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Kinetic Evidence for the Coexistence of Zwitterionic ($T^{\pm}$), Neutral (T^{0}) and Anionic (T^{-}) Intermediates during Rearrangement of *S*-(2-Oxotetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)isothiuronium Bromide to 5-(2-Hydroxyethyl)-2-(4-methoxyphenylimino)-1,3-thiazolidin-4-one

Jiří Váňa, Miloš Sedlák, and Jiří Hanusek*

Faculty of Chemical Technology, Institute of Organic Chemistry and Technology, University of Pardubice, Studentská 573, CZ-532 10 Pardubice, The Czech Republic

jiri.hanusek@upce.cz

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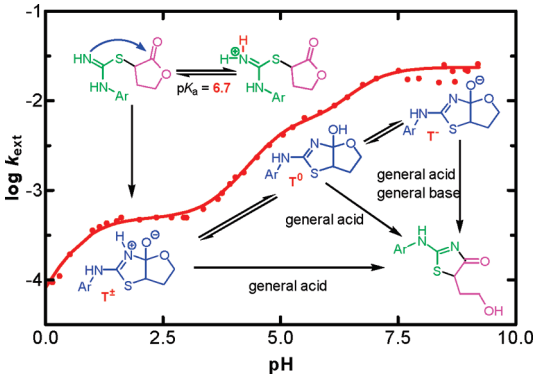

The kinetics and mechanism of rearrangement of *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)-isothiuronium bromide (**1**) into 5-(2-hydroxyethyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one have been studied under pseudo-first-order reaction conditions in aqueous buffer solutions and in diluted HCl at 25 °C. Multiple breaks in the pH profile establish the formation of three different kinetically detectable intermediates $\mathbf{T}^{\pm}$, $\mathbf{T}^{0}$, and $\mathbf{T}^{-}$. Treatment of **1** (pK_a = 6.7) with base produces reactive isothiourea, which undergoes cyclization to give $\mathbf{T}^{\pm}$ (rate limiting step at pH < 0.5). Intermediate $\mathbf{T}^{\pm}$ then undergoes either general acid-catalyzed, concerted ($\alpha = -0.47$) breakdown to **2** (rls at pH 2−3) or a water-mediated proton switch to $\mathbf{T}^{0}$ which is followed by its general acid-catalyzed breakdown (pH 3−6). The last reaction pathway involves the formation of $\mathbf{T}^{-}$ either from $\mathbf{T}^{\pm}$ or from $\mathbf{T}^{0}$ (pH > 6). The first possibility seems to be more likely because it is in accordance with kinetics observed in basic amine buffers, where the nonlinear increase of the k_{obs} with the c_{Buffer} changes to a linear increase as a general base-catalyzed pathway is introduced. Coexistence of all three kinetically detectable intermediates is very rare and is possibly due to relatively enhanced stability of these intermediates necessitating participation of an acid for progression to products.

Introduction

It is well-known that intramolecular reactions bear a striking resemblance to the reactions of enzymes and can give insight into the analogous enzymatic process.[1] Small molecules undergoing intramolecular cyclization reactions frequently have been used as models for understanding the nature of preorganizational effects and their relative contributions to the enhanced rates observed in enzymatic reactions.[1,2] Acyl groups have a prominent position in biochemistry and biology, and just their biochemical relevance has made acyl

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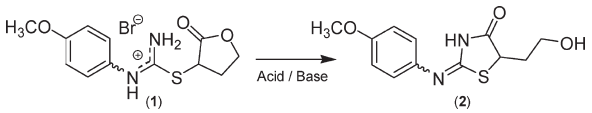
group transfer one of the most studied reactions in all of organic chemistry.[3] Intramolecular aminolysis are an specially important class of acyl-transfer reactions and are of great importance in biochemistry and medicinal chemistry, and a large amount of research has been devoted in this area.[4]

Rearrangements of heterocyclic compounds are also of great significance toward providing new routes to otherwise difficult to prepare biologically active compounds. This new approach to the synthesis of heterocycles has rapidly grown in the past several years.[5] In many cases, such transformations are subject to general acid−base catalysis and proceed under very mild conditions, even at physiological pH. This finding has great importance, not only for the synthesis of these compounds but also for their potential application in medicine (pro-drug approach[4k]). For example, the thiazolidine ring, which is the product formed in the present study, is an important pharmacophore.[6]

Recently, we have studied the structure[7] and reactivity[8] of substituted *S*-(1-phenylpyrrolidin-2-on-3-yl)isothiuronium salts which, in weakly basic medium, undergo an intramolecular rearrangement to give substituted 2-imino-5-[2-(phenylamino)-ethyl]-1,3-thiazolidin-4-ones. More recently, we have extended the scope of this transformation: replacing the γ-lactam ring with a γ-lactone ring.[9] The *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(substituted phenyl)isothiuronium bromides underwent[9]

SCHEME 1



rearrangement in acidic and basic medium to give 5-(2-hydroxyethyl)-2-phenylimino-1,3-thiazolidin-4-ones or 5-(2-hydroxyethyl)-2-phenylamino-4,5-dihydro-1,3-thiazol-4-ones in very good yields. This transformation proceeds readily under mild conditions in aqueous buffer solutions and is able to accept a relatively wide range of substituents in the benzene nucleus.

The aim of the work reported here was to carry out a detailed study of the mechanism of acid−base-catalyzed intramolecular rearrangement of *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)isothiuronium bromide (**1**) to 5-(2-hydroxyethyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one (**2**) (Scheme 1).

Results and Discussion

Kinetic Measurements. The acid−base-catalyzed transformation of isothiuronium salt **1** giving thiazolidin-4-one **2** as the only product was studied spectrophotometrically under pseudo-first-order conditions in aqueous hydrochloric acid solutions (c = 0.001−0.7 mol·L^{-1}) and in aqueous buffers (pH = 2−9) at constant ionic strength (I = 1 mol·L^{-1}) and at 25 °C. All spectra recorded during the rearrangement reaction showed sharp isosbestic points which prove[10] the existence of only two absorbing species; i.e., this result allows us to reject consecutive reaction mechanisms. In other words, only short-living intermediates in negligible concentration can occur on the reaction coordinate.

