Molecules **1996**, *1*, 170 – 174

Effect of *N*-Methyl Substituents in 2-Methoxycarbonylphenylsulfamides on Kinetics and Mechanism of Formation of (1*H*)-2,1,3-Benzothiadiazin-4(3*H*)-One-2,2-Dioxides

Miloš Sedlák*, Jaromír Kaválek, Vladimír Machácek, Vojeslav Šterba

Department of Organic Chemistry, Faculty of Chemical Technology, University of Pardubice, Cs. legií 565, 532 10 Pardubice, The Czech Republic; Fax: +42-40-514-530
(sedlak@hlb.upce.cz, kavalek@hlb.upce.cz, machacev@hlb.upce.cz)

Received: 19 October 1996 / Accepted: 3 January 1997 / Published: 4 February 1997

Abstract

The cyclization reactions of *N*-methyl-*N*'-(2-methoxycarbonylphenyl)sulfamide (**1a**), *N*-methyl-*N*-(2-methoxycarbonylphenyl)-sulfamide (**2a**), and 2-methoxycarbonylphenylsulfamide (**3a**) were studied in aqueous amine buffers (butylamine, ethanolamine, morpholine, glycinamide). The dependences observed between the rate constants and buffer concentrations show that the reactions are subject to base catalysis in all the three cases, the decomposition of the tetrahedral intermediate being rate limiting. The ratio of the relative rate constants of the base catalyzed cyclizations reactions of the three derivatives is **1a**: **2a**: **3a** = 1: 20000: 100.
The logarithm of rate constants of the base catalyzed cyclization reactions was plotted against the pK_a values of conjugated acids of the individual amines used as the buffers in the cyclization of compound **1a**, and the value of the *Brönsted* coefficient obtained was about 0.1, which means that the proton transfer from the intermediate to the basic buffer component is thermodynamically favorable. The intermediate is a much weaker base, and the reaction is controlled by diffusion. The slope of an analogous dependence for compound **2a** gradually decreases from values near to 0.5 to values near to zero, which means that the intermediate formed from compound **2a** ($pK_a \approx 9.3$) has a pK_a value comparable with that of the acid buffer component.

Keywords: Kinetics, Mechanism of cyclization, Sulfamides, (1*H*)-2,1,3-Benzothiadiazine-4(3*H*)-one-2,2-dioxides, Dissociation Constants

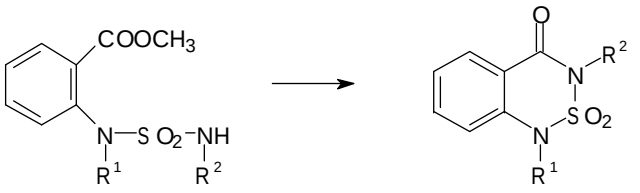
** To whom correspondence should be addressed*

† Presented at the Joint 12th Symposium on the Chemistry of Heterocyclic Compounds (SCHHC) and the 6th Blue Danube Symposium on Heterocyclic Chemistry (BDSHC), Brno, Czech Republic, September 1–4, 1996.

Introduction

We have found that the 2-methoxycarbonylphenylsulfamides can undergo both cyclization and solvolytic reactions depending on the medium used [1]. The

cyclization of *N*-(2-methoxycarbonylphenyl)-*N*'-isopropyl-sulfamide in methanolic sodium methoxide solution represents one of the possible industrial routes for the preparation of the commercial herbicide Bentazon[1]. Our investigation was focused on the kinetics and mechanism of cyclization of the following three derivatives: of *N*-methyl-*N*'-(2-methoxycarbonylphenyl)sulfamide (**1a**), *N*-methyl-*N*-(2-methoxycarbonylphenyl)sulfamide (**2a**), and 2-methoxycarbonylphenylsulfamide (**3a**) (Scheme 1).



1a-3a **1b-3b**

1a, b: R^1 = H; R^2 = CH_3
2a, b: R^1 = CH_3; R^2 = H
3a, b: R^1 = R^2 = H

Scheme 1

The cyclizations of all the three derivatives were studied in aqueous amine buffers in the pH region from 8 to 12.

