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Acid-catalyzed hydrolysis of 5-substituted-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxides (5-substituted benzosulfamides): kinetic behavior and mechanistic interpretations

Aliye Gediz Erturk[a]* and Yunus Bekdemir[b]

The acid-catalyzed hydrolysis of a series of 5-substituted-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxides has been investigated in aqueous solutions of sulfuric, perchloric, and hydrochloric acid at 85.0 ± 0.05 °C. Analysis of the kinetic data by the excess acidity method, Arrhenius parameters, the order of the catalytic effects of strong acids, the kinetic deuterium isotope effect, and the substituent effect have indicated that the hydrolysis of 5-substituted benzosulfamides 1a–d occur with a mechanistic switchover from A2 to A1 in the studied range: an A2 mechanism in low acidity regions and an A1 mechanism in high acid concentrations. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: acid-catalyzed hydrolysis; benzosulfamides; excess acidity; kinetics; mechanism

INTRODUCTION

The sulfamide functional group (-$HNSO_2NH$-), which is an important class of organosulfur compounds, is interesting because of the practical uses of the compounds as reagents in synthesis[1,2] or as possible medicinal agents.[3,4] This molecular framework is used as inhibitors of ATP-sensitive potassium channels[5] and carbonic anhydrase,[6] diuretics and anti-glaucoma agents, and it has recently emerged that they also have potential as anti-convulsant,[7] anti-tuberculous,[8] anti-obesity, anti-cancer, anti-pain and anti-infective drugs,[9] and as therapeutic actions against diabetes.[10] Cyclic sulfamides, in particular, are widely used as components of insecticide mixtures and as myorelax-anti-inflammatory agents.[11] Aryl-substituted seven-membered and eight-membered cyclic sulfamides inhibit HIV-1 protease, serine protease and metalloprotease.[9,12] However, despite its obvious importance, so far only Spillane and his coworkers[13] have studied the acid-catalyzed hydrolysis of N,N-diarylsulfamides in the pH range and measured the pK_a values of some cyclic sulfamides,[14] none of which were performed in a highly acidic medium. Likewise, in a previous work,[15] we examined thoroughly the hydrolysis mechanisms of open chain N,N′-diarylsulfamides in aqueous mineral acid solutions and the principal reaction pathways were hydrolyzed by an A2 mechanism at low acidity. At higher acidities, a changeover to an A1 mechanism was supported.

The aim of the present work is to gain further information on the hydrolysis of a series of 5-substituted-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxides **1a–d** (Scheme 1-referred to herein as 5-substituted benzosulfamides-) from cyclic sulfamides in aqueous solutions of mineral acids at elevated temperatures by using a range of physical organic mechanistic techniques.

EXPERIMENTAL

Materials and instruments

All chemical reagents were purchased from Sigma-Aldrich, Acros and Merck and were used without further purification. Product synthesis was carried out under microwave irradiation by using a domestic microwave oven (Bosch model HMT 812C 2450 MHz (Germany)) that was modified by fitting a reflux system and internal camera. Analytical thin layer chromatography (TLC) was performed on precoated plates (Merck silica gel 60, F_{254} (USA)), and visualization was achieved by ultraviolet light. All products were characterized by comparison of their physical data with samples prepared by conventional methods. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 MHz Spectrometer (Germany) at 200 and 50 MHz, respectively, with DMSO-d_6 as solvent. Chemical shifts were reported in parts per million (p.p.m) relative to TMS as the internal reference. Infrared (IR) spectra were recorded with a MATTSON 1000 FTIR Spectrophotometer (USA). Melting points were determined on an Electrothermal 9100 Melting Point Apparatus (China). All kinetic measurements of the sulfamides were performed on a GBC Cintra 20 model ultraviolet-visible (UV–VIS) spectrophotometer (Australia) with a fitted thermostated cell compartment.

* *Correspondence to: Aliye Gediz Erturk, Department of Chemistry, Faculty of Science and Arts, Ordu University – Cumhuriyet Campus, 52200, Ordu, Turkey. E-mail: aliyeerturk@gmail.com*

a *A. Gediz Erturk*
Department of Chemistry, Faculty of Science and Arts, Ordu University – Cumhuriyet Campus, 52200, Ordu, Turkey

b *Y. Bekdemir*
Department of Molecular Biology and Genetics, Faculty of Science and Arts, Canik Basari University – Gurgenyatak Campus, 55080, Canik/Samsun, Turkey

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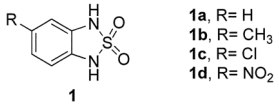


Scheme 1. The 5-substituted-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxides 1a–d

Preparation of 5-substituted-1*H*,3*H*-2,1,3-benzothiadiazole 2,2-dioxides (1a–d)[14,16]

We prepared a series of 5-substituted-benzosulfamides **1a–d** from the reaction of the corresponding substituted o-phenylenediamines with sulfamide in the presence of diglyme by using a modified domestic microwave oven at 900 W and irradiated for 5–8 min under reflux followed by using the general method.[17]

