KINETICS AND MECHANISM OF CYCLIZATION OF N-(2-METHOXYCARBONYLPHENYL)-N'-METHYLSULFONAMIDE TO 3-METHYL-(1*H*)-2,1,3-BENZOTHIADIAZIN-4(3*H*)-ONE 2,2-DIOXIDE

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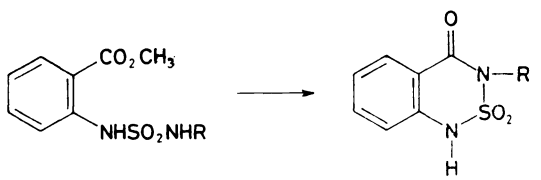
The cyclization kinetics of N-(2-methoxycarbonylphenyl)-N'-methylsulfonamide (*IIb*) into 3-methyl-(1*H*)-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide (*Ib*) has been studied in ethanolamine, morpholine, and butylamine buffers and in potassium hydroxide solutions. The cyclization is subject to general base and general acid catalysis. The value of the Brønsted coefficient β is about 0·1, which indicates that splitting off of the proton from negatively charged tetrahedral intermediate represents the rate-limiting and thermodynamically favourable step. In the solutions of potassium hydroxide the cyclization of dianion of the starting ester *IIb* probably becomes the rate-limiting step.

The derivatives *Ia*–*Ic* of 1*H*-2,1,3-benzothiadiazin-4(3*H*)-one 2,2-dioxide are used as broad-spectrum herbicides. The 3-isopropyl derivative *Ia*, known under the commercial names of Basagran and Bentazon, belongs to the most widely used herbicides and is employed in postemergent extirpation of dicotyledonous weeds in cereals. Its advantage lies in its low toxicity enabling its applications also in protected zones of drinking water resources[1–3].

The last step of one of the possible syntheses of Bentazon (*Ia*) consists in cyclization of N'-isopropyl-N-(2-methoxycarbonylphenyl)sulfonamide (*IIa*) in basic medium. As the cyclization of sulfonamide *IIa* proceeds very slowly in aqueous buffers, the hydrolysis of ester group being predominant, we have studied the cyclization of the corresponding methyl derivative *IIb*.



II *I*

In formulae *I* and *II*: *a*, R = H; *b*, R = CH_3; *c*, R = $CH(CH_3)_2$

The cyclizations of 3-($NHSO_2NH_2$)-alkanoic acids and their derivatives have low yields[4]; kinetics of these cyclizations have not been studied yet.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of compound *IIb* were measured at 400·13 and 100·62 MHz, respectively, with the help of an AM-400 Bruker spectrometer. The compound *IIb* was used as a 5% solution in deuteriochloroform. The chemical shifts $\delta(^1H)$ are referred to hexamethyldisiloxane, the chemical shifts $\delta(^{13}C)$ are referred to the middle signal of the solvent (δ 77·00).