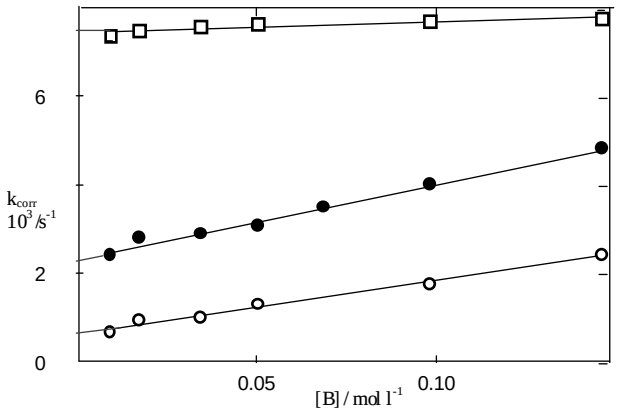


Fig. 1. *The dependence of the corrected rate constants $k_{corr}(s^{-1})$ of the cyclization reaction **1a** to **1b** on molar concentration [B] in the buffers: butylamine (□, pH = 11.1), ethanolamine (●, pH = 9.8), morpholine(○, pH = 8.9)*

Results and Discussion

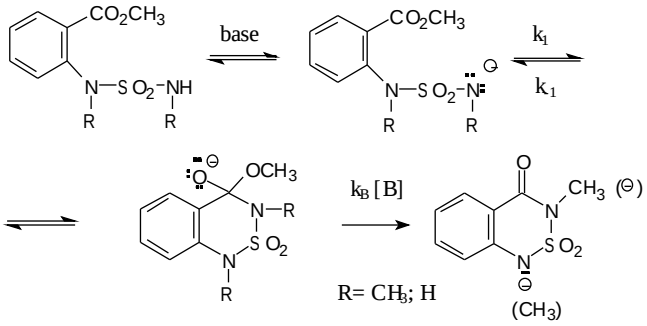
Figure 1 shows the dependences of corrected rate constants (k_{corr},the rate constant corrected with respect to the concentration of anion of substrate [2]) on the concentration of the basic buffer component for the cyclizaton of compound **1a** in the individual buffers. The analogous dependence for compound **2a** is of similar nature [3].

From the dependences obtained it is obvious that the corrected rate constant can be expressed by rate equation (1):

$$k_{corr} = k_{OH}[OH] + k_B [B] \quad (1)$$

The k_{OH} value corresponds to the intercept at zero buffer concentration, and k_B corresponds to the slope. This means that the cyclizations of compounds **1a** and **2a** are subject to OH ion catalysis and general-base-catalysis.

The Scheme 2 is valid for the two derivatives **1a** and **2a**: firstly the pre-equlibrium produces the anion which is then transformed into the intermediate. In this case the base catalyzed decomposition of the intermediate into the product is rate limiting.



Scheme 2

Figure 2 shows the dependence of the rate constant on the concentration of the basic buffer component for the third, unsubstituted derivative **3a** reacting in morpholine and glycinamide buffers. In contrast to the previous cases (derivatives **1a** and **2a**) the dependence shown has a different course – an increasing concentration of the basic buffer component slows down the reaction. This means that, at higher buffer concentration, the rate becomes independent of the buffer concentration and depends on the individual pH values. In the limiting case of a very high concentration of the buffer, the reaction changes from a general-base-catalyzed one to a specific-base-catalyzed one.

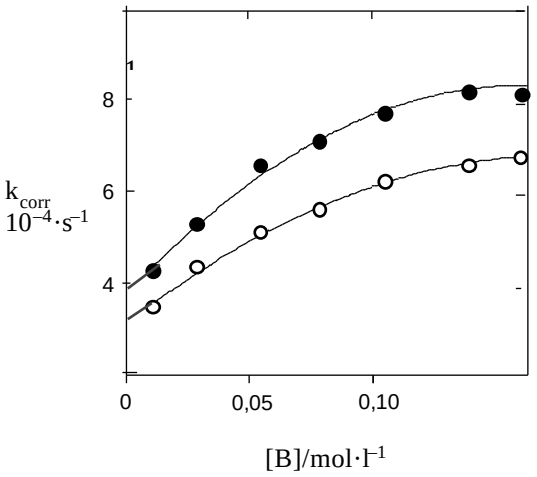
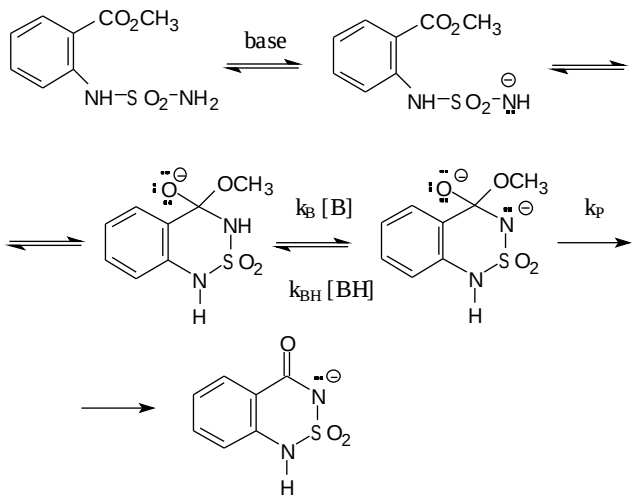


