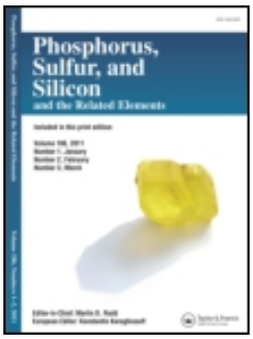

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THE SYNTHESIS AND ACID-CATALYZED HYDROLYSIS OF N-(4-SUBSTITUTEDPHENYL)-O-BENZENEDISULFONIMIDES

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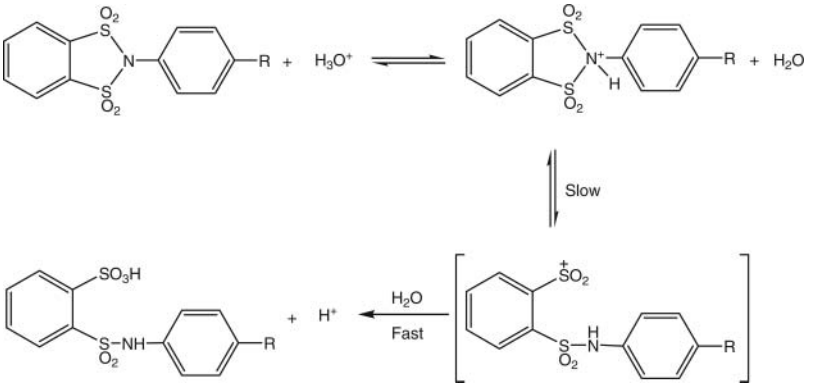
GRAPHICAL ABSTRACT



Abstract *The acid catalyzed hydrolyses of some cyclic disulfonimides, N-(4-substitutedphenyl)-o-benzenedisulfonimides (**1a–d**) have been studied in concentrated aqueous acidic solutions. Analysis of the data by the Excess Acidity Method, activation parameters, substituent, and solvent deuterium isotope effect are all indicate hydrolysis by an A-1 mechanism in the studied range.*

Keywords Disulfonimides; acid-catalysis; excess acidity; hydrolysis; mechanism

INTRODUCTION

Compounds containing sulfonamide groups (−SO_2NH−) have long been known as a result of their biological importance and chemical applications. They occupy a unique position in the drug industry with their antibacterial,[1] antitumor,[2] hypoglycemic,[3] and carbonic anhydrases enzyme (CA) inhibitory properties.[4] Disulfonimides are sulfonamide

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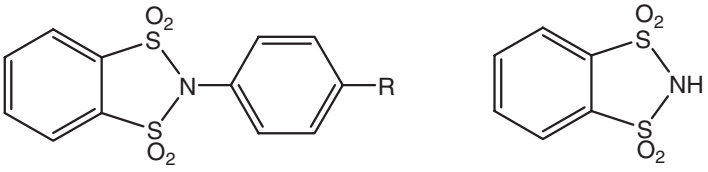
derivatives that contain two sulfone group connected to the nitrogen atom. They are also used in medicine for their antitumor effects and CA inhibitory properties.[5] Their complexes with transition metals are very common.[6] The complexes obtained from chiral derivatives of them used in asymmetric synthesis as catalysts.[7]

The derivatives of o-benzenedisulfonimide **2** are especially attractive as synthetic tools, since the two sulfonyl groups flanking nitrogen provide anionic charge stabilization so that the imide anion should be a good leaving group. Several N-substituted derivatives of it was used as an active source of electrophile in many substitution[8–10] and oxidation[11] reactions efficiently.



1 **a**; R= OCH_3
b; R= CH_3
c; R= H
d; R= Cl

2

Scheme 1

The acid catalyzed hydrolyses of sulfonamides[12] and sultams[13] (the corresponding cyclic sulfonamides) has been studied in some detail. Despite their obvious importance, there has been no systematic study of the acid-catalyzed hydrolysis of disulfonimides. We now report a detailed study of the acid-catalyzed hydrolysis of a series of N-(4-substitutedphenyl)-o-benzenedisulfonimides **1a–d** (Scheme 1) in concentrated aqueous acidic solutions.

