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

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The cyclization kinetics of N-(2-methoxycarbonylphenyl)-N-methylsulfonamide to 1-methyl-(1*H*)-2,1,3-benzothiadiazine-4(3*H*)-one-2,2-dioxide have been studied in glycinamide, morpholine, and butylamine buffers and in solutions of potassium hydroxide. The rate-limiting step consists in splitting off of the proton from the cyclic intermediate formed from the anion of the starting substrate. The value of the Brønsted coefficient β decreases with increasing pK_a value of the conjugate acid of buffer. The calculated pK_a value of the cyclic intermediate is 9·3.

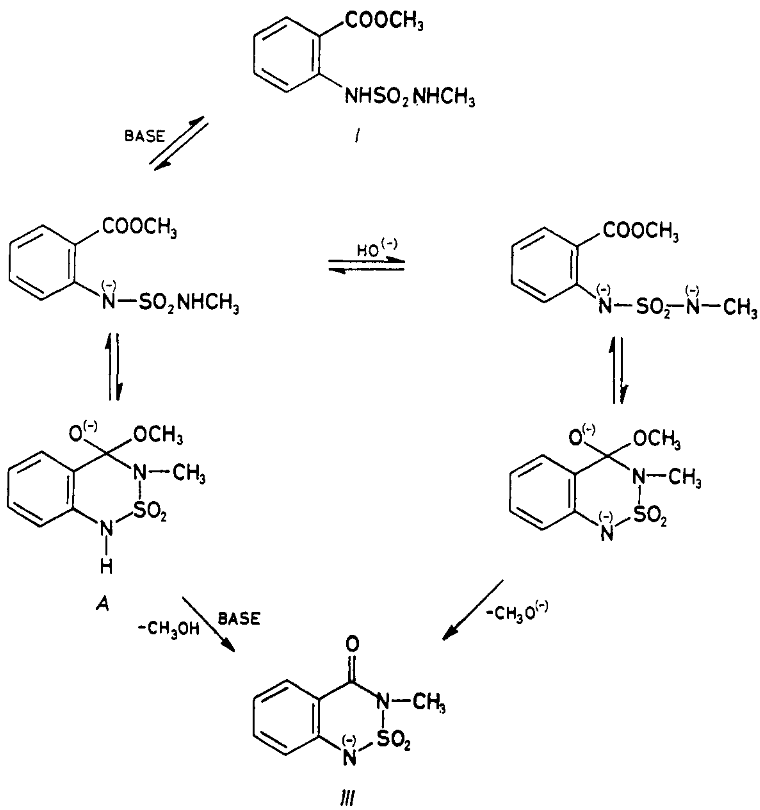
In our previous paper[1] we studied the cyclization kinetics of N-(2-methoxycarbonylphenyl)-N′-methylsulfonamide (*I*) to 3-methyl-(1*H*)-2,1,3-benzothiadiazine-4(3*H*)-one-2,2-dioxide (*III*) in ethanolamine, morpholine, and butylamine buffers and in solutions of potassium hydroxide. The cyclization was subject to general base catalysis. The value of the Brønsted coefficient β was ca 0·1, which suggests that the splitting off of the proton from the negatively charged tetrahedral intermediate represents the rate-limiting and thermodynamically favourable step. In the solutions of potassium hydroxide the rate-limiting step probably consisted in the cyclization of the dianion of the starting ester (Scheme 1). The present communication describes a kinetic study of base-catalyzed cyclization of N-(2-methoxycarbonylphenyl)-N-methylsulfonamide (*II*) to the anion of 1-methyl-(1*H*)-2,1,3-benzothiadiazine-4(3*H*)-one-2,2-dioxide (*IV*) (Scheme 2).

As there is a methyl group at the nitrogen atom adjacent to aromatic ring, no dianion can be formed, and in the rate-limiting step the proton must be split off from the nitrogen atom adjacent to carbonyl carbon atom. The aim of the present kinetic study is to establish the extent to which these differences will make themselves felt in the cyclization course and mechanism.