Syntheses of Substances

N-(2-*Methoxycarbonylphenyl*)-N′-*methylsulfonamide* (IIb). Chlorosulfuric acid (11·7 g, 0·1 mol) was added to 80 ml dry pyridine with stirring at −10 to 0°C during 45 min, whereafter the mixture was heated to 50°C, and 7·6 g (0·05 mol) methyl anthranilate was added thereto. After another 20 min, 7·8 g (0·25 mol) methylamine was added below the surface during 15 min, and the mixture was cooled to 48—50°C. After 30 min, the mixture was treated with 25 g (0·18 mol) phosphorus pentoxide, which increased its temperature to 70°C; this temperature was maintained for another 60 min. Then the mixture was cooled and diluted with 750 ml water[5]. The separated crystals were collected by suction and dried to give 200 mg (1·6%) substance with m.p. 121 to 132°C. Its purification by column chromatography (silica gel, toluene–ethyl acetate 5 : 1) gave 45 mg (0·4%) crystals melting at 134—136°C. For $C_9H_{12}N_2SO_4$ (244·26) calculated: 44·26% C, 4·95% H, 11·49% N, 13·11% S; found: 44·34% C, 5·07% H, 11·14% N, 12·86% S. ^1H NMR: 10·48 b, 2 H (NH, NH); 8·02 d, 1 H (H-3, $J(3, 4) = 7·7$); 7·66 d, 1 H (H-6, $J(5, 6) = 8·2$); 7·51 t, 1 H (H-5, $J(4, 5) = 7·7$); 7·06 t, 1 H (H-4, $J(4, 6) = 1·3$); 3·91 s, 3 H (OCH_3); 2·68 d, 3 H (NCH_3, $^3J = 5·3$). ^{13}C NMR: 140·97 (C-1), 114·79 (C-2), 131·29 (C-3), 122·07 (C-4), 134·71 (C-5), 117·63 (C-6), 52·45 (OCH_3), 28·24 (NCH_3), 168·37 (CO).

3-*Methyl*-(1H)-2,1,3-*benzothiadiazin*-4(3H)-*one* 2,2-*dioxide* (Ib). A mixture of 100 mg (0·4 mmol) N-(2-methoxycarbonylphenyl)-N′-methylsulfonamide (*IIb*) and 2 ml 22% ammonia was placed on a water bath and evaporated until dry. The evaporation residue was treated with 1 ml 36% hydrochloric acid, placed on a water bath, and evaporated until dry again. The residue was extracted with 2 ml methanol, and the extract was left to crystallize; it gave 50 mg (59%) compound with m.p. 200—203°C (ref.[6] gives m.p. 201—203°C).

Kinetic Measurements

The cyclization velocity was measured spectrophotometrically with a Specord UV-VIS (Zeiss) apparatus in aqueous buffers. The ionic strength was adjusted at $I = 1$ mol l^{-1} by addition of a 2M KCl solution. The buffer solution (2 ml) in a 1 cm quartz cell was placed in the thermostated cell compartment of the apparatus, and at $t = 25$°C methanolic solution of the substrate *IIb* (25 μl, $c = 0·03$ mol l^{-1}) was injected, whereupon the absorbance–time dependence was monitored at 345 nm. In dilute butylamine buffers the pH value was adjusted (by adding a potassium hydroxide solution) to be the same as that in the concentrated buffers, and then the substrate was added. The pH value of solutions with low buffer concentrations decreased because of the transformation of the substrate *IIb* into the anion and formation of the anionic product $Ib^{(-)}$. When this pH decrease was smaller than 0·1, then the obtained rate constant was additionally corrected according to Eq. (*2*) with application of the pK_a, k_{OH}, and k_B values found. If the pH

decrease was greater than 0·1 (at the buffer concentrations below 0·025 mol l^{-1}), the rate constant values were excluded.

The kinetic experiments carried out in the potassium hydroxide solutions (with the ionic strength adjusted at $I = 1$ mol l^{-1}) were monitored by the stopped-flow method using a Durrum D 110 apparatus. The cyclization rate constants k_{obs} (s^{-1}) were calculated from the equation $k_{obs}t = -2{\cdot}3 \log \Delta A + \text{const.}$, where $\Delta A = (A_\infty - A_t)$ or $(A_t - A_\infty)$.

Measurements of Dissociation Constants

The dissociation constants of compounds *Ib* and *IIb* were measured with the Specord UV-VIS spectrophotometer at 25°C. The measurements of compound *Ib* were carried out at 333 nm in chloroacetate buffer solutions. A 1 cm quartz cell was charged with 1 ml buffer solution and 1 ml substrate solution (the final ionic strength was adjusted with KCl at $I = 1$ mol l^{-1}). The reference cell contained the same buffer. The measurement of compound *IIb* was carried out in glycinamide, morpholine, and ethanolamine buffers prepared in similar way. The absorbances were measured at 262 nm for 2 min, whereupon an extrapolation was carried out to the time of mixing of both solutions. The pH values of the buffers were measured with an MV 870 apparatus (VEB Präcitronic, G.D.R.) using a combined glass and silver chloride electrode.