The o-Phenylenediamine (280 mg, 2.6 mmol) and sulfamide (250 mg, 2.6 mmol) were dissolved in diglyme. Diglyme was used as a neat solvent. The resulting solution was placed inside a modified domestic microwave oven at 900 W and irradiated for 8 min under reflux. The reaction was completed as determined by TLC monitoring, using ether/petroleum ether (3 : 1) as the eluent. The reaction mixture was removed from the oven, then cooled in ice, and filtered. The residue was dissolved in ether (20 mL) and washed successively with 2 N HCl (5 mL) three times and with saturated brine (3 mL). The ether solution was dried and benzylamine (1 mL) was added. The sulfamide salt was precipitated: it was filtered off, washed with ether and shaken with 2 N HCl (10 mL). The acidic solution was extracted with ether (5 mL) four times and the combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by crystallization from hot ethanol to yield pure **1a–d**.

1H,3H-2,1,3-benzothiadiazole 2,2-dioxide (1a)

White solid (355 mg, 80%); m.p. 176–177 °C; *Rf* (75% ether/benzene): 0.51; IR (KBr) (ν_{max}, cm^{-1}): 3280 (N-H), 3058, (Ar. C-H), 1600 (C = C), 1300 and 1160 (N-SO_2); ^{1}H-NMR (200 MHz, DMSO-d_6) (δ_H, p.p.m): 6.76–6.96 (4H, m, arom.), 10.90 (2H, s, 2NH); ^{13}C-NMR (50 MHz, DMSO-d_6,) (δ_C, p.p.m): 129.5, 121.3, 110.2.

4-Methyl-1H,3H-2,1,3-benzothiadiazole 2,2-dioxide (1b)

White solid (360 mg, 75%); mp 169–170 °C; *Rf* (75% ether/benzene): 0.55; IR (KBr) (ν_{max}, cm^{-1}): 3300 (N-H), 3080 (Ar. C-H), 2940 (C-H), 1610 (C = C), 1310 and 1165 (N-SO_2); ^{1}H-NMR (200 MHz, DMSO-d_6,) (δ_H, p.p.m): 2.23 (3H, s, Me), 6.68–6.62 (3H, m, arom.), 10.80 (2H, s, 2NH); ^{13}C-NMR (50 MHz, DMSO-d_6) (δ_C, p.p.m): 130.7, 129.8, 127.2, 121.6, 110.8, 110.3, 20.8.

4-Chloro-1H,3H-2,1,3-benzothiadiazole 2,2-dioxide (1c)

White solid (395 mg, 74%); mp 192–193 (Lit.[19] 199–200) °C; *Rf* (75% ether/benzene): 0.48; IR (KBr) (ν_{max}, cm^{-1}): 3270 (N-H), 3060 (Ar. C-H), 1605 (C = C), 1300 and 1155 (N-SO_2), 750 (C-Cl); ^{1}H-NMR (200 MHz, DMSO-d_6) (δ_H, p.p.m): 6.76–6.95 (3H, m, arom.), 11.30 (2H, s, 2NH); ^{13}C-NMR (50 MHz, DMSO-d_6) (δ_C, p.p.m): 130.5, 128.2, 125.0, 120.8, 111.2, 109.8.

4-Nitro-1H,3H-2,1,3-benzothiadiazole 2,2-dioxide (1d)

Yellow solid (308 mg, 55%); mp 190–191 (Lit.[20] 190) °C; *Rf* (75% ether/benzene): 0.38; IR (KBr) (ν_{max}, cm^{-1}): 3250 (N-H), 3040 (Ar. C-H), 1600 (C = C), 1550 (C-NO_2), 1310 and 1140 (N-SO_2); ^{1}H-NMR (200 MHz, DMSO-d_6) (δ_H, p.p.m) 6.65 (1H, d, J = 8.7 Hz, arom.), 7.56 (1H, d, J = 2.4 Hz, arom.), 7.84–7.90 (1H, dd, J = 6.4, 2.4 Hz), 11.77 (2H, s, 2NH); ^{13}C-NMR (50 MHz, DMSO-d_6); (δ_C, p.p.m): 140.7, 135.7, 129.0, 118.4, 108.7, 104.3.

Kinetic procedure

The hydrolysis rates of the cyclic substrates **1a–d** were measured at wavelengths in the range of 235–320 nm, using a UV–VIS spectrophotometer with a thermostated cell holder at 85.0 ± 0.05 °C. For all compounds, kinetic runs were initiated by injecting 50 μL of 3.0×10^{-4} M stock solution of the substrate in acetonitrile into 3.0 mL of the acid solution contained in a quartz cuvette and equilibrated at 85.0 ± 0.05 °C. The course of reactions was monitored over (at least) up to three-half lives and the absorbance values at infinity were obtained after ten-half lives in all cases. Good first-order behavior was observed with clean isosbestic points. The values of Pseudo first-order rate constants (k_1) were calculated from the plots of $ln(A–A\infty)$ against time using the least squares procedure, where A is the absorbance at time t and $A\infty$ is the absorbance at infinity. All acid reaction solutions were prepared from analytical grade concentrated acids, using deionized water and HPLC grade acetonitrile, making appropriate allowance for the water content of the acid. All kinetic runs were duplicated and the average deviation from the mean was less than 5%.

