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(Journal of the Korean Chemical Society)
Vol. 33, No. 1, 1989
Printed in the Republic of Korea

Styrylphenylsulfone 유도체의 가수분해 반응 메카니즘

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(1988. 8. 3. 접수)

The Kinetics and Mechanism of Hydrolysis of Styrylphenylsulfone Derivatives

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(Received August 3, 1988)

요 약. pH 0.0-14.00범위에서 Styrylphenylsulfone 유도체들의 가수분해반응에 대한 반응속도론적 연구가 25℃의 50% 메탄올-물속에서 자외선 분광법으로 이루어졌다. 반응속도식과 치환기 효과 (ρ= 1.85(pH7.0), ρ=1.54(pH 13.0))로부터, pH 11.0이상에서는 전형적인 Michael형의 친핵성 첨가반응, pH 9.0이하에서는 물분자에 의한 일반 염기촉매반응, 그리고 pH 9.0-11.0사이에서는 이들 두 반응이 경쟁적으로 일어남을 제안하였다.

ABSTRACT. The Kinetics of hydrolysis of styrylphenylsulfone derivatives in 50% methanol-water at 25℃ and ionic strength of 0.10 was investigated by UV spectrophotometry in the pH range of 0.0-14.0. The rate equations, which can be applied over a wide pH range, were obtained. The Hammett rho constants for the hydrolysis are 1.85 at pH 7.0 and 1.54 at pH 13.0, respectively. On the basis of the evidence, it is proposed that the general base-catalysis occurs in the hydrolysis of styrylphenylsulfone derivatives; above pH 11.0, Michael type nucleophilic addition take place, while below pH 9.0, the reaction is initiated by addition of water and from pH 9.0 to pH 11.0 these two reactions occur competitively.

INTRODUCTION

Nucleophilic additions to carbon-carbon double bonds are not so well documented as additions in which protonation or other electrophilic attack is the first step. When the electron density of carbon-carbon double bond is reduced by strongly electron-withdrawing substituents, nucleophilic attack at one of the vinylic carbons may occur. It has been shown that the hydrolysis of αβ-unsaturated compounds is catalyzed by general bases in buffer solutions and in the hydrolysis, the addition of anion is the rate determining step.[1-4]

In order to verify the mechanism of uncleophilic addition, in previous paper,[5,6] the authours have investigated the rate and mechanism of the addition of L-cysteine to styrylphe-

nylsulfone[5] and of thioglycolic acid to β-nitrostyrene derivatives[6]. In an effort to make more through investigations of the kinetics of the hydrolysis, including the effect of substituents and general base-catalysis, we carried out the studies on styrylphenylsulfone(**3**) derivatives in this paper.

EXPERIMENTAL

General. All chemicals used were reagent grade unless otherwise specifed. NMR spectra were obtained with a Varian 60MHz spectrometer, using tetramethylsilane as an internal standard. IR spectra were examined with a JASCO model DS701G spectrophotometer. Elemental analysis was performed by Perkin-Elmer 240 CHN Analyzer and UV spectra were obtained by a Pye-Unicam SP8800 spectrophotometer. GC/mass spectra were taken in a Hewlett Packard 5730A spectrometer. Melting points were measured with a Fisher Johns hot stage melting point apparatus.

Synthesis of para-sub. Styrylphenylsulfone (3) Derivatives. Phenylmercaptoacetic acid (**1**) was prepared by phase transfer catalysis of corresponding thiophenol and monochloroacetic acid, using butylammoniumhydrogensulfate (Aldrich) as catalyst[7]. Yield: 65%, mp.; 61.5~62.5 (*lit.* 59~61℃), NMR ($CDCl_3$/TMS) δppm; 11.25 (s. -OH), 3.62(s. -CH), 7.15~7.60(m. phenyl).