Observed rate constants, k_{obs}, were calculated in each buffer/acid solution from the absorbance vs time dependence of the absorptions at 260 or 273 nm and were plotted against the total buffer concentration ($c_{Buff} = c_B + c_{BH}$). It was found that in dichloroacetate (DCA), chloroacetate (CA), methoxyacetate (MEA), acetate (AC), hydroxylamine (HA), *N*-methylmorpholine (NMM), glycinamide (GA), tris-(hydroxymethyl)aminomethane (TRIS), and morpholine (MP) buffers the observed rate constant (k_{obs}) increases with both the total buffer concentration (c_{Buff}) and the basicity (pH) of the medium (Figures 1−3). From this observation, it is clear that the transformation involves general buffer catalysis as well as specific acid−base catalysis.

Two different dependences of k_{obs} on the total buffer concentration (c_{Buff}) were observed: in DCA, CA, MEA, AC, and partially in HA buffers, k_{obs} increases linearly with c_{Buff} (Figures 1 and 3), whereas in NMM, GA, TRIS, and MP buffers the slopes of plots decreased with increasing c_{Buff} until at sufficiently high buffer concentration the lines appear to approach linearity (Figures 2 and 3). With NMM, TRIS, and MP buffers, the linear portion, at high c_{Buff}, is easily discernible, and therefore, a more detailed analysis of those buffers was made (see below). Curved buffer dilution plots of k_{obs} reveal a change in the rate-limiting step with the change in the total buffer concentration at a constant pH, which in turn implies the presence of a reactive intermediate

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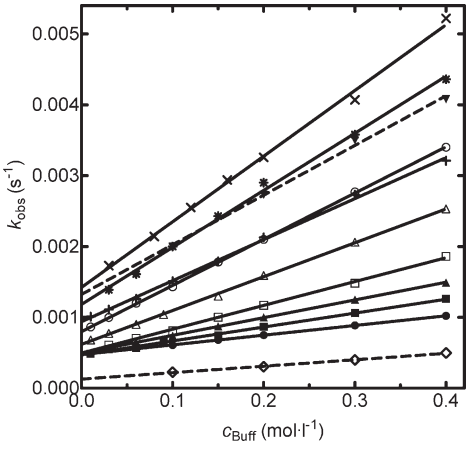

FIGURE 1. Dependence of the observed rate constant (k_{obs}, s^{-1}) on the total buffer concentration (c_{Buff}, mol·L^{-1}) measured at 25 °C in CA [(2:1a) pH 2.36 (●); (1:1) pH 2.68 (■); (1:1) pD 3.14 (◊); (1:2b) pH 2.94 (▲)], MEA [(2:1a) pH 3.04 (□); (1:1) pH 3.35 (△); (1:2b) pH 3.67 (○)] and AC buffers [(6:1a) pH 3.76 (+); (4:1a) pH 3.93 (∗); (3:1a) pH 4.04 (×); (1:1) pD 5.14 (▼)]: (a) acidic; (b) basic. Dashed lines correspond to measurements in D_2O. Note: Data for DCA (1:2b) and AC buffer ratios (2:1a, 1:1; 1:2b, 1:4b) are not depicted here for better clarity of the Figure but they are in the Supporting Information.

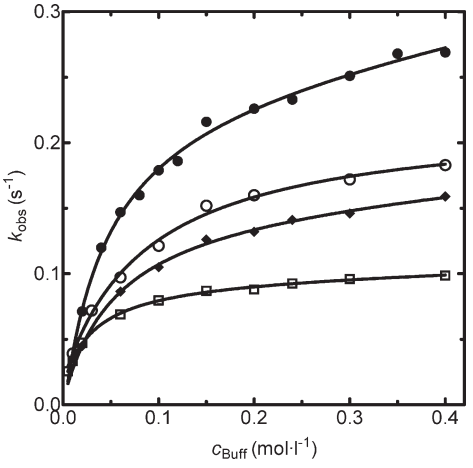

FIGURE 2. Dependence of the observed rate constant (k_{obs}, s^{-1}) on the total buffer concentration (c_{Buff}, mol·L^{-1}) measured at 25 °C in NMM [(1:1) pH 8.24 (□)]; TRIS [(1:1) pH 8.36 (♦)]; GA [(1:1) pH 8.65 (○)] and MP buffers [(1:1) pH 8.94 (●)]. Data for other buffer ratios are not depicted here for better clarity of the Figure but they are in the Supporting Information.

on the reaction coordinate.[4e,8b,11] Another possible reason for the nonlinear plots in Figure 2 is that the nitrogen buffers undergo some kind of complexation with **1** (pre-equilibria with amine/ammonium or H-bonding) and the complex becomes more reactive than uncomplexed **1**. However, this possibility seems to be unlikely because hydroxylamine buffers differ in their behavior dependent on the ratios of both components (Figure 3): a linear relationship is observed at a low fraction of free base (low pH) and a nonlinear relationship at a high fraction of free base (high pH). Therefore, it is clear that the nonlinearity of the plots is simply a function of pH, and similar observations have been reported for other reaction systems.[4e,11d]

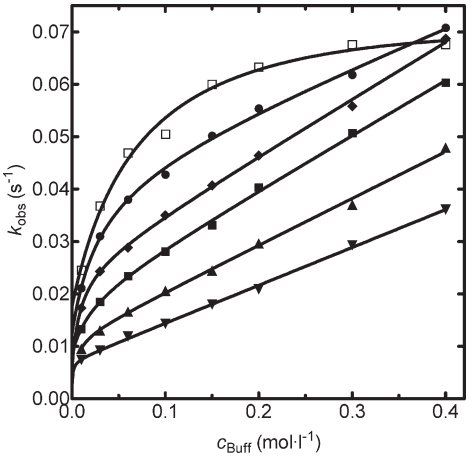

FIGURE 3. Dependence of the observed rate constant (k_{obs}, s^{-1}) on the total buffer concentration (c_{Buff}, mol·L^{-1}) measured at 25 °C in hydroxylamine (HA) buffers [(4:1a) pH 5.52 (▼); (2:1a) pH 5.85 (▲); (1:1) pH 6.15 (■); (1:2b) pH 6.42 (♦); (1:4b) pH 6.75 (●); (1:8b) pH 7.05 (□)]: (a) acidic; (b) basic.