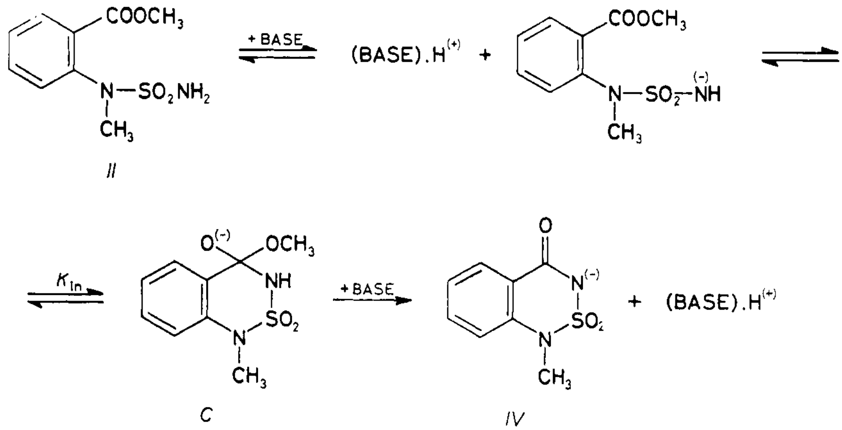
EXPERIMENTAL

Reagents

N-(2-*Methoxycarbonylphenyl*)-N-*methylsulfonamide* (II) was prepared by a known[2] procedure.



SCHEME 1



SCHEME 2

1-Methyl-(1H)-2,1,3-benzothiadiazine-4(3H)-one-2,2-dioxide (IV). Ester *II* (1 g, 4 mmol) was dissolved in 10 ml 4M sodium hydroxide. After 15 min, the reaction mixture was acidified with hydrochloric acid, and the separated solid was collected by filtration. The cyclizate was dissolved in a solution of hydrogencarbonate, filtered with charcoal, and precipitated from the filtrate by addition of hydrochloric acid. Yield 0·6 g (71%), m.p. 205–207°C in accordance with the value given by Cohen[3].

Kinetic Measurements

The cyclization rate of *II* → *IV* was measured spectrophotometrically using a Specord UV-VIS apparatus (Zeiss) in aqueous solutions of glycinamide, morpholine, and ethanolamine buffers. The ionic strength was adjusted at $I = 1 \text{ mol l}^{-1}$ by addition of 2M KCl solution. A 1 cm quartz cell was charged with 2 ml buffer solution (25°C), and at the time $t = 0$, 25 μl fresh methanolic solution of substrate *II* ($c \approx 0{\cdot}33 \text{ mol l}^{-1}$) was injected thereto, whereafter absorbance was monitored at the wavelength of 333 nm. In the experiments adopting solutions of butylamine buffers and potassium hydroxide the ionic strength was adjusted at $I = 1 \text{ mol l}^{-1}$, and the cyclization rate was measured by the stopped-flow method using a Durrum D-110 apparatus. One syringe contained a fresh solution of substrate *II* (ca $0{\cdot}75 \text{ mmol l}^{-1}$) in aqueous KCl. The other syringe contained an aqueous buffer solution. The 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 Constant

The dissociation constant of compound *IV* was measured in aqueous solutions of hydrochloric acid at $\lambda = 313$ nm at 25°C at the ionic strength $I = 1 \text{ mol l}^{-1}$. The pK_a values were calculated from the equation $pK_a = pH - \log P$, where P is the concentration ratio of the conjugate base and acid calculated from the measured absorbances.

RESULTS AND DISCUSSION

Figure 1 presents the dependence of $\log k_{obs}$ (extrapolated to zero buffer concentration, k_{corr}) on pH and that of $\log k_{obs}$ measured in solutions of potassium hydroxide on $(14 + \log a_{OH})$.

As the reactive species is the anion of ester *II* (the neutral ester *II* does not undergo the cyclization), at low pH values the values of logarithms of extrapolated k_{obs} increase linearly with pH (slope 1).

At higher pH values (butylamine buffers) a predominant part of substrate *II* is present in the form of anion. At these conditions the slope of the pH dependence of logarithm of rate constants should approach zero. In reality, however, the linear dependence is changed but a little (Fig. 1), and the change does not permit any estimation of pK_a of the ester. This fact can be explained by increasing extent of kinetic manifestation of splitting off of the proton from the intermediate *C* by hydroxyl ion in this pH region (Scheme 2).

This pK_a value could not be estimated by spectral methods either, since the half-life of the cyclization *II* → *IV* is less than 1 s in this region. Besides, the ester *II* is hydrolyzed in the stock solution, hence its concentration in the stock solution is continuously changing.