Product analysis

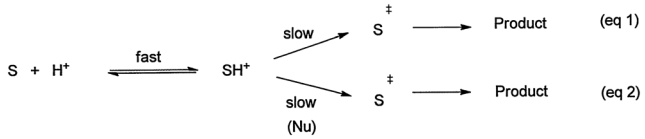
Analysis of the hydrolysis products was also determined by comparing the UV spectrum obtained after completion of the kinetic experiment with the spectrum of the expected product with the same concentration and under the same conditions. The UV–VIS spectra of the product of the acid-catalyzed hydrolysis of the compounds **1a–d** were found to be identical to the UV–VIS spectra of the corresponding substituted o-phenylenediamines recorded under the same conditions. (See Supplementary data). Also the product of the hydrolysis of a typical cyclic sulfamide (**1a**), which was isolated and recrystallized from benzene, was found to be o-phenylenediamine, m.p. 100-102 °C. The structure of this compound was confirmed by ^{1}H and IR spectra.

RESULTS AND DISCUSSIONS

Specific acid-catalyzed reactions, where the only protonation source is H_3O^+, can occur in two different ways. The catalysis also proceeds by fast, pre-equilibrium protonation before a rate-limited step for both mechanisms. If the protonated substrate (SH^+) evolves in the rate-determining step and subsequently turns speedily to products, a monomolecular mechanism −A1 is described (Eqn 1 in Scheme 2). If the protonated substrate (SH^+) is attacked by the nucleophile (Nu) in the rate-limited step, a bimolecular mechanism −A2 is formed (Eqn 2 in Scheme 2).[18]

In order to reliably designate reaction mechanisms at medium and high acidity levels, an array of criteria dealing with the kinetic data such as the catalytic order of strong acids,[19] shapes of profiles,[20] excess acidity method,[21] measurements of thermodynamic data,[22] kinetic deuterium isotope effect,[23] and substituent effects[24] are available.

The pseudo-first-order rate coefficients, k_1 for the hydrolysis of **1a–d** in aqueous solutions of mineral acids are given in Table 1. In Fig. 1, the hydrolysis of **1a** in sulfuric, perchloric, and hydrochloric acid shows that the catalytic effectiveness of the added acids was $HCl > H_2SO_4 > HClO_4$. Also for the hydrolysis of **1b–c,**



Scheme 2. Specific acid-catalyzed reactions. (1) Monomolecular reaction – A1, (2) Bimolecular reaction – A2

Table 1. Values of rate constants $10^5 k_1$ (s^{-1}) for the hydrolysis of **1a–d** in different aqueous acids at 85.0 ± 0.05 °C

$[H^+]$/(M)	**1a**			**1b**			**1c**			**1d**		
	H_2SO_4	$HClO_4$	HCl	H_2SO_4	$HClO_4$	HCl	H_2SO_4	$HClO_4$	HCl	H_2SO_4	$HClO_4$	HCl
1.00	0.19	0.16	0.81	0.19	0.20	1.71	0.22	0.17	2.12	1.98	1.32	5.37
2.00	0.50	0.33	1.28	0.37	0.37	3.47	0.87	0.49	3.29	2.93	1.98	7.15
3.00	1.24	0.68	3.08	0.56	0.60	5.98	1.79	0.87	5.16	3.21	2.35	9.47
4.00	2.10	1.25	8.02	1.03	1.29	9.36	3.36	1.74	9.16	5.14	3.83	15.32
5.00	3.55	2.29	13.81	2.11	2.89	13.34	6.51	3.68	17.14	8.95	7.04	24.81
6.00	6.26	3.79	21.09	4.47	6.41	20.69	12.15	7.77	31.40	19.04	10.48	34.43
7.00	10.33	5.76	38.50	8.09	11.50	29.11	20.48	11.42	42.54	31.55	9.08	45.24
8.00	17.19	4.63	92.99	12.32	9.05	39.17	28.11	9.20	28.59	39.02	5.77	59.82
9.00	18.58	2.66	82.79	14.74	4.71	26.23	22.72	4.43	7.55	30.78	3.32	32.07
10.00	9.86	1.77	28.69	8.72	2.43	17.38	10.76	1.98	1.61	15.11	2.41	19.55
10.53	6.80	1.42	20.28	4.32	1.88	14.30	5.08	0.88	0.93	7.44	2.15	15.11
11.00	4.66	—	16.58	3.06	—	11.41	4.16	—	0.85	4.44	—	10.84
11.44	3.14	—	12.70	2.77	—	9.70	3.33	—	0.78	3.12	—	9.23
12.00	1.65	—	—	3.63	—	—	2.78	—	—	1.57	—	—
13.00	2.03	—	—	7.01	—	—	1.80	—	—	1.06	—	—
14.00	4.44	—	—	14.65	—	—	1.21	—	—	0.90	—	—
15.00	10.10	—	—	30.42	—	—	2.72	—	—	1.87	—	—
16.00	20.92	—	—	54.53	—	—	6.78	—	—	4.16	—	—
17.00	36.82	—	—	76.06	—	—	16.53	—	—	6.82	—	—
17.85	57.71	—	—	90.17	—	—	32.51	—	—	9.21	—	—

