KINETICS AND MECHANISM OF SPIRO ADDUCT FORMATION FROM AND SMILES REARRANGEMENT OF N-METHYL-N-(2,4,6-TRINITROPHENYL)AMINOACETANILIDE. BASE-CATALYZED TRANSFORMATION OF N-(2,4,6-TRINITROPHENYLAMINO)-ACETANILIDE INTO 2-NITROSO-4,6-DINITROANILINE

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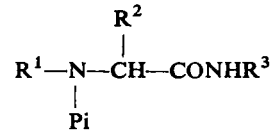
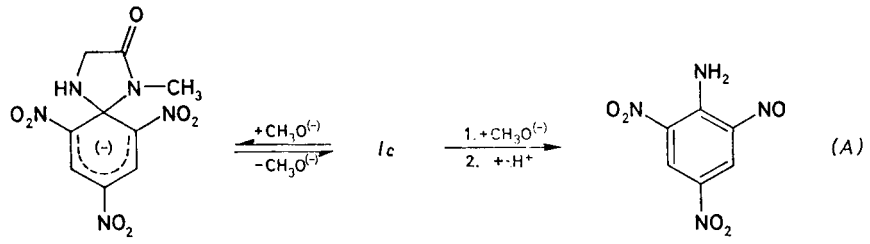
Dedicated to Prof. M. Večeřa on the occasion of his 65th birthday.

The paper deals with kinetics and mechanism of the reaction of N-(2,4,6-trinitrophenyl)amino-acetanilide (*IIa*) with methoxide ion and with the reaction kinetics and product structure of the reaction of N-methyl-N-(2,4,6-trinitrophenyl)aminoacetanilide (*IIb*) in methanolic buffers. The main product of the reaction of compound *IIa* with methoxide is 2-nitroso-4,6-dinitroaniline along with about 3% spiro adduct. The dependence of the experimental rate constant k_{exp} of the reaction with methoxide on the methoxide concentration is similar to that of the reaction of N-(2,4,6-trinitrophenyl)glycine methylamide, however, compound *IIa* reacts about 2·5 times faster and produces the spiro adduct in an about four times smaller amount. In basic acetate buffers, compound *IIb* is transformed quantitatively into the spiro adduct. In chloroacetate buffers, the reverse ring opening of the spiro adduct prevails. The ring opening takes two ways: A specific acid catalyzed one and a non-catalyzed one. Corresponding therewith is the non-catalyzed and specific base catalyzed formation of the spiro adduct. In aniline–anilinium chloride buffers, equilibrium is rapidly established between the spiro adduct and 2-methylamino-N-phenyl-N-(2,4,6-trinitrophenyl)acetamide hydrochloride. The mixture of the two compounds is transformed gradually into compound *IIb* which shows the highest thermodynamic stability in the given medium. At $[H^+] > 10^{-3}$ mol l^{-1} the thermodynamically most stable species is 2-methylamino-N-phenyl-N-(2,4,6-trinitrophenyl)acetamide hydrochloride.

In our previous papers[1-3] we studied the reactions of compounds *Ia–Ic* (Pi = = 2,4,6-trinitrophenyl) with methoxide ion. If R^1 or R^2 is a methyl group, then the substrate is cyclized to give the spiro adduct. If $R^1 = R^2 = H$ and $R^3 = CH_3$, then the yield of the spiro adduct is only about 12%, the main reaction product being 2-nitroso-4,6-dinitroaniline (reaction (*A*)).

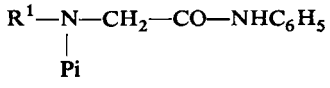


Ia, $R^1 = R^3 = CH_3$; $R^2 = H$
Ib, $R^1 = H$; $R^2 = R^3 = CH_3$
Ic, $R^1 = R^2 = H$; $R^3 = CH_3$



(A)

The present communication deals with a study of the reactions of compounds *IIa,b* with methoxide. Introduction of phenyl group instead of $R^3 = CH_3$ in compounds *Ib, c* should accelerate the ring opening of the spiro adduct and thereby enable the measurement of the reverse reaction rate and equilibrium constants. Another aim of our work was to determine the effect of the substitution mentioned (phenyl for methyl group) on the reaction product composition.



IIa, $R^1 = H$
IIb, $R^1 = CH_3$

EXPERIMENTAL

The NMR *spectra* (^1H and ^{13}C) were measured with a JNM FX-100 apparatus (JEOL) at 99·602 and 25·047 MHz, respectively. For the measurements the samples were dissolved in hexadeuteriodimethyl sulphoxide and tetradeuteriomethanol, respectively. The chemical shifts $\delta(^1H)$ are related to the solvent signal (δ 2·55 in hexadeuteriodimethyl sulphoxide) and to that of hexamethyldisiloxane (δ 0·05 in tetradeuteriomethanol), resp. The chemical shifts $\delta(^{13}C)$ are related to the central signal of the multiplet of solvent (δ 39·6 for hexadeuteriodimethyl sulphoxide, δ 49·0 for tetradeuteriomethanol).

Glycine anilide was prepared by the reaction of chloroacetanilide[4] with ethanolic ammonia[5], m.p. of the dihydrate is 56—60°C, ref.[5] gives m.p. 62°C. N-Methylglycine anilide hydrochloride was prepared similarly from chloroacetanilide and ethanolic methylamine. After evaporation of the reaction mixture the residue was recrystallized from 1% aqueous HCl. M.p. 228—232°C, ref.[6] gives m.p. 229—231°C.

2,4,6-*Trinitrophenylaminoacetanilide* (IIa): A suspension of 3·5 g (22 mmol) glycine anilide dihydrate and 2 g (24 mmol) $NaHCO_3$ in 30 ml methanol was treated with 5 g (20 mmol) 1-chloro-2,4,6-trinitrobenzene added with stirring. After 2 h stirring at room temperature, the precipitate was collected by suction and washed with 5 ml methanol, then it was transferred into a solution of 15 ml 1 mol l^{-1} HCl in 50 ml water, thoroughly mixed, again collected by suction, and washed with water. Yield 5·4 g (75%), m.p. 229—232°C (glacial acetic acid). For $C_{14}H_{11}N_5O_7$ (361·3) calculated: 46·53% C, 3·07% H, 19·39% N; found: 46·75% C, 3·25% H, 19·33% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(NHCO) 10·43 (1 H, broad singlet); δ(NH) 9·8 (1 H, a very broad band); δ(Pi) 9·02 (2 H, singlet); $\delta(C_6H_5)$ 7·60 (*ortho*), 7·38 (*meta*), 7·15 (*para*) (5 H, multiplet); $\delta(CH_2)$ 3·99 (2 H, singlet).