RESULTS AND DISCUSSION

The cyclization kinetics of ester *IIb* into anion $Ib^{(-)}$ was monitored in morpholine, ethanolamine, and butylamine buffers and in potassium hydroxide solutions at ionic strength $I = 1$ mol l^{-1} at 25°C. The reaction was of the pseudo-first order, and the spectral records showed well-developed isosbestic points except for the kinetic runs with low concentrations of the morpholine buffer. The rate constants k_{obs} increase with both buffer concentration and basicity of medium. As the reactant proper is the ester anion (whereas the neutral ester does not undergo cyclization but only undergoes a slow hydrolysis similar to that of other derivatives of methoxycarbonylphenylsulfonamide[7]), the k_{obs} values were related to the anion concentration by dividing them by the fraction $f = ([III] + [IV])/([III] + [IV] + [IIb])$. The corrected rate constant values k_{corr} were calculated from Eq. (*1*) where the f values were calculated from pK_a of ester *IIb* and pH of solution.

$$k_{corr} = k_{obs}/f = k_{obs}(1 + 10^{(pK_a - pH)}) \qquad (1)$$

Figures 1 and 2 show the dependences of the corrected rate constants k_{corr} on the concentration of base in buffers. Figure 3 gives the dependence of $\log k_{corr}$ on the value $(14 + \log [OH])$ for the measurements carried out in the potassium hydroxide solutions. At the same time, Fig. 3 presents the logarithms of the rate constants obtained by extrapolations of the dependences in Figs 1 and 2 to the zero buffer concentration, on pH.

The dependences of k_{corr} on base concentration are linear in all the cases, but the slopes of these dependences increase with increasing content of acidic buffer com-

ponent. That means that the cyclization is catalyzed by both the basic and acidic buffer components. Hence, k_{corr} is given by Eq. (2).

$$k_{corr} = k_{OH}[OH] + k_B[B] + k_{BH}[BH] \qquad (2)$$

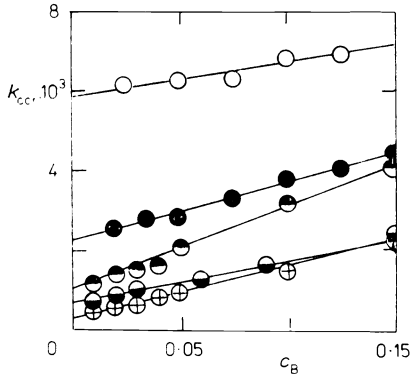


FIG. 1

The dependence of the corrected rate constants k_{corr} (s^{-1}) of the cyclization reaction $IIb \rightarrow Ib^{(-)}$ on molar concentration c_B in the buffers: ethanolamine 3 : 1 basic (○), ethanolamine 1 : 1 (●), ethanolamine 3 : 1 acidic (◓), morpholine 3 : 1 basic (◒), morpholine 1 : 1 (⊕)

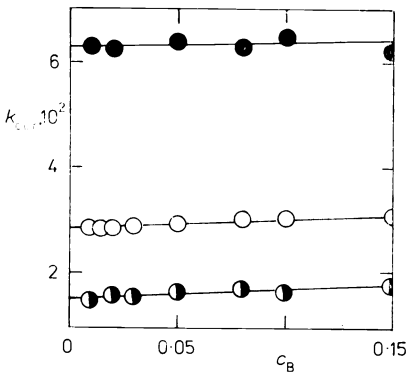


FIG. 2

The dependence of the corrected rate constants k_{corr} (s^{-1}) of the cyclization reaction $IIb \rightarrow Ib^{(-)}$ on the molar concentration c_B of base in the butylamine buffers: 2 : 1 basic (●), 1 : 1 (○), 2 : 1 acidic (◑)