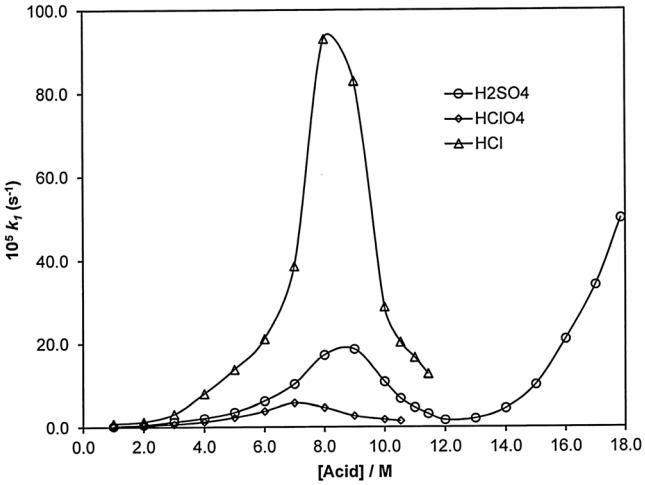


Figure 1. Plots of rate constants (k_1) for acid-catalyzed hydrolysis of 1a in aqueous acidic solutions at 85.0 ± 0.05 °C. Δ: HCl; ○: H_2SO_4; ◊: $HClO_4$

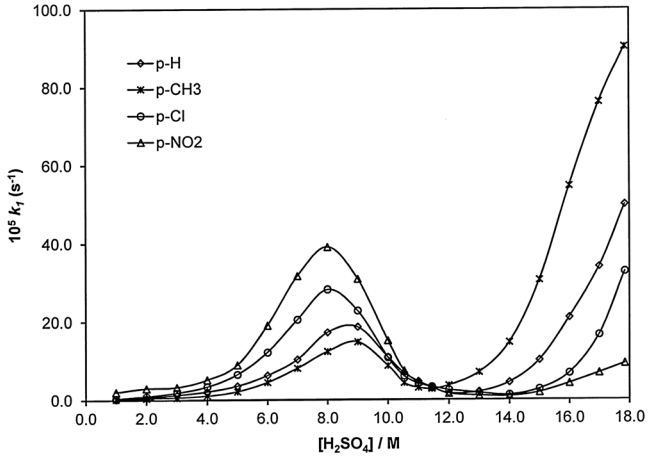


Figure 2. Rate profiles for hydrolysis of 1a–d in sulfuric acid at 85.0 ± 0.05 °C. Δ: p-NO_2; ○: p-Cl; ◊: p-H; *: p-CH_3

this order varied in a similar way, as expected. Bunton and his coworkers[19,25] have suggested that such an order is characteristic of a bimolecular (A2) mechanism, because the transition state of the positive character is being preferentially stabilized by small anions of high charge density such as Cl^-. On the contrary, the transition states of the unimolecular A1 mechanism are preferred for stabilization by anions of low charge density such as ClO_4^-, so the order of the A1 reaction is $HClO_4 > H_2SO_4 > HCl$.

Profiles of the acid-catalyzed hydrolysis of the benzosulfamides **1a–d** in aqueous solutions of sulfuric acid at 85.0 ± 0.05 °C are shown in Fig. 2. For **1a**,**b** in the 1.00–9.00 M (for **1c**,**d** in the 1.00–8.00 M) region, the rate of hydrolysis increased with increasing acid concentration. While **1a**,**b** show a clearly defined rate maximum at 9.00 M (for **1c**,**d** at 8.00 M), after that the rates decrease, pass a minimum for **1a**,**b** around 10.00–12.00 M (for **1c**,**d** around 10.00–14.00 M) and finally increase again for **1a**,**b** after 12.00 M (for **1c**,**d** after 14.00 M). Similar rate maxima have been observed for acid-catalyzed hydrolysis of other compounds such as sultams,[26] N-arylsulfinylphthalimides,[27] hydroxamic acids,[21,28] primary acetate esters,[29] N-acetylsulfonimidic esters[30] and N,N′-diarylsulfamides.[15] The initial downward curvatures, which were exhibited are typical of an A2 reaction in which extensive protonation of the 5-substituted benzosulfamides occurs in the regions of acidity in which the activity of the water is falling. The rates of hydrolysis of the 5-substituted benzosulfamides at higher concentrations of the sulfuric acid solutions pass through a minimum and then increase sharply. An upward linear region is typical of an A1 process. In addition, the final increases are associated with a changeover of mechanism from A2 to A1 with increasing concentration of the acid. Similar behavior has also been observed for acid-catalyzed hydrolysis of seconder alkyl and benzyl esters.[20]