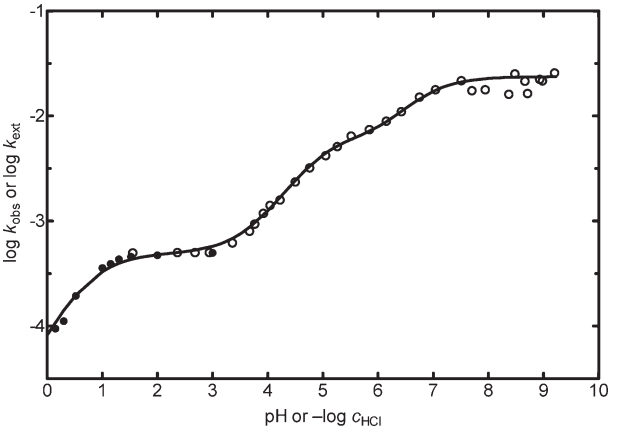

FIGURE 4. pH profile (log k_{ext} vs pH) for rearrangement of **1** to **2** in buffers (○) and (log k_{obs} vs −log c_{HCl}) in hydrochloric acid (●). The line represents the best fit of all data points using eq 2 or eq 5 with parameters given in the text.

Extrapolation of the plots of k_{obs} vs c_{Buff} to zero buffer concentration provided, as intercepts, the values of the catalytic constants (k_{ext}). In this case, the only catalytic species are the hydroxide anion and hydroxonium ion, whose concentrations are given by the ratio of both buffers components (c_B / c_{BH}) or by concentration of the hydrochloric acid. From this data the corresponding pH profile (Figure 4) can be generated whose shape, in the pH region 0−3, is similar to that observed for cyclization of *S*-(ethoxycarbonylmethyl)isothiuronium chloride.[12]

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TABLE 1. Catalytic Rate Constants k_{BH}^{cor} and k_B' for Individual Buffer Components

base buffer component (B)	pK_a(BH)[29]	k_{BH}^{cor} ($L \cdot mol^{-1} \cdot s^{-1}$)	k_B'
H_2O	−1.74	2460[a]	
dichloroacetate (DCA)	1.29	175 ± 5	
chloroacetate (CA)	2.86	48.0 ± 3	
methoxyacetate (MEA)	3.53	22.6 ± 0.8	
acetate (AC)	4.76	6.3 ± 0.2	
hydroxylamine (HA)	5.96	1.6 ± 0.1[b]	
N-methylmorpholine (NMM)	7.41		0.12 ± 0.01[c]
TRIS	8.10		0.26 ± 0.02[c]
glycinamide (GA)	8.00		0.24 ± 0.01[c]
morpholine (MP)	8.39		0.48 ± 0.02[c]

[a]From the plateau at pH 2−3 (Figure 4). $k_H = k_1k_2/k_{-1}$. [b]From buffer with c_B/c_{BH} 1:4. [c]From buffers with c_B/c_{BH} 1:1.

There are five breaks in the pH profile in Figure 4. In hydrochloric acid solutions, the log k_{obs} increases with pH up to ca. 1.5. Between pH 1.5 and 3.0, the values of log k_{obs} (log k_{ext}) are pH-independent and then linearly increase again with exceptionally low slope (ca. 0.45; a slope +1 has been observed for similar cyclization[12]). The third slight break downward occurs at pH ~5, and then log k_{ext} gradually increases again with pH (slope ca. 0.3) up to pH 7. The last break downward to zero slope occurs at pH ~7. The values of log k_{ext} are somewhat scattered above pH 7 because the extrapolation from nonlinear dependences (basic buffers) is less precise as compared with extrapolation from linear dependences found for substituted acetate buffers.

Since the isothiuronium salt **1** (= $\mathbf{SH}^+$) itself does not undergo rearrangement, it was necessary to relate k_{obs} to the concentration of free isothiourea (**S**). The corrected rate constants (k_{cor}) were calculated from the pK_a of the isothiuronium salt **1** and pH of the buffer solution according to eq 1. A pK_a of 6.7 was adopted for this purpose (for details of the pK_a estimation, see below)

$$k_{cor} = k_{obs}\frac{K_a}{K_a + [H^+]} = k_{obs}(1 + 10^{(pK_a - pH)}) \qquad (1)$$

For buffers showing linear dependence of k_{cor} vs c_{Buff} (substituted acetates, acidic HA buffers), the catalytic constants k_{Buff} were determined from the slopes of the plots. A second plot of k_{Buff} values against the ratio c_B/c_{Buff} then provides a linear dependence from which it is possible to determine the catalytic constants of both buffer components: extrapolation to $c_B/c_{Buff} = 0$ and 1 gives the catalytic constants k_B^{cor} and k_{BH}^{cor}, respectively. For the reactions monitored here, no significant general base-catalyzed rearrangement (k_B^{cor}) was observed in all the substituted acetate buffers. Only the acid−buffer component catalyzes the reaction, i.e., the reaction is general acid catalyzed. The catalytic constant k_{BH}^{cor} for the individual general acids is given in Table 1. A Brønsted plot of log k_{BH}^{cor} vs pK_a(BH) is linear with the slope $\alpha = -0.47$ (Figure 5). The point corresponding to catalysis by H_3O^+ can be calculated from the plateau at pH 2−3, and this point falls 0.5 log units below the extrapolated straight line in Figure 5.

For basic buffers (Figure 6) when k_{cor} is plotted against concentration of the base−buffer component (c_B), the linear portions of nonlinear dependences (at high c_{Buff}) are almost parallel. From this observation it can be concluded that the reaction in concentrated amine buffers involves general-base catalysis. In dilute buffers, both acid as well as base−buffer component can catalyze the reaction.

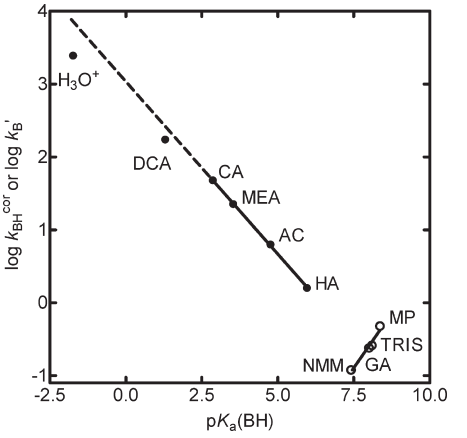

FIGURE 5. Brønsted plot of log k_{BH}^{cor} vs pK_a(BH) (●) and log k_B' vs pK_a(BH) (○).

