Amidines. VIII. A Kinetic Study of Alcoholysis of N^1-Arenesulfonyl-N^1,N^2-diarylacetamidines

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Alcoholysis of N^1-arenesulfonyl-N^1,N^2-diarylacetamidines (1—30) was studied kinetically. The rate of the reaction between the substrates and ethoxide ion depended on the electron-withdrawing resonance effect of the substituents on both the N^1-aryl and N^2-aryl groups to a similar extent. The rate of the neutral alcoholysis depended on the resonance effect of the N^1-aryl substituent to a larger extent than in the former reaction, and depended hardly at all on the electron-releasing resonance effect of the N^2-aryl substituent, showing that the reaction does not proceed by the solvolysis mechanism.

A reaction mechanism is proposed in which the rate-determining attack of the nucleophile is accompanied by the concerted departure of the *N*-arylarenesulfonamide group.

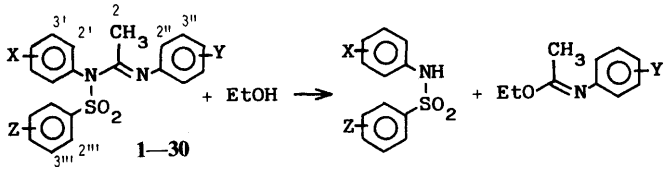
Keywords kinetic study; alcoholysis; N^1-arenesulfonyl-N^1,N^2-diarylacetamidine; concerted mechanism; tetrahedral intermediate; Hammett's plot; Yukawa–Tsuno equation

In previous papers we reported the reactions between N^1-arenesulfonyl-N^1,N^2-diarylamidines and various nucleophiles, *i.e.*, ethoxide ion,[1,2] *p*-nitroaniline[3] and amides.[2,4] The reactions took place at the amidine central carbon, and gave imidates, unsymmetrical amidines and acylamidines, respectively, with departure of *N*-arylarenesulfonamides.

In this work, we studied the alcoholysis of N^1-arenesulfonyl-N^1,N^2-diarylacetamidines (**1—30**) kinetically to elucidate the electronic effect of the three substituents X, Y and Z on the reaction rate (Chart 1).

The reaction was allowed to proceed in the presence of sodium ethoxide. The second-order rate constant, k^{EtO}, was correlated to the nucleophilic substituent constant, σ^-, of the substituents X and Y to a moderate extent in Hammett's relation.

The attack of ethoxide ion on the amidine central carbon is expected to be rate-determining on the basis that the *N*-arylarenesulfonamide group is a better leaving group than the ethoxide group if the metastable tetrahedral intermediate exists. The contribution of the resonance effect of the substituent X to the reaction rate suggests that there is a significant change in the charge of the sulfonamide nitrogen in the transition state. This implies that the rate-determining attack of ethoxide ion is accompanied by the concerted departure of the sulfonamide group.



1—30

	X	Y	Z		X	Y	Z
1	*p*-Cl	*m*-NO_2	*p*-Cl	**16**	*p*-NO_2	*m*-CH_3O	*p*-CH_3
2	*m*-Cl	*m*-NO_2	*p*-Cl	**17**	*p*-NO_2	*m*-Cl	*p*-CH_3
3	*p*-CF_3	*m*-NO_2	*p*-Cl	**18**	*p*-NO_2	*m*-NO_2	*p*-CH_3
4	*p*-CN	*m*-NO_2	*p*-Cl	**19**	*p*-NO_2	*p*-CN	*p*-CH_3
5	*p*-NO_2	*m*-NO_2	*p*-Cl	**20**	*p*-NO_2	*p*-NO_2	*p*-CH_3
6	*p*-NO_2	*p*-Cl	*p*-CH_3	**21**	*p*-NO_2	*p*-CH_3O	*m*-NO_2
7	*p*-NO_2	*p*-Cl	H	**22**	*p*-NO_2	*p*-CH_3	*m*-NO_2
8	*p*-NO_2	*p*-Cl	*p*-Cl	**23**	*p*-NO_2	*p*-isoPr	*m*-NO_2
9	*p*-NO_2	*p*-Cl	*m*-NO_2	**24**	*p*-NO_2	*p*-(*tert*-Bu)	*m*-NO_2
10	*p*-NO_2	H	*p*-CH_3	**25**	*p*-NO_2	*p*-CH_3S	*m*-NO_2
11	*p*-NO_2	H	H	**26**	*p*-CF_3	*p*-CH_3O	*m*-NO_2
12	*p*-NO_2	H	*p*-Cl	**27**	*m*-NO_2	*p*-CH_3O	*m*-NO_2
13	*p*-NO_2	H	*m*-NO_2	**28**	*p*-CN	*p*-CH_3O	*m*-NO_2
14	*p*-NO_2	*p*-CH_3O	*p*-CH_3	**29**	*p*-NO_2	*p*-CH_3O	H
15	*p*-NO_2	*p*-CH_3	*p*-CH_3	**30**	*p*-NO_2	*p*-CH_3O	*p*-Cl

Chart 1

Experimental

All melting points are uncorrected. The ultraviolet (UV) spectra were measured on a Hitachi spectrophotometer, model 139. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on JEOL PMX 60 and JEOL GX 400 NMR spectrometers with tetramethylsilane as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), double double doublet (ddd) and broad (br).

Materials N^1-Tosyl-N^1-(*p*-nitrophenyl)-N^2-(*p*-chlorophenyl)acetamidine (**6**),[1] N^1-tosyl-N^1-(*p*-nitrophenyl)-N^2-(*p*-methoxyphenyl)acetamidine (**14**),[4] N^1-tosyl-N^1-(*p*-nitrophenyl)-N^2-(*p*-methylphenyl)acetamidine (**15**),[4] N^1-tosyl-N^1-(*p*-nitrophenyl)-N^2-(*m*-nitrophenyl)acetamidine (**18**),[4] N^1-tosyl-N^1,N^2-di(*p*-nitrophenyl)acetamidine (**20**)[3] and N^1-(*p*-methoxyphenyl)-N^2-(*p*-nitrophenyl)acetamidine[3] were prepared according to the cited references.

Preparation of N^1-Arenesulfonyl-N^1,N^2-diarylacetamidines by Beckmann Rearrangement N^1-Arenesulfonyl-N^1,N^2-diarylacetamidines were prepared according to the previous papers[1,4] by method A and method B. Method A: Substituted acetophenoxime tosylate (0.01 mol) and the sodium salt of *N*-arylarenesulfonamide (0.01 mol) were heated with an appropriate solvent. Method B: Substituted acetophenoxime (0.01 mol), tosyl chloride (0.01 mol) and Et_3N (0.01 mol) were dissolved in an appropriate solvent under ice-cooling. The mixture was kept for 1 d in an ice-box, and filtered. The sodium salt of substituted *N*-arylarenesulfonamide (0.01 mol) was added to the filtrate, and the mixture was heated under reflux. The results are shown in Table I. ^{1}H-NMR data for N^1-arenesulfonyl-N^1,N^2-diarylacetamidines ($CDCl_3$, 400 MHz) are shown in Table II.