RESULTS AND DISCUSSION

Profiles for the acid catalyzed hydrolysis of **1a–d** in sulfuric acid solutions at 60.0 ± 0.1 °C are shown in Fig. 1. In all cases, the rates of hydrolysis increased continuously with increasing acid concentration in the studied range (13.00–16.00 M). There is no indication of a rate maximum even at quite high acidity. The hydrolysis reaction was very slow and cannot be followed by an ultraviolet (UV) spectrometer in lower acidic solutions. So, it was impossible to obtain reproducible results. Because of this, no kinetic data were obtained for HCl and $HClO_4$.

The kinetic data in Table 1 were also analyzed by the Excess Acidity treatment of Cox and Yates.[14–16] The appropriate kinetic equation for mainly unprotonated substrates Eq. (1) was used;

$$\log k_1 - \log C_{H^+} - \log C_S/(C_S + C_{SH^+}) = m^{\neq} m^* X + \log a_{Nü} + \log(k_0/k_{SH^+}) \qquad (1)$$

Owing the extremely low basicity of the cyclic disulfonimides studied, the protonation correction term, $[\log C_S/(C_S + C_{SH}{}^+)]$ can be neglected. In the equation, k_1 is the pseudo first order rate constant in aqueous acid concentration $C_H{}^+$ and of excess acidity X.

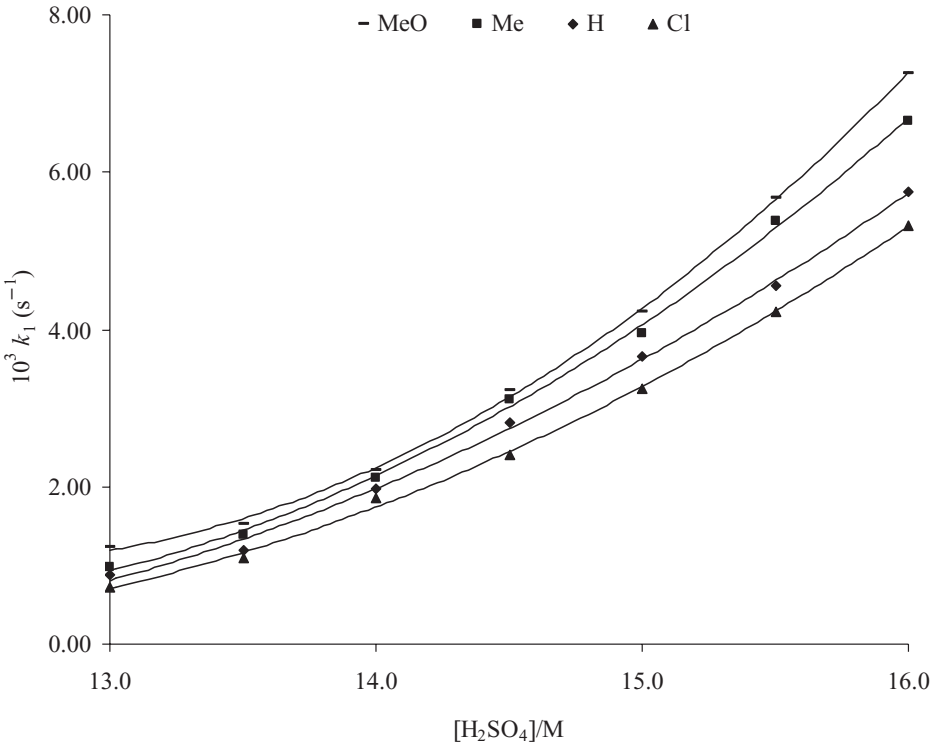


Figure 1 Plots of k_1 for acid-catalyzed hydrolysis of N-(4-substitutedphenyl)-o-benzenedisulfonimides **1a–d** in sulfuric acid solutions at 60.0 ± 0.1°C.