phenylsulfonylacetic acid (**2**) was prepared by oxidation of (**1**) in the mixed solvent of glacial acetic acid and hydrogen peroxide[8]. Yield; 57%, mp.; 113℃ (*lit.* 112-114℃, IR (KBr) λmax. cm^{-1}, 3018(w. CH- st.), 1175(w. CO_2H st.), 1725(s. CO st.), 1320-1355, 1180(s. SO_2 st.), 720~725(s. phenyl st.). Styrylphenylsulfone(**3a**), p-methoxystyrylphenylsulfone (**3b**), p-chlorostyrylphenylsulfone (**3c**) and p-nitrostyrylphenylsulfone (**3d**) derivatives were prepared by condensation of corresponding various para-substituted benzaldehyde and (**2**)[9]. Melting points were determined after recrystallization in diethyl ether and ethanol. The analytical and spectral data of (**3**) derivatives are shown in *Table* 1.

Kinetic. The reaction rate reported herein were determined UV spectrophotometrically by procedures which have been previously described[5,6]. The pH of solution was adjusted by a Fisher Accumet model 525 digital pH/ion meter. The solvent system used in the present work is 50% methanol. Ionic strength was kept constant at 0.10M by adding sodium chloride solution, and all reactions were run at 25℃.

Product Analysis. One gram of (**3a**) dissolved in the methanol solution was added to the proper buffer solution containing 50% methanal. The mixture was refluxed for 4~5 hours and dried in vacuo until a paste was obatined. The paste was washed many times with distilled water and dried for a week in a vaccum

Table 1. Analytical and spectral data of *para*-substituted styrylphenylsulfone (3) derivatives

Compds	Yield *(lit.[a])* (%)	mp *(lit.[b])* (℃)	UV^{c}*max.* (log ε) (nm)	Formula	Cal.(%) C	H	N	Found(%) C	H	N	IR(cm^{-1})[d]	MS(M^+) (m/e%)
(3a)	30(39)	75(74-75)	270(4.60)	$C_{14}H_{12}SO_2$	68.8	4.92	–	68.6	5.00	–	3060, 1310, 1150, 920, 860	244.5(14.5)
(3b)	15(19)	119(120)	275(3.40)	$C_{15}H_{14}SO_3$	65.7	5.11	–	65.6	5.10	–	3070, 1295, 1140, 960, 845	274(8.5)
(3c)	55(63)	128(129)	282(4.39)	$C_{14}H_{11}SO_2Cl$	60.3	3.98	–	60.4	4.00	–	1510, 1340, 969, 830, 720	279(20)
(3d)	45(50)	169(170)	300(4.41)	$C_{14}H_{11}NSO_4$	58.1	3.81	4.8	58.0	4.00	4.6	1520, 1320, 1110, 800, 725	289(12.5)

[a]ref. 8, [b]All mps are without corrected., [c]in methyl alcohol, [d]KBr disc.

desicator, and recrystallized twice from ether (Yield, 65%). The mp. 89~90℃ (*lit.* 88~89℃), agreed with phenylmethylsulfone. Anal, calc. ($C_{17}H_8SO_2$ (156)): Calc. (%); C 53.85, H 5.13, found (%); C 54.0, H 5.08. And from the filtrate, benzaldehyde was identified by Brady reagent.

Table 2. First order rate constants ($k10^7$ obs. sec^{-1}) for the hydrolysis of styrylphenylsulfone (3) derivatives[a]