The cyclization rate in buffer solutions is defined by Eq. (*1*),

$$v = k_{obs}c_{SH} = (k'_0 + k'_{OH}a_{OH} + k'_B[B])\, c_{SH} = $$
$$= (k_0 + k_{OH}a_{OH} + k_B[B]\ [S^{-1}] \qquad (1)$$

hence Eqs (*2*) and (*3*) are valid.

$$k_B = k'_B c_{SH}/c_{S^-} = k'_B(1 + 10^{pK_a - pH}) \qquad (2)$$

$$k_0 + k_{OH}a_{OH} = (k'_0 + k'_{OH}a_{OH})\, c_{SH}/c_{S^-} = k_{corr}(1 + 10^{pK_a - pH}), \qquad (3)$$

where k'_B are the values determined for given buffer ratios from the dependence of k_{obs} vs base concentration.

From Eq. (*2*) and from the k'_B values measured in four series of butylamine buffers (Table I) it was possible to find the pK_a value of 10·75 ± 0·10 for the ester *II* and the value $k_B = (54 \pm 3)\ s^{-1}$ for butylamine.

As the k_B value is of basic importance, it was also estimated from the dependence of k_{obs} measured in mixtures of butylamine buffer (1 : 15 basic) in 0·02M KOH (at these conditions pH did not change with the buffer concentration), the butylamine concentration being varied from 0·01 to 0·06 mol l^{-1}. As the proportion of the ester *II* anion is greater than 97% in this medium, we can write Eq. (*4*).

$$k_{obs} = \text{const.} + k_B[B] \qquad (4)$$

The calculated value is $k_{obs} = (55 \pm 5)\ l\ mol^{-1}\ s^{-1}$. The extrapolation of k_{obs} from five butylamine buffers to the zero buffer concentration and application of

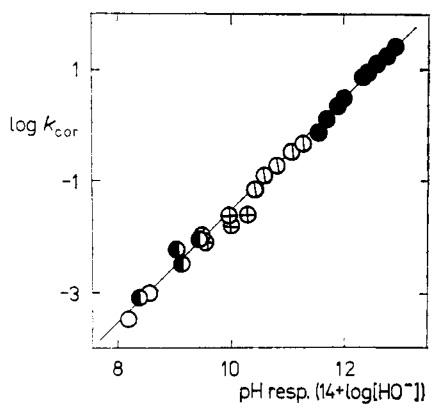


FIG. 1

The dependence of logarithms of observed rate constants of the reaction *II*→*IV* (extrapolated to zero buffer concentration), k_{obs} (s^{-1}), on the pH values of buffers or (for the KOH solutions) on (14 + log . . [OH⁻]). For denotation of points see Fig. 2

Eq. (*3*) gave the values of $(k_0 + k_{OH}a_{OH})$, and their dependence on a_{OH} (Fig. 3) provided the values $k_{OH} = (205 \pm 30)\ l\ mol^{-1}\ s^{-1}$, and $k_0 = (0.21 \pm 0.02)\ s^{-1}$.

The measurements of the cyclization in solutions of potassium hydroxide gave the value of $k_{OH} = (260 \pm 15)\ l\ mol^{-1}\ s^{-1}$.

With regard to the fact that in the first case the calculation concerns the extrapolated values and activities (instead of concentrations) and, in addition, the values

TABLE I

The k_B values ($l\ mol^{-1}\ s^{-1}$) calculated from Eq. (*2*) for a series of butylamine buffers (1 : 4 acidic, 1 : 2 acidic, 1 : 2 basic, 1 : 4 basic)