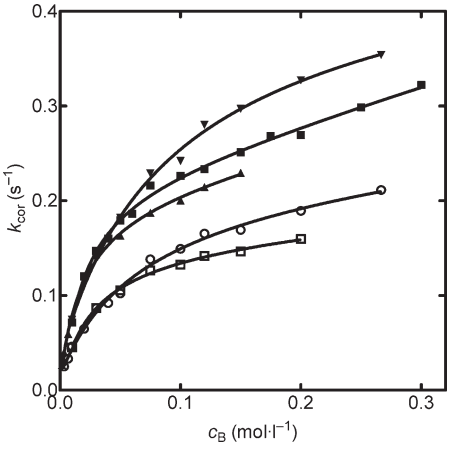

FIGURE 6. Dependence of the corrected rate constant (k_{cor}, s^{-1}) on the concentration of base-buffer component (c_B, $mol \cdot L^{-1}$) measured at 25 °C in morpholine (MP) buffers [(2:1a) pH 8.63 (▲); (1:1) pH 8.93 (■); (1:2b) pH 9.21 (▼)] and TRIS buffers [(1:1) pH 8.37 (□); (1:2b) pH 8.70 (○)]: (a) acidic; (b) basic.

A solvent kinetic isotope effect was also studied in (1:1) chloroacetate and acetate buffer (Figure 1). Both dependences of k_{obs} *vs* c_{Buff} in D_2O were linear (like in water), and the values for chloroacetate $k_{ext}^H/k_{ext}^D = 3.55$, $k_{Buff}^H/k_{Buff}^D = 2.14$ and for acetate $k_{ext}^H/k_{ext}^D = 1.83$, $k_{Buff}^H/k_{Buff}^D = 2.36$ were obtained.

Estimation of the pK_a of Isothiuronium Salt 1. Knowledge of the pK_a value is essential for correct evaluation of all kinetic data. It was not possible to measure the thermodynamic pK_a value of **1** because of the very high rates of cyclization at pH 6−8, but a pK_a(**1**) around 7 would be reasonable for an *N*-phenylisothiuronium salt. The pK_a of *S*-methyl-*N*-phenylisothiuronium is 7.14.[13] The lactone group in **1** will have an acidifying effect (through polar effects as well as due to intramolecular hydrogen bond), whereas a methoxy group in the *para*-position will have an opposite effect. In our case, the best fit of all data points in

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Figure 4 using eq 2 or 5 with parameters given below was achieved for $pK_a(\mathbf{1}) = 6.7$.

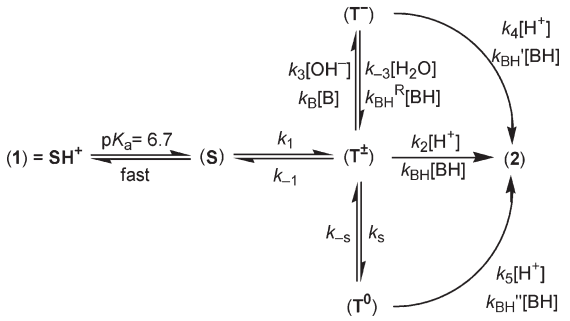
We also verified this $pK_a(\mathbf{1})$ value using the SPARC program,[14a] which was successfully tested[14b] by estimation of more than 4300 ionization pK_a's. The SPARC program gave $pK_a(\mathbf{1})$ 6.2 and 7.3, respectively, for both possible canonical structures.

Mechanism of the Rearrangement and Evaluation of the Kinetic Data. The bimolecular[15] and intramolecular[4] aminolyses of esters that have been studied to date have shown large differences in the detailed mechanism. However, it is generally accepted that, with most esters, the attack of amine to form the labile intermediate $\mathbf{T}^{\pm}$ is rapid and reversible, and the rate-determining step at high pH is the trapping of this intermediate by proton removal with a general base giving $\mathbf{T}^{-}$, a proton switch through water ($\mathbf{T}^{\mathbf{0}}$), or direct breakdown of $\mathbf{T}^{\pm}$ to products. Only in very few cases when the intermediate $\mathbf{T}^{\pm}$ or $\mathbf{T}^{-}$ is too unstable to permit proton transfer to take place in a discrete step before its breakdown, a concerted mechanism or enforced concerted mechanism of catalysis is possible in order to avoid this labile intermediate.[3c,16,17] The existence of such labile tetrahedral intermediates has been proven indirectly on the basis of curved pH profiles,[4d,15e,f] curved buffer dependence plots,[4e,8b,11] curved Brønsted plots,[15d,f] kinetic isotope effects,[3f,4c] and quantum chemical calculations.[18] The intramolecular aminolysis of alkyl esters involves[4c−e,h] either breakdown of $\mathbf{T}^{-}$ or its general base-catalyzed formation from $\mathbf{T}^{\mathbf{0}}$. However, for cyclization of *S*-(ethoxycarbonylmethyl)isothiuronium chloride, which best resembles the rearrangement of our lactone, the rate-limiting formation and breakdown of $\mathbf{T}^{\pm}$ was reported.[12] To the best of our knowledge, the coexistence of all three kinetically detectable intermediates $\mathbf{T}^{\pm}$, $\mathbf{T}^{\mathbf{0}}$, and $\mathbf{T}^{-}$ during an aminolysis reaction has not yet been published.

In our case, the transitions in the pH profile (Figure 4) above pH 1 and 4.5 establish the formation of at least two different kinetically detectable intermediates, whose rate of formation and breakdown to product are pH dependent.[19] The break at pH ~7 gives either the value of the apparent ionization constant pK_{app} for **1** or is caused by appearance of another kinetically detectable intermediate (cf. behavior in buffers where at pH >6 linear dependences of k_{obs} vs c_{Buff} change to nonlinear). The combination of both possibilities is also conceivable.

It is impossible to neglect break at pH 5, although it is very slight, because the slope of the straight line crossing the points between pH 3.2−6.0 would be only 0.45. It is well-known that the slopes in pH profiles have mostly integral values giving whole number reaction orders.[20] Only in very rare systems, involving autocatalysis or autoinhibition, are the ratios of small integers such as 1/2 allowed (mostly in the gas phase). However, in a relatively narrow pH region (approximately two pH units), the slopes can change from one integral value to another, giving intermediate values as, for example, during hydrolysis of aspirin.[21]

SCHEME 2



According to the literature and kinetic measurements, the following Scheme 2 can be suggested for rearrangement of **1** to **2**. (For structures of particular intermediates, see Scheme 3.)