pH	(3a)	(3a)[b]	(3b)	(3c)[c]	3d)[d]
0.0	0.330	0.398	0.20	2.48	9.46
0.5	0.450	0.398	0.20	2.25	13.2
1.0	0.455	0.398	0.20	2.04	16.8
1.5	0.398	0.398	0.30	2.31	16.9
2.0	0.405	0.398	0.19	2.40	13.2
2.5	0.402	0.398	0.16	2.50	17.0
3.0	0.378	0.398	0.29	2.50	14.2
3.5	0.400	0.398	0.38	2.50	17.2
4.0	0.425	0.398	0.30	2.73	13.5
4.5	0.450	0.398	0.25	2.25	16.8
5.0	0.450	0.398	0.28	3.15	17.0
5.5	0.450	0.398	0.15	2.15	19.0
6.0	0.405	0.398	0.26	2.41	16.6
6.5	0.397	0.398	0.30	2.43	15.5
7.0	0.342	0.398	0.25	2.33	17.5
7.5	0.380	0.398	0.20	2.35	17.0
8.0	0.365	0.402	0.33	2.25	17.5
8.5	0.400	0.411	0.25	2.35	18.0
9.0	0.402	0.437	0.25	4.85	18.0
9.5	0.550	0.520	0.38	6.40	23.0
10.0	0.550	0.783	0.32	7.50	30.0
10.5	1.37	1.610	0.35	4.35	31.5
11.0	3.45	4.25	2.15	5.55	133.
11.5	16.0	12.40	5.00	21.5	165.
12.0	33.5	37.90	13.5	25.8	804.
12.5	134.	120.	44.2	65.5	2100.
13.0	371.	371.	145.	180.	6680.
13.5	1240.	1171.	488.	600.	34200.
14.0	3340.	3700.	1550.	2500.	66000.

[a]The ionic strength was mintained at 0.1M by the addition of sodium chloride solution except below pH 1.0 and above pH 13.0., [b]The values were calculated using the equation (6)., [c]ref. 10a., [d]ref. 10b.

RESULT

The logarithmic plots of the absorbance (log OD) of (3) vs. times were linear and used to calculated the first-order rate constants. The hydrolysis rate constants at various pH are given in *Table* 2, and *Fig.* 1 shows the log*k* against pH. The solid line in *Fig.* 1 is a theoretical value calculated according to the equation (6) and circles are experimental points.

General base catalysis rate constants were extrapolated to zero buffer concentration and the values are determined at various acetate ion concentration as shown in *Fig.* 2.

DISCUSSION

Substitution Effect. The Hammett plot[11] of the constant of the hydrolysis leads to a straight line a slope of $\rho=1.85$ at pH 7.0 and $\rho=1.54$ at pH 13.0, respectively. Therefore, the rate of hydrolysis of (3) derivatives is accelerated by electron withdrawing groups at all pH range, suggesting that the hydrolysis proceeds through similar mechanism in acidic and basic media. The $\rho>0$ value would be large for those reactions, in which bond making occurs prior to bond breaking.

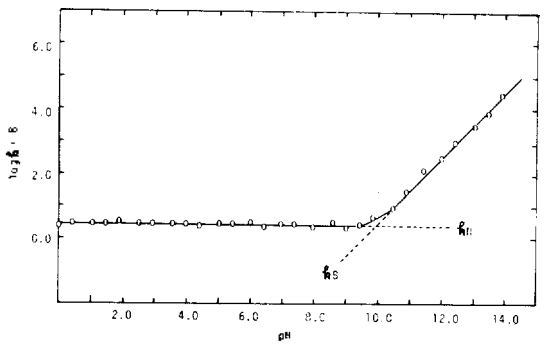


Fig. 1. Plots of log obs. against pH for the hydrolysis of styrylphenylsulfone (3a) in 50% methanol. (The points are experimental and solid line is calculated according to the equation (6).

