Kinetic Study on Acid-Base Catalyzed Hydrolysis of Azimsulfuron, a Sulfonylurea Herbicide

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ABSTRACT: Pseudo-first-order rate constants (k_{obs}) for hydrolysis of a sulfonylurea herbicide, azimsulfuron, AZIM®, {N-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbony]-1-methyl-4-(2-methyl-2H-tetrazol-5-yl)-1H-pyrazole-5-sulfonamide} (AZS) follow an empirical relationship: $k_{obs} = \alpha_1 + \alpha_2[^-OH] + \alpha_3[^-OH]^2$ within the [NaOH] range of 0.1–2.0 M at different temperatures ranging from 40 to 55°C. The contribution of $\alpha_3[^-OH]^2$ term is small compared with $\alpha_2[^-OH]$ term and this turns out to be zero at 60°C. Pseudo-first-order rate constants (k_{obs}) for hydrolysis of AZS within the [H$^+$] range from 2.5×10^{-6} to 1.4 M follow the relationship: $k_{obs} = (\alpha_1 K_a + \beta_1[H^+] + \beta_2[H^+]^2)/([H^+] + K_a)$ where pK_a = 4.37 at 50°C. The value of β_1 is nearly 25 times larger than that of α_1. The rate of alkaline hydrolysis of AZIM is weakly sensitive to ionic strength. © 1999 John Wiley & Sons, Inc., Int J Chem Kinet 31: 253–260, 1999

INTRODUCTION

Azimsulfuron (AZS) {N-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-1-methyl-4-(2-methyl-2H-tetra-zol-5-yl)-1H-pyrazole-5-sulfonamide}, originally known as DPX-A8947, AZS is one of the most effective sulfonylurea herbicides for weed control in wet rice paddies. Sulfonylurea herbicides have a common functional group ($-SO_2NHCONH-$) in which the carbonyl carbon is the most likely electrophilic site for nucleophilic attack by water and other nucleophiles in the aqueous degradation of these herbicides.
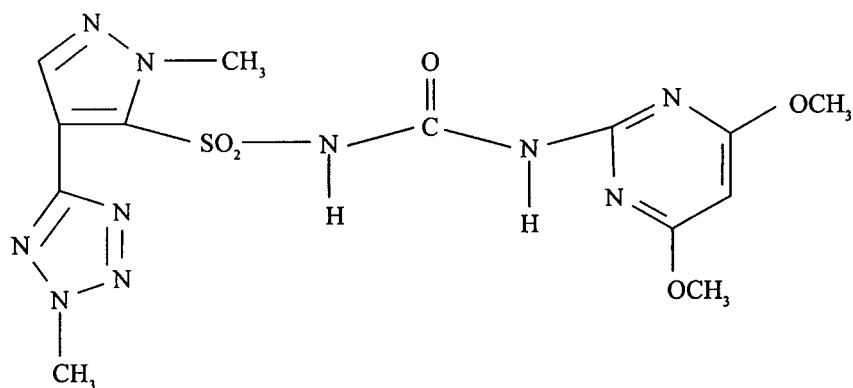
AZS

The acid-base catalyzed hydrolysis of urea has been the subject of several reports [1–4] partly because of its relevance as a model system for urease-catalyzed hydrolysis reactions. The sulfonylurea herbicides are subject to both chemical hydrolysis and microbial degradation in soils [5,6]. Although AZS is *N,N′*-disubstituted urea, its aqueous stability is expected to be low compared with urea due to chemical modification on the leaving ability of the leaving group. There is a paucity of kinetic information on the acid-base catalyzed hydrolysis of AZS. Such an *in-vitro* study on AZS may be useful in the rationalization of degradation data obtained in the presence of soils of different pH and physico-chemical characteristics. The aim of the present study was to investigate the mechanistic details of hydrolytic cleavage of AZS under acidic and alkaline pH. The experimental results and their probable explanations are described in this article.