Preparation of N^1-Mesyl-N^1-(*p*-nitrophenyl)-N^2-(*p*-methoxyphenyl)acetamidine (31) *p*-Methoxyacetophenoxime (1.65 g, 0.01 mol), tosyl chloride (1.91 g, 0.01 mol) and Et_3N (1.01 g, 0.01 mol) were dissolved in 20 ml of anhydrous tetrahydrofuran (THF) under ice-cooling. The mixture was kept for 1 d in an ice-box and filtered. The sodium salt of *N*-(*p*-nitrophenyl)methanesulfonamide (2.38 g, 0.01 mol) and 50 ml of anhydrous THF were added to the filtrate. The whole was stirred for 5.5 h at room temperature, and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in 50 ml of $CHCl_3$. The $CHCl_3$ solution was washed successively with 1 N NaOH and H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was washed with a small amount of AcOEt, and recrystallized from AcOEt to give 1.08 g (30%) of **31**, mp 141 °C. *Anal.* Calcd for $C_{16}H_{17}N_3O_5S$: C, 52.88; H, 4.72; N, 11.56. Found: C, 53.04; H, 4.75; N, 11.45. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.81 (3H, s, 2-position), 3.46 (3H, s, CH_3SO_2), 3.81 (3H, s, OCH_3), 6.80 (2H, d, J=9 Hz, 2″- and 6″-positions), 6.90 (2H, d, J=9 Hz, 3″- and 5″-positions), 7.63 (2H, d, J=9 Hz, 2′- and 6′-positions), 8.33 (2H, d, J=9 Hz, 3′- and 5′-positions).

Preparation of Ethyl *N*-Arylacetimidates Ethyl *N*-(*p*-methoxyphenyl)-acetimidate,[1] ethyl *N*-(*p*-methylphenyl)acetimidate,[5] ethyl *N*-phenylacetimidate,[5] ethyl *N*-(*p*-chlorophenyl)acetimidate,[5] ethyl *N*-(*m*-chlorophenyl)acetimidate[5] and ethyl *N*-(*p*-nitrophenyl)acetimidate[6] were prepared

TABLE I. Preparation of N^1-Arenesulfonyl-N^1,N^2-diarylacetamidines[a)]

Compd. No.	Method	React. solvent	React. time (h)	Yield (%)	mp (°C)	Molecular formula	Analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1	A	Xylene	8	50	178	$C_{20}H_{15}Cl_2N_3O_4S$	51.73	3.26	9.05	51.66	3.24	9.07
2	A	Xylene	8	41	211	$C_{20}H_{15}Cl_2N_3O_4S$	51.73	3.26	9.05	51.48	3.30	9.14
3	A	Toluene	17	28	166	$C_{21}H_{15}ClF_3N_3O_4S$	50.66	3.04	8.44	50.71	3.02	8.41
4	A	Toluene	13	22	222	$C_{21}H_{15}ClN_4O_4S$	55.45	3.32	12.32	55.42	3.22	12.17
5	A	Toluene	7	29	203	$C_{20}H_{15}ClN_4O_6S\cdot$ 1/2AcOEt	50.92	3.69	10.80	50.78	3.64	10.89
7	A	Dioxane	2	30	193	$C_{20}H_{16}ClN_3O_4S$	55.88	3.75	9.77	55.87	3.73	9.73
8	A	Dioxane	1.5	42	184	$C_{20}H_{15}Cl_2N_3O_4S$	51.73	3.26	9.05	51.71	3.22	9.02
9	A	Dioxane	2	46	192	$C_{20}H_{15}ClN_4O_6S$	50.59	3.18	11.80	50.77	3.15	11.87
10	B	Dioxane	2.5	62	218	$C_{21}H_{19}N_3O_4S$	61.60	4.68	10.26	61.59	4.63	10.26
11	B	Dioxane	4	70	190	$C_{20}H_{17}N_3O_4S$	60.75	4.33	10.63	60.84	4.26	10.61
12	B	Dioxane	4	57	185	$C_{20}H_{16}ClN_3O_4S$	55.88	3.75	9.77	55.88	3.71	9.75
13	B	Dioxane	2	59	158	$C_{20}H_{16}N_4O_6S$	54.54	3.66	12.72	54.59	3.59	12.64
16	B	THF	2	53	178	$C_{22}H_{21}N_3O_5S$	60.12	4.82	9.56	60.04	4.74	9.50
17	B	Dioxane	12	24	183	$C_{21}H_{18}ClN_3O_4S$	56.82	4.09	9.47	56.83	4.07	9.39
19	A	Toluene	6.5	25	198	$C_{22}H_{18}N_4O_4S\cdot$ 1/2AcOEt	60.24	4.63	11.71	60.28	4.55	11.72
21	B	THF	7	23	152	$C_{21}H_{18}N_4O_7S$	53.61	3.86	11.91	53.61	3.80	11.72
22	B	THF	10	57	152	$C_{21}H_{18}N_4O_6S$	55.50	3.99	12.33	55.48	3.93	12.20
23	B	THF	5	23	155	$C_{23}H_{22}N_4O_6S$	57.25	4.60	11.61	57.12	4.58	11.51
24	B	THF	7	34	162	$C_{24}H_{24}N_4O_6S$	58.05	4.87	11.28	57.89	4.83	11.26
25	B	THF	7	29	164	$C_{21}H_{18}N_4O_6S_2$	51.84	3.73	11.52	51.73	3.84	11.41
26	B	THF	2	11	132	$C_{22}H_{18}F_3N_3O_5S$	53.55	3.68	8.52	53.53	3.68	8.42
27	B	THF	3	22	133	$C_{21}H_{18}N_4O_7S$	53.61	3.86	11.91	53.72	3.86	11.84
28	B	THF	2	24	150	$C_{22}H_{18}N_4O_5S$	58.66	4.03	12.44	58.69	3.96	12.18
29	B	THF	1	23	165	$C_{21}H_{19}N_3O_5S$	59.28	4.50	9.88	59.20	4.53	9.87
30	B	THF	4	33	170	$C_{21}H_{18}ClN_3O_5S$	54.84	3.95	9.14	54.90	3.92	9.19

a) All samples were recrystallized from ethyl acetate except for **22**, **27** and **28**. Compounds **22** and **27** were recrystallized from a mixture of ethyl acetate and petroleum benzin (4 : 1), and compound **28** was recrystallized from benzene.

TABLE II. ^{1}H-NMR Spectral Data for N^1-Arenesulfonyl-N^1,N^2-diarylacetamidines (δ, $CDCl_3$)