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The excess acidity method has been put forward as a powerful device for the mechanistic explanation of a wide variety of reactions in highly acidic aqueous media, particularly in sulfuric acid. The kinetic data for sulfuric acid solution in Table 1 were analyzed by the excess acidity treatment of Cox and Yates.[31–34] The kinetic equation for mainly unprotonated substrates – Eqn 3 was used;

$$\log k_1 - \log C_{H^+} - \log C_S/(C_S + C_{SH^+}) = m^*m^{\neq} X + r \log a_{Nu} + \log (k_o/K_{SH^+}) \quad \text{(eq 3)}$$

The pseudo-first-order rate constants, k_1, in sulfuric acid obey the Eqn 3 in the case of the A2 mechanism. In this equation, C_S and C^+_{SH} are the concentrations of the unprotonated and protonated substrate in the aqueous acid with concentration C^+_H [= c (H_2SO_4)]. Because of the extremely low basicity of the 5-substituted benzosulfamides studied, the protonation correction term [log $C_S/(C_S + C^+_{SH})$] can be neglected in the low acidity region (up to 8.00 or 9.00 M). X is the excess acidity and a_{Nu} is the water activity (C^+_H, X,[32,35] and a_{Nu}[36] were corrected according to temperature, and the recent molarity-based log a_{Nu} values by Cox[33] were used because of their correct standard state) and r is the number of water molecules in the transition state.[33,35] $m^*m^{\neq}$ are the combined slope parameters, where m^* gives information about the protonation site (for the nitrogen compounds m^* is in the range of 0.7–1.0),[20] while $m^{\neq}$ accounts for the characteristics of the transition state (for A1 reactions $m^{\neq} > 1$).[31] k_o stands for the medium-independent rate constant of the rate-limiting step and K^+_{SH} for the thermodynamic dissociation constant of the protonated form of the substrate.

For the hydrolysis of **1a–d** in sulfuric acid solutions, a plot of the left-hand side of this equation (log k_1 – log C^+_H) versus X yields a curve (Fig. 3). If we focus on the 3.00–9.00 M acidity region in Fig. 3, where the acidity is low, then the protonation can be almost neglected because of the low basicity of the sulfamides. The slightly downward curvature of this region allows easy distinction of A2 reactions involving water in the rate-determining step. Similar behavior has been observed for the hydrolysis of iminosulfonate esters,[37] benzohydroxamic acids,[21] sultams,[26] sulfinylphthalimides,[27] and N,N′-diarylsulfamides.[15]

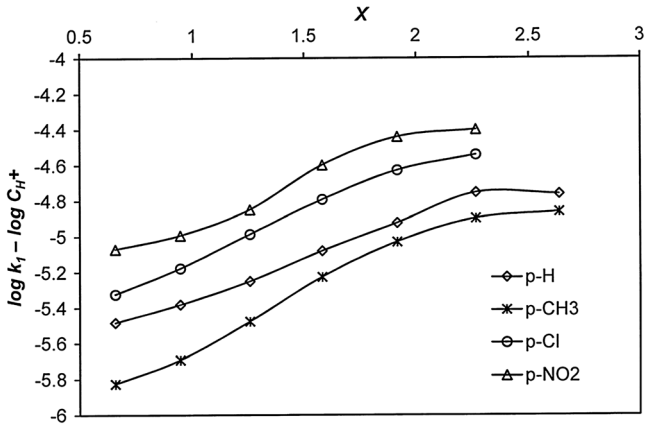

Figure 3. (log k_1 – log C_H^+) versus X (temperature corrected) plot of the acid-catalyzed hydrolysis in 3.0–8.0 M H_2SO_4 region for 1a, b and in 3.0–9.0 M H_2SO_4 region for 1c,d at 85.0 ± 0.05 °C. Δ: p-NO_2; ○: p-Cl; ◊: p-H; *: p-CH_3

The increasing values of log activity of the species reacting with SH^+ are subtracted from the left-hand side of the equation until linearity of the result against X is achieved.[31] In the 5-substituted benzosulfamides hydrolysis process, subtraction one of the water activity from the left-hand side of Eqn 3 is required to obtain good straight line correlations, which implies involvement of one water molecule in the transition state for 5-substituted benzosulfamides (Fig. 4 and Eqn 3 where $r = 1$). In the light of this evidence, we can say that the first parts of the profiles (3.00–8.00 M or 3.00–9.00 M) proceed with an A2 mechanism involving one water molecule in the transition state, where r is 1. The slope and intercept values of the lines obtained in Fig. 4 for **1a–d** are given in Table 2. According to Ghosh and Cox, $m^*m^{\neq} > 1$ is for A1 processes, and $m^*m^{\neq} < 1$ is for A2 processes.[21,38] For **1a–d**, values of $m^*m^{\neq}$ have been found, which are lower than 1, which implies an A2 mechanism on the left-hand side of the rate maxima in sulfuric acid profiles. Similar plots and slope values ($m^{\neq}$ m^*) were obtained for the hydrolysis of benzohydroxamic acids, classified as an A2 mechanism.[21,38]