Plots of $\log k_1 - \log C_{H^+}$ versus X are shown in Fig. 2 for the hydrolyses of **1a–d** in sulfuric acid solutions. The resulting straight lines with high correlations (r^2: 0.989–0.997) for all compounds are typical of an A-1 mechanism in the studied range of acid, which means there is no involvement of nucleophile in the transition state. Similar behavior has been observed for the hydrolyses of some sulfamates[17] and a number of sulfonimidic esters at higher acidity region.[18]

The values of the rate constants for the hydrolysis of all compounds (**1a–d**) at different temperatures were also obtained as shown in Table 2. The temperature dependence of the

Table 1 Values of $10^3 k_1$ (s^{-1}) for the hydrolysis of **1a–d** in sulfuric acid solutions at 60.0 ± 0.1 °C

	$10^3 k_1$ (s^{-1})			
H_2SO_4 (M)	**1a**	**1b**	**1c**	**1d**
13.00	1.24	0.97	0.88	0.72
13.50	1.52	1.38	1.20	1.10
14.00	2.22	2.12	1.98	1.85
14.50	3.22	3.11	2.82	2.41
15.00	4.23	3.96	3.65	3.25
15.50	5.68	5.37	4.55	4.23
16.00	7.25	6.65	5.75	5.32

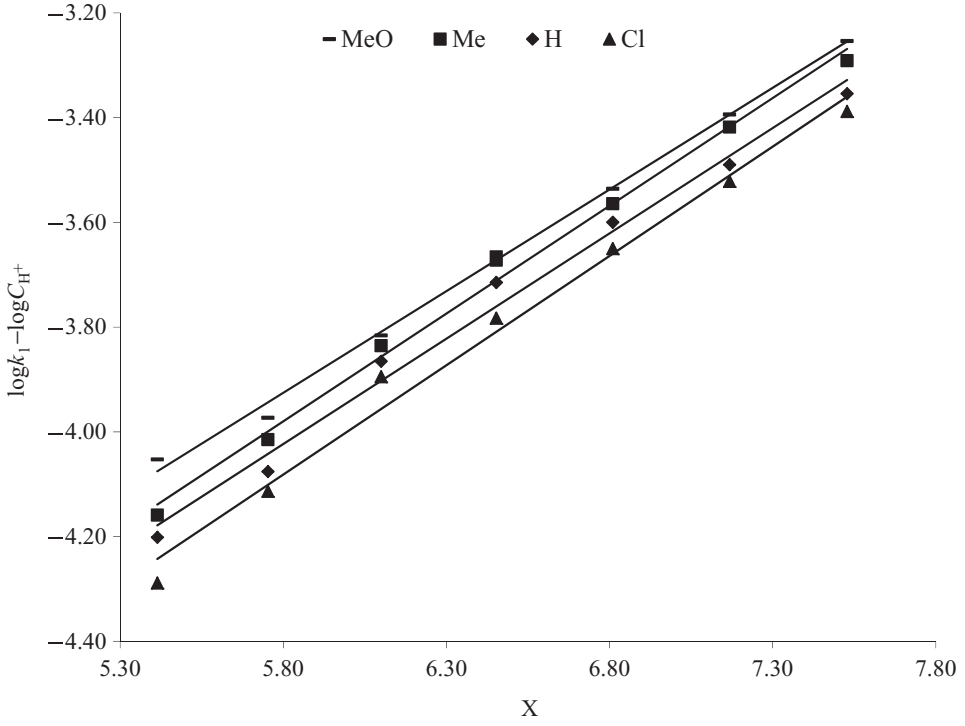


Figure 2 Plot of logk_1 – logC_{H+} vs. excess acidity for the acid catalyzed hydrolysis of **1a–d** in sulfuric acid solutions at 60.0 ± 0.1°C.