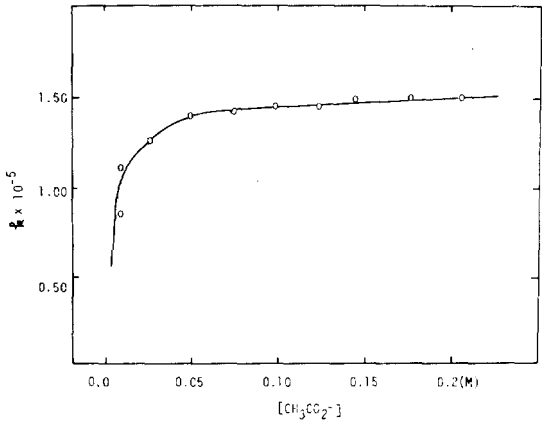


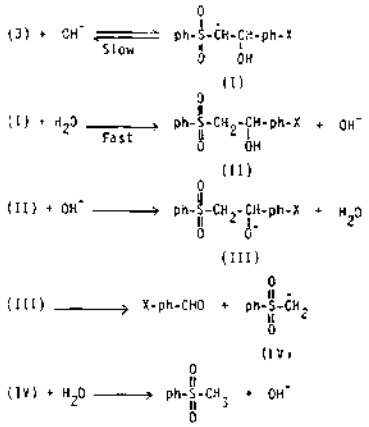
Fig. 2. General base catalyzed hydrolysis of p-nitrostyrylphenylsufone (**3d**) at pH 4.75 and 25℃. Extrapolated to zero buffer concentration. (The circles are experimental and curve is drawn according to equation (4-3).

General base Catalysis. As shown in *Fig.* 2, to make sure that this reaction is catalyzed by general base, the rate constants were determined at various acetate ion concentration $[Ac^-]$ at pH 4.75[12]. From the equation (4), k_2 step shows general base catalysis; k_N depends only on the concentration of acetate ion at constant pH 4.75, whereas, the reaction velocity is not a linear function of catalyst concentration. *Fig.* 2 shows that k values calculated by equation (3-3), are in good agreement with observed values and experimental values.

Rate Equation and Mechanism. As shown in *Fig.* 1, the change of log$k$ vs. pH is complicated; below pH 9.0, the log$k$ remains almost constant, whereas above pH 11.0, the slope is ca. 1.0, i.e., k values are directly proportional to the hydroxide ion concentration. Analysis of *Fig.* 1 shows that the rate constant (kt) can be divided into two part; one part is directly proportional to hydroxide ion concentration and the other is not. Therefore, the observed rate constants of the catalyzed hydrolysis can be expressed to be base catalyzed hydrolysis as equation (1), where k_N is the first order rate constant for the spontaneous hydrolysis below pH9.0 and k_B is the catalytic rate constant for the base catalyzed reactions above pH 11.0.

$$k_1 = k_N + k_B[OH^-] \quad (1)$$

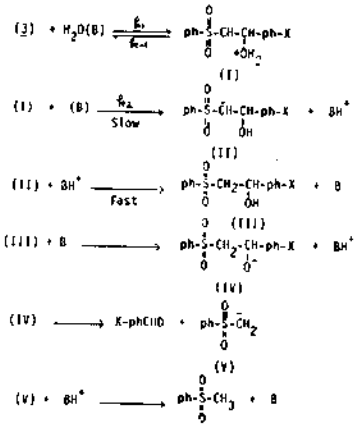
From the substituent effect ($\rho > 0$), and the k_B part where the rate constant is proportional to hydroxide ion concentration[6] ($k_{obs} = k_B[OH^-]$), can be given a rate equation of the Michael type reaction. Hence, the mechanism of the hydrolysis is proposed as *Scheme* 1.



Scheme 1

The observed rate constant below pH 9.0 was almost constant irrespective of hydroxide ion concentration, the hydrolysis is catalyzed by the general bases, the hydrolysis rate is not proportional to the concentration of hydroxide ion. Therefore, the reaction would proceed via the reaction path different from that of *Scheme* 1. These facts suggest that the reaction mechanism is complicated as the case of β-nitrostyrene[13], and from the results of substitution effect ($\rho > 0$) and general base catalysis (*Fig.* 2), following mechanism in proposed as *Scheme* 2.