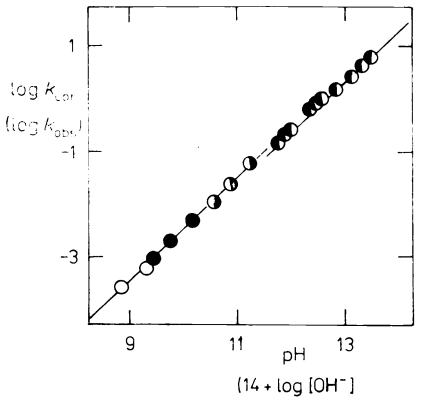


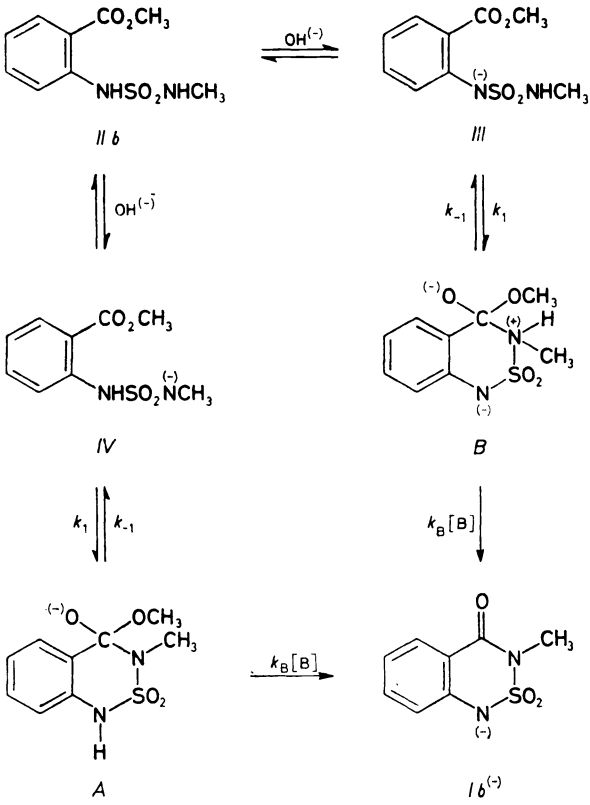
FIG. 3

The pH dependence of log k_{corr} (s^{-1}) (extrapolated to zero buffer concentration) in ethanolamine (●), morpholine (○), and butylamine (◑) buffers, and the dependence of log k_{obs} (s^{-1}) on (14 + log [$OH^{(-)}$]) for solutions of potassium hydroxide (◑)

When plotting k_{corr} against $([B^-] + r[BH])$ we obtained linear dependences with the same slopes for a given buffer type, and the following k_B and r values were obtained from these dependences: morpholine buffers: $k_B = (8{\cdot}3 \pm 0{\cdot}3) \cdot 10^{-3}$ l. . mol^{-1} s^{-1}, $r = 0{\cdot}8$; ethanolamine buffers: $k_B = (9{\cdot}1 \pm 0{\cdot}3) \cdot 10^{-3}$ l mol^{-1} s^{-1}, $r = 0{\cdot}6$; butylamine buffers: $k_B = (12 \pm 1) \cdot 10^{-3}$ l mol^{-1} s^{-1}, $r = 0{\cdot}3$.

From the Brønsted dependence of log k_B vs pK_a of the acid buffer component we obtained the value $\beta \sim 0{\cdot}1$, which corresponds to a thermodynamically favourable proton transfer from the intermediate to the basic buffer component[8].

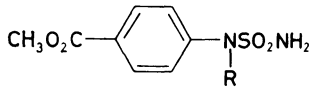
The general-base-catalyzed cyclization of ester *IIb* can be described by the mechanism given in Scheme 1.