rate constants of the hydrolysis reaction was analyzed by a least-square procedure and calculated activation enthalpy and entropy values are shown in Table 3. The hydrolysis of all compounds have $\Delta S^{\neq}$ of small negative or positive values. It is consistent with an A-1 mechanism that substrat molecule has more rotational and translational freedom in the transition state, where a water molecule does not involved. The acid-catalyzed hydrolysis of esters and amides[19] proceeding by an A-1 mechanism have $\Delta S^{\neq} \approx 0$ to -41.8 JK^{-1}mol^{-1}, while those proceeding by an A-2 mechanism have $\Delta S^{\neq} \approx -62.8$ to -125.5 JK^{-1}mol^{-1}. Over the range 14.00–16.00 molar sulfuric acid, the values of $\Delta S^{\neq}$ for the hydrolysis

Table 2 Values of $10^3\, k_1$ (s^{-1}) for the hydrolysis of the **1a–d** at different temperatures

H_2SO_4 (M)	Compound	55.0°C	60.0°C	65.0°C	70.0°C
14.00	**1a**	1.35	2.22	3.56	5.61
	1b	1.33	2.12	3.40	5.51
	1c	1.19	1.98	2.85	5.21
	1d	1.26	1.85	3.48	5.32
16.00	**1a**	3.68	7.25	11.20	18.50
	1b	3.65	6.65	10.40	16.50
	1c	3.42	5.75	9.58	15.20
	1d	3.21	5.32	8.87	13.90

Table 3 Arrhenius parameters for the hydrolysis of **1a–d**

Compound	H_2SO_4 (M)	$\Delta S^{\neq}$ ($JK^{-1}mol^{-1}$)	$\Delta H^{\neq}$ ($kJmol^{-1}$)	r^2
1a	14.00	−12.86	94.59	0.997
	16.00	+9.58	98.89	0.999
1b	14.00	−30.89	88.55	0.999
	16.00	−8.03	93.18	0.996
1c	14.00	−17.77	93.16	0.994
	16.00	−8.25	93.36	0.999
1d	14.00	−25.55	90.56	0.998
	16.00	−13.48	91.83	0.999

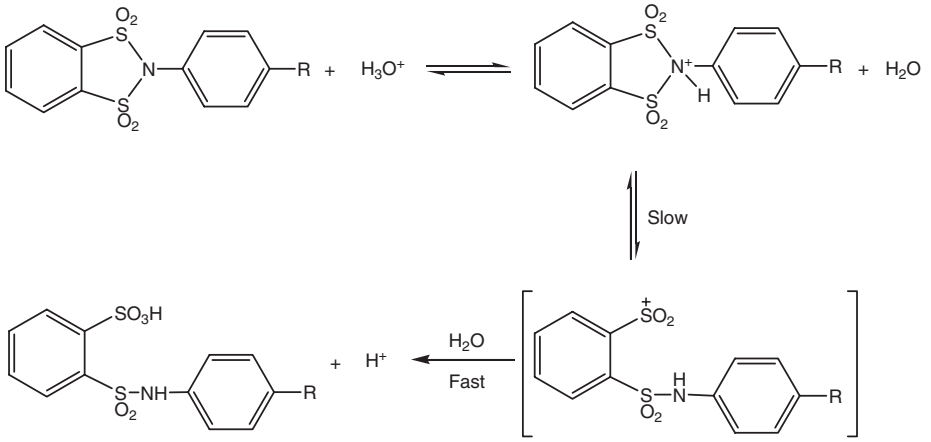
of **1a–d** become increasingly less negative with increase of acidity suggests that the A-1 mechanism becomes more dominant at higher acidities (Table 3).