N-*Methyl*-N-(2,4,6-*trinitrophenyl*)*aminoacetanilide* (IIb) was prepared in the same way from 5 g (20 mmol) 1-chloro-2,4,6-trinitrobenzene, 4 g (20 mmol) N-methylglycine anilide hydrochloride, and 4 g (48 mmol) $NaHCO_3$. Yield 7·1 g (95%). A suspension of 1 g (2·66 mmol) raw compound *IIb* in 20 ml methanol was treated with 3 ml 1 mol l^{-1} sodium methoxide. The mixture was stirred until dissolution of all compound *IIb*, the solution was filtered, and 3 ml 1 mol . . l^{-1} methanolic HCl was added. During 4 h standing the solution separated the pure compound *IIb*. Yield 0·9 g, m.p. 173—176°C (decomp.). For $C_{15}H_{13}N_5O_7$ (375·3) calculated: 48·00% C, 3·49% H, 18·66% N; found: 48·13% C, 3·54% H, 19·00% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ (NH) 10·05 (1 H, a broadened singlet); δ(Pi) 8·94 (2 H, singlet); $\delta(C_6H_5)$ 7·57 (*ortho*), 7·35 (*meta*), 7·15 (*para*) (5 H, multiplet), $\delta(CH_2)$ 3·94 (2 H, singlet); $\delta(CH_3)$ 3·02 (3 H, singlet). ^{13}C NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(CO) 166·09; δ(Pi) 143·21 (C-1), 143·62 (C-2), 125·66 (C-3), 138·23 (C-4); $\delta(C_6H_5)$ 138·54 (C-1), 119·46 (C-2), 128·95 (C-3), 123·90 (C-4); $\delta(CH_2)$ 58·50; $\delta(CH_3)$ 41·65.

Spiro adduct IIIb, *triethylammonium salt*: A suspension of 0·5 g (1·33 mmol) compound *IIb* in 10 ml $CHCl_3$ was treated with 0·3 ml (0·22 g; 2·1 mmol) triethylamine. After 10 min, 40 ml ether was added. The product separated overnight was collected by suction under argon and dried by passing argon therethrough and then 1 h in vacuum. Yield 0·45 g (71%), m.p. 128 to 132°C. For $C_{21}H_{28}N_6O_7$ (476·5) calculated: 52·93% C, 5·92% H, 17·64% N; found: 52·86% C, 6·20% H, 17·74% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(Ar) 8·57 (2 H, singlet), $\delta(C_6H_5)$ 6·9—7·4 (5 H, multiplet); $\delta(CH_2)$ 3·61 (2 H, singlet); $\delta(\overset{(+)}{N}CH_2)$ 3·12 (6 H, quartet, J = 7·3 Hz), $\delta(NCH_3)$ 2·30 (3 H, singlet); $\delta(CH_3)$ 1·20 (9 H, triplet). ^{13}C NMR spectrum (hexadeuteriodimethyl sulphoxide): δ(CO) 170·71; δ(Ar) 118·35, 126·30, 127·29, 127·65, 129·22, 130·51, 136·31; δ_1 84·70; $\delta(CH_2)$ 57·03; $\delta(\overset{(+)}{N}CH_2)$ 45·98; $\delta(NCH_3)$ 34·22; $\delta(CH_3)$ 8·83.

2-*Methylamino*-N-*phenyl*-N-(2,4,6-*trinitrophenyl*)*acetamide hydrochloride* (IVb): A suspension of 1·9 g (5 mmol) compound *IIb* in 25 ml absolute ethanol was treated with 6 ml methanolic 1 mol l^{-1} butylamine. The solution of compound *IIIb* formed by heating at 40°C was treated with 5 ml methanolic 3·5 mol l^{-1} HCl added at once with stirring. The crystalline solid separated overnight was collected by suction under argon, washed with a mixture of 5 ml absolute ethanol and 0·5 ml methanolic 1 mol l^{-1} HCl, dried by passing argon therethrough and by evacuation. Yield 1·6 g (77%), m.p. 136—139°C (decomp.). For $C_{15}H_{14}N_5O_7Cl$ (411·8) calculated: 43·75% C, 3·43% H, 8·61% Cl, 17·01% N; found: 43·84% C, 3·73% H, 9·05% Cl, 16·75% N. ^{1}H NMR spectrum (tetradeuteriomethanol + one drop of methanolic HCl): δ(Pi) 9·05 (2 H, singlet), $\delta(C_6H_5)$ 7·47 (5 H, singlet); $\delta(CH_2)$ 4·17 (2 H, a broadened singlet); $\delta(CH_3)$ 2·65 (3 H, a broadened singlet). ^{13}C NMR spectrum (tetradeuteriomethanol + one drop of methanolic HCl): δ(CO) 168·11; δ(Pi) 148·03 (C-1), 149·01 (C-2), 125·71 (C-3), 137·75 (C-4); $\delta(C_6H_5)$ 133·36 (C-1), 128·93 (C-2), 131·66 (C-3), 131·32 (C-4); $\delta(CH_2)$ 51·00; $\delta(CH_3)$ 33·70 .

The kinetic measurements were carried out in methanolic solutions at 25°C with the ionic strength adjusted at 0·04 by addition of NaCl. The apparatus used was a Zeiss Specord UV VIS. The kinetics of the reverse reactions *IIb* ⇄ *IIIb* were measured in the following two ways: *a*) 20 μl methanolic solution of compound *IIb* ($5 . 10^{-3}$ mol l^{-1}) was added to 2 ml methanolic acetate or chloroacetate buffer ([$ClCH_2COONa$]/[$ClCH_2COOH$] = 5), and the absorbance increase was measured at 510 nm. *b*) 20 μl methanolic solution of compound *IIIb* ($5 . 10^{-3}$ mol . $. l^{-1}$) was added to 2 ml methanolic chloroacetate buffer and the absorbance decrease was measured at 510 nm. The solution of compound *IIIb* was prepared by addition of 0·1 ml 1 mol l^{-1} CH_3ONa to 10 ml $5 . 10^{-3}$ mol l^{-1} methanolic *IIb*. The methanolic acetate buffers were prepared by mixing fresh solutions of 1 mol l^{-1} acetic acid and sodium acetate. The methanolic chloroacetate buffers were prepared by mixing 0·5 mol l^{-1} chloroacetic acid and 0·25 mol l^{-1} sodium chloroacetate (the latter was prepared by neutralization of 0·5 mol l^{-1} chloroacetic acid with 0·5 mol l^{-1} sodium methoxide in methanol).

