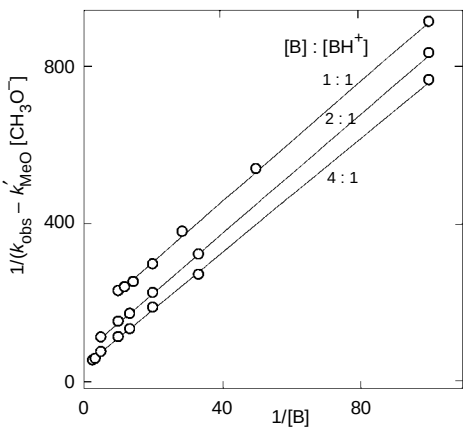


FIG. 8
Dependence of $1/(k_{obs} - k'_{MeO}[CH_3O^-])$ (s) upon 1/[B] in *N*-methylmorpholine buffers

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