First step (k_1) reaction of the above mechanism (*Scheme* 2) is inintiated by attack of nucleophile, water molecule (B), and produces zwi-



Scheme 2

tter ionic intermediate (Ⅰ). Second step (k_2) shows general base catalysis, and (Ⅱ) would swiftly accept a proton to produce (Ⅲ) by third step. Therefore, the over-all reaction rate should be controlled by the second step of the *Scheme* 2. But, at the range of lower pH in the sponteneous hydrolysis (pH 0.0～9.0), where proton concentration is high as compared to hydroxide ion concentration the zwitter ionic intermediate (Ⅰ) should be protonated at the anionic center rather than losing a proton to a general base. Therefore, rate determining step (k_2) may be change to another step[14]. In general, among all the possible mechanism, first step reaction of *Scheme* 2 is reversible, whereas second step is irreversible and (Ⅰ) is very unstable. During the reaction, if (Ⅰ) is present in small amount and do not change in its concentration and a steady-state approximation is applicable with respect to (Ⅰ),[6,15]

$$\text{Rate}=-\frac{d[3]}{dt}=k_N[3]=\frac{k_1k_2[3]\Sigma[B]}{k_{-1}+k_2\Sigma[B]} \quad (2)$$

Then k_N is given as following;

$$1/k_N=1/k_{-1}+1/k_1/k_{-1}k_2\Sigma[B] \quad (3)$$

$$k_N=\frac{k_1\Sigma k_2[B]}{k_{-1}+\Sigma k_2[B]} \quad (4)$$

From the equation (4), it can be shown that if the concentration of general base is high ($k_2[B] \gg k_{-1}$), then k_N will take limiting value,[5,6] $k_1=k_N$.[16]

Fig. 2 shows the rate constants for the hydrolysis of (**3d**) at various acetate ion concentrations at pH 4.75. Consequently, k_N depends only upon the concentration of the acetate ion at constant pH[12], while, acetate ion acts as a general base catalyst[17]. Since, at low pH, the concentrations of hydroxide ion and acetate ion are negligile compared to water concentration, k_N is given as equation (5).

$$k_N=\frac{(k_1/k_{-1})k_2^{H_2O}[H_2O]}{1+(k_2^{H_2O}[H_2O]/k_{-1})} \quad (5)$$

The values of constants in equation (5) shows the efficiency of hydroxide ion and water as the base catalyst.[18] As the result, in case of (**3a**)[19] overall rate constant (k_1) becomes equation (6).

$$(\mathbf{3a});k_1=\frac{7.74\times10^{-15}+4.11\times10^{-12}[OH^-]}{1.94\times10^{-7}+3.0\times10^{-5}[OH^-]}+3.70\times10^{-4}[OH^-] \quad (6)$$

Fig. 1 and *Table* 2 show that the values of over-all rate constant, calculated by equation (6), are in good agreement with observed values, similarly, the rate equations obtained for the derivatives of (**3b-3d**) are as follows;

$$(\mathbf{3b});k_1=\frac{1.63\times10^{-15}+7.70\times10^{-11}[OH^-]}{8.13\times10^{-8}+2.17\times10^{-3}[OH^-]}+1.45\times10^{-4}[OH^-] \quad (7)$$

$$(\mathbf{3c});k_1=\frac{2.14\times10^{-13}+2.37\times10^{-9}[OH^-]}{9.26\times10^{-7}+4.88\times10^{-2}[OH^-]}+1.75\times10^{-4}[OH^-] \quad (8)$$

$$(\mathbf{3d});k_1=\frac{2.95\times10^{-11}+5.40\times10^{-8}[Ac^-]}{1.76\times10^{-5}+3.44\times10^{-3}[Ac^-]}+6.52\times10^{-3}[OH^-] \quad (9)$$

On the basis of rate equations (6)～(9), substituent effect, general base catalysis and hydrolysis products analysis, the mechanism of the hydrolysis of (**3**) derivatives over wide pH range is fully explained. One may draw a conclusion

as following; below pH 9.0, the hydrolysis is initiated by the addition of water but above pH 11.0, Michael type addition occurs by addition of hydroxide ion. And from pH 9.0 to pH 11.0, these two reactions occur competitively.[20]

