KINETICS AND MECHANISM OF DESULFURIZATION REACTION OF 1-METHYL-2-PHENYLQUINAZOLINE-4(1*H*)-THIONES

Jiří HANUSEK[1,*], Miloš SEDLÁK[2], Roman KEDER[3] and Vojeslav ŠTĚRBA[4]

Department of Organic Chemistry, Faculty of Chemical Technology, University of Pardubice, Nám. Čs. legií 565, 532 10 Pardubice, Czech Republic; e-mail: [1] jiri.hanusek@upce.cz, [2] milos.sedlak@upce.cz, [3] roman.keder@upce.cz, [4] vojeslav.sterba@upce.cz

Received June 29, 2004
Accepted September 9, 2004

Dedicated to Professor Otto Exner on the occasion of his 80th birthday.

Kinetics and mechanism of desulfurization reaction of 1-methyl-2-(substituted phenyl)-quinazoline-4(1*H*)-thiones in sodium methoxide solutions have been studied, giving the corresponding 1-methyl-2-(substituted phenyl)quinazolin-4(1*H*)-ones. The reaction proceeds in two steps. The first step involves splitting off of sulfur in the form of SH^- and is much faster than the second step, whose rate is almost independent of the concentration of water in methanol. At lowest concentrations of methoxide, the rate of the first step increases linearly, but at higher concentrations a gradual decrease in the rate takes place. The rate of the second step, i.e. the transformation of the intermediate formed **In** into 1-methyl-2-(substituted phenyl)quinazolin-4(1*H*)-one (**2a**–**2e**), is independent of the methoxide concentration but increases with increasing concentration of water in methanol. On the basis of the kinetic dependences, the mechanism for both steps of desulfurization and the structure of intermediate **In** were proposed.

Keywords: Kinetics; Mechanism; Desulfurization; Quinazolines; Quinazoline-4(1*H*)-thiones; Methanolysis; Hydrolysis.

In analogy to the transformation of carbonyl group into thiocarbonyl group, there exist a large number of reactions involving the opposite process, i.e. replacement of sulfur by oxygen. This problem was dealt with in an extensive review article[1] in 1998, which also mentions desulfurizations of heterocyclic compounds. Most often, desulfurization is achieved by the action of oxidizing agents and by hydrolytic processes combined with treatment with transition metal salts. Besides the review article mentioned, there exist a couple of papers particularly dealing with the desulfurization of quinazoline-4-thione derivatives.

Most preparative desulfurizations involve *S*-alkylation of quinazoline-4-thione with methyl iodide[2a,2b], diazomethane[2c], 1-bromo-(2-diethylamino)ethane[2d], or 1-(chloroacetyl)piperidine[2d], and subsequent hydrolysis of the 4-(alkylsulfanyl)quinazoline or 4-(alkylsulfanyl)quinazolinium iodide formed, the hydrolysis being realized in acid or base media, possibly in the presence of hydrogen peroxide. Other desulfurization methods are based on the application of benzonitrile oxide and triethylamine in benzene[2b] or mercury(II) acetate in acetic acid[2e]. However, we are not aware of any reference of desulfurization mediated by alkoxides.

EXPERIMENTAL

Measurements

Kinetic measurements were carried out on an HP UV/VIS 8453 diode array apparatus. A 1-cm quartz cell was charged with 2 ml of dried methanolic sodium methoxide (water content 200 ppm) at 25 °C, then 50 µl of a methanolic solution of substrate **1a**–**1e** was injected and the absorbance at 388 nm was measured. The resulting concentration of substrate $c \approx 1 \times 10^{-4}$ mol l^{-1}. After completing the first step, the reaction mixture was treated with aqueous sodium hydroxide of the same concentration, and the spectra corresponding to the second step were recorded (see Table III). The values of both observed rate constant (k_{obs}) were calculated from the spectral records. The measurements of the effects of water on the first step were carried out in mixtures of sodium methoxide and sodium hydroxide in methanol–water (see Table II).