The thermodynamic parameters were calculated from an Arrhenius equation with a least squares procedure by using the values of specific rate constant at different temperatures. Table 3 tabulates the calculated activation enthalpy and entropy values. The entropies in 1.00 and 7.00 M sulfuric acid are negative (−97.92 and −87.28 J mol^{-1} K^{-1}) and would support a bimolecular mechanism exclusively for **1a**. In 14.00 M $\Delta S^{\neq}$ is reasonably positive (+214.16 J mol^{-1} K^{-1}) and would indicate a monomolecular mechanism for **1a**. The values for the hydrolysis of **1b–c** change in a similar way, as expected. The acid-catalyzed hydrolysis

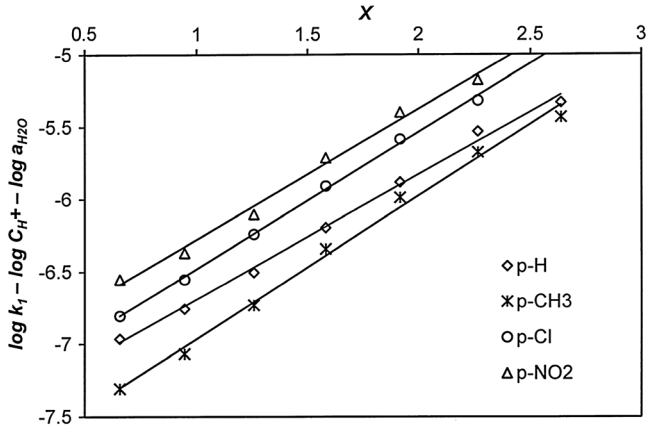

Figure 4. (log k_1 – log C_H^+ – log a_{H2O}) versus X plot of the acid-catalyzed hydrolysis in 3.0–8.0 M H_2SO_4 region for 1a,b and in 3.0–9.0 M H_2SO_4 region for 1c,d at 85.0 ± 0.05 °C, showing the involvement of one water molecule – A2 mechanism. Δ: p-NO_2; ○: p-Cl; ◊: p-H; *: p-CH_3

Table 2. Excess acidity of treatment into the acid-catalyzed hydrolysis of the cyclic sulfamides **1a–b** (for 3.00–8.00 M H_2SO_4 region) and **1c,d** (for 3.00–9.00 M H_2SO_4 region)

Compound	Slope ($m^*m^{\neq}$)	Intercept [log (k_o/K^+_{SH})]	R^2
1a	0.863	−7.56	0.996
1b	0.989	−7.96	0.994
1c	0.946	−7.43	0.998
1d	0.903	−7.18	0.992

Table 3. Values of rate constants $10^5 k_1$ (s^{-1}) and thermodynamic parameters for the hydrolysis of the 5-substituted-1*H*, 3*H*-2,1,3-benzothiadiazole 2,2-dioxides **1a–d** at different temperatures

Compound	H_2SO_4	80.0 °C	85.0 °C	90.0 °C	95.0 °C	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (J mol^{-1} K^{-1})	R^2
1a	7.00	7.02	10.33	14.82	21.42	80.24 ± 0.04	−97.92 ± 0.12	0.9999
	10.00	6.32	9.86	15.02	22.42	109.50 ± 0.06	−68.17 ± 0.18	0.9999
	16.00	8.12	20.92	51.82	114.20	189.95 ± 0.35	214.16 ± 0.98	0.9993
1b	7.00	5.05	8.09	12.82	20.00	96.96 ± 0.13	−53.11 ± 0.35	0.9997
	10.00	3.02	4.72	7.18	10.72	101.12 ± 0.14	−41.16 ± 0.40	0.9996
	16.00	20.20	54.53	151.20	414.20	218.53 ± 0.22	302.25 ± 0.61	0.9998
1c	7.00	11.94	20.48	33.72	53.42	107.49 ± 0.6	−16.23 ± 0.44	0.9995
	10.00	5.12	10.76	19.92	37.82	142.72 ± 0.27	76.57 ± 0.75	0.9993
	16.00	2.80	6.78	15.72	36.42	184.70 ± 0.05	190.22 ± 0.15	0.9999
1d	7.00	18.50	31.55	54.82	95.20	104.49 ± 0.16	−21.10 ± 0.46	0.9995
	10.00	8.12	15.11	27.82	51.42	133.18 ± 0.09	53.12 ± 0.24	0.9999
	16.00	1.71	4.16	9.68	21.42	181.76 ± 0.15	177.91 ± 0.42	0.9999

of the esters and amides[22] proceed with an A1 mechanism, $\Delta S^{\neq} \sim 0$–41.8 J mol^{-1} K^{-1}, while those proceeding with an A2 mechanism have $\Delta S^{\neq} \sim -62.8$ to -125.5 J mol^{-1} K^{-1}. It is suggested that the negative values of $\Delta S^{\neq}$ for an A2 mechanism are a reflection of the loss of rotational and translational freedom of the water molecules in the transition state, where the water molecule acts as a nucleophile. The positive values of $\Delta S^{\neq}$ in 14.00 M acid, for the hydrolysis of **1a–d**, indicate that no water molecule is involved in the rate-determining step, and so a monomolecular mechanism is proposed. Thus, the bimolecular mechanism proposed for hydrolysis at low acid concentrations and the monomolecular mechanism for the high acid concentrations are further supported by this change in $\Delta S^{\neq}$.[39]