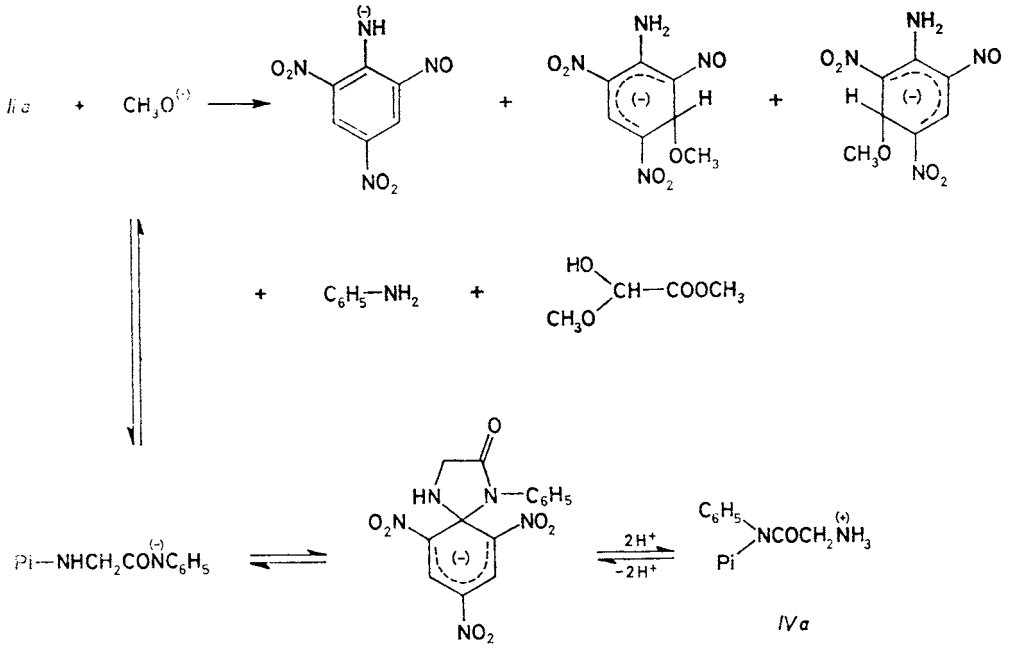
Estimation of the equilibrium constant of the reaction *IIIb* ⇄ *IVb* and estimation of the rate constant of the transformation *IIIb* + *VIb* ⇄ *IIb*. At the time $t = 0$, 0·4 ml methanolic $2·5 . . 10^{-4}$ mol l^{-1} compound *IIIb* was added to 1·6 ml methanolic aniline–anilinium chloride buffer ([$C_6H_5NH_3Cl$]/[$C_6H_5NH_2$] = 1 to 9) and the absorbance decrease at 510 nm and increase at 370 nm were measured. The reference cell contained 1·6 ml of the same buffer and 0·4 ml methanol. The resultant anilinium chloride concentration was 0·04 mol l^{-1} in all the cases. The solution of compound *IIIb* was prepared by addition of 0·2 ml 1 mol l^{-1} methoxide to 20 ml $2·5 . 10^{-4}$ mol l^{-1} solution of compound *IIb*.

RESULTS AND DISCUSSION

Reaction of 2,4,6-*Trinitrophenylaminoacetanilide* (IIa) *with Methoxide*

After addition of the methoxide solution to the solution of compound *IIa* an equilibrium mixture is rapidly formed which contains the anion and the adducts with methoxide ion of 2-nitroso-4,6-dinitroanilline (95 ± 3%) and the spiro adduct *IIIa* (spiro[(1-phenyl-5-imidazolone)-2,1′-(2′,4′,6′-trinitrobenzenide)]) (about 3%) (Scheme 1). The amounts of the spiro adduct *IIIa* and of 2-nitroso-4,6-dinitroaniline were estimated in the same way as in the case of the reaction products from compound *Ic* and methoxide[3], in which case the spiro adduct was formed in the amount of about 12%.

The reaction of compound *IIa* with methoxide obeys the pseudo-first-order kinetics in the whole range studied (*i.e.* 4–5 halflives). The dependence of log k_{exp} on log [$CH_3O^{(-)}$] is presented in Fig. 1 which also gives the corresponding dependence for the reaction of N-(2,4,6-trinitrophenyl)glycine methylamide with methoxide[3]. The two dependences have the same character, hence it can be presumed that the mechanism of the two reactions is the same, too[3] (Scheme 2). At lower methoxide concentrations the main reaction pathway consists in the transformation of the conjugated base of compound *IIa* into the nitroso compound with formation of the aziridinone intermediate as the rate-limiting step, the rate constant k_{exp} being defined by Eq. (*1*). The equilibrium constant of formation of the equilibrium mixture



SCHEME 1

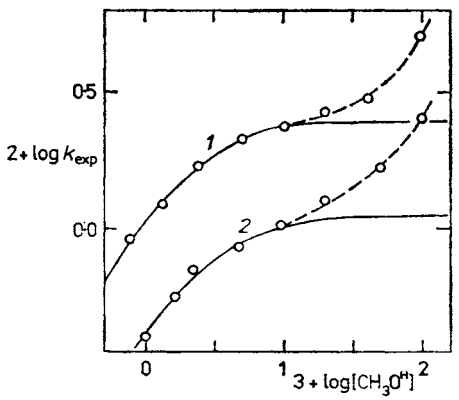
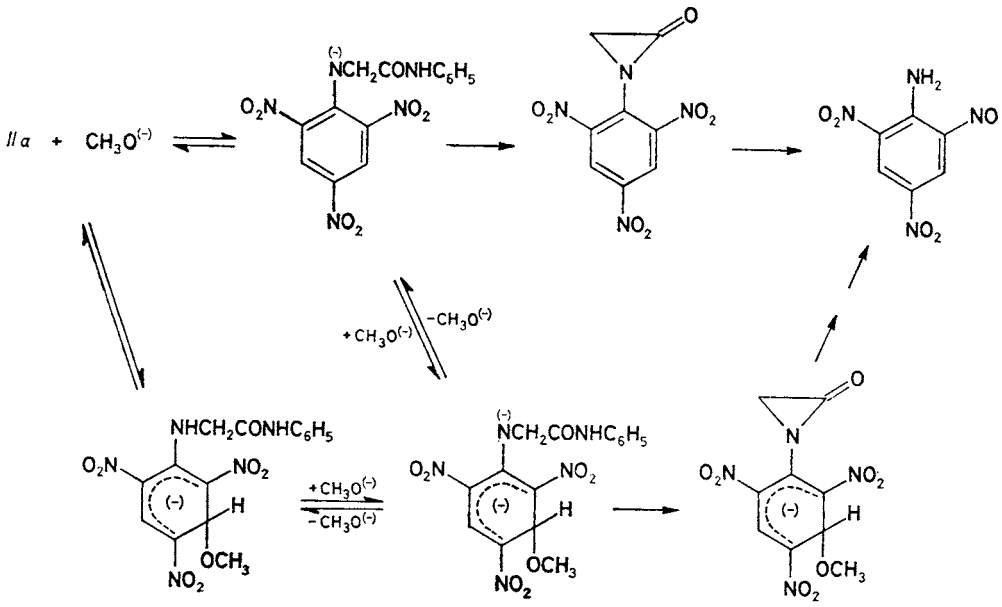