pH	k_B	k'_B
10·40	56·7	17·5
10·74	51·6	25·5
11·20	51·1	37·7
11·54	54·6	47·0

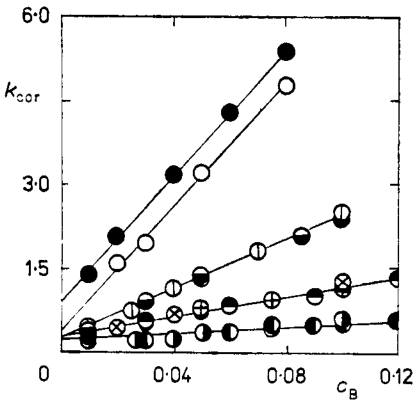


FIG. 2

The dependence of the corrected rate constants $k'_{corr} = k_{corr}(1 + 10^{pK_a - pH})$ (s^{-1}) of the reaction *II* → *IV* on the base concentration c_B ($mol\ l^{-1}$) in the following buffers: butylamine 1 : 4 basic (●); 1 : 2 acidic (○); glycinamide 1 : 1 (◑); 1 : 3 basic (◐); morpholine 1 : 3 basic (◓); 1 : 3 acidic (⊗); 1 : 1 (⊕); ethanolamine 1 : 3 acidic (◒), 1 : 1 (⦶)

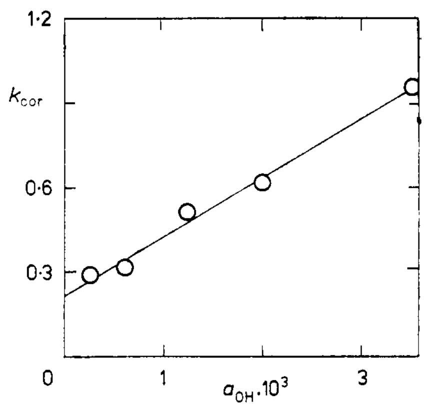


FIG. 3

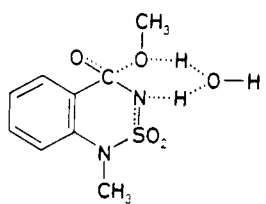
The dependence of $k_{corr} = k_0 + k_{OH}a_{OH}$ (s^{-1}) on the activity a_{OH} of hydroxyl ion for the reaction *II* → *IV* in butylamine buffers (Eq. (*3*)) corrected with respect to the base concentration, we accept the value obtained (205) as an informative one only, and its approximative agreement with the value (260) obtained by direct measurement as evidence in favour of the mechanism suggested.

Figure 2 presents the dependence of $k_{corr}(1 + 10^{pK_a - pH})$ on the base concentration for all the values measured in series of glycinamide, morpholine, and ethanolamine buffers and for two series of butylamine buffers. With the glycinamide, morpholine, and ethanolamine buffers all the values (for a given type of base) lie at a common straight line in accordance with the fact that the catalysis by the acid buffer component does not make itself felt and the straight lines extrapolate to a single point which determines $k_0 = (0{\cdot}20 \pm 0{\cdot}04)\ s^{-1}$. The dependence of k_{corr} on c_B was used to estimate the individual k_B values ($l\ mol^{-1}\ s^{-1}$): 54 for butylamine, 22·5 for ethanolamine, 9·8 for morpholine, and 3·7 for glycinamide.

With the butylamine buffers, the relationships of the rate constants $k_{corr}(1 + 10^{pK_a - pH})$ on the base concentration (Fig. 2) have – for both ratios – the same slope ($k_B = 54\ l\ .\ mol^{-1}\ s^{-1}$) but different intercepts, since the catalysis by hydroxyl ion is kinetically significant.

The cyclization of ester *II* substantially differs from that of ester *I* in several aspects:

1) Although in the cyclization of ester *I* the splitting off of H^+ from the intermediate by the base buffer component was thermodynamically advantageous, the hydroxyl ion reacted faster by more than 3 orders of magnitude. This fact was explained by the cyclization of dianion being the main reaction pathway (Scheme 1) at higher concentrations of hydroxyl ion. With the ester *II*, dianion is not formed, and the rate constant k_{OH} is only ca five times higher than the rate constant k_B of the reaction with butylamine, which confirms the above interpretation.

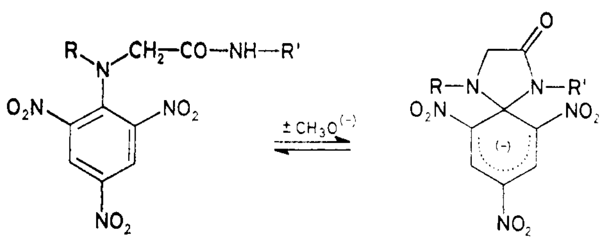


D

2) The transformation of the intermediate *A* formed in the cyclization of ester *I* to product *III* was also catalyzed by the acidic buffer component. In the intermediate *C* formed from ester *II* the N—H bond is in the neighbourhood of methoxy group. During splitting of this methoxy group the acidity of the proton bound to nitrogen steeply increases (pK_a of product *IV* is equal to 1·11). Therefore the splitting of methoxy group can be facilitated by the bond being formed (through a water molecule) with the proton of NH group (structure *D*). Therefore, protonated amines (which are relatively weak acids) are kinetically insignificant. The intramolecular catalysis is also indicated by the k_0 value found for the "noncatalyzed" transformation of intermediate *C* into product.