EXPERIMENTAL

Materials

Reagent and commercial grades of AZS {*N*-[[(4,6-dimethoxy-2-pyrimidinyl)amino]carbonyl]-1-methyl-4-(2-methyl-2H-tetrazol-5-yl)-1H-pyrazole-5-sulfonamide} were obtained as a generous gift from Du Pont Far East Inc. 2-Amino-4,6-dimethoxypyrimidine was obtained from Maybridge Chem. Co. Ltd., UK. All other chemicals used were commercial products of reagent grade. Glass-distilled water was used throughout the kinetic study. Stock solutions of AZS were pre-

pared frequently in acetonitrile. The values of water solubility of azimsulfuron at 25°C are 72 mg/L at pH 5 and 1050 mg/L at pH 7 [7].

Kinetic Measurements

Apparently, the base-catalyzed hydrolysis products of AZS absorbed much more strongly than AZS at 285 nm in alkaline medium. However, in acidic medium, AZS showed a stronger absorption than the hydrolysis products at 240 nm. The reaction rates of aqueous cleavage of AZS under alkaline and acidic pH were studied spectrophotometrically by monitoring the appearance of products at 285 nm and disappearance of reactant (AZS) at 240 nm, respectively. The ionic strength of the reaction medium was kept constant at 2.0 M with sodium chloride. The acetate buffer solutions of desired pH were prepared just before the start of the kinetic runs.

In a typical kinetic run, all the reaction ingredients (except AZS) required for an appropriate experimental condition were put in a 25 mL reaction vessel, which was then placed in a thermostatted water bath. A total volume of 9.9 mL of reaction solution was allowed to equilibrate for about 15 min at the desired temperature. The reaction was then initiated by adding 0.1 mL (using a 100 μl Hamilton syringe) of 0.015 M AZS. An aliquot of nearly 2.5 mL was quickly withdrawn from the reaction mixture and transferred to a 3 mL quartz cuvette. The cuvette was then quickly placed into the thermostatted cell compartment of a Shimadzu model UV-2101/3101PC UV-VIS-NIR scanning spectrophotometer. The absorbance of the reaction mixture (A_{obs})

was recorded at a fixed wavelength of either 285 nm or 240 nm and the reaction mixture (i.e., aliquot) was transferred back quickly into the thermostatted bulk reaction mixture. There was always a maximum lapse of nearly 30 s on the average between the time of removal of the aliquots and the time when their absorbance was recorded. Reactions were generally followed up to >80% completion with at least 13 data points as well as a reading after 24–240 h. The pH values of the reaction mixtures containing acetate buffers were determined with WITEG W500 Digital pH/mV/Temp meter.

Entire kinetic runs were carried out under pseudo-first-order kinetic conditions. Pseudo-first-order rate constants (k_{obs}) were calculated from eq. (1) and eq. (2) for the reactions where disappearance of reactant and appearance of product(s), respectively, were monitored as a function of reaction time (t). In eqs. (1) and (2), A_{obs}, A_∞, and A_0 represent absorbance at any time, t, at $t = \infty$, and $t = 0$, respectively, E_{app} is the apparent molar absorption coefficient, and $[X]_0$ is the initial concentration of AZS.

$$A_{obs} = E_{app}[X]_0 \exp(-k_{obs}t) + A_\infty \qquad (1)$$

$$A_{obs} = E_{app}[X]_0[1 - \exp(-k_{obs}t)] + A_0 \qquad (2)$$

The nonlinear least-squares technique was used to calculate three unknown parameters, k_{obs}, E_{app}, and A_∞ or A_0 from eqs. (1) or (2). The observed data were found to fit reasonably well with eq. (1) or eq. (2) for almost all the kinetic runs. The percentage deviations between the observed and calculated absorbance values were less than 2% for up to 6–8 halflives for most of the kinetic runs.