FIG. 1

The dependence of log k_{exp} on log [$CH_3O^{(-)}$] for the reaction of 2,4,6-trinitrophenylaminoacetanilide *IIa* (*1*) or N-(2,4,6-trinitrophenyl)glycine methylamide[3] (*2*) with methoxide. The heavy lines were calculated from Eq. (*I*) with application of the values $K_1 = 600\,l\,mol^{-1}$ and $k_1 = 2{\cdot}5 \cdot 10^{-2}\,s^{-1}$ (for compound *IIa*) and $K_1 = 500\,l\,mol^{-1}$ and $k_1 = 1{\cdot}1 \cdot 10^{-2}\,s^{-1}$ (for N-(2,4,6-trinitrophenyl)glycine methylamide[3])



SCHEME 2

of the conjugated base and 1,3-adduct (Scheme 2) is

$$k_{exp} = k_1 K_1 [CH_3O^{(-)}]/(1 + K_1[CH_3O^{(-)}]) \qquad (I)$$

$K_1 = 600\,\mathrm{l\,mol^{-1}}$. The expression $K_1[CH_3O^{(-)}]/(1 + K_1[CH_3O^{(-)}])$ gives the proportion of the conjugated base and 1,3-adduct of *IIa* in the reaction mixture, and k_1 means the overall rate constant of their conversion into the nitroso compound and spiro adduct *IIIa* ($k_1 = 2{\cdot}5 \,.\, 10^{-2}\,\mathrm{s^{-1}}$).

The Reactions in the System IIb ⇌ IIIb ⇌ IVb

After addition of the methoxide solution to methanolic solution of compound *IIb*, the spiro adduct *IIIb* (with λ_{max} 420 and 510 nm) is rapidly formed. Addition of methanolic hydrogen chloride causes a practically instantaneous transformation of the spiro adduct into light yellow 2-methylamino-N-phenyl-N-(2,4,6-trinitrophenyl)acetamide hydrochloride (*IVb*) (Fig. 2). The structure of the two compounds was determined by means of ^{1}H and ^{13}C NMR spectra. From the character of electronic spectra of compounds *IIIb* and *IVb* it is obvious that practicaly no 2-nitroso-4,6-dinitroaniline is formed in the reaction of compound *IIb* with methoxide (the electronic spectra would enable the detection of the nitroso compound, if it

were formed in an amount greater than 2%). The equilibrium between the spiro adduct *IIIb* and compound *IIb* is also established in acetate buffers, the ratio being $[IIIb]/[IIb] = 10$ in a buffer with the concentration ratio $[CH_3COONa]/[CH_3COOH] = 1$.

In the chloroacetate buffers – except the most basic ones ($[ClCH_2COONa]/[ClCH_2COOH] = 5$) – the equilibrium is shifted in favour of the starting compound *IIb*. After addition of compound *IIIb* into aniline–anilinium chloride buffers, the equilibrium *IIIb* ⇄ *IVb* is established instantaneously, and the equilibrium mixture is transformed slowly and practically irreversibly into the starting compound *IIb*.

The cyclization kinetics of compound *IIb* to the spiro adduct *IIIb* was studied in acetate buffers ($[CH_3COONa]/[CH_3COOH] = 1$ to 4). The spectra measured during the reaction course in the wavelength region 330–630 nm showed an isosbestic point, but the absorbance increase measured at 510 nm was (in the initial phase) faster than it should be according to the pseudo-first-order kinetics. The absorbance–time dependence can be expressed by Eq. (*2*).

$$A_\infty - A_t = (A_\infty - A_0)(0{\cdot}15 \exp(-k_a t) + 0{\cdot}85 \exp(-k_b t)) \qquad (2)$$

Both rate constants increased linearly with the methoxide concentration (determined by the buffer components ratio), being independent of the buffer concentration and of the ionic strength. The rate constants ratio k_a/k_b is about 3·5. The kinetic equation (*2*) is consistent either with a system of consecutive reactions (*B*) or with a system of parallel reactions (*C*) having the same product (A and B denote the two isomers of the starting compound).

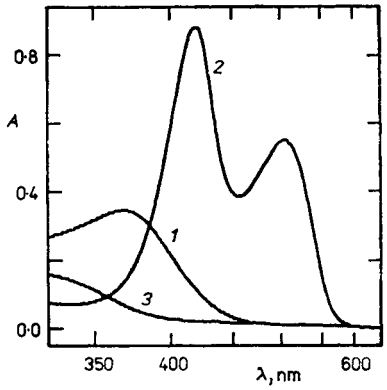


FIG. 2

Electronic spectra of compounds *IIb* (*1*), *IIIb* (*2*), and *IVb* (*3*) at the concentrations of $3{\cdot}5 \cdot 10^{-5}$ mol l^{-1} in methanol

$$A \rightleftharpoons B \rightarrow C \qquad (B)$$

$$A \rightarrow C \leftarrow B \qquad (C)$$

The ^1H and ^{13}C NMR spectra of compound *IIb* (measured in hexadeuteriodimethyl sulphoxide because of very low solubility of compound *IIb* in methanol), however, showed no signs of the presence of the second isomer.