SCHEME 1

The ratio of the anions $[III]/[IV]$ can be estimated from the pK_a values of compounds *Va* (9·87), *Vb* (8·37), and *IIc* (9·53) and *IIb* (9·30). Under the presumption that the replacement of NH group by NCH_3 group has no substantial effect on the

dissociation of the proton from the groups NH_2 and $NHCH_3$, respectively, the proportions of anions of compound *Vb* are in a ratio of 30 : 1 in favour of the anion



Va, R = CH_3
Vb, R = H

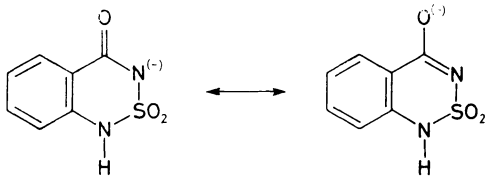
type C_6H_5—$N^{(-)}$–. The pK_a value of compound *IIb* is one unit higher than that of ester *Vb*, which is obviously due to the intramolecular hydrogen bond between NH group and carbonyl group in compound *IIb*. Hence it is likely that the concentration of anion *III* is greater than that of anion *IV* by a factor of only 2–3.

As the rate-limiting step of the base catalyzed cyclization consists in the thermodynamically favourable proton transfer from the cyclic intermediate to the basic buffer component, the decisive factor for a choice of reaction pathway is the relative stability of the intermediates *B* and *A*. It is doubtless that the stability of the intermediate *B* (which carries a positive charge at the nitrogen atom adjacent to SO_2 group) is much smaller than that of the intermediate *A*, hence the reaction goes via the intermediate *A* (Scheme 1).

The thermodynamically favourable proton transfer means that the pK_a value of negatively charged intermediate *A* must be smaller than that of the conjugated acid of morpholine[9] by more than one unit and, hence, smaller than that of neutral ester *IIb* by 2 units.

A certain idea about the effect of cyclization on the pK_a value can be obtained from comparison of pK_a of ester *IIc* (9·53) with that of anion of its cyclization product (*Ic*$^{(-)}$, pK_a 8·20, ref.[10]).

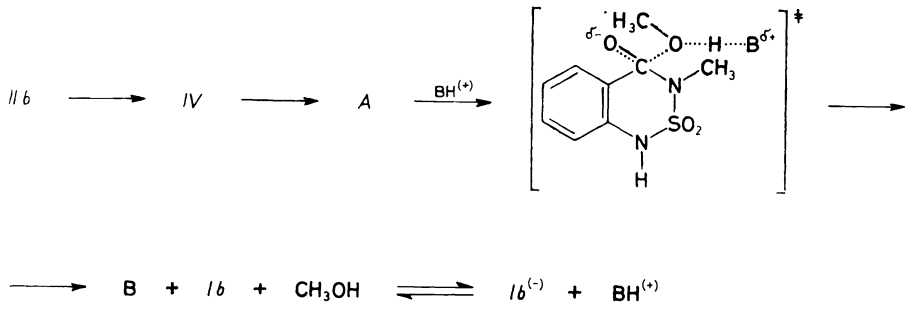
A considerable acidity difference was observed between noncyclic and cyclic β-diketones and β-ketoesters[11,12], and the cyclization of ureidoesters[13,14] is accompanied by a considerable acidity increase, too.



Ic$^{(-)}$

The general-acid-catalyzed cyclization of anion *IV* can be explained in similar way as the cyclization of ethyl esters of thiohydantoic acid[14] (Scheme 2).