The mass spectra were measured with a mass spectrometer VG Platform II with chemical ionization at atmospheric pressure (APCI) and quadrupole analyzer (0–3000 Da). Before the mass spectrometer, there was a separation unit involving a high-pressure pump Waters 616, an autosampler Waters 717, UV detector Waters 996, and HPLC column filled with Separon SGX C18 (150 × 3 mm, particle size 7 µm). The mobile phase consisted of a mixture of 70% acetonitrile and 30% redistilled water. The outlet of the liquid chromatograph was connected directly to the quadrupole mass spectrometer with APCI for recording positive ions. The data were obtained in the range of *m/z* 15–600. The ion source temperature was 100 °C, and that of the APCI probe was 500 °C. The voltage imposed on the conical input electrode was 10 V.

Procedure

The starting 1-methyl-2-(substituted phenyl)quinazoline-4(1*H*)-thiones (**1a**–**1e**) and their desulfurization products 1-methyl-2-(substituted phenyl)quinazolin-4(1*H*)-ones were prepared by a procedure described in our previous paper[3,4] that also included their characterization. The desulfurization reaction was carried out for the 4-chloro derivative on preparative scale as follows:

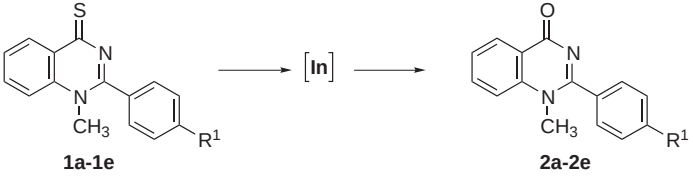
A 100-ml flask was charged with 2-(4-chlorophenyl)-1-methylquinazoline-4(1*H*)-thione (**1d**; 0.32 g, 1.12 mmol) and 0.35 M sodium methoxide (50 ml). The reaction mixture was refluxed until decolorization (ca. 30 min) and then cooled and neutralized with acetic acid to pH ≈ 7–8. Methanol was distilled off and collected in a flask cooled with a dry ice–

acetone mixture. The residue after evaporation was triturated with water and the undissolved portion (0.2 g, 67%) melting at 216–219 °C was recrystallized from a water–ethanol (2:1) mixture to give white crystals of 2-(4-chlorophenyl)-1-methylquinazolin-4(1*H*)-one (**2d**), m.p. 218–220 °C. The identity of product was verified by ^{1}H and ^{13}C NMR spectra. The distillate was treated with 1-fluoro-2,4-dinitrobenzene (0.42 g, 2.25 mmol) and sodium hydroxide (0.1 g, 2.5 mmol). The mixture was left to stand at room temperature for 12 h and then analyzed by HPLC/MS, which revealed 2,4-dinitrobenzenethiol MS (*m/z*): $[M + H]^+$ – 200.7.

RESULTS AND DISCUSSION

In our previous paper[3] we studied the kinetics and mechanism of base-catalyzed cyclization giving derivatives of quinazolin-4(1*H*)-one and quinazoline-4(1*H*)-thione. Studying this reaction, we found out that in the case of 1-methyl-2-(substituted phenyl)quinazoline-4(1*H*)-thiones (**1a**–**1e**), the desulfurization reactions in methanolic sodium methoxide at room temperature took place leading to the corresponding quinazolin-4-one. The aim of our work was a detailed investigation of kinetics and mechanism of this desulfurization reaction.

The reaction was studied by UV/VIS spectrophotometry in 0.1–1.6 M solutions of sodium methoxide. The desulfurization of compound **1d** was also carried out on preparative scale in order to verify the reaction course. We found out that the desulfurization proceeds kinetically as a system of two consecutive reactions. The first, much more faster step produces a desulfurized intermediate, which subsequently decomposes to the final product (oxygen-containing derivative) (Scheme 1).



1a-1e **2a-2e**

1, 2	a	b	c	d	e
R^1	H	OCH_3	CH_3	Cl	NO_2

SCHEME 1

At the lowest concentrations of methoxide, the rate of formation of **In** depends linearly upon $[CH_3O^-]$ (Fig. 1). The second-order rate constants *k* corresponding to this reaction step are given by the slopes of the straight lines (Table I). The dependence of log *k* on the σ constants of substituents is linear (Fig. 2), the value of reaction constant ρ = 0.40 ± 0.01 being in accor-

dance with the fact that the attack of the reaction center by the nucleophile occurs in a large distance from the substituent.