Product Characterization

The most probable electrophilic sites for oxy nucleophilic attack are the carbon of —CO— or sulfur of —SO₂NH— groups in AZS. But the electrophilicity of carbonyl carbon is much larger than the sulfur of sulfonamide for nucleophilic attack by nucleophiles containing oxygen and nitrogen as nucleophilic sites [8]. Thus, in the hydrolysis of AZS, the attack by $^-$OH or H_2O should occur at the carbonyl carbon of the herbicide. The expected immediate stable products should be **1** and **2,** whether —SO₂NH₂ or —NH₂ moiety leaves as a result of nucleophilic attack at carbonyl carbon.
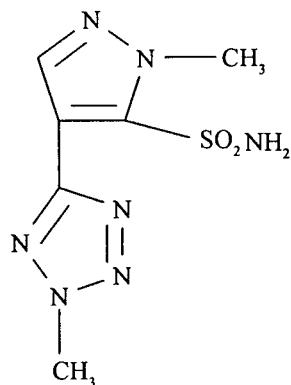
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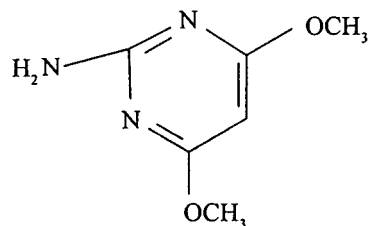
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It is difficult to ascertain whether —SO₂NH₂ or —NH₂ is better leaving group because the pK_a of $C_6H_5SO_2NH_2$, $C_6H_5NH_2$, and **3** at 50°C are 10.11 [9], 27 [10], and 8.4 [11], respectively.

3

Recently, it has been reported that the main products of hydrolysis of sulfonylurea herbicides, ArSO₂NHCONHHet, are ArSO₂NH₂, H₂NHet, and CO_2 and anionic sulfonylurea herbicides, ArSO₂N⁻CONHHetM⁺, are inert toward hydrolysis

[6,12]. However, rimsulfuron rapidly hydrolyzed in both acidic and alkaline conditions through contraction of the sulfonylurea bridge [5].

The values of pseudo-first-order rate constants for hydrolysis of a few sulfonylurea herbicides are shown in Table I. It is evident from Table I that thifensulfuron methyl and thifensulfuron hydrolyzed 4–5 times and 10–300 times slower than rimsulfuron at pH 5 and 9, respectively. The initial steps in the acidic and alkaline hydrolyses of thifensulfuron methyl and thifensulfuron involved the cleavage of the sulfonylurea bridge, whereas rimsulfuron hydrolyzed through contraction of the sulfonyl bridge. The rate of hydrolysis of rimsulfuron increased 3–6 times with each 10°C increase in temperature [5]. Thus, the allowance of temperature difference made k_{obs} larger for rimsulfuron than that for AZS by more than 6-fold and 190-times at pH 5 and 9, respectively. But the values of k_{obs} for AZS differ from corresponding k_{obs} for thifensulfuron methyl by the factors of 2–3 and 3–4 at pH 5 and 9, respectively (Table I). These results suggest that the acidic and alkaline hydrolysis of AZS involve the cleavage of the sulfonylurea bridge.

In a typical kinetic run, the products of the reaction mixture containing 1.5×10^{-4} M AZS and 0.6 M NaOH were analyzed using a mass spectrometric technique. The mass spectra of the reaction products obtained at different time intervals (2 min; 3, 12, and 25 days) showed a strong peak at m/z 156 which may be due to **2**. Although the mass spectrum of the reaction mixture at reaction time ∼2 min did not show a peak at m/z equivalent to the molecular ion peak for **1**, the presence of a peak for **2** suggested that the immediate products of the aqueous cleavage of AZS were **1** and **2**. The uv spectra of an authentic sample of **2** showed a weak absorption at 285 nm ($\varepsilon = 270 \pm 60$ M^{-1} cm^{-1} where ε represents molar extinction coefficient) within the [NaOH] range of 0.1–2.0 M at 2 M ionic strength. An authentic sample of **1** could not be obtained to check its ultraviolet spectra under the reaction conditions of the kinetic runs. However, the value of k_{obs} (= 1.44×10^{-4} min^{-1} at 50°C) for the reaction of monoanionic AZS with H$_2$O obtained by monitoring the appearance of products at 285 nm is not significantly different from the value of k_{obs} (1.90×10^{-4} min^{-1} at 50°C) obtained by monitoring the disappearance of AZS at 240 nm and pH 5.6. These results suggest that the rate of hydrolysis of AZS monitored at both 285 and 240 nm under mild pH corresponds to the same slow reaction step. Furthermore, if **1** and **2** were not the immediate products in the hydrolytic cleavage of AZS, then it was highly unlikely for reaction kinetics to obey a simple first-order rate law under both acidic and alkaline conditions.