3) The rate constant k_B for butylamine is more than 3 orders greater with ester *II* as compared to ester *I*, although in both the cases the rate of the proton transfer proper approaches that of a diffusion-controlled reaction. This difference is caused by the difference between the stabilities of the intermediates as well as by the fact that the ester *I* is in equilibrium with two conjugate bases (Scheme 1) but the calculation of k_B adopts the total (experimental) dissociation constant which is several times greater than the dissociation constant for the produced bases from which the cyclic product is formed[1] (Scheme 1). Hence the real k_B values are several times higher than the values calculated from the overall dissociation constant.

In our opinion, the main reason of the large difference between the stabilities of the intermediates lies in the location of methyl group in the intermediate. A methyl group at nitrogen atom adjacent to aromatic ring increases the ring-forming tendency by several orders. With N-methyl-N-(2,4,6-trinitrophenyl)glycinamide (*Va*) the equilibrium constant of formation of spiro adduct was higher by as much as 8 orders of magnitude as compared with that of the analogous derivative *Vb* bearing the methyl group at the other nitrogen atom[4].



Va, R = CH_3; R' = H
Vb, R = H; R' = CH_3

4) The value of the Brønsted coefficient β found for the cyclization of ester *I* was ca 0·1. In the cyclization of ester *II* the value is substantially higher and increases with decreasing pK_a value of the conjugate acid of buffer. These findings suggest that the proton transfer to the basic buffer component is thermodynamically little favourable or (with weaker bases) even unfavourable. The following scheme and the therewith corresponding equation (*5*) were suggested by Eigen[5] for the proton transfer between electronegative atoms (O—N):

$$\mathrm{SH + B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{SH\cdots B} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{S\cdots HB} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{S + HB}$$

SCHEME 3

$$k_T = k_1k_2k_3/(k_{-1}k_{-2} + k_{-1}k_3 + k_{-2}k_3) \tag{5}$$

The values of k_1, k_{-3}, and k_{-1}, k_3 are the rate constants of diffusion of reactants to and from each other, and k_2, k_{-2} are the rate constants of the proton transfer itself.

The value of $5 . 10^9 \, l \, mol^{-1} \, s^{-1}$ frequently used for k_1 and k_2 was determined in the reaction of azide ion with reactive carbenium ions[6]. For k_{-1} and/or k_3 the proposed value is $10^{-11} \, s^{-1}$, and for k_2, k_{-2} the proposed[7] value is $10 \exp(10{\cdot}3 \pm \Delta pK_a)$, but somewhat different values were adopted too[8,9].

ΔpK_a is the difference between pK_a values of the acids SH and BH (Scheme 3). The rate constant k_T is defined by Eq. (*5*).

The k_B values found experimentally represent a product of K_{In} (the equilibrium constant of formation of the intermediate *C*) and the rate constant k_T of the proton transfer from the intermediate.

$$k_B = k_T K_{In} \tag{6}$$

In the reaction with hydroxyl ion the rate of proton transfer is controlled by diffusion (the reaction is considerably favourable thermodynamically), and for k_T one can adopt the value of $1{\cdot}4 . 10^{10} \, l \, mol^{-1} \, s^{-1}$ found[5] for the reaction of phenol with OH^- ion and thus estimate $K_{In} = 1{\cdot}85 . 10^{-8}$.

Using this K_{In} value we can calculate k_T for the other bases employed. From Eq. (*6*) and the k_T values given for primary amines it was possible to calculate (by the method of stepwise approximation) the value of 9·3 for pK_a of the intermediate (Scheme 2 and Table I).

The higher acidity of N—H proton in intermediate *A* as compared with that of the intermediate *C* formed from ester *II* is probably caused by the polar effect of the adjacent aromatic ring and larger distance from the negatively charged oxygen atom.

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