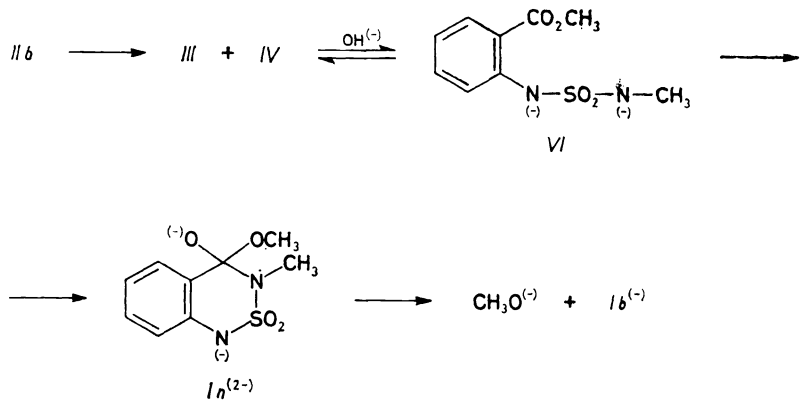
The considerable catalytic effect (which is even observed with the acids as weak as the protonated ethanolamine or butylamine) is due to the great tendency of the intermediate *A* to ring opening with formation of anion *IV* as a consequence of the much less nucleophilicity of $-SO_2-N^{(-)}-CH_3$ group as compared with $-CS-N^{(-)}-C_6H_5$ group (pK_a of phenylthiourea is about 13 in water[15] and pK_a of ester of 5-phenylthiohydantoic acid will only be slightly lower). This is in accordance with the rule[16] that a catalysis makes itself felt the more the more it is needed. The cyclization of 5-phenylhydantoic acid (CO instead of CS), which acid is by 3 orders of magnitude weaker an N-acid than is the thio derivative[14], showed such a slight acid catalysis even in phosphate buffers that the linear increase in k_{obs} with increasing buffer concentration was misinterpreted, being considered a specific effect of buffer on solvation of the reacting components[14].



SCHEME 2

Figure 3 gives plots of log k_{corr} (extrapolated to zero concentration of buffer) on pH and log k_{corr} vs $(14 + \log [OH^{(-)}])$ for kinetic experiments in potassium hydroxide solutions. Both the dependences are linear with the slope equal to 1, but the straight line of the pH dependence is shifted upwards by 0·1. The activity coefficient of $OH^{(-)}$ ion at $I = 1$ mol l^{-1} is smaller than one, hence the concentration of $OH^{(-)}$ ion is higher than the activity of $OH^{(-)}$ obtained from pH measurement.

The k_{OH} value determined from the dependence of k_{corr} on concentration of $OH^{(-)}$ ion is $30 \pm 1{\cdot}5$ l mol^{-1} s^{-1}, i.e. more than 3 orders of magnitude greater than the k_B values, although the proton transfer from the intermediate *A* to the basic buffer component is thermodynamically favourable and its rate approaches the rates of diffusion-controlled reactions. In the diffusion-controlled proton transfers the values of rate constants for the reaction of hydroxyl ion are greater than those for other bases by less than one order of magnitude[7]. The difference of more than 3 orders means that the hydroxyl-ion-catalyzed reaction goes by another pathway, most likely via the dianion *VI* (Scheme 3).