Applying a steady-state approximation to the tetrahedral intermediates $\mathbf{T}^{\pm}$, $\mathbf{T}^{\mathbf{0}}$, and $\mathbf{T}^{-}$, we obtained eq 2 for the reaction at zero buffer concentration where K_a is the ionization constant of **1** (= $\mathbf{SH}^{+}$) and $K_W = 10^{-14}$ (at 25 °C) is the ion product of water.

$$k_{ext} = \frac{k_1 \frac{K_a}{K_a + [H^+]}}{k_{-1} + k_2[H^+]}\left(k_2[H^+] + \frac{k_S k_5 [H^+]}{k_{-S} + k_5[H^+]} + \frac{k_3 k_4 K_W}{k_{-3}[H_2O] + k_4[H^+]}\right) \quad (2)$$

The three terms in parentheses concern the acid-catalyzed breakdown of the intermediates $\mathbf{T}^{\pm}$, $\mathbf{T}^{\mathbf{0}}$, and $\mathbf{T}^{-}$. Fitting the pH profile using eq 2 is not sufficient to determine all nine rate constants, and only products or ratios of particular rate constants are accessible.

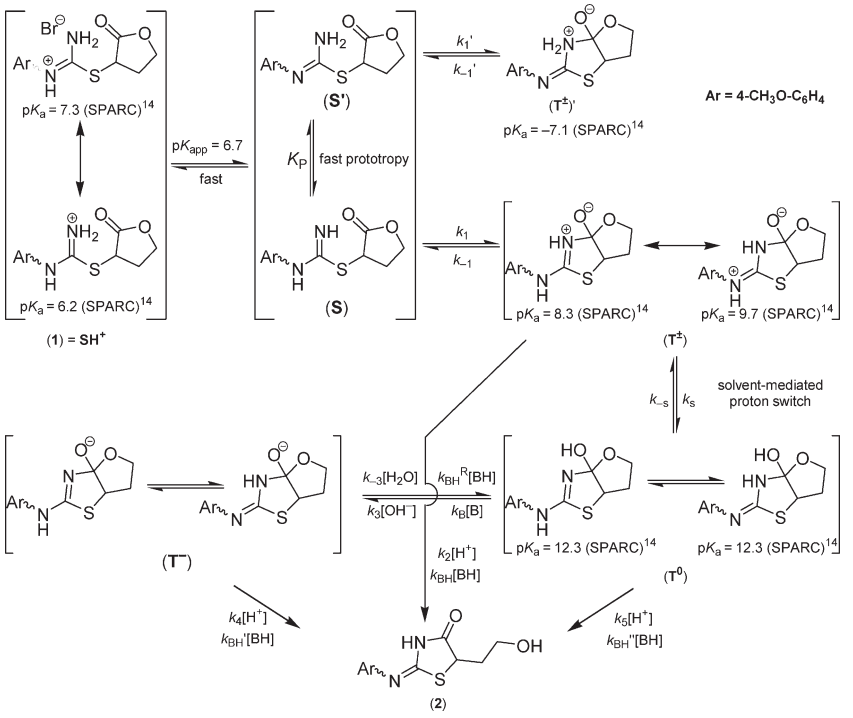
At pH 0−2.5, the starting compound is present almost entirely as the protonated species $\mathbf{SH}^{+}$, since the pK_a is 6.7, and the last two terms in parentheses can be neglected. Simultaneously, the ratio $K_a/(K_a + [H^+]) = K_a/[H^+]$ and eq 2 can be rewritten to eq 3, which is completely consistent with the previously reported equation.[12]

$$k_{ext} = \frac{k_1 k_2 K_a}{k_{-1} + k_2[H^+]} \quad (3)$$

The values $k_1 = 492\ s^{-1}$ and $k_2/k_{-1} = 5\ L \cdot mol^{-1}$ were obtained from the data (pH 0.5−2.5) using nonlinear regression. The optimized k_1 value which is the rate constant for cyclization of **S** to $\mathbf{T}^{\pm}$ is 40-fold less than the value found for cyclization of *S*-(ethoxycarbonylmethyl)isothiuronium chloride ($k_c = 2 \times 10^4\ L \cdot mol^{-1} \cdot s^{-1}$).[12] The reason lies in the presence of the 4-methoxyphenyl group, which lowers the nucleophilicity of the distant nitrogen (polar as well as steric effects). The break at pH 1.5 indicates a change in the rate-limiting step. At pH <0.5,

(14) (a) http://ibmlc2.chem.uga.edu/sparc/. (b) Hilal, S. H.; Karickhoff, S. W.; Carreira, L. A. *Quant. Struc. Act. Rel.* **1995**, *14*, 348–355.
(15) (a) Bunnett, J. F.; Davis, G. T. *J. Am. Chem. Soc.* **1960**, *82*, 665–674. (b) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1960**, *82*, 675–681. (c) Bruice, T. C.; Mayahi, M. F. *J. Am. Chem. Soc.* **1960**, *82*, 3067–3071. (d) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1968**, *90*, 2622–2637. (e) Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638–2645. (f) Satterthwait, A. C.; Jencks, W. P. *J. Am. Chem. Soc.* **1974**, *96*, 7018–7031. (g) Kovach, I. M.; Belz, M.; Larson, M.; Rousy, S.; Schowen, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 7360–7365.
(16) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425–432.
(17) Williams, A. In *Concerted Organic and Bio-organic Mechanisms*; CRC Press: Boca Raton, 2000.
(18) (a) Ilieva, S.; Galabov, B.; Musaev, D. G.; Morokuma, K.; Schaefer, H. F., III. *J. Org. Chem.* **2003**, *68*, 1496–1502. (b) Sung, D. D.; Koo, I. S.; Yang, K.; Lee, I. *Chem. Phys. Lett.* **2006**, *426*, 280–284.
(19) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993–3002.
(20) Birk, J. P. *J. Chem. Educ.* **1976**, *53*, 704–707.
(21) (a) Edwards, L. J. *Trans. Faraday Soc.* **1950**, *46*, 723–735. (b) Garrett, E. R. *J. Am. Chem. Soc.* **1957**, *79*, 3401–3408.