At higher methoxide concentrations, the observed rate constants k_{obs} become independent of the methoxide concentration, and at $[CH_3O^-] > 0.8$ mol l^{-1} they decrease (Fig. 1). The presence of water has only a slight effect on the value of k_{obs}; the rate of formation of intermediate mildly decreases with increasing water concentration (Table II). In aqueous solutions of sodium hydroxide, the rate of desulfurization is very low, about 10 times lower than that in methanol. The rate of transformation of **In** into the product is almost independent of the methoxide concentration, but it rapidly increases in a linear way with increasing amount of added water (Table III). If the MeOH used had been dried with Mg (water content 200 ppm), then the decomposition of **In** was very slow, and the formation

TABLE I
Second-order rate constants for **1a**–**1e** → **In**

Compound	**1a**	**1b**	**1c**	**1d**	**1e**
k, l mol s^{-1}	2.15 ± 0.05	2.40 ± 0.05	2.89 ± 0.07	3.43 ± 0.11	5.82 ± 0.33

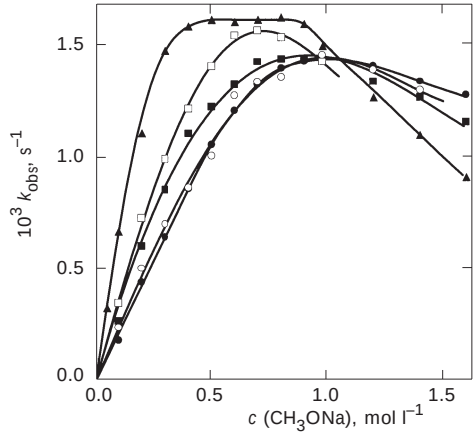


FIG. 1
Dependence of the observed rate constant (k_{obs}) for desulfurization of 1-methyl-2-(4-substituted phenyl)quinazoline-4(1*H*)-thiones **1a** (■), **1b** (●), **1c** (○), **1d** (□) and **1e** (▲) on sodium methoxide concentration c at 25 °C. The curves depict the character of the dependences and are given for better guidance

of compounds **2a**–**2e** practically ceased: the solution contained only the unreacted intermediate. Several attempts to isolate the intermediate **In** failed. After separation from the reaction mixture, we always obtained only the starting substance or the desulfurization product.

The low effect of water concentration on the rate of formation of **In** (Table II) and, in particular, its slow decomposition into products, indicate that the desulfurization itself takes place during the reaction of the sub-

TABLE II
Observed rate constants for reaction **1d** → **In** in 0.5 M sodium methoxide with addition of water

Vol.% H_2O	0	5	10	20
$k_{obs} \times 10^3$, s^{-1}	1.40	1.27	1.13	0.92

TABLE III
Dependence of the observed rate constants for reaction **In** → **2d** in 0.5 M sodium methoxide at various concentrations of water. (Note: the measurements cannot be carried out at water contents above 5%, because the product crystallizes from the reaction mixture.)

Vol.% H_2O	1	2	3	4	5
$k_{obs} \times 10^4$, s^{-1}	1.68	3.42	5.45	8.31	10.2

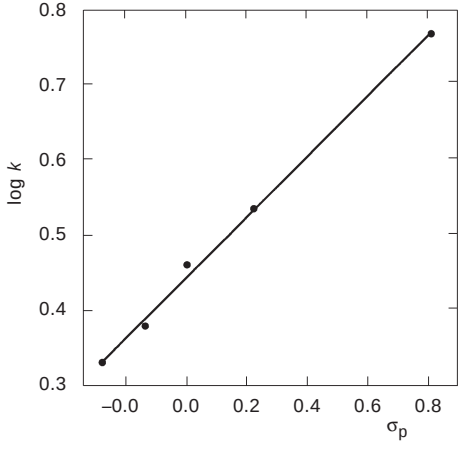
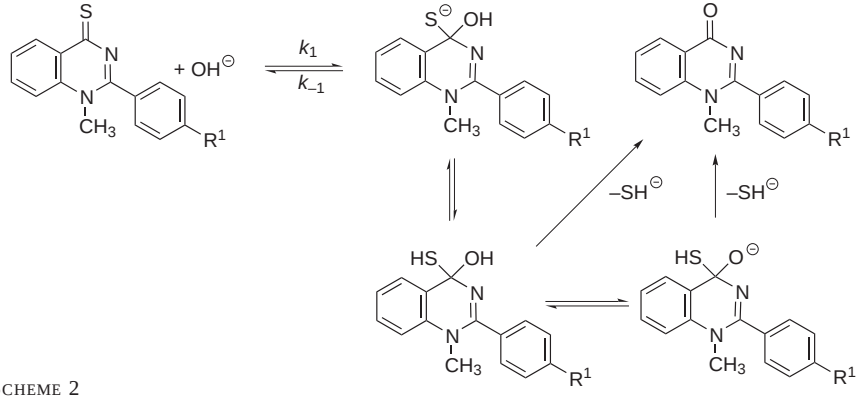