In chloroacetate buffers, the rate constants of formation of the equilibrium mixture *IIb* ⇌ *IIIb* were measured at 510 nm from the absorbance decrease of compound *IIIb*. In the most basic chloroacetate buffer used, the rate of establishing of the equilibrium was also measured in the direction *IIb* → *IIIb*. In these buffers the absorbance–time dependences have an exponential character typical of reactions of the first or pseudo-first order. The concentration ratio $R = [IIIb]/[IIb]$ was calculated from Eq. (*3*)

$$R = (A - A_{II})/(A_{III} - A_{II}), \qquad (3)$$

in which A means the absorbance of the equilibrium mixture of compounds *IIb* and *IIIb* in the given buffer, A_{II} means the absorbance of compound *IIb* in 10^{-4} mol . l^{-1} methanolic HCl, and A_{III} means the absorbance of compound *IIIb* at the same concentration (always measured at 510 nm). The experimental rate constant k_{exp} of formation of the equilibrium mixture of compounds *IIb* and *IIIb* is the sum of the rate constants in both directions of the reaction (*4*). Eq. (*5*) applies to the equilibrium state,

$$k_{exp} = k_f + k_r \qquad (4)$$

$$k_f[IIb] = k_r[IIIb] \qquad (5)$$

and combination of Eqs (*3*), (*4*), and (*5*) provides relations for calculation of the rate constants in both directions (Eqs (*6*) and (*7*)). The results are given in Table I.

$$k_f = k_{exp}R/(R + 1) \qquad (6)$$

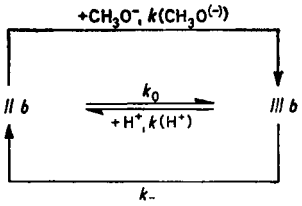
$$k_r = k_{exp}/(R + 1) \qquad (7)$$

The rate constants k_f of formation of the spiro adduct *IIIb* increase linearly with the methoxide concentration, those of the reverse reaction (k_r) increase linearly with the proton concentration. In the chloroacetate buffers with the component ratios $[ClCH_2COOH]/[ClCH_2COONa] = 4$ and 8, the k_r values were obtained by extrapolation to zero buffer concentration. The concentrations of H^+ and $CH_3O^{(-)}$ ions were calculated from pK_A of chloroacetic acid (7·96), the activity coefficients calculated[7] from Eq. (*8*), and the pK_S value (16·92) of methanol[8].

$$\log \gamma = -1{\cdot}9\sqrt{0{\cdot}04}/(1 + 2{\cdot}5\sqrt{0{\cdot}04}) \qquad (8)$$

The slope of the dependence of the k_r constant on $[H^+]$ gives the rate constant value of the acid-catalyzed tranformation of the spiro adduct *IIIb* into compound *IIb* ($k_{H^+} = (4{\cdot}7 \pm 0{\cdot}3) \cdot 10^3$ l mol^{-1} s^{-1}), the corresponding intercept gives the rate constant value of the non-catalyzed ring opening in the spiro adduct *IIIb* ($k_- = (2{\cdot}9 \pm 0{\cdot}2) \cdot 10^{-4}$ s^{-1}).

Similarly, the dependence of k_f on $[CH_3O^{(-)}]$ was used for determination of the rate constant of the base-catalyzed ($k(CH_3O^{(-)}) = (8{\cdot}5 \pm 0{\cdot}4) \cdot 10^4$ l mol^{-1} s^{-1}) and non-catalyzed ($k_0 = (5 \pm 0{\cdot}5) \cdot 10^{-5}$ s^{-1}) cyclization of compound *IIb* to the spiro adduct *IIIb* (Scheme 3).



SCHEME 3

TABLE I

The rate constants k_{exp}, k_f, and k_r of the reversible transformation *IIb* ⇄ *IIIb* in methanolic chloroacetate buffers at the ionic strength of 0·04 mol l^{-1}

$\frac{[ClCH_2COOH]}{[ClCH_2COONa]}$	$[ClCH_2COOH] \cdot 10^2$ mol l^{-1}	$\frac{[IIIb]}{[IIb]}$	$k_{exp} \cdot 10^4$ s^{-1}	Measured in the direction	$k_f \cdot 10^4$ s^{-1}	$k_r \cdot 10^4$ s^{-1}
	0·2	1·53	7·7	*IIIb* → *IIb*	4·65	3·05
0·2	0·2	1·53	7·7	*IIb* → *IIIb*	4·65	3·05
	0·8	1·53	8·4	*IIb* → *IIIb*	5·10	3·30
	0·8	1·50	7·85	*IIIb* → *IIb*	4·70	3·15
	4	0·26	6·30	*IIIb* → *IIb*	1·30	5·00
1	1	0·27	6·15	*IIIb* → *IIb*	1·30	4·85
	16	0·066	12·30	*IIIb* → *IIb*	0·76	11·50
4	4	0·067	11·40	*IIIb* → *IIb*	0·72	10·7
	32	0·03	20·60	*IIIb* → *IIb*	~0·60	20·00
	26	0·045	19·30	*IIIb* → *IIb*	~0·80	18·50
8	19	0·04	18·30	*IIIb* → *IIb*	~0·70	17·60
	13	0·035	17·00	*IIIb* → *IIb*	~0·60	16·50
	6·5	0·03	17·10	*IIIb* → *IIb*	~0·50	16·60
	6·5[a]	0·035	17·10	*IIIb* → *IIb*	~0·60	16·50

[a] The ionic strength 0·008 mol l^{-1} was not adjusted by addition of NaCl.

In the acetate buffers, the $k(CH_3O^{(-)})$ value ($(10{\cdot}6 \pm 0{\cdot}8) \cdot 10^4$ l mol^{-1} s^{-1}) was found with the use of the k_b value of Eq. (2) corrected for the reverse reaction *IIIb* → *IIb*. The methoxide concentration was calculated in similar way as that in the chloroacetate buffers with the use of the pK_A (9·52) of acetic acid[7]. The equilibrium constants of the equations (*D*) and (*E*) are defined by Eqs (*9*) and (*10*), respectively.

$$IIb + CH_3O^{(-)} \overset{K_2}{\rightleftharpoons} IIIb + CH_3OH \qquad (D)$$

$$IIb \overset{K_2'}{\rightleftharpoons} IIIb + H^+ \qquad (E)$$

$$K_2 = [IIIb]/[IIb]\,[CH_3O^{(-)}] = k(CH_3O^{(-)})/k_- = 2{\cdot}9 \cdot 10^8 \text{ l mol}^{-1} \qquad (9)$$

$$K_2' = [IIIb]\,[H^+]/[IIb] = k_0/k_{H^+} = 1{\cdot}1 \cdot 10^{-8} \text{ mol l}^{-1} \qquad (10)$$