Compd. No.	2	2′	3′	4′	5′	6′	2″	3″	4″	5″	6″	2‴	3‴	4‴	5‴	6‴	Other signals
1	1.69	7.47	7.27				7.49		7.94	7.47	7.02	7.84	7.47				
2	1.69	7.36		7.24	7.44	7.49	7.50		7.94	7.47	7.02	7.85	7.49				
3	1.71	7.49	7.77				7.51		7.95	7.48	7.03	7.84	7.49				
4	1.72	7.49	7.81				7.50		7.96	7.48	7.02	7.81	7.49				
5	1.76	7.53	8.36				7.51		7.96	7.50	7.03	7.82	7.49				
7	1.76	7.53	8.32				6.57	7.25				7.87	7.50	7.64			
8	1.73	7.46	8.33				6.62	7.28				7.79	7.46				
9	1.75	7.55	8.37				6.63	7.29				8.75		8.48	7.70	8.20	
10	1.78	7.52	8.30				6.66	7.30	7.07			7.75	7.28				CH_3 (Ts), 2.44
11	1.77	7.54	8.31				6.64	7.29	7.08			7.88	7.49	7.62			
12	1.74	7.53	8.32				6.69	7.32	7.10			7.81	7.45				
13	1.76	7.56	8.36				6.68	7.32	7.11			8.73		8.46	7.69	8.23	
16	1.78	7.52	8.30				6.20		6.62	7.19	6.24	7.75	7.28				CH_3 (Ts), 2.44; CH_3O, 3.78
17	1.77	7.51	8.32				6.64		7.04	7.21	6.55	7.74	7.29				CH_3 (Ts), 2.46
19	1.76	7.52	8.33				6.72	7.58				7.75	7.31				CH_3 (Ts), 2.48
21	1.79	7.55	8.35				6.65	6.86				8.76		8.45	7.68	8.19	CH_3O, 3.80
22	1.76	7.56	8.35				6.59	7.12				8.73		8.45	7.68	8.21	CH_3, 2.32
23	1.78	7.56	8.35				6.62	7.13				8.72		8.45	7.68	8.22	CH_3, 1.24; CH, 2.89
24	1.78	7.56	8.35				6.63	7.33				8.72		8.46	7.69	8.23	CH_3, 1.31
25	1.77	7.55	8.36				6.64	7.23				8.75		8.46	7.69	8.20	CH_3S, 2.48
26	1.75	7.49	7.76				6.64	6.86				8.79		8.44	7.67	8.21	CH_3O, 3.79
27	1.79	8.19		8.37	7.71	7.75	6.65	6.86				8.75		8.47	7.70	8.22	CH_3O, 3.80
28	1.77	7.49	7.79				6.64	6.86				8.74		8.45	7.68	8.19	CH_3O, 3.80
29	1.80	7.54	8.31				6.60	6.84				7.87	7.48	7.61			CH_3O, 3.79
30	1.77	7.53	8.31				6.64	6.87				7.80	7.44				CH_3O, 3.79

according to the cited references. The following imidates were prepared by the reaction of ethyl orthoacetate and arylamines.[7)] Ethyl *N*-(*p*-isopropylphenyl)acetimidate, bp 131 °C/13 mmHg, yield 88%. *Anal.* Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 75.66; H, 9.51; N, 6.74. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.23 (6H, d, J=7 Hz, CH_3 of isopropyl), 1.33 (3H, t, J=7 Hz, CH_2CH_3), 1.83 (3H, s, 2-position), 2.86 (1H, septet, J=7 Hz, CH of isopropyl), 4.21 (2H, q, J=7 Hz, CH_2CH_3), 6.68 (2H, d, J=9 Hz, 2′- and 6′-positions), 7.12 (2H, d, J=9 Hz, 3′-

and 5'-positions). Ethyl *N*-(*p*-(*tert*-butyl)phenyl)acetimidate, bp 139 °C/18 mmHg, yield 78%. *Anal.* Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.53; H, 9.84; N, 6.43. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.30 (9H, s, *tert*-Bu), 1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.83 (3H, s, 2-position), 4.22 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.68 (2H, d, J=9 Hz, 2'- and 6'-positions), 7.28 (2H, d, J=9 Hz, 3'- and 5'-positions). Ethyl *N*-(*p*-methylthiophenyl)acetimidate, bp 156 °C/15 mmHg, yield 80%. *Anal.* Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.03; H, 7.45; N, 6.78. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.30 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.80 (3H, s, 2-position), 2.42 (3H, s, SCH_3), 4.25 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.73 (2H, d, J=9 Hz, 2'- and 6'-positions), 7.28 (2H, d, J=9 Hz, 3'- and 5'-positions). Ethyl *N*-(*p*-cyanophenyl)acetimidate, bp 164 °C/13 mmHg, mp 75 °C (petroleum ether), yield 82%. *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.15; H, 6.43; N, 14.77. ^{1}H-NMR ($CDCl_3$, 60 MHz) δ: 1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.80 (3H, s, 2-position), 4.23 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.83 (2H, d, J=9 Hz, 2'- and 6'-positions), 7.58 (2H, d, J=9 Hz, 3'- and 5'-positions). Ethyl *N*-(*m*-nitrophenyl)acetimidate, bp 169 °C/22 mmHg, yield 64%. *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.77; H, 5.85; N, 13.28. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.36 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.85 (3H, s, 2-position), 4.24 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.10 (1H, ddd, J=8, 2, 1 Hz, 6'-position), 7.44 (1H, t, J=8 Hz, 5'-position), 7.62 (1H, t, J=2 Hz, 2'-position), 7.90 (1H, ddd, J=8, 2, 1 Hz, 4'-position). Ethyl *N*-(*m*-methoxyphenyl)acetimidate, bp 141 °C/22 mmHg, yield 91%. *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.46; H, 7.98; N, 7.58. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 1.33 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.83 (3H, s, 2-position), 3.78 (3H, s, OCH_3), 4.21 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.32 (1H, t, J=2 Hz, 2'-position), 6.35 (1H, ddd, J=8, 2, 1 Hz, 6'-position), 6.59 (1H, ddd, J=8, 2, 1 Hz, 4'-position), 7.17 (1H, t, J=8 Hz, 5'-position).

Preparation of *N*-Arylarenesulfonamides *N*-(*p*-Chlorophenyl)-*p*-chlorobenzenesulfonamide,[8] *N*-(*m*-chlorophenyl)-*p*-chlorobenzenesulfonamide,[8] *N*-(*p*-nitrophenyl)-*p*-chlorobenzenesulfonamide,[8] *N*-(*p*-trifluoromethylphenyl)-*p*-chlorobenzenesulfonamide,[9] *N*-(*p*-nitrophenyl)-*m*-nitrobenzenesulfonamide,[10] *N*-(*p*-trifluoromethylphenyl)-*m*-nitrobenzenesulfonamide,[11] *N*-(*m*-nitrophenyl)-*m*-nitrobenzenesulfonamide[12] and *N*-(*p*-nitrophenyl)methanesulfonamide[13] were prepared according to the cited references.

N-(*p*-Cyanophenyl)-*p*-chlorobenzenesulfonamide was prepared by the usual method. mp 181.5 °C (AcOEt), yield 66%. *Anal.* Calcd for $C_{13}H_9ClN_2O_2S$: C, 53.34; H, 3.10; N, 9.57. Found: C, 53.33; H, 3.05; N, 9.51. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 7.18 (2H, d, J=8 Hz, 2'- and 6'-positions), 7.19 (1H, br s, NH), 7.48 (2H, d, J=8 Hz, 3- and 5-positions), 7.56 (2H, d, J=8 Hz, 3'- and 5'-positions), 7.78 (2H, d, J=8 Hz, 2- and 6-positions). *N*-(*p*-Cyanophenyl)-*m*-nitrobenzenesulfonamide, mp 195 °C (AcOEt), yield 75%. *Anal.* Calcd for $C_{13}H_9N_3O_4S$: C, 51.48; H, 2.99; N, 13.85. Found: C, 51.61; H, 2.99; N, 13.74. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 7.29 (2H, d, J=9 Hz, 2'- and 6'-positions), 7.75 (2H, d, J=9 Hz, 3'- and 5'-positions), 7.90 (1H, t, J=8 Hz, 5-position), 8.25 (1H, ddd, J=8, 2, 1 Hz, 6-position), 8.49 (1H, ddd, J=8, 2, 1 Hz, 4-position), 8.56 (1H, t, J=2 Hz, 2-position), 11.31 (1H, br s, NH).