FIG. 2
Hammett correlation of second-order rate constants

strate with methoxide in the first reaction step. This is also confirmed by a low value of λ (235 nm), which is typical (Fig. 3) of formation of the tetrahedral intermediate **In**. For the reaction of the substrate with OH^- in water, it is possible to presume the formation of the following intermediates leading to the products (Scheme 2).



SCHEME 2

The lifetime of intermediates given in Scheme 2 is substantially lower than 1 s in the given medium, which means that the transformation of substrate into product by reaction with OH^- does not reveal any spectral manifestation of intermediate, as this is the case in the reaction of carbonyl compounds[5]. Since from the above-mentioned findings follows that the

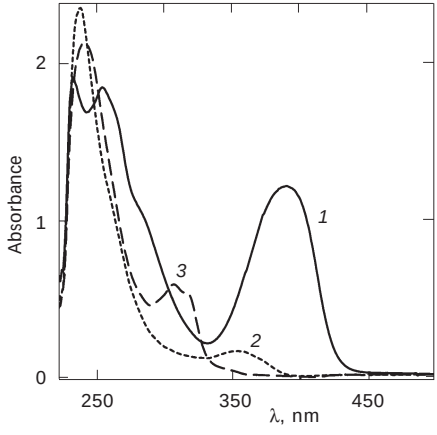
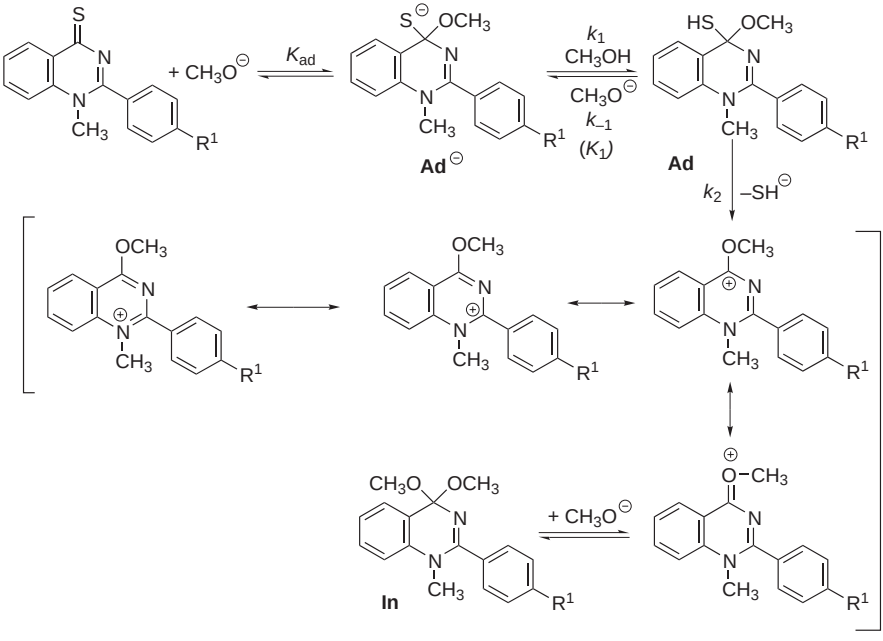


FIG. 3

Spectra of starting substance (*1*), intermediate (*2*) and product (*3*). The spectrum after reaction is identical with that of the product prepared by independent synthesis in the same medium

desulfurization of substrate is exclusively caused by the action of methoxide, **In** is very stable at the given conditions (zero rate of transformation into product in the absence of water), it can justifiably be presumed that **In** has the structure of a dimethoxy adduct. Its formation including splitting off of sulfur in the form of SH^- are presented in Scheme 3.