The kinetic solvent isotope effect (k_1D_2O/k_1H_2O) observed for the hydrolysis of **1c** is shown in Table 4. The values obtained in 13.50 and 16.00 molar sulfuric acid solutions are 1.80 and 2.08 respectively that is also consistent with an A-1 mechanism. Generally, for an A-2 mechanism, values of k_1D_2O/k_1H_2O lie closer to unity, on the other hand it is expected to be around 2–4 for an A-1 mechanism.[20,21]

In the studied acidity range, electron-donating substituents produce the highest rate of hydrolysis (i.e., **1a** > **1d**), and the substituent effects are well correlated by a satisfactory Hammett $\rho\sigma$ plot [at 14.00 M H_2SO_4, $\rho = -0.157$ (corr. 0.991) and at 16.00 M H_2SO_4, $\rho = -0.281$ (corr. 0.961)], i.e., as shown in Fig. 3 for 14.00 M H_2SO_4. Clearly, at these acidities, electron-donating substituents facilitate both protonation of the substrate and stabilize the sulfur cation in the A-1 mechanism.

There is no direct evidence concerning the site of the protonation of o-benzenedisulfonimides, however, the protonation of sultams[13] and sulfinamides[22] occur preferentially at the nitrogen atom.

As a result of all these observations, we propose that the acid catalyzed hydrolysis of N-(4-substitutedphenyl)-o-benzenedisulfonimides occur by an A-1 mechanism in the studied range, as shown in Scheme 2. A rapid protonation on nitrogen atom is followed by S–N bond cleavage in the rate determining step.



Scheme 2

Table 4 Deuterium solvent isotope effect for the hydrolysis of N-fenil-o-benzendisulfonimit **1c** in sulfuric acid solutions at 60 ± 0.1°C

Acid (M)	$10^3\,k_1$ (s^{-1})	k_{D_2O}/k_{H_2O}
H_2SO_4 (13.50)	1.20	1.80
D_2SO_4 (13.50)	2.16	
H_2SO_4 (16.00)	5.75	2.08
D_2SO_4 (16.00)	12.00	

EXPERIMENTAL

Material

N-(4-Substitutedphenyl)-o-benzenedisulfonimides **1a–d** were prepared as described by Sorbye et al.[8] by making minor changes. The modified process: o-Benzenedisulfonyl chloride was dissolved in benzene and stirred under reflux. The solution of corresponding p-substituted aniline (1 eq.) and triethylamine (1 eq.) in benzene was added stepwise into the stirring solution. The reaction was allowed to reflux for 5 h. The heterogenous mixture obtained was cooled and filtered to remove triethylamine hydrochloride. The liquid phase was placed in a flask again. While stirring the system, potassium tert-butoxide (1.5 eq.) and catalytic amounts of 18-crown-6 were added in portions, respectively. Then, the reaction was allowed to reflux for additional 20 h. The reaction mixture was cooled, filtered, and the