Preparation of *p*-Cyanoacetophenoxime Tosylate The compound was prepared by the same method as used for the preparation of *m*-nitroacetophenoxime tosylate.[4] mp 120 °C (AcOEt), yield 85%. *Anal.* Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 60.92; H, 4.42; N, 8.84. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 2.36 (3H, s, 2-position), 2.45 (3H, s, CH_3 of Ts), 7.38 (2H, d, J=8 Hz, 3''- and 5''-positions), 7.67 (2H, d, J=9 Hz, 3'- and 5'-positions), 7.71 (2H, d, J=9 Hz, 2'- and 6'-positions), 7.92 (2H, d, J=8 Hz, 2''- and 6''-positions).

Kinetic Runs The alcoholysis reaction was allowed to proceed in EtOH–THF (99 : 1, v/v) solution in the presence or absence of NaOEt at 25 °C unless otherwise noted. The ionic strength was maintained at 0.02 by the addition of NaBr unless otherwise noted.

Preparation of the Reaction Solution A THF solution (1 ml) of the substrate (2 to 8 × 10^{-3} M) was added to EtOH or EtOH containing NaOEt in a 100 ml volumetric flask which had been prewarmed to the desired temperature, and the mixture was diluted to the mark with the same EtOH solution.

Alcoholysis in the Presence of NaOEt The UV spectra of **15** and *N*-(*p*-nitrophenyl)-*p*-toluenesulfonamide in the presence of NaOEt and ethyl *N*-(*p*-methylphenyl)acetimidate in EtOH–THF (99 : 1, v/v) are shown in Fig. 1. The proportion of *N*-(*p*-nitrophenyl)-*p*-toluenesulfonamide was calculated from the absorbance of the reaction solution at 390 nm. The reactions of **5**—**20** were followed in the same manner. The UV spectra of N^1-(*p*-chlorobenzenesulfonyl)-N^1-(*p*-trifluoromethylphenyl)-N^2-(*m*-nitrophenyl)acetamidine (**3**), *N*-(*p*-trifluoromethylphenyl)-*p*-chlorobenzenesulfonamide and ethyl *N*-(*m*-nitrophenyl)acetimidate are shown in Fig. 2. The proportions of **3** and the sum of sulfonamide and imidate were calculated from the absorbancies of the reaction solution at 235, 240, 245, 250, 255 and 260 nm by the least-squares method for two variables. The reactions of **1**—**4** were followed in the same manner.

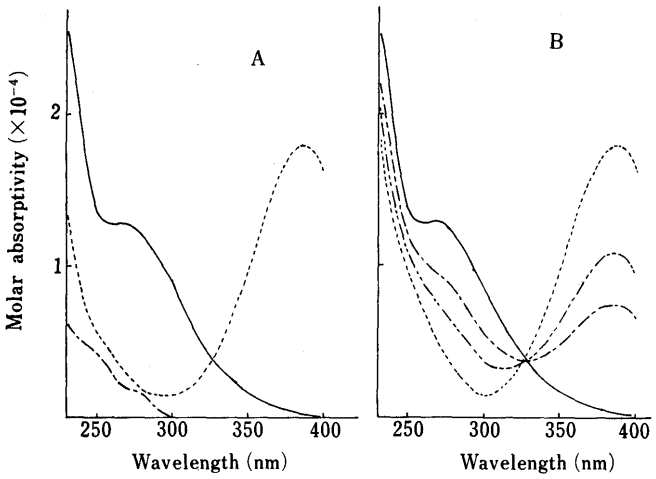


Fig. 1. A: Absorption Spectra of **15** (——) and *N*-(*p*-Nitrophenyl)-*p*-methylbenzenesulfonamide (– – –) in EtOH–THF (99 : 1, v/v) in the Presence of 0.02 M NaOEt, and Ethyl *N*-(*p*-Methylphenyl)acetimidate (—·—) in EtOH–THF (99 : 1, v/v) at 25 °C

B: Absorption Spectra of **15** in EtOH–THF (99 : 1, v/v) in the Presence of 0.02 M NaOEt, Immediately after Dissolution (——), at 990 min after Dissolution (—·—), at 1840 min after Dissolution (— – —) and the Sum of the Spectra of *N*-(*p*-Nitrophenyl)-*p*-methylbenzenesulfonamide and Ethyl *N*-(*p*-Methylphenyl)acetimidate (– – –) at 25 °C

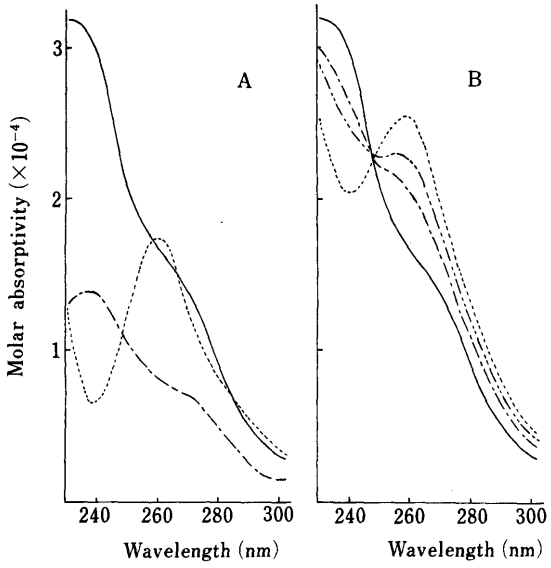


Fig. 2. A: Absorption Spectra of **3** (——) and *N*-(*p*-Trifluoromethylphenyl)-*p*-chlorobenzenesulfonamide (– – –) in EtOH–THF (99 : 1, v/v) in the Presence of 0.02 M NaOEt, and Ethyl *N*-(*m*-Nitrophenyl)acetimidate (—·—) in EtOH–THF (99 : 1, v/v) at 25 °C

B: Absorption Spectra of **3** in EtOH–THF (99 : 1, v/v) in the Presence of 0.02 M NaOEt, Immediately after Dissolution (——), at 160 min after Dissolution (—·—), at 320 min after Dissolution (— – —), and the Sum of the Spectra of *N*-(*p*-Trifluoromethylphenl)-*p*-chlorobenzenesulfonamide and Ethyl *N*-(*m*-Nitrophenyl)acetimidate (– – –) at 25 °C

Alcoholysis under Neutral Conditions The UV spectra of N^1-(*m*-nitrobenzenesulfonyl)-N^1-(*p*-nitrophenyl)-N^2-(*p*-methoxyphenyl)acetamidine (**21**), *N*-(*p*-nitrophenyl)-*m*-nitrobenzenesulfonamide and ethyl *N*-(*p*-methoxyphenyl)acetimidate are shown in Fig. 3. The proportions of **21** and the sum of sulfonamide and imidate were calculated from the absorbancies of the reaction solution at 265, 270, 305 and 310 nm by the

TABLE III. Second-Order Rate Constants, k^{EtO}, of Alcoholysis of **1**—**20** in 1% THF–EtOH in the Presence of EtONa at 25 °C; Ionic Strength 0.02[a,b]