SCHEME 3



the term $k_2[H^+] \gg k_{-1}$ and eq 3 can be simplified as follows, $k_{ext} = k_1K_a/[H^+]$, and the formation of $\mathbf{T}^{\pm}$ is rate-limiting. At pH >1.5, $k_2[H^+] \ll k_{-1}$, and $k_{ext} = k_1k_2K_a/k_{-1}$ is pH-independent. The acid-catalyzed breakdown of $\mathbf{T}^{\pm}$ is now the rate-limiting step of the rearrangement. The value of the solvent kinetic isotope effect $k_{ext}^{H}/k_{ext}^{D} = 3.55$ measured in chloroacetate buffer ($c_B/c_{BH} = 1$, pH 2.67) must be consistent with the simplified form of eq 3 at pH >1.5 (plateau). It can be presumed that the solvent kinetic isotope effect for the formation and reverse breakdown of $\mathbf{T}^{\pm}$ will be negligible ($K_1^{H}/K_1^{D} \approx 1$). Solvent kinetic isotope effect for the ionization constant $K_a^{H}/K_a^{D} \approx 3$ can be estimated from fractionation factors. The value of k_2^{H}/k_2^{D} which corresponds to the H_3O^+-catalyzed breakdown of $\mathbf{T}^{\pm}$ is then 1.18. This value is substantially lesser than the value found for chloroacetic acid $k_{Buff}^{H}/k_{Buff}^{D} = 2.14$.[4c] This result can be explained by different transition-state geometry. In the case of weak acids (BH), the proton has almost a central position between $\mathbf{T}^{\pm}$ and acid in the transition state (as seen from $\alpha = -0.47$; i.e., $\mathbf{T}^{\pm}\cdots H\cdots B$), whereas in the case of much stronger H_3O^+ the transition state closely resembles reactants (early transition state $\mathbf{T}^{\pm}\cdots H{-}OH_2^+$ for which α should approach zero, as can be seen from the point falling below the straight line in Figure 5).

At pH >2.5 a new reaction pathway through $\mathbf{T}^{\mathbf{0}}$ gradually opens, and the second term in eq 2 becomes kinetically significant. k_{ext} is given by eq 4.

$$k_{ext} = \frac{k_1K_a}{k_{-1}}\left(k_2 + \frac{k_Sk_5}{k_{-S} + k_5[H^+]}\right) \qquad (4)$$

Using the parameters mentioned above, the ratios $k_{-S}/k_5 = 1.3 \times 10^{-5}$ mol·L^{-1} and $k_S/k_{-1} = 8.8 \times 10^{-4}$ were obtained by optimization of the data in pH profile. From the break at pH 4.9, it can be concluded that a change in the rate-limiting step occurs again. At pH <4.9, the formation of $\mathbf{T}^{\mathbf{0}}$ is rate-limiting, whereas at pH >4.9 its acid-catalyzed breakdown is involved. The value of solvent kinetic isotope effect $k_{ext}^{H}/k_{ext}^{D} = 1.83$ measured in acetate buffer ($c_B/c_{BH} = 1$, pH 4.61) is much less than observed in chloroacetate buffer. This observation is consistent with eq 4 under the following presumptions. Solvent kinetic isotope effect is still $K_a^{H}/K_a^{D} \approx 3$, but the ratio of fractions $(k_S^{H}k_5^{H}/(k_{-S}^{H}+k_5^{H}[H^+]))/(k_S^{D}k_5^{D}/(k_{-S}^{D}+k_5^{D}[D^+]))$ must be less than 1 because the concentration of D^+ is 3 times less than $[H^+]$ in buffer with the same c_B/c_{BH}. The value 1.83 refers to the rearrangement of $\mathbf{T}^{\pm}$ to $\mathbf{T}^{\mathbf{0}}$ (K_S^{H}/K_S^{D}) as well as to acid-catalyzed decomposition of $\mathbf{T}^{\mathbf{0}}$ (k_5^{H}/k_5^{D}).

The last reaction pathway (at pH > 5) involves the trapping of $\mathbf{T}^{\pm}$ by proton removal with a base giving $\mathbf{T}^{-}$. The nonlinear regression of all experimental data points using previously optimized parameters with eq 2 gave the values of $k_{-3}/k_4 = 2.6 \times 10^{-8}$ s^{-1} and $k_3/k_{-1} = 7 \times 10^3$ l·mol^{-1}.

Although the values of individual rate constants are not directly accessible from optimization of the measured data, they can be estimated as follows. Proton transfer from $\mathbf{T}^{\pm}$ to the strong base hydroxide ion will be thermodynamically favorable, so that the value of k_3 is taken as 10^{10} L·mol^{-1}·s^{-1} for hydroxide ion.[22] The rate constant for the reverse breakdown of $\mathbf{T}^{\pm}$ to **S** is then $k_{-1} = 1.4 \times 10^6$ s^{-1}. This value is approximately 2 orders of magnitude lesser than the estimated rate constant $k_{-1} = 6.6 \times 10^8$ s^{-1} for expulsion of amine from the related cyclic zwitterionic intermediate.[23] The value estimated by us is not totally unreasonable because our $\mathbf{T}^{\pm}$ is resonance-stabilized (Scheme 4), and therefore, its reverse breakdown would be slower. If the value of k_{-1} is 1.4×10^6 s^{-1}, then $k_2 = 7.0 \times 10^6$ L·mol^{-1}·s^{-1} and $k_S = 1260$ s^{-1}.

The two proton transfers that convert $\mathbf{T}^{\pm}$ to $\mathbf{T}^{\mathbf{0}}$ could occur either in a stepwise mechanism through $\mathbf{T}^{+}$, with the

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(23) Barnett, R. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1969**, *91*, 2358–2369.

rate constants k_{OH} and k_H (not shown in Schemes 2 and 3) or in a single concerted step with the rate constant k_S, which may include one to two water molecules. Water acts as a bifunctional catalyst for proton transfer through a five- or eight-membered ring. Experimental distinction between the two mechanisms can be done by measuring a solvent isotope effect. Bifunctional concerted catalysis is in accord with a solvent isotope effect less than 2.[24] In our case, the k_{ext}^{H}/k_{ext}^{D} obtained from linear dependences of k_{obs} *vs* c_{Buff} measured in acetate buffer (1:1) in H_2O and D_2O is only 1.83, which supports the idea of water-mediated proton switch. The values of k_S are generally in the range[4d,15f,25] $10^5-10^8\ s^{-1}$. Our value $k_S = 1260\ s^{-1}$ is quite small (perhaps due to mentioned resonance stabilization of $\mathbf{T}^{\pm}$).