Fig. 2. *The depence of the corrected rate constants k_{corr} (s^{-1}) of the cyclization reaction* ***3a*** *to* ***3b*** *on molar concentration [B] in the buffers: morpholine(●, pH = 8.9), glycinamide(○, pH = 8.2)*



Scheme 3

The experimental dependences (Fig. 2) can be explained by the decomposition of the intermediate given in Scheme 3. The path from left to right predominates at low buffer concentration, i.e. the rate is given by the k_B constant.

At higher buffer concentrations, the concentration of the acidic buffer component increases, and the reverse path becomes significant, which means that the k_{BH} constant to make itself felt. Thus the overall reaction rate is lowered. The corrected rate constant (k_{corr}) is given by rate equation (2):

$$k_{corr} = k_0 + \frac{k_B[B]}{k_{BH}/k_p\,[BH]+1} \qquad (2)$$

The value $k_B = 2.2\times10^{-2}$ l·mol· s^{-1} and the ratio $k_{BH}/k_P = 3.3$ were found in the morpholine buffer of 1:1 concentration ratio with pH 8.9, and value $k_B = 1.9\times10^{-3}$ l·mol·s^{-1} and the ratio $k_{BH}/k_P = 2.8$ were found in the glycinamide buffer of 1:1 concentration ratio with pH 8.2.

Table 1 presents the k_B values, i.e. the rate constants of the base-catalyzed transformation of the intermediate (Scheme 2) into product, for derivatives **1a** and **2a**.

Table 1. *The pK_a values of the conjugated acids of the amines used in the buffers and k_B constants ($l\cdot mol\cdot s^{-1}$) for compound* ***1a*** *and* ***2a****.*

Compound	**k_B/l·mol·s^{-1}**			
1a	-	8.3×10^{-3}	9.1×10^{-3}	12.1×10^{-3}
2a	3.7	9.8	22.5	54.0
Amine	**glycin-amide**	**morpholine**	**ethanol-amine**	**butyl-amine**
pK_a	8.32	8.82	9.68	11.38

Figure 3 represents the dependences of the logarithm of the k_B constants on the pK_a values of the conjugated acids of the individual amines used in the buffers. The following conclusions can be made from the dependences obtained:

1. The slope is close to zero for compound **1a**, which means that the proton transfer from the intermediate to the basic buffer component is thermodynamically favourable - the intermediate is a much weaker base, and the reaction is controlled by diffusion.

2. For compound **2a** the slope gradually decreases from values close to 0.5 down to values near to zero, which means that the proton transfer from the intermediate gradually becomes less favorable. From this dependence it was possible to estimate the pK_a value of the intermediate (Fig. 4), namely 9.3.

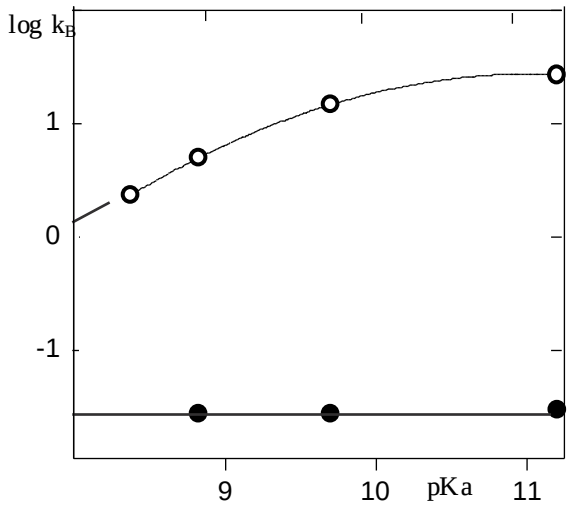


Fig. 3. *The dependence of the logarithm of k_B on the pK_a values of the protonated amines used in the buffers for compounds* ***1a*** *(●) and* ***2a*** *(○).*