Compd. No.	X	Y	Z	$10^4 k^{EtO}$ ($M^{-1}s^{-1}$)	Compd. No.	X	Y	Z	$10^4 k^{EtO}$ ($M^{-1}s^{-1}$)
1	*p*-Cl	*m*-NO_2	*p*-Cl	3.77 (0.206)	**11**	*p*-NO_2	H	H	4.70 (0.122)
2	*m*-Cl	*m*-NO_2	*p*-Cl	10.2 (0.323)	**12**	*p*-NO_2	H	*p*-Cl	8.74 (0.610)
3	*p*-CF_3	*m*-NO_2	*p*-Cl	22.9 (0.622)	**13**	*p*-NO_2	H	*m*-NO_2	43.4 (3.49)
4	*p*-CN	*m*-NO_2	*p*-Cl	117 (4.4)	**15**	*p*-NO_2	*p*-CH_3	*p*-CH_3	1.68 (0.301)
5	*p*-NO_2	*m*-NO_2	*p*-Cl	259 (4.9)	**16**	*p*-NO_2	*m*-CH_3O	*p*-CH_3	4.69 (0.154)
6	*p*-NO_2	*p*-Cl	*p*-CH_3	12.8 (0.71)	**17**	*p*-NO_2	*m*-Cl	*p*-CH_3	16.0 (0.69)
7	*p*-NO_2	*p*-Cl	H	20.8 (0.62)	**18**	*p*-NO_2	*m*-NO_2	*p*-CH_3	75.9 (2.26)
8	*p*-NO_2	*p*-Cl	*p*-Cl	41.6 (1.00)	**19**	*p*-NO_2	*p*-CN	*p*-CH_3	136 (6.2)
9	*p*-NO_2	*p*-Cl	*m*-NO_2	187 (7.7)	**20**	*p*-NO_2	*p*-NO_2	*p*-CH_3	284 (5.5)
10	*p*-NO_2	H	*p*-CH_3	3.05 (0.102)					

a) The precise k^{EtO} for **14** could not be obtained. *b*) Standard deviations are shown in parentheses.

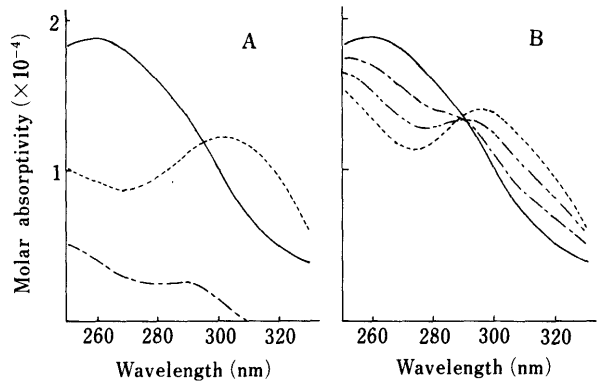


Fig. 3. A: Absorption Spectra of **21** (——), *N*-(*p*-Nitrophenyl)-*m*-nitrobenzenesulfonamide (– – –) and Ethyl *N*-(*p*-Methoxyphenyl)acetimidate (—·—) in EtOH–THF (99:1, v/v) at 25 °C

B: Absorption Spectra of **21** in EtOH–THF (99:1, v/v), Immediately after Dissolution (——), at 45 min after Dissolution (—·—), at 130 min after Dissolution (—··—), and the Sum of the Spectra of *N*-(*p*-Nitrophenyl)-*m*-nitrobenzenesulfonamide and Ethyl *N*-(*p*-Methoxyphenyl)acetimidate (– – –) at 25 °C

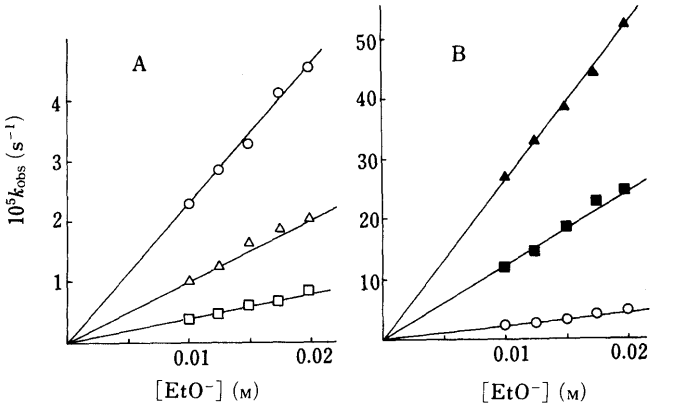


Fig. 4. Plots of the Apparent Rate Constants, k_{obs}, of Alcoholysis of **1**—**5** in EtOH–THF (99:1, v/v) in the Presence of NaOEt *versus* [EtO^-] at 25 °C

Ionic strength 0.02. A: □, **1**; △, **2**; ○, **3**. B: ○, **3**; ■, **4**; ▲, **5**.

least-squares method for two variables. The reactions of **14**, **21**—**25**, **29** and **30** were followed in the same manner. The reactions of **26**—**28** were followed in the same manner as those of **1**—**4** after the addition of NaOEt to the reaction solution immediately before UV measurement.

Alcoholysis of 31 under Neutral Conditions The reaction proceeded in two ways; by alcoholysis at the amidine central carbon to give *N*-(*p*-nitrophenyl)methanesulfonamide and ethyl *N*-(*p*-methoxyphenyl)acetimidate (k_1^0), and by alcoholysis at the sulfonamide nitrogen to give N^1-(*p*-methoxyphenyl)-N^2-(*p*-nitrophenyl)acetamidine and ethyl methanesulfonate (k_2^0). The alcoholysis of **31** was carried out by allowing an EtOH–THF (60:40, v/v) solution of **31** to stand for 8 d at 25 °C. The ^{1}H-NMR (DMSO-d_6) spectrum of the crude product showed the presence of all the substances mentioned above. In the kinetic runs (25 °C, EtOH–THF (99:1, v/v)), the proportions of **31**, amidine, and the sum of sulfonamide and imidate were calculated from the absorbancies at 275, 280, 305, 310, 355 and 360 nm (near λ_{max} of each substance) by the least-squares method for three variables. The value of k_1^0 was 5.78 (0.062) × 10^{-6} s^{-1}, and k_2^0 was 1.03 (0.106) × 10^{-6} s^{-1}. Standard deviations are shown in parentheses.

Alcoholysis of 21 in the Presence of HCl Ionic strength of the reaction solution was maintained at 0.02 by the addition of LiCl. The proportions of **21** and *N*-(*p*-nitrophenyl)-*m*-nitrobenzenesulfonamide were calculated from the absorbancies at 300, 320, 325 and 375 nm of the reaction solution, to which NaOEt was added immediately before the UV measurement, by the least-squares method for two variables (absorption by imidate could be neglected at the cited wavelengths).