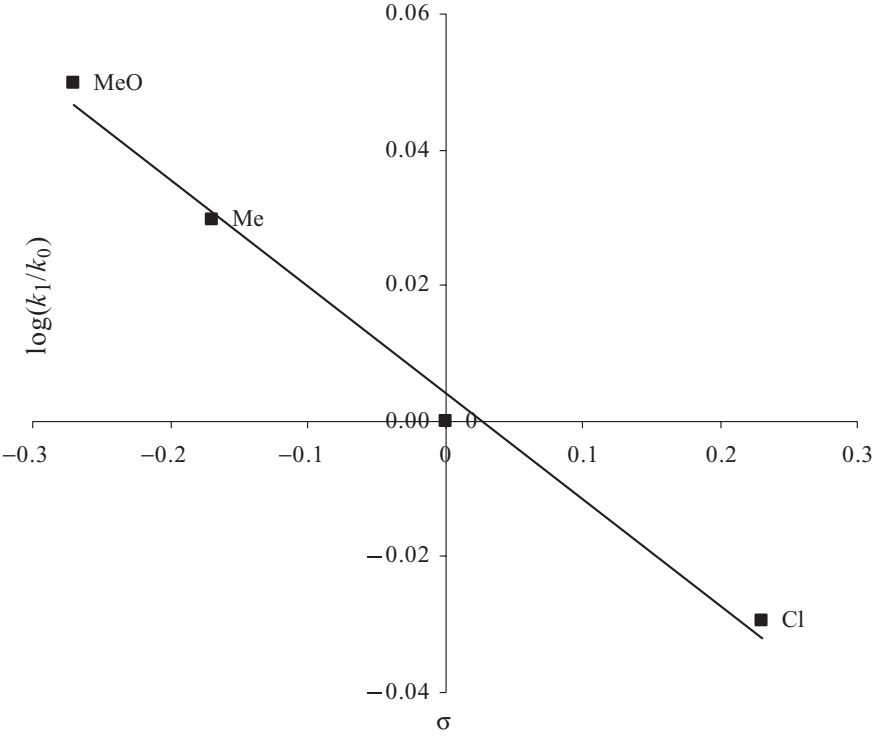


Figure 3 The plot of log k_1 vs. Hammett σ values for the acid-catalyzed hydrolyses (14.00 M H_2SO_4) of N-(4-substitutedphenyl)-o-benzenedisulfonimides (**1a–d**) at 60.0 ± 0.1°C.

solvent was stripped of under vacuum up to half volume and was left to crystallization in the same solvent. By repeating the benzene recyrstallization, pure cyristalline products **1a–d** was obtained with 34–40% yield. Elemental analyses were performed by Test Analyses Laboratory (ATAL) of TUBİTAK in Ankara, Turkey. Disulfonimide **1a** had m.p. 185–186 °C; ^{1}H NMR ($CDCl_3$), δ 8.15–7.90 (m, 4H), 7.57 (d, 2H), 7.07 (d, 2H), 3.80 (s, 3H); found C, 48.65; H, 3.80; N, 4.27; S, 19.63; calc. for $C_{13}H_{11}NS_2O_5$ C, 47.98; H, 3.41; N, 4.31; S, 19.71%; **1b** had m.p. 216–218 °C; ^{1}H NMR ($CDCl_3$), δ 8.20–7.83 (m, 4H), 7.67–7.36 (m, 4H), 2.45 (s, 3H); found C, 51.65; H, 3.85; N, 4.55; S, 20.28; calc. For $C_{13}H_{11}NS_2O_4$ C, 50.46; H, 3.59; N, 4.53; S, 20.73%; **1c** had m.p. 193–195 °C (lit.[23] 195 °C); ^{1}H NMR ($CDCl_3$), δ 7.61–7.80 (m, 5H), 7.96–8.20 (m, 4H); **1d** had m.p. 242–245 °C; ^{1}H NMR ($CDCl_3$), δ 8.21–7.90 (m, 4H), 7.67–7.48 (m, 4H); found C, 44.32; H, 2.39; N,4.20; S, 19.83; calc. for $C_{12}H_8NS_2O_4Cl$ C, 43.70; H, 2.45; N, 4.25; S, 19.45%.

Kinetic Procedure

The rates of hydrolysis of the disulfonimides were followed at 215 nm with using a GBC Cintra 20 model UV–VIS spectrophotometer fitted with a thermostated cell holder (±0.05 °C). Good first-order behavior was observed with clean isobestic points. Values of the first order rate coefficients k_1 were calculated from the standard equation using a least-squares procedure. All kinetic measurements were duplicated and the average deviation from the mean was <5%.

Product Analysis

The product of the hydrolysis was determined by comparing the UV spectrum obtained at the completion of the kinetic experiment with the spectrum of the expected product that was run at the same concentration and under the same conditions. The UV spectra of the hydrolysis of N-phenyl-o-benzenedisulfonimide (**1c**) were shown to be identical to that of corresponding 2-(phenylsulfamoyl)benzenesulfonic acid, m.p. 91–95 °C (dec). This compound was prepared by treating water with the product, which was obtained from the reaction of o-benzenedisulfonyl chloride and aniline in benzene. Its structure was confirmed by IR and ^{1}H-NMR techniques.

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