An alternative mechanism is proposed in Scheme 3, together with corresponding eq 5. The only difference between mechanisms in Scheme 2 and 3 is that the cleavage of a proton proceeds from $\mathbf{T}^{\mathbf{0}}$ instead of $\mathbf{T}^{\pm}$.[4c]

$$k_{ext} = \frac{k_1\dfrac{K_a}{K_a+[H^+]}}{k_{-1}+k_2[H^+]}\left(k_2[H^+]+\frac{k_S k_5[H^+]}{k_{-S}+k_5[H^+]} + \frac{k_S k_3 k_4 K_W}{(k_{-S}+k_5[H^+])(k_{-3}[H_2O]+k_4[H^+])}\right) \quad (5)$$

Optimized values of $k_1, k_2/k_{-1}$, and k_{-S}/k_5 are the same as those obtained from eq 2. From the last two terms of eq 5 the ratios $k_S/k_{-1} = 8.0\times10^{-4}$, $k_{-3}/k_4 = 3.0\times10^{-7}\ s^{-1}$, and $k_3K_S/k_{-1} = 6\times10^4\ L\cdot mol^{-1}$ were optimized. In order to calculate the rate constants k_{-1} and k_S the value of K_S is needed. K_S can be estimated from the values of $pK_a(\mathbf{T}^{\pm}) = 8.3 - 9.7$ (cf. $pK_a(\mathbf{T}^{\pm}) = 9.8$ determined for a similar intermediate[8c]) and $pK_a(\mathbf{T}^{\mathbf{0}}) = 12.3$ which were calculated using SPARC.[14] From them, $K_S = k_S/k_{-S} = 4\times10^2 - 1\times10^4$.

If the value of k_3 is taken as $10^{10}\ L\cdot mol^{-1}\cdot s^{-1}$ and K_S is in the range $4\times10^2-1\times10^4$, then $k_{-1} = 6.7\times10^7-1.7\times10^9\ s^{-1}$, $k_2 = 3.4\times10^8-8.3\times10^9:\cdot mol^{-1}\cdot s^{-1}$, and $k_S = 5.4\times10^5-1.3\times10^6\ s^{-1}$, which conforms well with the literature mentioned above. The decision as to which mechanism is correct can be made from measurements in buffers.

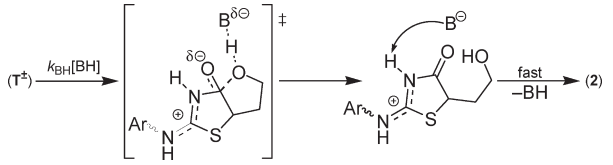
In all buffer solutions, the reaction involves general acid−base catalysis; therefore, at least one buffer component must also catalyze the rearrangement of **1** to **2**, and extended kinetic eqs 6 and 7 derived from Schemes 2 and 3 can be written:

$$k_{obs} = k_{ext} + \frac{k_1\dfrac{K_a}{K_a+[H^+]}}{k_{-1}+k_{BH}[BH]}\left(k_{BH}[BH]+\frac{k_S k_{BH}'[BH]}{k_{-S}+k_{BH}'[BH]} + \frac{k_B k_{BH}''[B]}{k_{BH}^{R}+k_{BH}''}\right) \quad (6)$$

$$k_{obs} = k_{ext} + \frac{k_1\dfrac{K_a}{K_a+[H^+]}}{k_{-1}+k_{BH}[BH]}\left(k_{BH}[BH]+\frac{k_S k_{BH}'[BH]}{k_{-S}+k_{BH}'[BH]} + \frac{k_S k_B k_{BH}''[B]}{(k_{-S}+k_{BH}'[BH])(k_{BH}^{R}+k_{BH}'')}\right) \quad (7)$$

(24) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1981**, *103*, 580–587.

SCHEME 4



No significant general base-catalyzed reaction (k_B) was observed in substituted acetate buffers; therefore, the last term in parentheses in both eq 6 and eq 7 can be neglected. All dependences of k_{obs} *vs* c_{Buff} are linear, which means that $k_{BH}[BH] \ll k_{-1}$ (general acid BH is much weaker than H_3O^+) and $k_{BH}'[BH] \gg k_{-S}$. Equations 1 and 6 or 7 can be combined to eq 8, where $k_{BH}^{cor} = K_1k_{BH}$, $K_1 = k_1/k_{-1}$, and $k_0^{cor} = k_{ext}(K_a + [H^+])/K_a + K_1k_S$.

$$k_{cor} = k_0^{cor} + k_{BH}^{cor}[BH] \quad (8)$$

A Brønsted plot of $\log k_{BH}^{cor}$ vs $pK_a(BH)$ is linear, and the slope $\alpha = -0.47$ (Figure 5) must reflect a rate-limiting step involving proton transfer from general acid to $\mathbf{T}^{\pm}$ which is concerted with C−O bond breaking (Scheme 4). The reaction may occur by a "one-encounter" mechanism in which the same molecule of catalyzing acid (BH) donates a proton to the poorly leaving alkoxide and removes it from the nitrogen[15e] in order to avoid thermodynamically unfavorable protonated intermediate/product ($pK_a \approx -7$).

In basic amine buffers, the catalytic power of general acid BH decreases and the dependences of k_{obs} vs c_{Buff} are no longer linear because the term $k_{BH}[BH]$ is low and the term $k_{BH}'[BH]$ becomes comparable with k_{-S}. Furthermore, a general base-catalyzed pathway gradually opens in those buffers (eqs 9 and 10). Only eq 9 is consistent with the observation of linear increase of k_{cor} with c_B in concentrated buffers (Figure 6) because the eq 10 predicts saturation kinetics. The mechanism in Scheme 2 is therefore more plausible.

$$k_{cor} = k_{ext}^{cor} + K_1\left(\frac{k_S k_{BH}'[BH]}{k_{-S}+k_{BH}'[BH]} + \frac{k_B k_{BH}''[B]}{k_{BH}^{R}+k_{BH}''}\right) \quad (9)$$

$$k_{cor} = k_{ext}^{cor} + K_1\left(\frac{k_S k_{BH}'[BH]}{k_{-S}+k_{BH}'[BH]} + \frac{k_S k_B k_{BH}''[B]}{(k_{-S}+k_{BH}'[BH])(k_{BH}^{R}+k_{BH}'')}\right) \quad (10)$$

From the linear portions of nonlinear dependences (at high c_B), the slopes give $k_B' = K_1k_{BH}''k_B/(k_{BH}^{R}+k_{BH}'')$ for particular base−buffer components (Table 1). The Brønsted plot of $\log k_B'$ vs $pK_a(BH)$ is linear, and the slope $\beta_{obs} = 0.6$ (Figure 5). This value cannot be interpreted in terms of simple proton transfer from $\mathbf{T}^{\pm}$ to the base (B) because k_B' is the composite constant. It can be presumed that the dependence of $\log k_B$ vs $pK_a(BH)$ should have a slope approaching unity[4c,15e] (Eigen-type Brønsted correlation); therefore, the difference between the predicted and observed

(25) (a) Chang, K. C.; Grunwald, E. *J. Phys. Chem.* **1976**, *80*, 1422–1425. (b) Grunwald, E.; Chang, K. C.; Skipper, P. L.; Anderson, V. K. *J. Phys. Chem.* **1976**, *80*, 1425–1431. (c) Bensaude, O.; Dreyfus, M.; Dodin, G.; Dubois, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 4438–4446.

slope $\Delta\beta = 0.4$ corresponds to two proton transfers (k_{BH}^{R} and k_{BH}'') from general acid to $\mathbf{T}^{-}$.