Results

The Effect of the Substituent X on the Reaction Rate The apparent rate constant of alcoholysis in the presence of NaOEt k_{obs}, is represented by Eq. 1.

$$k_{obs} = k^0 + k^{EtO}[EtO^-] \quad (1)$$

Plots of k_{obs} *vs.* [EtO^-] were linear (Fig. 4), and the second-order rate constants, k^{EtO}, are shown in Table III. The k^{EtO} values for **1**—**5** (Y = *m*-NO_2, Z = *p*-Cl) showed a linear logarithmic relation with the corrected Hammett's substituent constant[14] according to the Yukawa–Tsuno equation (2),[15] $\sigma + r(\sigma^- - \sigma)$, with a ρ value of 2.50 and an r value of 0.41 (Fig. 5). The correlation coefficient, R, was 0.9983.

$$\log k^{EtO} = \rho\{\sigma + r(\sigma^- - \sigma)\} + \log k_H^{EtO} \quad (2)$$

Willi[16] reported that the dissociation constant of *N*-arylarenesulfonamides correlated well with σ^- of the aryl substituents ($\rho^- = 1.74$). The r value of 0.41 in Fig. 5 suggests that the resonance effect of the substituent X plays a role to in stabilizing the transition state to a moderate extent.

The Effect of the Substituent Z on the Reaction Rate Plots of k_{obs} *vs.* [EtO^-] for **6**—**13** are shown in Fig. 6. The k^{EtO} values for **6**—**9** (X = *p*-NO_2, Y = *p*-Cl) (Table III) showed a linear logarithmic relation with σ of the substituent Z with a ρ value of 1.33, R = 0.9999 (Eq. 3).

$$\log k^{EtO} = \rho\sigma + \log k_H^{EtO} \quad (3)$$

The effect of the substituent Z on the reaction rate was less than that of X. In these experiments, substrates carrying a

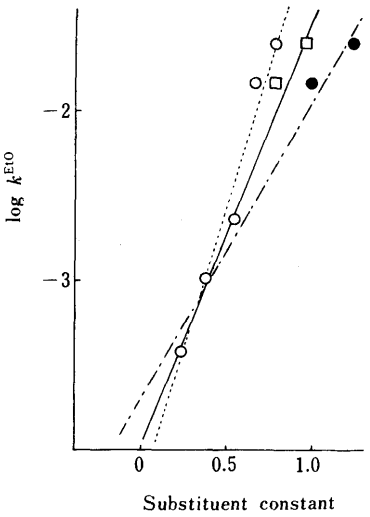


Fig. 5. Hammett's Plots of k^{EtO} for the Substituent X (**1**—**5**) (Y=*m*-NO_2, Z=*p*-Cl)

○, σ; ●, σ^-; □, $\sigma+r(\sigma^- -\sigma)$. ——, log k^{EtO} *versus* $\sigma+r(\sigma^- -\sigma)$ ($\rho=2.50$, $R=0.9983$); – – –, log k^{EtO} *versus* σ ($\rho=3.38$, $R=0.9869$); —·—, log k^{EtO} *versus* σ^- ($\rho^-=1.76$, $R=0.9921$).

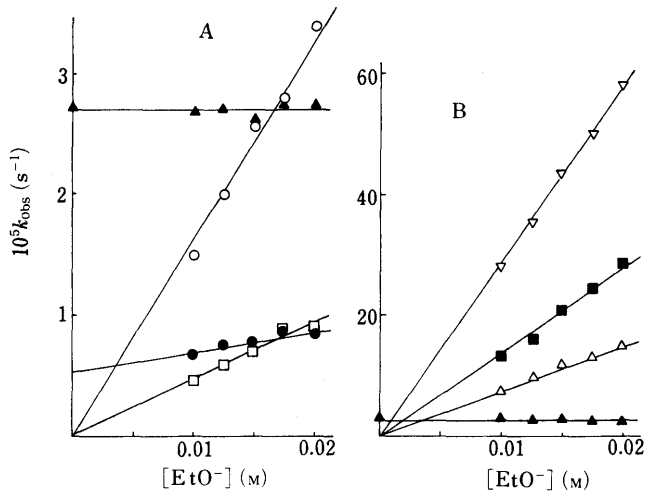


Fig. 7. Plots of the Apparent Rate Constants, k_{obs}, of Alcoholysis of **14**—**20**, in EtOH–THF (99 : 1, v/v) in the Presence of NaOEt *versus* [EtO^-] at 25 °C

Ionic strength 0.02. A: ▲, **14**; ●, **15**; □, **16**; ○, **17**. B: ▲, **14**; △, **18**; ■, **19**; ▽, **20**.

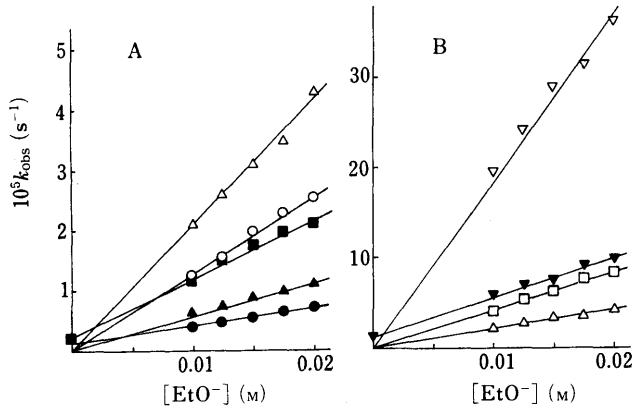


Fig. 6. Plots of the Apparent Rate Constants, k_{obs}, of Alcoholysis of **6**—**13** in EtOH–THF (99 : 1, v/v) in the Presence of NaOEt *versus* [EtO^-] at 25 °C

Ionic strength 0.02. A: ○, **6**; △, **7**; ●, **10**; ▲, **11**; ■, **12**. B: △, **7**; □, **8**; ▽, **9**; ▼, **13**.

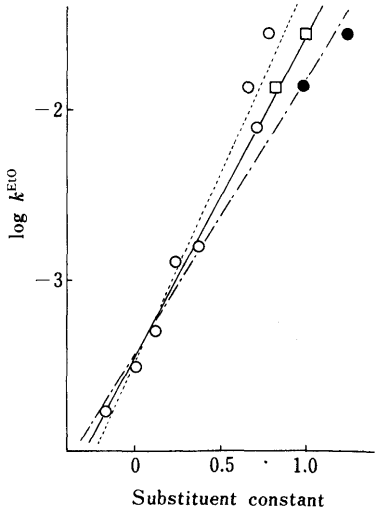


Fig. 8. Hammett's Plots of k^{EtO} for the Substituent Y (**6**, **10** and **15**—**20**) (X=*p*-NO_2, Z=*p*-CH_3)

○, σ; ●, σ^-; □, $\sigma+r(\sigma^- -\sigma)$. ——, log k^{EtO} *versus* $\sigma+r(\sigma^- -\sigma)$ ($\rho=1.92$, $R=0.9965$); – – –, log k^{EtO} *versus* σ ($\rho=2.26$, $R=0.9829$); —·—, log k^{EtO} *versus* σ^- ($\rho^-=1.62$, $R=0.9901$).

strongly electron-withdrawing Z at the para position to the sulfonyl group were not examined because these compounds readily undergo Smiles rearrangement to give trisubstituted amidines.[2)]

The k^{EtO} values of **10**—**13** (X=*p*-NO_2, Y=H) (Table III) also correlated well with σ of the substituent Z ($\rho=1.32$, $R=0.9982$). The electronic properties of the substituents Y (Y=H and *p*-Cl) do not affect the sensitivity of the reaction rate to the electronic effect of Z.