RESULTS AND DISCUSSION

Effect of [NaOH] on Rate of Hydrolysis of AZS

A series of kinetic runs was carried out within the [NaOH] range of 0.1–2.0 M at 40°C and 2.0 M ionic strength. Pseudo-first-order rate constants k_{obs}, as shown in Figure 1, revealed an increase with the increase in [NaOH]. Similar observations were obtained at different temperatures ranging from 40 to 60°C. The observed data were treated with the following empirical equation.

$$k_{obs} = \alpha_1 + \alpha_2[^-OH] + \alpha_3[^-OH]^2 \qquad (3)$$

The empirical parameters, α_1, α_2, and α_3, were calculated using the least-squares technique, and these results are summarized in Table II. The fitting of the observed data to eq. (3) is evident from the plots of Figure 1 where solid lines are drawn through the least-squares calculated points. Most of the α_1 values are

Table I   Values of Pseudo-First-Order Rate Constants (k_{obs}) for Hydrolysis of Sulfonylurea Herbicides at Different pH

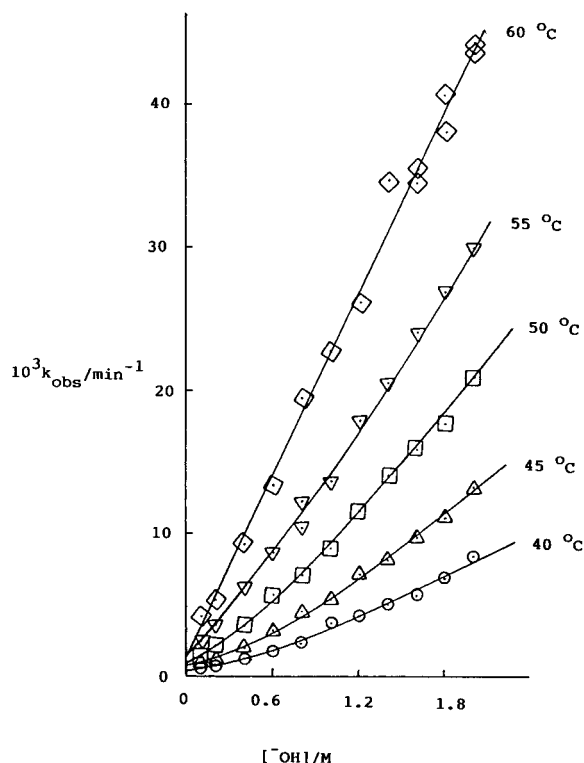| Herbicide	Temp/°C	pH =	$10^5 k_{obs}$/min^{-1}		
			4	5	9
Thifensulfuron methyl[a]	28		23.3	2.17	<11.8
Derivative of thifensulfuron methyl[a]	28		14.0	3.67	–
Thifensulfuron[a]	28		11.6	3.17	0.35
Derivative of thifensulfuron[a]	28		25.8	5.83	<0.53
Rimsulfuron[b]	25		–	10.2	120
Azimsulfuron[c]	50		353	35.0	∼14.4

[a] Ref. 6
[b] Ref. 5
[c] This study

Figure 1 Effects of [⁻OH] on pseudo-first-order rate constants (k_{obs}) for the cleavage of AZS at 40 (○), 45 (△), 50 (□), 55 (▽), and 60°C (◇).

associated with high standard deviations which make them rather unreliable. The maximum contribution of α_1 is <50% compared to other terms of eq. (3) under the experimental conditions imposed. A relatively more reliable value of α_1 was determined from k_{obs} obtained within the [NaOH] range of 0.001–0.050 M at 50°C. Under such conditions, α_3 [⁻OH]² term may

be neglected in eq. (3), and the linear least-squares calculated values of α_1 and α_2 are $(1.44 \pm 0.02) \times 10^{-4}$ min⁻¹ and $(7.32 \pm 0.08) \times 10^{-3}$ M⁻¹ min⁻¹, respectively.

It may be worth mentioning that the contribution of the α_3[⁻OH]² term compared with other terms of eq. (3) is <40% under the experimental conditions of entire kinetic runs. The standard deviations associated with α_3 values are rather high and because of the low contribution of the α_3[⁻OH]² term, the values of α_3 (Table II) may be considered to be less reliable.