Conclusions

Treatment of the isothiuronium salt 1 (= $\mathbf{SH}^{+}$) with base produces reactive isothiourea in a fast pre-equilibrium ($pK_a = 6.7$). The resulting isothiourea can exist in the form of two prototropic tautomers (**S** and **S′**) that are rapidly interchanging with one another. In principle, both tautomers can undergo cyclization to the zwitterionic intermediate ($\mathbf{T}^{\pm}$ or $\mathbf{T}^{\pm\prime}$). However, only the tautomer **S** provides (k_1) the resonance-stabilized $\mathbf{T}^{\pm}$ whose estimated $pK_a(\mathbf{T}^{\pm}) = 8.3-9.7$ is not very different from $\mathbf{SH}^{+}$ so that there is not a large favorable free energy for proton transfer from $\mathbf{SH}^{+}$ to catalyzing base, and concerted catalysis cannot be expected for either the formation or breakdown of the zwitterionic intermediate.[3c] The stepwise process involving fast pre-equilibrium with subsequent cyclization is in accord with the "libido" rule.[1d,17,26] On the other hand, the cyclization of **S′** (k_1') would provide $\mathbf{T}^{\pm\prime}$, which is not resonance-stabilized, and its $pK_a(\mathbf{T}^{\pm\prime})$ should be around −7 (i.e., far from starting SH^{+}). Therefore, $\mathbf{T}^{\pm\prime}$ is not directly involved in reaction, but the K_P can influence the apparent ionization constant of SH^{+}. The existence of the zwitterionic intermediate $\mathbf{T}^{\pm}$ is proven by the break in pH profile (Figure 4) at pH 1.5 (see the section dealing with kinetic data evaluation). Zwitterionic intermediate $\mathbf{T}^{\pm}$ then undergoes either acid-catalyzed concerted[27] breakdown to product (pH 2−3) or water-mediated proton switch from N to O (pH 3−5). Such proton transfers between electronegative base pairs in hydroxylic solvents often occur by relay through one or more solvent molecules.[17] The last reaction pathway (pH > 5) involves the formation of anionic intermediate $\mathbf{T}^{-}$ either from $\mathbf{T}^{\pm}$ or from $\mathbf{T}^{0}$. The first possibility involving reaction $\mathbf{T}^{\pm} \rightarrow \mathbf{T}^{-}$ (Scheme 2) seems to be more likely because it is in accordance with behavior in basic amine buffers, where linear increase of the observed rate constant with c_B is observed. To the best of our knowledge, the coexistence of all three kinetically detectable intermediates $\mathbf{T}^{\pm}$, $\mathbf{T}^{0}$, and $\mathbf{T}^{-}$ in aminolysis is unique throughout the literature. We have found only one example of kinetic evidence for three species of the tetrahedral intermediate during lactonization of 4,6,8-trimethylcoumarinic acid.[28] We believe that this coexistence is possible only due to enhanced stability of all mentioned intermediates whose easy formation and slow breakdown reflects the advantage of an intramolecular reaction and the presence of a relatively poor leaving group (alkoxide) necessitating participation of an acid.

Experimental Section

Compounds. Preparation and characterization of *S*-(2-oxotetrahydrofuran-3-yl)-*N*-(4-methoxyphenyl)isothiuronium bromide (**1**) and 5-(2-hydroxyethyl)-2-[(4-methoxyphenyl)imino]-1,3-thiazolidin-4-one (**2**) was described elsewhere.[9]

Kinetic Measurements. All of the kinetic measurements were carried out in a 1 cm closable cell using a Hewlett-Packard 8453 diode array spectrophotometer at 25 ± 0.1 °C. The observed pseudo-first-order rate constants k_{obs} were calculated from absorbance−time dependences at the wavelengths of 260 and 273 nm and at the substrate concentrations of ca. 5×10^{-5} mol·L^{-1}. Ionic strength $I = 1$ mol·L^{-1} was adjusted by KCl. In all kinetic runs, the standard deviation in the fit was always less than 1% of the quoted value and was more usually between 0.2 and 0.4% of the quoted value. The pH of individual buffers was measured using PHM 93 Radiometer Copenhagen apparatus equipped with glass electrode. Redistilled water, commercially available substituted acetic acids, amines, and potassium chloride (p.a.) for adjustment of ionic strength of buffer solutions were used. The solvent kinetic isotope effect was measured in chloroacetate and acetate buffers ($c_B/c_{BH} = 1:1$) of the same composition and ionic strength which were prepared from potassium chloride, sodium hydroxide, chloroacetic anhydride/acetic anhydride, and H_2O or D_2O (99.8% D). Rapid deuteration of isothiuronium moiety in D_2O, which can cause a slight secondary kinetic isotope effect, was confirmed by ^{1}H NMR experiment. The starting salt **1** was dissolved in D_2O, and the ^{1}H NMR spectrum was measured immediately. All NH and NH_2 protons completely disappeared due to very fast exchange with solvent. This observation also proves that there is a rapid establishment of equilibrium between the salt and its conjugate base (proton transfer from/to nitrogen has the rate constant k about 10^{10} L·mol^{-1}·s^{-1}).[22]

The dissociation constant of particular buffer components (substituted acetic acids and ammonium cations) was taken from the literature.[29]

Acknowledgment. Financial support by the Ministry of Education, Youth, and Sports of the Czech Republic (Project MSM 002 162 7501) is gratefully acknowledged.

Supporting Information Available: All kinetic data (the observed rate constants measured in buffers and HCl) and selected spectral records. This material is available free of charge via the Internet at http://pubs.acs.org.

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