The Effect of the Substituent Y on the Reaction Rate Plots of k_{obs} *vs.* [EtO^-] for **14**—**20** are shown in Fig. 7. The k^{EtO} values of **6**, **10** and **15**—**20** (X=*p*-NO_2, Z=*p*-CH_3) (Table III) were analyzed by the use of Eq. 2 to give a ρ value of 1.92 and an r value of 0.51, with $R=0.9965$ (Fig. 8). The results showed that the resonance effect of the substituent Y plays a role in stabilizing the transition state to a similar extent to that of the substituent X.

A remarkable contribution of the term k^0 to the reaction rate of N^1-tosyl-N^1-(*p*-nitrophenyl)-N^2-(*p*-methoxyphenyl)acetamidine (**14**), which carries electron-releasing Y and electron-withdrawing X, was observed (Fig. 7), while the k^{EtO} value for the same substrate was too small to allow us to obtain a precise value. The alcoholysis of **14** proceeded in EtOH–THF (99 : 1, v/v) solution without any added catalyst. The k^0 value was evaluated to be 2.72 (0.029) × 10^{-5} s^{-1} at 25 °C (standard deviation in parenthesis).

Alcoholysis under Neutral Conditions Alcoholysis of the substrates carrying electron-releasing Y and electron-withdrawing X and Z (**9**, **13**, **21**—**25** and **26**—**28**) proceeded with measurable rates under neutral conditions (Table IV).

The reaction of **21** was also undertaken in the presence of hydrogen chloride for the purpose of discriminating whether the reaction proceeds *via* the conjugate acid of **21** or not. The apparent rate constants, k_{obs}, are represented by Eq. 4

TABLE IV. Pseudo First-Order Rate Constants, k^0, of Alcoholysis of **9**, **13**, **14** and **21**—**30**; Ionic Strength 0.02[a]

Compd. No.	X	Y	Z	10^5k^0 (s^{-1}) 18 °C	25 °C	32 °C	39 °C	46 °C	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal K^{-1} mol^{-1})
9	p-NO_2	p-Cl	m-NO_2		0.202 (0.0021)					
13	p-NO_2	H	m-NO_2		1.14 (0.083)	3.26 (0.071)	8.29 (0.413)	18.6 (1.05)	24.5 (0.67)	0.60 (2.16)
14	p-NO_2	p-CH_3O	p-CH_3		2.72 (0.029)					
21	p-NO_2	p-CH_3O	m-NO_2	5.18 (0.189)	14.2 (0.42)	33.3 (2.59)	73.2 (3.63)		22.1 (0.99)	−2.1 (1.98)
22	p-NO_2	p-CH_3	m-NO_2		4.31 (0.128)					
23	p-NO_2	p-isoPr	m-NO_2		4.21 (0.207)					
24	p-NO_2	p-(*tert*-Bu)	m-NO_2		3.86 (0.250)					
25	p-NO_2	p-CH_3S	m-NO_2		1.86 (0.129)					
26	p-CF_3	p-CH_3O	m-NO_2		1.04 (0.023)					
27	m-NO_2	p-CH_3O	m-NO_2		2.74 (0.038)					
28	p-CN	p-CH_3O	m-NO_2		6.04 (0.026)					
29	p-NO_2	p-CH_3O	H		3.18 (0.108)					
30	p-NO_2	p-CH_3O	p-Cl		4.81 (0.134)					

a) Standard deviations are shown in parentheses.

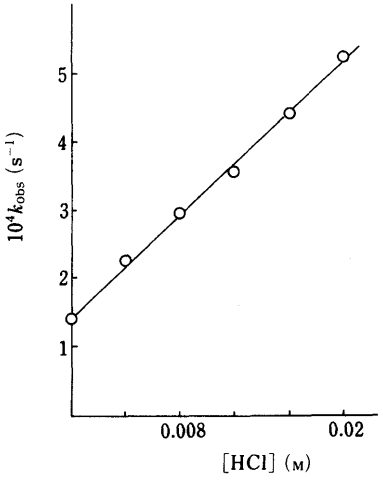


Fig. 9. Plot of the Apparent Rate Constants, k_{obs}, of Alcoholysis of **21** in EtOH–THF (99 : 1, v/v) in the Presence of HCl *versus* [HCl] at 25 °C
Ionic strength 0.02.

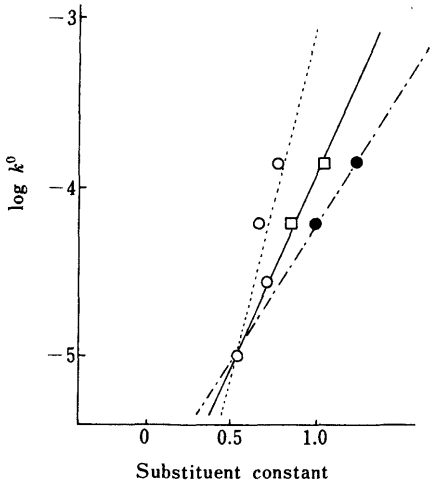


Fig. 10. Hammett's Plots of k^0 for the Substituent X (**21** and **26**—**28**) (Y = p-CH_3O, Z = m-NO_2)
○, σ; ●, σ^-; □, $\sigma+r(\sigma^- -\sigma)$. ——, log k^0 *versus* $\sigma+r(\sigma^- -\sigma)$ (ρ = 2.26, R = 0.9973); – – –, log k^0 *versus* σ (ρ = 4.22, R = 0.8719); — · —, log k^0 *versus* σ^- (ρ^- = 1.57, R = 0.9928).

$$k_{obs}=k^0+\frac{[H^+]k^H}{[H^+]+K_{BH^+}} \quad (4)$$

where K_{BH^+} and k^H are the dissociation constant of the conjugate acid of the substrate and the rate constant of the reaction between the conjugate acid and ethanol, respectively. If the basicity of the substrate is low enough, $K_{BH^+} \gg [H^+]$, Eq. 4 reduces to Eq. 5.

$$k_{obs}=k^0+\frac{k^H}{K_{BH^+}}[H^+] \quad (5)$$

The plot of k_{obs} *vs.* [HCl] was linear showing that Eq. 5 is valid under these conditions (Fig. 9). The value of k^H/K_{BH^+} was calculated to be 1.90 (0.066) × 10^{-2} M^{-1} s^{-1} (standard deviation in parenthesis). Based on the autoprotolysis constant of ethanol (pK_s = 19.1), the value of k^0 is estimated to be 5.36 × 10^{-12} s^{-1} if the reaction proceeds *via* the conjugate acid of the substrate under neutral conditions. Since k^0 = 1.42 × 10^{-4} s^{-1} experimentally (Table IV), the reaction must proceed between the neutral substrate and ethanol. The k^0 values of **9**, **13**, and **21**—**25** (X = p-NO_2, Z = m-NO_2) (Table IV) were analyzed according to Yukawa–Tsuno equation (6) to give a ρ value of −3.37, and an r value of 0.09, with R = −0.9926.

$$\log k^0=\rho\{\sigma+r(\sigma^+-\sigma)\}+\log k_H^0 \quad (6)$$

The reaction rate hardly depends at all on the resonance effect of the substituent Y. The k^0 values of **21** and **26**—**28** (Y = p-CH_3O, Z = m-NO_2) (Table IV) were analyzed according to Eq. 2 to give a ρ value of 2.26 and an r value of 0.58, with R = 0.9973 (Fig. 10). The enhanced r value of the substituent X as compared with that of the same substituent for the term k^{EtO} suggests that there is a larger change in the charge of sulfonamide nitrogen in the transition state of the neutral alcoholysis as compared with that of the attack of ethoxide ion.