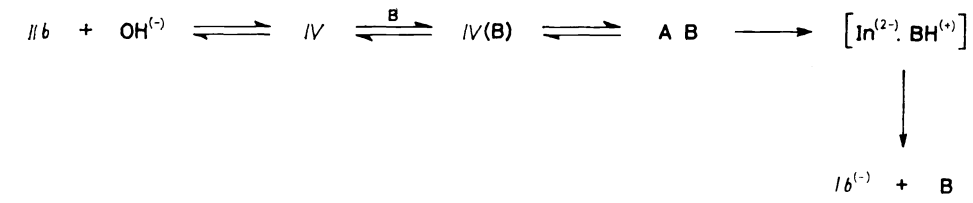


SCHEME 3

The pK_a value of the equilibrium reaction $III + IV \rightleftarrows VI + H^+$ cannot be determined experimentally; a rough assessment can only be made. The pK_a value for the second dissociation of 1,3-bis(3-nitrophenyl)sulfonamide is 12·8 (ref.[17]). A 3-nitro group is similar to 4-methoxycarbonyl group in its polar effect on dissociation of N—H bond. The pK_a value of sulfuric diamide[17] ($NH_2SO_2NH_2$) is 10·42 (after statistical correction for one amino group it is 10·72). That is by 2·35 pK_a units more than with the 4-methoxycarbonyl derivative *Vb*. Presuming that the same difference also applies to the dissociation to the second degree, we can assess the pK_a value of the mixture of anions *III* and *IV*, i.e. c. 12·8 + 2·35 ≐ 15·15. The activating effect of SO_2 group on the acidity of hydrogen atom in NHR group (R = = methyl or 3-nitrophenyl) is much smaller in the monoanion $Ar—N^{(-)}—SO_2NHR$ than in the neutral compound, hence the polar effect of the group R on the dissociation of the second proton will be more important. Thus e.g. the ϱ value for dissociation of substituted formanilides[18] is 1·53, being 2·85 for substituted anilines in which the polar effect of the formyl group does not operate[19]. The pK_a value of the mixture of anions *III* and *IV* will thus be greater than 15·15; probably 16 – 17.

The hydroxyl ion makes itself felt kinetically also in the reaction pathway in Scheme 1, being involved in splitting off of the proton from the intermediate *A*. But in comparison with the other reaction pathway via the dianion *VI* the share of $OH^{(-)}$ ion will be several % at the most. In comparison with the basic components of buffer the relative participation of hydroxyl ion in the first reaction pathway will be increased with increasing pH and with decreasing buffer concentration. Therefore, its importance will be the greatest in the butylamine buffers in which (especially at the lowest buffer concentrations) probably a rather large part of the intermediate *A* will be transformed into $In^{(2-)}$ by the reaction with hydroxyl as compared with the participation of butylamine.

The value of k_d for a diffusion-controlled proton transfer to a base is c. 10^{10} s^{-1} (refs[8,9]). The value of rate constant for the proton transfer from the intermediate to basic buffer component (k_H in Scheme 1) obviously approaches this value. As it is $k_B = k_H K_{In}$ (where K_{In} means the equilibrium constant of formation of *In* from the anions *IV*), it is $K_{In} < 10^{-11}$. At the highest buffer concentrations it is $k_H[B] \leqq 10^9$ (s^{-1}). As the dependence of k_{corr} on the base concentration remains linear even at the highest buffer concentrations (Figs 1, 2), the rate constant k_{-1} of decomposition of intermediate A to anion *IV* must be at least one order of magnitude greater (i.e. $k_{-1} = 10^{10}$ s^{-1}). It is possible that the intermediate is so unstable ($k_{-1} < 10^{11}$ s^{-1}) that its reversible transformation to anion *IV* is faster than the reverse diffusion of the catalyst base into the solution, and the reaction proceeds by the so-called preassociation mechanism[20] (Scheme 4).



SCHEME 4

The catalyst is present beside the anion in the moment of formation of the intermediate *A*, and the proton transfer takes place immediately after formation of *A*. Most probably the base stabilizes the activated complex only by formation of a hydrogen bond, hence the value of the Brønsted coefficient β is small[20].

Conclusions. The cyclization of *IIb* to *Ib* in aqueous buffers goes via the anion *IV*. The rate-limiting step consits in the splitting off of the proton from intermediate *A* which is catalyzed by the basic buffer component. The value of the Brønsted coefficient β (0·1) indicates that pK_a of intermediate *A* is smaller than that of the acidic buffer component, hence the proton transfer is thermodynamically favourable. Beside the base catalysis, the splitting off of methoxy group from intermediate *A* catalyzed by the acidic buffer component also makes itself felt to a relatively small extent. In solutions of potassium hydroxide the main reaction pathway probably consists in the formation of intermediate $In^{(2-)}$ from dianion *VI*.

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