SCHEME 3

The relationship (*1*) for k_{obs} can be defined on the basis of Scheme 3 on the assumption that the reacting species is the adduct **Ad**, which irreversibly splits off the SH group. As the adduct **Ad** is highly unstable and its concentration is negligibly low compared to those of the reactants, it is possible to apply the Bodenstein approximation. The concentration of adduct $\mathbf{Ad}^-$ can be expressed by the equilibrium constant K_{ad}; so the final form of Eq. (*1*) reads as follows:

$$k_{obs} = \frac{K_{ad} k_1 k_2 [CH_3ONa]}{k_{-1}[CH_3ONa] + k_2} . \qquad (1)$$

Since the SH^- concentration in solution is very low, the reverse reaction practically does not occur. This means that the formation of **In** is, in fact, a consecutive two-step reaction consisting of formation of carbocation and

its reaction with CH_3O^- to give **In**. As the rate constant of formation of **In** from carbocation is high, its value cannot be determined. The gradual decrease in the slope of the dependence k_{obs} vs $[CH_3O^-]$ at higher methoxide concentrations (Fig. 1) can be due either to the fact that practically all the substrate has reacted with methoxide to give non-reactive negatively charged species or to a change in the rate-limiting step. Since the negatively charged adduct of substrate with methoxide **Ad**$^-$ is an anion of thioacetal, and the starting substrate **1a**–**1e** is stabilized by delocalization of the electron pair of N-1 nitrogen, its reverse decomposition is very fast, much faster than the addition of methoxide to the substrate. This was confirmed by the fact that the absorption (at λ_{max} = 388 nm) of the substrate several seconds after the addition of substrate to 0.5 M methoxide was the same as that of the substrate alone (in methanol). This means that the observed decrease in the slope of the dependence k_{obs} vs $[CH_3O^-]$ is due to a change in the rate-limiting step.

The only alternative that can be taken into account as the rate-limiting step of the reaction in the region of linear increase is the reaction of negatively charged adduct **Ad**$^-$ with methoxide, which is strongly endothermic and very slow. Thus the formation of **Ad**$^-$ is preceeded by a fast established equilibrium directly proportional to CH_3O^- concentration, with small equilibrium constant K_{ad}.

In the region where the k_{obs} constant is independent of methoxide concentration, the rate-limiting step consists in splitting off of SH^- from adduct **Ad** with concomitant formation of the resonance stabilized carbocation. The change in rate-limiting step depends on the ratio of the reaction rates of the reverse and consecutive reactions of **Ad** (Scheme 3). When the rate of reverse reaction is lower than that of the transformation into carbocation (at low $[CH_3O^-]$), the rate-limiting step is the reaction of **Ad**$^-$ with methanol; in the opposite case it is the rate of splitting off of SH^- from **Ad** to give the carbocation. When $k_{-1}[CH_3O^-] = k_2$, **Ad** is transformed back to **Ad**$^-$ and forward to the carbocation as well, and k_{obs} should have a half value of that attained at the plateau (zero slope of the dependence k_{obs} vs $[CH_3O^-]$). In reality, this value is partially distorted by the retardation of reaction due to the change in medium and, to an increasing extent, due to decreasing values of σ constants of the substituents (see Fig. 1).

On the basis of pK_a = 9.43 for phenylmethanethiol[6], the equation for calculation of pK_a of tertiary alcohols and thiols in water[7] and methanol[8], and the σ_I constants of the substituents, we have assessed the difference between pK_a of methanol and adduct **Ad** in methanol. The difference is 7–8 orders of magnitude, which means that the reaction is strongly exothermic

and the rate constant of reaction of **Ad**$^-$ with methanol approaches that of diffusion-controlled processes (k_{-1} is about 10^8 s^{-1}). As the rough calculation of methoxide concentrations in the equation $k_{-1}[CH_3O^-] = k_2$ gave the values from 0.12 mol l^{-1} (4-NO_2) to 0.4 mol l^{-1} (4-OCH_3), the rate constant k_2 of splitting off of SH^- should range from ca. 0.12×10^7 s^{-1} (4-NO_2) to 0.4×10^7 s^{-1} (4-OMe).