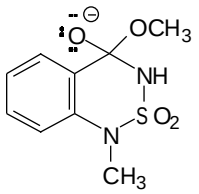


Fig. 4. Structure of intermediate of compound IIa ($pK_a \approx 9.3$)

The relative rate constants of base-catalyzed cyclization of the individual compounds can be summarized as follows. The derivative **1a**, which has the methyl group at its terminal nitrogen atom, is cyclized more slowly than the unsubstituted derivative **3a** by a factor of 100. The derivative **2a** which has the methyl group at its first nitrogen atom (neighbour on benzene ring), is cyclized faster than the unsubstituted derivative IIIa by a factor 200. This means that the shift of methyl group from one nitrogen atom to the other will cause a change of four orders of magnitude in the cyclization rates.

These findings can be interpreted as follows:

1.Derivative **2a** provides a smaller number of conformers due to its methyl substituent present at the first nitrogen atom, hence the cyclization is more favourable from the point of view of the entropy.

2. The rate decrease observed with the derivative **1a**, which has the methyl group at the terminal nitrogen atom, can be due to steric hindrance of the methyl group to the addition to carbonyl group.

The pK_a values measured by us for both the starting substances (**1a**-**3a**) and cyclizates (**1b**-**3b**) are given in Table 2.

Table 2. The pK_a values of compounds **1a**-**3a** and **1b**-**3b**

Compound	pK_a	Compound	pK_a
1a	9.30 ± 0.05	**1b**	2.33 ± 0.02
2a	10.75 ± 0.03	**2b**	1.11 ± 0.04
3a	9.39 ± 0.02	**3b**	2.39 ± 0.03
			8.20 ± 0.04

Compounds **1a** and **3a** have very similar pK_a values, which reflect the splitting of the proton from the first nitrogen atom. The pK_a value of derivative **2a** is higher by about 1.5 units, which corresponds to the splitting off of the proton from the terminal nitrogen atom. Comparison of pK_a values of the cyclizates **1b** and **3b** revels an interesting acidity increase due to *N*-methyl substituent in compound **1b**.

Experimental section

Kinetic measurements

The cyclization rate **1a**-**3a** to **1b**-**3b** was measured spectrophotometrically using a HP 8453 Diode Array Spectrophotometer in aqueous solutions of glycinamide, morpholine and ethanolamine buffers. The ionic strength was adjusted at I = 1 mol·l^{-1} by addition of 2*M* KCl solution. A 1 cm quartz cell was charged with 2 ml buffer solution (25 °C), and at the time t = 0, 25 ml fresh methanolic solution of substrate (c = 0.33 mol.l^{-1}) was injected, whereafter absorbance was monitored at the wavelengths from 260 nm to 360 nm. The rate constants k_{obs} (s^{-1}) were calculated from the equation: $k_{obs}t = -2.3\log DA + const.$, where $D A = (A_{oo} - A_t)$ or $(A_t - A_{oo})$.

Measurements of Dissociation Constants

The dissociation constants of compounds **1a**,**b** – **3a**,**b** were measured spectrophotometrically using HP 8453 Diode Array Spectrophotometer. The measurements of compounds **1b**, **2b** and **3b** (pK_{a1}) were carried out in chloroacetate buffer solutions. A 1 cm quartz cell was charged with 1 ml buffer solution and 1 ml substrate solution (the final ionic strenght was adjusted with KCl at I = 1 mol·l^{-1}). The reference cell contained the same buffer. The meas-

urement of compounds **1a**, **2a**, **3a** and **3b** (pK_{a2}) was carried out in glycinamide, morpholine and ethanolamine buffers prepared in a similar way. The pH values of the buffers were measured with an Radiometer PHM 93 Copenhagen using a combined glass and silver chloride electrode.

Syntheses of Substrates

Preparation of compounds **1a**,**b** – **3a**,**b** were described in previous papers [1–3].

References and Notices

1. Kaválek, J.; Králíková, U.; Machácek, V.; Sedlák, M.; Šterba, V. *Collect.Czech.Commun.* **1990**, *55,* 202.
2. Kaválek, J.; Machacek, V.; Sedlák, M.; Šterba, V. *Collect.Czech.Chem.Commun.* **1992**, *56*,1701.
3. Kaválek, J.; Machacek, V.; Sedlák, M.; Šterba, V. *Collect.Czech.Chem.Commun.* **1993**, *57*,1282.