It is interesting to note that the value of $\alpha_2(= 3.55 \times 10^{-4}$ M⁻¹ s⁻¹) is slightly more than 800-fold larger than the corresponding value of 4.28×10^{-7} M⁻¹ s⁻¹ obtained in the alkaline hydrolysis of urea at 60°C [4]. However, the pseudo-first-order rate constant ($k_{obs} = 3.77 \times 10^{-4}$ s⁻¹) for hydrolysis of AZS at 1.0 M NaOH and 60°C is nearly 370-fold larger than k_{obs} (= 1.02×10^{-6} s⁻¹) obtained for hydrolysis of urea under similar experimental conditions [4]. Significantly larger rate of alkaline hydrolysis of AZS than that of urea may be attributed to increased leaving ability of the leaving group in AZS compared to that in urea.

Effect of Acidic pH on Rate of Hydrolysis of AZS

The rate of hydrolysis of AZS was also studied under the [HCl] range of 0.001–1.4 M at a constant ionic strength of 2.0 M (by NaCl) and under the pH range 3.6–5.6 at 50°C. The observed pseudo-first-order rate constants, k_{obs}, as summarized in Table III, were found to fit to the following empirical equation:

$$k_{obs} = (\alpha_1 K_a + \beta_1[H^+] + \beta_2[H^+]^2)/([H^+] + K_a) \qquad (4)$$

Table II Values of Empirical Parameters, α_1, α_2, and α_3, Calculated from Eq. (3)[a]

Temp °C	$10^4 \, \alpha_1$ min⁻¹	$10^3 \, \alpha_2$ M⁻¹ min⁻¹	$10^4 \, \alpha_3$ M⁻² min⁻¹	[NaOH] range M
40	2.00 ± 2.51[b]	2.37 ± 0.56[b]	7.28 ± 2.53[b]	0.1 − 2.0
45	4.12 ± 1.18	3.86 ± 0.42	12.1 ± 2.0	0.1 − 2.0
50	7.11 ± 2.65	5.81 ± 0.70	24.2 ± 2.9	0.1 − 2.0
	2.52 ± 1.57	7.86 ± 0.46	11.5 ± 2.4	0.001 − 2.0[c]
	5.00 ± 3.01	7.38 ± 0.70	13.4 ± 3.3	0.1 − 2.0[c]
55	14.3 ± 7.5	11.2 ± 1.7	14.8 ± 8.2	0.1 − 2.0
60	11.0 ± 11.4	22.1 ± 2.5	−0.4 ± 1.1	0.1 − 2.0
	13.8 ± 7.4	21.3 ± 0.6	0	0.1 − 2.0

[a] Conditions: 1.5×10^{-4} M AZS, $\lambda = 285$ nm, 2.0 M ionic strength, 1% (v/v) acetonitrile in the aqueous solvent, unless otherwise stated, reagent grade AZS was used.

[b] Error limits are standard deviations.

[c] In these kinetic runs, the commercial grade AZS was used.

Table III   Pseudo-First-Order Rate Constants (k_{obs}) for Hydrolysis of AZS Under Acidic pH[a]

[HCl] (pH)/M	$10^4 k_{obs}$/min^{-1}	$10^4 k_{calcd}$[b]/min^{-1}
(5.6)	1.90 ± 0.40[c]	3.57
(5.0)	3.50 ± 0.40	8.74
(4.6)	12.3 ± 0.9	15.6
(4.0)	35.3 ± 4.0	28.4
(3.6)	30.5 ± 2.0	34.3
0.001	34.8 ± 4.3	38.3
0.005	36.4 ± 2.6	39.6
0.01	43.6 ± 2.3	39.9
0.05	41.4 ± 2.4	40.6
0.1	43.0 ± 1.0	41.3
0.2	42.9 ± 0.9	42.7
0.4	45.8 ± 1.0	45.6
0.6	46.0 ± 1.1	48.4
0.8	52.8 ± 1.2	51.3
1.0	55.7 ± 1.4	54.2
1.2	58.7 ± 1.8	57.0
1.4	57.3 ± 1.9	59.9

[a] Conditions: 1.5×10^{-4} M AZS, λ = 240 nm, unless otherwise noted ionic strength is 2.0 M, 1% (v/v) acetonitrile in the aqueous solvent, 50°C.
[b] Calculated from eq. (4) using the values of β_1, β_2, and K_a as mentioned in the text.
[c] Parenthesized values are pH (maintained by the use of acetate buffer, 0.2 M total buffer concentration, where ionic strength was not adjusted by using any inert salt).