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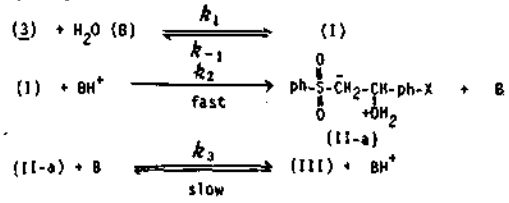
14. 
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16. Which is maximum point $k_1=1.57\times10^{-5}$ (**3d**) in *Fig.* 2 and $k_1=1.37\times10^{-7}$ (**3a**) at pH 10.5 in *Fig.* 1. If water and hydroxide ion are general base present in the solution, equation (4) becomes equation (4−1).

$$k_N=k_1k^{H_2O}[H_2O]+k_1k_2^{OH^-}[OH^-]/k_{-1}+k_2^{H_2O}[H_2O]+k_2^{OH^-}[OH^-] \quad (4-1)$$

17. The acetate ion acts as a general base catalyst, equation (4) becomes as (4−2),

$$k_N=\frac{(k_1/k_{-1})k_2^{H_2O}[H_2O]+(k_1/k_{-1})k_2^{OH}[OH^-]+(k_1/k_{-1})k_2^{Ac}-[Ac^-]}{1+(k_2^{H_2O}[H_2O]/k_{-1})+k_2^{OH}[OH^-]/k_{-1})+k_2^{Ac}\cdot[Ac^-]} \quad (4-2)$$

In case of (**3d**), k_N constants becomes equation (4−3).

$$k_N=\frac{2.95\times10^{-11}+5.40\times10^{-3}[Ac^-]}{1.76\times10^{-5}+3.44\times10^{-3}[Ac^-]} \quad (4-3)$$

18. In case of (**3a**), the value of $(k_1/k_{-1})k_2^{H2O}[H_2O]$ can be determined form the $k_1=1.37\times10^{-7}$ sec.$^{-1}$ at pH ,10.5 and observed rate constant, $k=3.98\times10^{-8}$ sec.$^{-1}$ at pH 1.50, and is found to be $(k_1/k_{-1})k_2^{H2O}[H_2O]=5.16\times10^{-8}$ according to equation (5). By substituting $k=5.50\times10^{-8}$ sec.$^{-1}$ at pH 9.50 and $(k_1/k_{-1})k_2^{H2O}[H_2O]=5.61\times10^{-8}$ into equation (4−1), $(k_1/k_{-1})k_2^{OH^-}[OH^-]=1.13\times10^{-3}$ can be obtained. As a result, If only water and hydroxide ion are present, apparent rate constant, k_N becomes equation (4−4).

$$k_N=\frac{7.74\times10^{-15}+4.11\times10^{-2}[OH^-]}{1.94\times10^{-7}+3.00\times10^{-5}[OH^-]} \quad (4-4)$$

The various contants in equation (5) used to calculate the k_N value of (3) derivatives are summerized as follow.

Compounds	k_1	$(k_1/k_{-1})k_2^{H2O}[H_2O]$	$(k_1/k_{-1})k_2^{OH^-}[OH^-]$
(3a)	1.37×10^{-7}	5.61×10^{-8}	1.13×10^{-3}
(3b)	3.55×10^{-8}	4.58×10^{-8}	2.17×10^{-3}
(3c)	4.85×10^{-5}	4.41×10^{-6}	4.88×10^{-3}
(3d)	1.57×10^{-7}	1.88×10^{-7}	6.47×10^{-2}

19. The nucleophilic addition constant of hydroxide ion, $k_B=3.70\times10^{-4}$ sec.$^{-1}$ is determined by substituting the value of $k=3.45\times10^{-7}$ sec.$^{-1}$ at pH 11.0 and $k=3.34\times10^{-4}$ sec.$^{-1}$ at pH 14.0, into equation (1).
20. The ratios of contribution of water and hydroxide ion on the hydrolysis of **(3a)** are given as follow.

pH	9.0	9.5	10.0	10.5	11.0	11.5
$(OH^-/H_2O)^a$	0.1	0.3	1.0	3.0	10.	30.

[a]calculated by equation (6).