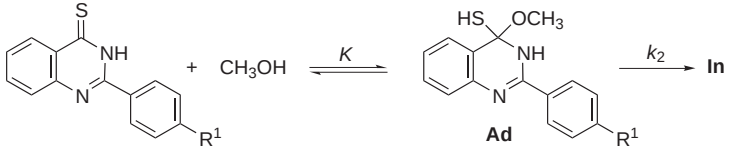
Although it is presumed that acetals and ketals and their thio analogs are stable in neutral and basic media, a very slow but measurable spontaneous hydrolysis has been found[9,10] with some acetals containing good leaving groups.

A fast spontaneous hydrolysis takes place in the case of 4-H_2N-C_6H_4-CH(OEt)SC_6H_5 (k_{obs} = 40 s^{-1}); a mechanism with ion pair separation rate-limiting step was suggested[11]. The driving force is (like with **Ad**) stabilization of carbocation by delocalization of the electron pair from nitrogen to carbon. The delocalization of electron pair is accompanied by increased aromatization of the six-membered ring.

Generally, the decrease in reaction rates at methoxide concentrations above 0.8 mol l^{-1} can be due to another change in the rate-limiting step, but in the present case such a variant is groundless.

The drop in k_{obs} at sodium methoxide concentrations above 0.8 mol l^{-1} is due to the effect of a change in activity coefficients of the individual reactants and in the transition state of the rate-limiting step. For instance, the activity coefficient of methanol in 1.6 M sodium methoxide[12] $\gamma = 0.8$.

At methoxide concentrations above 0.8 mol l^{-1}, the rate-limiting step is splitting off of SH^- from adduct **Ad** for all the derivatives. In this case, the reaction mechanism can be described by simplified Scheme 4.

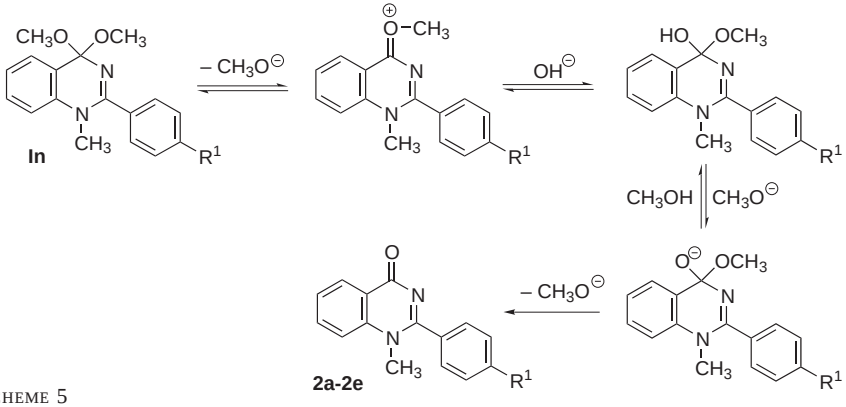


SCHEME 4

The change of the reaction medium affects the values of equilibrium constants *K*. However, the decreases found are substantially larger with the 4-Cl derivative and much larger with the 4-NO_2 derivative (inversion of the dependences), and this means that the change of the medium must have a considerable effect also on the rate-limiting step, i.e. on the k_2 constant. The spontaneous decomposition of 4-$(CH_3)_2N$-C_6H_4-CH(OEt)SC_6H_5 involved the rate-limiting separation of the ion pair formed. Although the

splitting off of SH^- is by 5–6 orders of magnitude faster, an internal return of the ion pair formed in this case obviously takes place, the difference being in that the rates of internal return and ion-pair separation differ substantially less. The rate of internal return increases with increasing σ constants of substituents, and the separation of carbocation and SH^- becomes more and more rate-limiting. The rate of separation of SH^- decreases to the same extent as the stabilization of SH^- by formation of H-bonds. The latter decreases with increasing methoxide concentration, because the activity coefficient of methanol is decreasing. A decrease in stabilization of SH^- by H-bonds by a value of 1.6 kJ mol^{-1} decreases the reaction rate almost to one half.