where α_1 is calculated from eq. (3), β_1 and β_2 are empirical parameters, and K_a is the ionization constant of acidic group in AZS. The nonlinear least-squares calculated values of β_1, β_2, and K_a are $(3.99 \pm 0.13) \times 10^{-3}$ min^{-1}, $(1.43 \pm 0.19) \times 10^{-3}$ M^{-1} min^{-1}, and $(4.29 \pm 1.12) \times 10^{-5}$ M, respectively, with $\alpha_1 = 1.44 \times 10^{-4}$ min^{-1}. The fitting of the observed data to eq. (4) appeared to be good, as is evident from the calculated values of rate constants shown in Table III.

Effect of Temperature on Rate of Alkaline Hydrolysis of AZS

Pseudo-first-order rate constants, k_{obs}, obtained at a constant [NaOH] and within the temperature range of 40–60°C, were found to obey the Eyring equation {eq. (5)}, where all the symbols have their usual meanings. The nonlinear least-squares technique was used to calculate ΔH^* and ΔS^* from eq. (5)

$$k_{obs} = (kT/h) \exp(\Delta S^*/R) \exp(-\Delta H^*/RT) \quad (5)$$

and these calculated values of ΔH^* and ΔS^* are summarized in Table IV. Although k_{obs} increased by nearly 10- to 15-fold with the increase in [NaOH] from 0.1–

2.0 M at a constant temperature, no regular trend was observed in the variation of ΔH^* and ΔS^* values with the change in [NaOH] (Table IV).

Effect of Ionic Strength on Alkaline Hydrolysis of AZS

The effect of ionic strength on rate of alkaline hydrolysis of AZS was studied by carrying out the kinetic runs within the [NaCl] range of 0.0–3.0 M at 0.6 M NaOH and 50°C. Pseudo-first-order rate constants, k_{obs}, showed an increase of nearly 22% with the increase in ionic strength from 0.6–3.6 M (Table V). An effect of ionic strength was not observed in the alkaline hydrolysis of urea [4]. Although the ionic strength effect appears to be small, it is certainly real. The pK_a of the most acidic hydrogen in AZS should be ca. 4 [13]. Thus, at 0.6 M NaOH, the reactants in the hydrolysis of herbicide should be ionized AZS (S$^-$) and $^-$OH; hence the rate of hydrolysis should be sensitive to ionic strength. The alkaline hydrolysis of saccharin (at 1.0 M NaOH) containing a similar reactive functional group as AZS, was found to be more sensitive to ionic strength [14]. But the value of α_3/α_2 (= 1.8 M^{-1} at 60°C) for saccharin was significantly larger (>6 times) than that for AZS. It should be noted that the negative charge in S$^-$ is not localized as in $^-$OH and that is why the rate of reaction between S$^-$ and $^-$OH showed a weak ionic strength effect.

Mechanistic Speculations

The rate constant [$^-$OH] profiles (Figure 1) indicate that there is a change in the rate-determining steps with the change in [$^-$OH]. A similar conclusion was first advanced by Biechler and Taft in the interpretation of

Table IV   Values of Activation Parameters at Different [NaOH] Calculated from Eq. (5) Using k_{obs}

[NaOH]/M	ΔH^*/kcal mol^{-1}	ΔS^*/cal K^{-1} mol^{-1}
0.1	22.61 ± 1.26[a]	9.8 ± 3.8[a]
0.2	19.45 ± 1.27	18.8 ± 3.8
0.4	19.20 ± 1.78	18.4 ± 5.4
0.6	18.79 ± 0.70	19.0 ± 2.1
0.8	21.25 ± 1.61	10.9 ± 4.9
1.0	19.32 ± 0.72	16.4 ± 2.2
1.2	17.33 ± 0.60	22.0 ± 1.8
1.4	19.58 ± 0.81	14.8 ± 2.4
1.6	17.54 ± 0.98	20.8 ± 3.0
1.8	16.86 ± 0.82	22.7 ± 2.5
2.0	16.37 ± 0.42	23.9 ± 1.3

[a] Error limits are standard deviations.