In Fig. 3, the logarithms of the first-order (k_0 and k_-) and pseudo-first-order rate constants ($k(CH_3O^{(-)})\,[CH_3O^{(-)}]$ and $k_{H^+}[H^+]$) are plotted against log $[H^+]$. At the proton concentration of about 10^{-8} mol l^{-1}, the reaction rates of *IIb* ⇌ *IIIb* are the same in both directions. The spiro adduct *IIIb* is predominantly formed in the methoxide-catalyzed reaction, whereas in the reverse direction mainly the non-catalyzed ring opening makes itself felt. At $[H^+] = 6 \cdot 10^{-8}$ mol l^{-1}, when the equilibrium mixture contains about 15% of the spiro adduct *IIIb*, the non-catalyzed and catalyzed processes are equally significant in both directions ($k_{H^+}[H^+] = k_-$; $k(CH_3O^{(-)})\,[CH_3O^{(-)}] = k_0$).

In the aniline–anilinium chloride buffers, both the spiro adduct *IIIb* and the amide *IVb* are rapidly converted into an equilibrium mixture of both the compounds which is then slowly transformed into the starting compound *IIb*, the last being

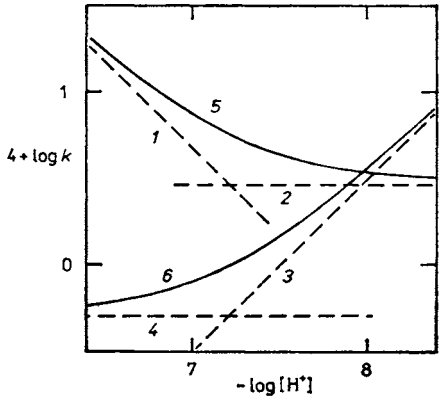
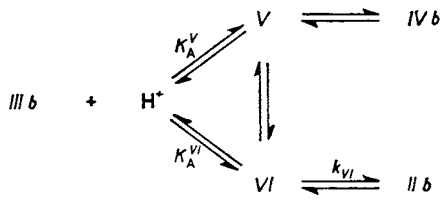


FIG. 3

The dependences of logarithms of the rate constants of the catalyzed ($k(CH_3O^{(-)})$ (*3*)) and non-catalyzed (k_0 (*4*)) cyclization *IIb* → → *IIIb*, and the catalyzed ($k_{H^+}[H^+]$ (*1*)) and non-catalyzed (k_-(2)) decomposition of the spiro adduct *IIIb* → *IIb* on log $[H^+]$. The heavy lines represent the logarithms of sums of the constants log ($k(CH_3O^{(-)})\,[CH_3O^{(-)}] + k_0$) (*6*) and log ($k_{H^+}[H^+] + k_-$) (*5*)

the most stable thermodynamically in the medium given. In this case the acid-catalyzed transformation *IIIb* → *IIb* only makes itself felt. The reactions taking place are represented in Scheme 4, structures of the dipolar ions *V* and *VI*



SCHEME 4

will be discussed below. The concentration of the dipolar ion *V* is higher than that of *VI* by many orders of magnitude. The equilibrium constant of the reaction *IIIb* + 2 H^+ ⇌ *IVb* (Eq. (*11*)) was calculated from Eq. (*12*)

$$K_3 = [\mathrm{IVb}]/[\mathrm{IIIb}]\,[\mathrm{H^+}]^2 = (9{\cdot}1 \pm 0{\cdot}4)\,.\,10^{10}\ \mathrm{l^2\ mol^{-2}} \qquad (11)$$

$$\log([\mathrm{IVb}]/[\mathrm{IIIb}]) = \log K_3 + 2\log K_A + 2\log r\,, \qquad (12)$$

where $K_A = 10^{-5{\cdot}09}$ is the dissociation constant of anilinium ion in methanol[9], and r means the ratio of the buffer components ($[C_6H_5\overset{(+)}{N}H_3]/[C_6H_5NH_2]$). The concentration ratio [*IVb*]/[*IIIb*] was calculated from Eq. (*13*),

$$[IVb]/[IIIb] = (A_{III} - A)/(A - A_{IV})\,, \qquad (13)$$

where A_{III} and A_{IV} are absorbances of the compounds *IIIb* and *IVb*, respectively, and A is the absorbance of the equilibrium mixture of compounds *IIIb* and *IVb* in the aniline–anilinium chloride buffer extrapolated to the zero time. When studying the equilibria, we could start only from the stock solutions of the spiro adduct *IIIb*, because in the stock solutions of compound *IVb* the compound *IIb* is formed slowly and irreversibly, hence the concentration of compound *IVb* gradually decreases.

From Scheme 4 it is possible to derive the expressions (*14*)–(*16*) for the rate of transformation of the equilibrium mixture *IIIb* + *IVb* into compound *IIb*.

$$v = k_{exp}([IIIb] + [IVb]) = k_{VI}[VI] \qquad (14)$$

$$[VI] = [\mathrm{H^+}]([IIIb] + [IVb])/(1 + K_3[\mathrm{H^+}]^2)\,K_A^{VI} \qquad (15)$$

$$k_{exp} = k_{VI}[\mathrm{H^+}]/(1 + K_3[\mathrm{H^+}]^2)\,K_A^{VI} = k_{H^+}[\mathrm{H^+}]/(1 + K_3[\mathrm{H^+}]^2) \qquad (16)$$

Table II presents the measured and the calculated values of the rate constants k_{exp} for various aniline–anilinium chloride buffers. The best agreement between the measured and the calculated k_{exp} values was reached for the value $k_{H^+} = 2{\cdot}85 \cdot 10^3$ l mol^{-1} s^{-1}. The k_{H^+} value found in this way is smaller than that measured in chloroacetate buffers by the factor of 1·65. The difference between the two k_{H^+} values is acceptable with regard to the fact that the measurements were carried out in two different buffer types and with pK_A values found by different authors[7,9] and with respect to the necessity to take into account the correction for the ionic strength effect in the calculations.