The solvent effect could be taken into account for the transition state. There might be some differences in solvation structure, but from the initial state to transition state in both mechanisms has quite similar solvation requirements, because both have protonated substrate in the rate-determining step. As Long and Schalenger reported, large negative values of $\Delta S^{\neq}$ imply an A2 mechanism due to attaching water molecules where it loses some freedom. Still these values need to be supported with other criteria such as Hammett plots and catalytic activity of the acids and so on for the proposed mechanism.[22,40]

The kinetic deuterium isotope effect (KDIE) for the acid-catalyzed hydrolysis of **1a** was measured in D_2O/D_2SO_4 and H_2O/H_2SO_4 solutions and was found to be $k_{D2O}/k_{H2O} = 1.07$ (in 6.00 M) and 1.85 (in 16.00 M) (Table 4). The former value supports a bimolecular A2 pathway whereas the latter value shows a monomolecular A1 mechanism. In the A1 mechanism, the rate-determining step is not affected significantly by the change of solvent because it does not involve the solvent or transfer of proton. Thus, the main effect of changing the solvent from H_2O to D_2O lies in its influence on the first step involving the protonation equilibrium. In the A1 mechanism, $k_D \sim k_H$ and the ratio k_{D2O}/k_{H2O} are influenced by the K_{SD}^+/K_{SH}^+ ratio. In D_2O, the concentration of the conjugate acid of the substrate [SD^+] is higher than [SH^+] in H_2O because most acids are stronger in H_2O than in D_2O. Therefore, the ratio is expected to be around 2–4.[23,41,42] For example, the k_{D2O}/k_{H2O} ratios for the acid-catalyzed hydrolysis of ethylene oxide[42] and t-butyl acetate[23] are 2.2 and 2.0, respectively. The ratio k_{D2O}/k_{H2O} is controlled not only by the K_{SD}^+/K_{SH}^+ ratio but also by the difference between the k_D and k_H rate constants. Generally, for the A2 mechanism in the rate-determining step, when the nucleophilic attacks of water take place on the protonated substrate, the values of k_{D2O}/k_{H2O} lie closer to unity than those observed for the A1 mechanism. Values of 1.02 and 1.19 were obtained for the acid-catalyzed hydrolyses of N-(4-substituted-arylsulfinyl)phthalimides[27] and arylsulfonyl phthalimides,[43] respectively. The mechanistic changeover is also supported by the values of the KDIEs.[44]

Table 4. Kinetic data and kinetic isotope effects at 85.0 ± 0.05 °C for the hydrolysis of **1a** in sulfuric acid solutions

(Acid)/M	$10^5 k_1$ (s^{-1})	k_{D2O}/k_{H2O}
6.00 M D_2O/D_2SO_4	6.70	1.07
6.00 M H_2O/H_2SO_4	6.26	
11.00 M D_2O/D_2SO_4	2.58	0.55
11.00 M H_2O/H_2SO_4	4.66	
16.00 M D_2O/D_2SO_4	38.77	1.85
16.00 M H_2O/H_2SO_4	20.92	

Additionally, in 11.00 M acid, k_{D2O}/k_{H2O} was measured as 0.55. This concentration lies on the right side of the maxima of the rate profile. Because of high protonation and decreasing activation of the water in this region, an increase in the rate of H_2O solution involved, is observed. Also this increase has arisen from the larger nucleophilicity of H_2O with respect to D_2O. Similar results were obtained from the hydrolysis of amidosulfides and cyclic sulfonamides. In comparison, for the amidosulfides, k_{D2O}/k_{H2O} was measured as 0.58 for 4.61 M $HClO_4$ which was taken on the right side of the maxima,[20] and for the cyclic sulfonamides this ratio was evaluated as 0.51 at 14.50 M acid.[45]

Structure-reactivity effects were investigated by studying the effect of changing the substituents (*X*) in compound 1 in 2.00, 10.00, and 17.85 M H_2SO_4 at 85.0 ± 0.05 °C, on the rates of reaction. Hammett plots illustrate these effects (See Supplemental materials). The substituent effects are well correlated by a satisfactory Hammett plot.[24] The slope of the Hammett plot (log $k/k_o = \rho\sigma$) gives the ρ value. As a general convention, if the ρ value is positive it implies that electron-withdrawing groups accelerate the rate of reaction and electron releasing groups retard the