Table V   Effect of Ionic Strength on Alkaline Hydrolysis of AZS[a]

Ionic Strength/M	$10^4 \, k_{obs}/min^{-1}$
0.6	47.6 ± 1.4[b]
0.6	44.7 ± 0.4
1.1	48.2 ± 0.6
1.6	50.6 ± 0.9
2.6	52.6 ± 0.6
3.1	52.7 ± 0.7
3.6	56.3 ± 1.5

[a] Conditions: 1.5×10^{-4} M AZS, $\lambda = 285$ nm, 1% (v/v) acetonitrile in the aqueous solvent, 0.6 M NaOH, 50°C, ionic strength was maintained by the use of NaCl.
[b] Error limits are standard deviations.

kinetic data on the alkaline hydrolysis of trifluoroacetanilide and *N*-methylanilides [15]. These authors proposed, for the first time, the existence of highly unstable oxydianionic tetrahedral (ODT) intermediates in the hydrolysis of anilides under highly alkaline medium. The existence of ODT intermediates have been proposed in many related studies [16]. In an earlier study on alkaline hydrolysis of formamide it was concluded that the existence of an ODT intermediate is not an implicit function of either alkalinity of the reaction medium or the structural features of the substrate but rather is a composite function of both effects. The existence of an ODT intermediate was also proposed in the alkaline hydrolysis of urea [4]. The existence and non-existence of trianionic tetrahedral intermediates in the alkaline hydrolysis of saccharin [14] and phthalimide [17], respectively, were attributed to the stronger electron withdrawing ability of $\rangle SO_2$ group compared to the $\rangle CO$ group [18]. The stronger electron withdrawing nature of the $\rangle SO_2$ group compared to that of the $\rangle CO$ group could also be seen in the difference between the pK_a of saccharin (1.31) [8a] and that of phthalimide (8.3) [19], (9.5) [20].

The approximate value of pK_a of $-SO_2NH-$ group may be estimated as follows. The pK_a of saccharin is 1.3 [8a] and pK_a values of phthalimide are 8.3 [19] and 9.5 [20a]. Thus, the replacement of CO by SO_2 causes the reduction in pK_a by nearly $7-8$ pK units. The reported value of pK_a of diacetylamine ($CH_3CONHCOCH_3$) is 12.9 [21]; hence, the expected pK_a value for $CH_3SO_2NHCOCH_3$ is $5-6$. The kinetically determined value of pK_a (= 4.37) therefore appears to be for the $-SO_2NHCO-$ group of AZS.

The values of pK_a of protonated triazine ($3H^+$) and the side chain amino group of 3 are 1.5 and 8.4, respectively [11]. Thus, the pK_a of the primary amino group of 2 should be nearly $8-9$. The values of pK_a of NH_3, $C_6H_5NH_2$, CH_3CONH_2, and $CF_3CONHC_6H_5$

are 35 [22], 27 [10], 15.4 [19], and 9.5 [23], respectively. In view of these results it seems that the pK_a of $-CONH-$ group of AZIM should be < 4.

The measured pK_a value of $4H^+$ is 4.37 at 39°C [24]; hence the kinetically determined pK_a (= 4.37) may be assigned for pyrimidinium ion of AZS.

4H⁺
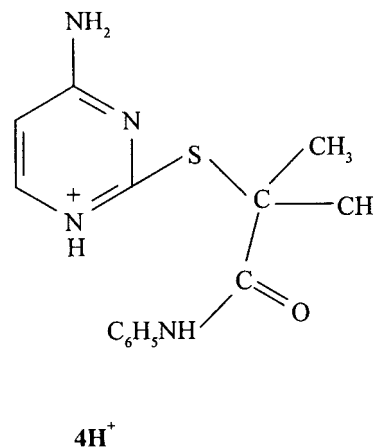
The previous discussion reveals that the pK_a value of 4.37 cannot be assigned with certainty to either $-SO_2NHCO-$, $-CONH-$, or pyrimidinium ion of AZS. However, nearly 25-fold larger value of β_1 than that of α_1 creates doubt about pyrimidinium ion being an acidic group of pK_a 4.37, because the acidic site is quite far from the expected reaction site.

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