The k^0 values of **14**, **21**, **29** and **30** (X = p-NO_2, Y = p-CH_3O) (Table IV) showed a linear logarithmic relation with σ of the substituent Z with a ρ value of 0.84. R = 0.9917. The effect of the substituent Z on the reaction rate was reasonably less than those of X and Y.

Discussion

Schmir *et al.*[17] reported that the rate constants of the

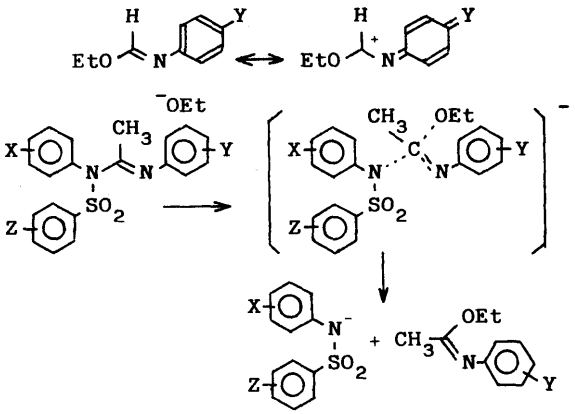


Chart 2

step of hydroxide ion attack in the alkaline hydrolysis of ethyl *N*-arylformimidates were well correlated with σ^- of aryl substituents with a ρ^- value of 1.68.[18] As is shown in Chart 2, the resonance effect of electron-withdrawing aryl substituents enhances the electrophilicity of the reaction site. In the present reaction, the resonance effect of the substituent Y influenced the second-order rate constant, k^{EtO}, to a moderate extent ($r=0.51$), while that of X also did so to a similar extent ($r=0.41$). Probably the attack of ethoxide ion on the amidine central carbon is accompanied by the concerted departure of the arenesulfonamide group so that the negative charge on the sulfonamide nitrogen increases in the transition state (Chart 2).

From a study on the exchange of isotopic carbonyl oxygen with oxygen of the medium, Bender[19] proposed that the hydrolysis of the ester proceeds through a tetrahedral intermediate. Since his proposal, it has been widely accepted that the carbonyl addition and related reactions proceed not by a nucleophilic substitution on the sp^2 carbon but by an addition and subsequent elimination mechanism. If the tetrahedral intermediate is too unstable to have a sufficient lifetime, however, the possibility remains that the reaction proceeds by a concerted mechanism with properties similar to those expected for the first step. Jencks and Gilchrist[20] claimed that the tetrahedral intermediate in the aminolysis of aryl acetate does not have a sufficient lifetime to reach equilibrium with respect to proton transfer on the basis of the fact that tertiary amines react with aryl acetate with the same reaction characteristics as primary and secondary amines.

In the alcoholysis under neutral conditions, the reaction rate hardly depends on the electron-releasing resonance effect of the substituent Y ($r=0.09$). The reaction would not, therefore, proceed by a solvolysis mechanism (Chart 3). Heck and Winstein[21] reported that the rate of acetolysis of neophyl *p*-bromobenzenesulfonate correlated with σ^+ of the substituents on the neophyl group. They proposed a mechanism in which the reaction proceeds with anchimeric assistance, and the existence of the cationic three-membered ring intermediate was proved. The possibility can not be ruled out that the cationic intermediate formed by the solvolysis mechanism reacts directly with ethanol without forming the three-membered structure so that the rate of reaction does not correlate with σ^+ of the substituent Y. However, the situation requires that the rate of reaction should be correlated with σ^- of the substituent X, *i.e.*, the

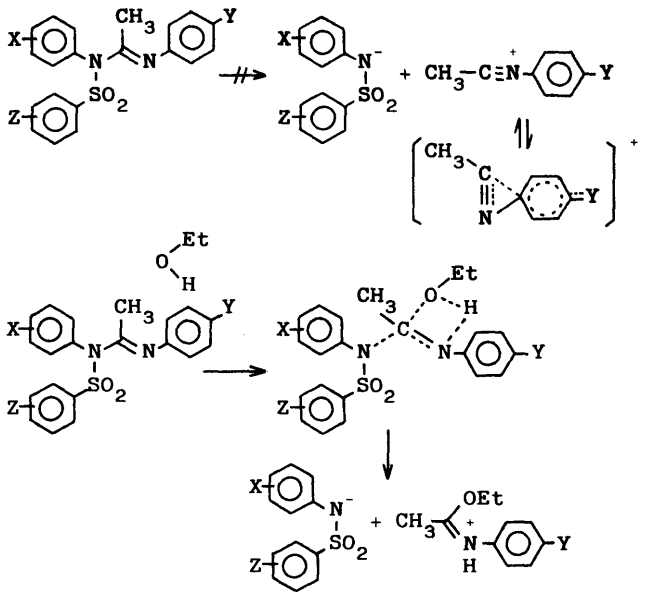


Chart 3

r value should be unity or near to it. The *r* value for the substituent X (0.58) is only slightly greater than that for the attack of ethoxide ion (0.41) suggesting that the two reactions proceed by similar mechanisms. The tetrahedral intermediate of the alcoholysis, if it exists at all, is structurally crowded, and is expected to readily expel the *N*-arylarenesulfonamide group to release the steric strain. As a result, the rate-determining attack of ethoxide ion or ethanol is accompanied by the concerted departure of the sulfonamide group (Charts 2 and 3). Jencks and Gilchrist[20] pointed out that the rate of the reaction between the esters and nucleophiles depends sharply on the basicity of both the attacking nucleophile and the leaving group as the basicity of the nucleophile decreases. The situation accords with the results that the *r* value for X in the neutral reaction (0.58) was greater than in the attack of ethoxide ion (0.41). In the neutral alcoholysis, the imino nitrogen probably assists the attack of ethanol on the amidine central carbon as an intramolecular general base catalyst as judged from the large negative value (-3.37) of ρ for substituent Y (Chart 3).[22]

Fersht and Kirby[23] reported that the activation entropy, $\Delta S^{\neq}$, is -22.5 eu for the intramolecular general base-catalyzed hydrolysis of acetylsalicylic acid. The values of $\Delta S^{\neq}$ for the neutral alcoholysis of **13** and **21** were nearly zero (Table IV). The large difference in the activation entropies of the two reactions would be attributable to the structural features of their transition states. Probably the eight-membered chelate structure for the intramolecular general base catalysis of acetylsalicylic acid hydrolysis requires a large negative activation entropy, while the present reaction proceeds *via* the four-membered chelate intermediate which would be expected to require a less negative activation entropy (Chart 3).

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22) Another possible mechanism for the neutral alcoholysis would be based on the enhancement of the electrophilicity of the amidine central carbon by charge transfer from the imino nitrogen to the aromatic ring of the arenesulfonyl group. This mechanism accords well with the large negative ρ value for the substituent Y. However, this mechanism was ruled out by the fact that the neutral alcoholysis of N^1-mesyl-N^1-(*p*-nitrophenyl)-N^2-(*p*-methoxyphenyl)acetamidine (**31**) also proceeded with a rate constant of $5.78 \times 10^{-6}\,s^{-1}$ (see Experimental).
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