From the equilibrium constants K_3 and K_2' it is possible to calculate the equilibrium constant K_4 of the reaction $IVb \rightleftharpoons IIb + H^+$ (Eq. (*17*)). This means that at the concentration

$$K_4 = [IIb]\,[H^+]/[IVb] = 1/K_2'K_3 = 9{\cdot}7 \cdot 10^{-4}\ \text{mol l}^{-1} \qquad (17)$$

$[H^+] > 10^{-3}$ mol l^{-1}, compound *IVb* is the most stable of all the three compounds (*IIb*, *IIIb*, *IVb*) thermodynamically, whereas in the regions $10^{-3} > [H^+] > 10^{-8}$ mol . l^{-1} and $[H^+] < 10^{-8}$ mol l^{-1} the most stable compounds are *IIb* and *IIIb*, respectively.

The transformation of the negatively charged spiro adduct *IIIb* into the positively charged amide *IVb* must proceed through the phase of the dipolar ion. The formation of the dipolar ion could not be detected even spectrally in the case of the spiro adduct *IIIb*. We suppose, however, that the dipolar ion *V* has an analogous structure to that of the dipolar ion formed by protonation of the spiro adduct derived from N-(2,4,6-trinitrophenyl)alanine methylamide which was identified by means of the ^{1}H NMR spectrum[2]. So far, this neutral spiro adduct is the single product which has been detected in both methanolic solution and dimethyl sulphoxide (the pK_A

TABLE II

A survey of the equilibrium and rate constants of the catalyzed and non-catalyzed cyclization *IIb* → *IIIb* ($k(CH_3O^{(-)})$, k_0) and of the catalyzed and non-catalyzed decomposition of the adduct *IIIb* → *IIb* (k_{H^+}, k_-)

$k(CH_3O^{(-)})$, l mol^{-1} s^{-1}	$(8{\cdot}5 \pm 0{\cdot}4) \cdot 10^4$
	$(10{\cdot}6 \pm 0{\cdot}8) \cdot 10^4$[a]
k_0, s^{-1}	$(5 \pm 0{\cdot}5) \cdot 10^{-5}$
k_{H^+}, l mol^{-1} s^{-1}	$(4{\cdot}7 \pm 0{\cdot}3) \cdot 10^3$
k_-, s^{-1}	$(2{\cdot}9 \pm 0{\cdot}2) \cdot 10^{-4}$
$K_2 = k(CH_3O^{(-)})/k_-$, l mol^{-1}	$(2{\cdot}9 \pm 0{\cdot}2) \cdot 10^8$
$K_2' = k_0/k_{H^+}$, mol l^{-1}	$1{\cdot}1 \cdot 10^{-8}$

[a] In methanolic acetate buffers.

value of this dipolar ion is 5·87 (ref.[2])). In the other cases the dipolar ion obviously is more acidic, hence at the proton concentration suitable for a study of equilibria between the spiro adduct and the dipolar ion most of the spiro adduct is already transformed into the amide type *IV*.

The reversible transformation of compound *IIb* into the spiro adduct *IIIb* takes two pathways (Scheme 3). Mechanism of formation of the spiro adduct *IIIb* in the methoxide-catalyzed reaction is described by Eq. (*F*).

$$IIb + CH_3O^{(-)} \overset{K_5}{\rightleftharpoons} PiN(CH_3)—CH_2CO—\overset{(-)}{N}—C_6H_5 \underset{k_-}{\overset{k_2}{\rightleftharpoons}} IIIb \qquad (F)$$

The rate constant of the base-catalyzed reaction is defined as $k(CH_3O^{(-)}) = K_5k_2$.

In the other reaction pathway the decomposition of the spiro-adduct *IIIb* to compound *IIb* is subject to acid catalysis. The acid catalysis can be specific or general. For the general acid catalysis there exist two possibilities: *a*) The reaction proceeds in two steps – the ring opening of the spiro adduct *IIIb* is followed by the rate-limiting protonation at the nitrogen atom (*G*).

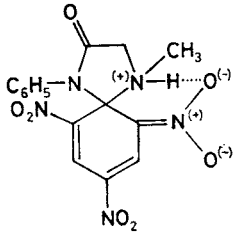
$$IIIb \rightleftharpoons PiN(CH_3)CH_2\overset{(-)}{C}ONC_6H_5 \xrightarrow{HA} IIb + A^{(-)} \qquad (G)$$

As the protonation of the nitrogen is thermodynamically favourable, the rate constants of the proton-catalyzed and the chloroacetic acid-catalyzed reactions would have to be comparable. In reality, the proton catalysis already prevails at $[H^+] > > 10^{-7}$ mol l^{-1}. *b*) The reaction involes simultaneous formation of the N—H bond and splitting of N—C bond. But this mechanism is improbable either, since the attack of the acid on the electron pair at the nitrogen atom incorporated in conjugation within an amidic group would be energetically unfavourable. The dependence of the rate constant of the ring opening on the chloroacetic acid concentration is not linear, its slope being increased with increasing concentration of the acid. At the highest chloroacetic acid concentration used (0·32 mol l^{-1}), the rate constant is by only about 25% higher than that obtained by extrapolation to the zero buffer concentration. Hence, the most probable reason of the acceleration of the decomposition of the spiro adduct into compound *IIb* lies in the effect of chloroacetic acid on the character of medium. Obviously, the ring opening of the spiro adduct *IIIb* is subject to specific catalysis and not to general catalysis.

The non-catalyzed cyclization *IIb* ⇄ *IIIb* corresponds to the specific acid-catalyzed ring opening of the spiro adduct *IIIb* to compound *IIb*, Eq. (*H*):

$$IIb \underset{k_{VI}}{\overset{k_0}{\rightleftharpoons}} VI \rightleftharpoons IIIb + H^+ \qquad (H)$$

The structure of the dipolar ion *VI* differs by position of a proton from that of *V*, the latter being the intermediate in the formation of *IVb* from *IIIb*. The proton in the dipolar ion *VI* could be bound to the amidic nitrogen. Thermodynamic stability of such an ion can only be roughly estimated. The pK_A value of N-protonated