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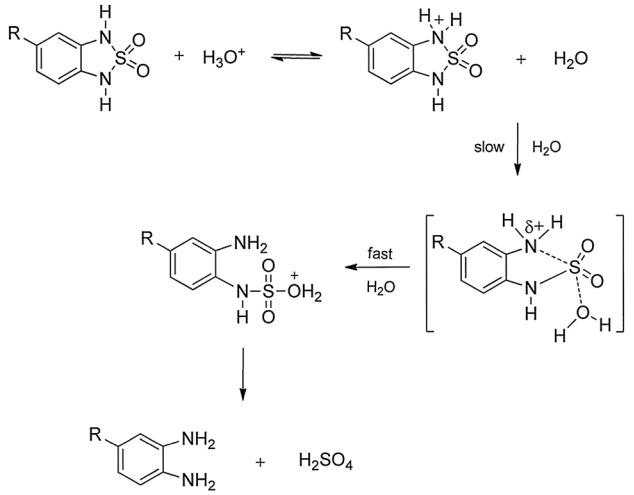
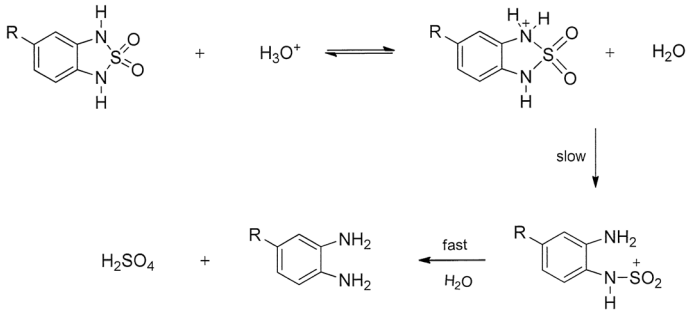


Scheme 3. Suggested A2 mechanism of acid-catalyzed hydrolysis of 5-substituted benzosulfamides 1a–d



Scheme 4. Suggested A1 mechanism of acid-catalyzed hydrolysis of 5-substituted benzosulfamides 1a–d

reaction (A2 mechanism). A negative ρ value simply implies the opposite contribution of the substituent (A1 mechanism).[46,47]

The values of Hammett ρ are 0.957 (R^2: 0.9992) at 2.00 M H_2SO_4 and 0.247 (R^2: 0.9939) at 10.00 M H_2SO_4. The electron-withdrawing substituents produce the highest rate of hydrolysis (i.e., **1d** > **1b** in Fig. 1). Clearly at these acidities [up to 12.00 (or 14.00) M (H^+)], the electron-withdrawing substituents increase the positive charge on the sulfur atom, so the nucleophilicity of the water molecule becomes more effective because of the positively charged sulfur atom in the rate-determining transition state for the A2 mechanism. The ρ value is −1.0371 [R^2: 0.9991] at 17.85 M H2SO_4. At acidity levels higher than 12.00 (or 14.00) M [H^+], the electron-donating substituents produce the highest rate of hydrolysis (i.e., **1b** > **1d** in Fig. 1). With these acidities, the electron-donating substituents increase the basicity and assist protonation of the 5-substituted benzosulfamides. Electron-donating substituents also facilitate heterolysis of the sulfur-nitrogen bond, and thus, a strong negative substituent effect can be expected for an A1 mechanism. Also, the position of the rate maximum on the rate profiles parallels the electronic properties of the substituents (Fig. 2).

We studied the ionization ratio (C^+_{BH}/C_B) of 5-substutited benzosulfamides and observed shifts of absorption peak position with increasing acidity due to the medium effects. We could not see any good isosbestic point at ambient temperature. It is presumed that the medium effects prevented the family of spectral curves from passing through an isosbestic point.[48–50] The values of $pK_{BH}+$ and m* could not be estimated. So the direct evidence concerning the site of protonation of 5-substituted benzosulfamides could not be obtained. However, the protonation behaviors of the sultams and sulfamate esters were studied. The values of $pK_{BH}+$ of the substituted sultams = 5.96–8.3.[26] Sulfamate esters have pK_a values of ≈ 8 in water-organic media.[51] Sulfamides have two electron donor nitrogen atoms. So protonation of the sulfamides might take place on nitrogen as observed for the sultams[52] and sulfinamides.[53] When both the mechanisms are examined, the possible hydrolysis products are arylsulfamic acids and their corresponding amines. However, we could not observe any o-aminoarylsulfamic acids. Phenylsulfamic acid has already been studied by Spillane and his coworkers,[13] and they found the rate of hydrolysis of phenylsulfamic acid was around 100× faster than the rate of hydrolysis of diphenylsulfamide. Accordingly, the final products of the hydrolysis of **1a–d** are found to correspond to the o-phenylenediamines.

CONCLUSIONS

The accumulated evidence from the above range of physical organic mechanistic techniques have indicated that the acid-catalyzed hydrolysis mechanism of the cyclic sulfamides **1a–d** proceeds with an A2 mechanism at low acidities (for **1c**,**d** 1.00–8.00 M and for **1a**,**b** 1.00–9.00 M), as shown in Scheme 3. In this first step, rapid pre-equilibrium protonation of the 5-substituted benzosulfamides is involved. It is assumed that the protonation occurs on the nitrogen atom, and subsequently, a water molecule attacks the sulfur atom as the nucleophile in the rate-determining step. At acidity levels higher than 12.00 M (H^+) for **1a**,**b** [14.00 M (H^+) for **1c**, **d**], rapid protonation on the nitrogen atom is followed by S–N bond cleavage in the transition step, and the acid-catalyzed hydrolysis mechanism of the 5-substituted benzosulfamides **1a–d** could be described as an A1 reaction mechanism as shown in Scheme 4.

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