The transformation of intermediate **In** into product is very slow; its rate increases only moderately with the methoxide concentration, but it increases linearly with water concentration. In Mg-dried methanol, the transformation proceeded at a negligible rate. This is in accordance with the following reaction sequence (Scheme 5). The process closely resembles the extensively studied acetal hydrolysis.



SCHEME 5

CONCLUSIONS

The kinetic study of desulfurization of **1a**–**1e** in sodium methoxide solutions shows that the reaction proceeds in two steps. At low methoxide concentrations, the rate of the first step is determined by the reaction of Ad^- with methanol to give **Ad**; at higher concentrations, the splitting off of SH^- from adduct **Ad** becomes rate-limiting. This behavior is supported by the finding that the observed rate constant first increases with the methoxide concentration, but then becomes independent of this concentration (de-

creasing with water concentration), which excludes the possibility of manifestation of the reaction pathway given in Scheme 2. The intermediate formed by desulfurization probably has the dimethyl acetal structure and is in equilibrium with the carbocation. Relative stability of the carbocation is determined by its proneness to aromatization, and the only pathway of its decomposition to the final product **2a**–**2e** is the reaction with present hydroxide ion and/or water. This interpretation is supported by the fact that the intermediate decomposition is strongly accelerated in the presence of water and/or hydroxide.

The authors thank the Ministry of Education, Youth and Sports of the Czech Republic (Project CI MSM 253 100 001) for the financial support.

REFERENCES

1. Corsaro A., Pistarà V.: *Tetrahedron* **1998**, *54*, 15027.
2. a) Fry D. J., Kendall J. D., Morgan A. J.: *J. Chem. Soc.* **1960**, 5062; b) Legrand L., Lozac'h N.: *J. Heterocycl. Chem.* **1984**, *21*, 1615; c) Walter W., Voss J.: *Justus Liebigs Ann. Chem.* **1966**, *698*, 113; d) Chaurasia M. R., Sharma S. K.: *Heterocycles* **1981**, *16*, 621; e) Legrand L., Lozac'h N.: *Bull. Soc. Chim. Fr.* **1960**, 2088.
3. Hanusek J., Sedlák M., Šimůnek P., Štěrba V.: *Eur. J. Org. Chem.* **2002**, 1855.
4. Hanusek J., Hejtmánková L., Kubicová L., Sedlák M.: *Molecules* **2001**, *6*, 323.
5. a) Sorensen P. E., Logager T., Kanagasabapathy V. M., McClelland R. A.: *Bull. Soc. Chim. Fr.* **1988**, 313; b) Sorensen P. E., Pedersen K. J., Pedersen P. R., Kanagasabapathy V. M., McClelland R. A.: *J. Am. Chem. Soc.* **1988**, *110*, 5118; c) Guthrie J. P.: *J. Am. Chem. Soc.* **2000**, *122*, 5529.
6. Kreevoy M. M., Harper E. T., Duvall R. E., Wilgus H. S., Ditsch L. T.: *J. Am. Chem. Soc.* **1960**, *82*, 4899.
7. Fox J. P., Jencks W. P.: *J. Am. Chem. Soc.* **1974**, *96*, 1436.
8. a) Crampton M. R. in: *The Chemistry of the Thiol Group 1* (S. Patai, Ed.), p. 379. J. Wiley, London 1974; b) Charton M.: *J. Org. Chem.* **1964**, *29*, 1222; c) Charton M. in: *Progress in Physical Organic Chemistry* (R. W. Taft, Ed.), Vol. 13, p. 119. Academic Press, New York 1981.
9. Fife T. H.: *Acc. Chem. Res.* **1972**, *5*, 264.
10. Young P. R., Jencks W. P.: *J. Am. Chem. Soc.* **1977**, *99*, 8238.
11. Jensen J. L., Jencks W. P.: *J. Am. Chem. Soc.* **1979**, *101*, 1476.
12. Terrier F.: *C. R. Acad. Sci., Ser. C* **1967**, *265*, 1433.