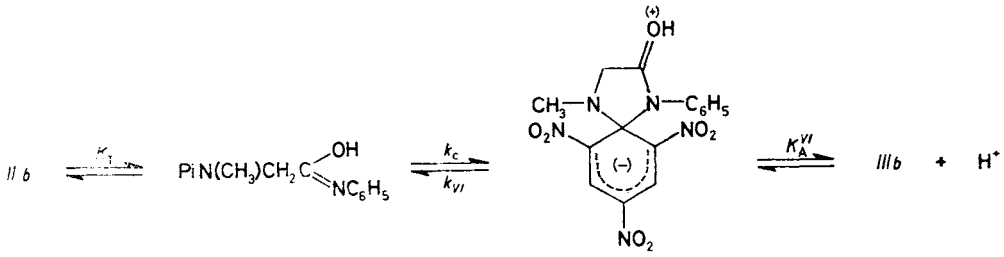
V

N-methylacetamide is −7·8 (ref.[10]); that of acetanilide will even be substantially more negative. The acidity of the proton at amidic nitrogen of the dipolar ion *VI* would be, furthermore, strongly enhanced by the polar effect of methylamino group at the α carbon atom and by the polar effect of cyclohexadienide group which, in spite of its negative charge, represents a considerable electron-acceptor group. These effects would only be slightly compensated by the strong hydrogen bond to the oxygen atom of nitro group[11]. So, *e.g.*, the pK_A value of the dipolar ion *VII* (6·64) is lower than that of methylamine itself[12] by 4 orders of magnitude. This means that the dissociation constant of the dipolar ion formed by protonation of the amidic nitrogen would have to be higher than 10^{10}. From the bimolecular rate constant of the proton-catalyzed transformation of the spiro adduct *IIIb* to compound *IIb* ($k_{H^+} = 4{\cdot}7 \cdot 10^3\ l\ mol^{-1}\ s^{-1}$) and from Scheme 4, we obtain for the rate constant k_{VI} the following relation: $k_{VI} \gg k_{H^+} \cdot 10^{10} > 10^{14}\ s^{-1}$. As the value of $10^{13}\ s^{-1}$ is considered to be the upper limit for a rate constant of transformation of a viable species[13], the dipolar ion with the proton bound to the amidic nitrogen cannot be able of existence.

The proton in the dipolar ion *VI* could be bound to the carbonyl oxygen atom. The pK_A value of acetanilide is −1·54 for the protonation at oxygen in water[14]. The dissociation constant value of the spiro adduct protonated at oxygen atom would be (very roughly) 10^2. Hence, such an ion would not be so unstable as to be unable of existence in the given medium. On the basis of these considerations it is possible to suggest, for the acid-catalyzed decomposition of the spiro adduct *IIIb*, the mechanism represented in Scheme 5.

The equilibrium constant of formation of the tautomeric form of amide *IIb*, K_T, can be estimated from pK_A of the acetanilide protonated at the oxygen (−1·54) and pK_A of the N-protonated N-phenyl-O-ethylethanimidic acid (4·63, ref.[15]):

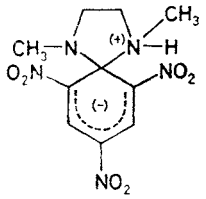
$K_T \approx 10^{-6}$. From Scheme 5 it is possible to derive kinetic equations for the rate constants of the acid-catalyzed splitting of the spiro adduct *IIIb*, k_{H^+}, and non-catalyzed cyclization of compound *IIb*, k_0: $k_{H^+} = k_{VI}/K_A^{VI} = 4{\cdot}7 \cdot 10^3\ l\ mol^{-1}\ s^{-1}$



VI

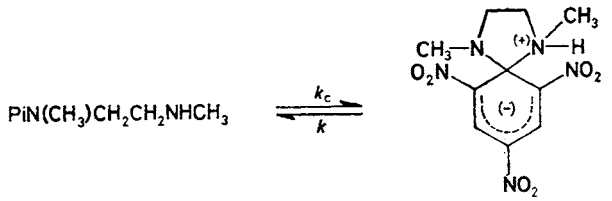
SCHEME 5

and $k_0 = K_T k_c = 5 \cdot 10^{-5}\ s^{-1}$. For the rate constants k_{VI} and k_c we then obtain the values $k_{VI} \approx 4{\cdot}7 \cdot 10^5\ s^{-1}$ and $k_c = 5 \cdot 10^2\ s^{-1}$. For the rate constants of the cyclization to the dipolar ion *VII* and reverse splitting of the latter it is given by



VII

Bernasconi[16]: $k_{VI} = 1{\cdot}93 \cdot 10^5\ s^{-1}$ and $k_c = 1{\cdot}2 \cdot 10^3\ s^{-1}$. When comparing pairs of the rate constants, we clearly see that the roughly estimated K_T and K_A^{VI} constants are reasonable and the suggested mechanism (Scheme 5) can be considered real.



(*I*)

The replacement of $CONHCH_3$ group by $CONHC_6H_5$ (compounds *Ia* and *IIb*) will increase – in the reaction with methoxide – the concentration of the reactive anion with simultaneous decreasing of the cyclization rate constant of this anion.

The bimolecular cyclization rate constant $k(CH_3O^{(-)})$ for the phenyl derivative *IIb* and the methyl derivative[1] *Ia* has the values of $8{\cdot}5 \cdot 10^4$ and $1{\cdot}75 \cdot 10^2$ l mol^{-1} s^{-1}, respectively. Hence, the replacement of methyl group by phenyl group increases the cyclization rate by almost 3 orders of magnitude. The decisive factor is the enhancement of acidity of the amidic hydrogen atom, the N—C bond being formed only to a small extent in the cyclization transition state. This is also supported by a comparison of the rate constants of the reverse reaction of the phenyl derivative *IIIb* and of the spiro adduct formed from the methyl derivative *Ia* ($k_- = 2{\cdot}9 \cdot 10^{-4}$ and $(2 \text{ to } 3) \cdot 10^{-6}$ s^{-1}, respectively).

When comparing the rates of formation of the spiro adducts from compounds *IIa* and *IIb*, it is necessary to take into account, in the case of compound *IIa*, the equilibrium constant of the splitting off of the proton from the nitrogen atom bound to the 2,4,6-trinitrophenyl group ($K = 600$ l mol^{-1}), the rate constant of formation of the products ($k = 2{\cdot}5 \cdot 10^{-2}$ s^{-1}), and the relative population of the spiro adduct in the reaction products (about 0·03). Then we can obtain the rate constant $k(CH_3O^{(-)}) = 600 \cdot 2{\cdot}5 \cdot 10^{-2} \cdot 0{\cdot}03 = 0{\cdot}45$ l mol^{-1} s^{-1} for the cyclization of compound *IIa* to the spiro adduct. Replacement of hydrogen atom in the NH group of compound *IIa* by a methyl group (compound *IIb*) increases the cyclization rate by the factor of about $2 \cdot 10^5$.

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