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Kinetic Investigation on the Hydrolysis of Aryl(fluoro)(phenyl)-λ⁶-sulfanenitriles

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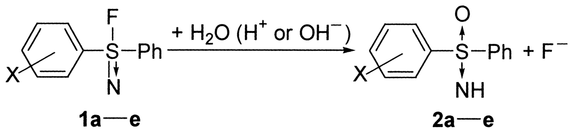
A kinetic investigation on the hydrolysis of aryl(fluoro)(phenyl)-λ^6-sulfanenitriles was carried out in some aqueous and mixed aqueous-organic solutions. The pH-rate profiles showed that the hydrolysis consists of pH-independent, acid-catalyzed and base-catalyzed reactions. The neutral hydrolysis of fluoro-λ^6-sulfanenitriles was found to proceed via an S_N1 or an *S*-nitrilosulfonium cation-like transition state, which is characterized by a large negative Hammett ρ-value ($\rho = -1.76$ in water; -1.85 in CH_3CN/H_2O(1/4, v/v); -2.35 in TFE/H_2O (1/1, v/v)), relatively large *m*-values (ca. 0.83 for fluoro(diphenyl)-λ^6-sulfanenitrile; ca. 0.82 for fluoro(*p*-nitrophenyl)(phenyl)-λ^6-sulfanenitrile against the solvent ionizing power Y_{OTs}-values in acetonitrile–water), a common ion effect in TFE/H_2O, and a small salt effect. The large negative activation entropies (-60—-101 J K^{-1} mol^{-1}) were presumed to be due to strong solvation of F^- with H_2O in the reaction systems. The ease of ion dissociation of the S–F bond was examined by a theoretical calculation in a DFT method, to show that the S_N1-like transition state is caused by a facile tendency of dissociation of the S–F bond of fluoro-λ^6-sulfanenitriles. The acid-catalyzed hydrolysis was found to proceed via a more cation-like transition state involving a concerted proton transfer to the fluorine atom and breaking of the sulfur-fluorine bond in the λ^6-sulfanenitrile. The alkaline hydrolysis probably takes place via an S_N2 mechanism.

Aryl(fluoro)(phenyl)-λ^6-sulfanenitriles,[1] ArPhFS(N) **1** bearing an SN triple bond are interesting unusual organic compounds. We previously reported[2] that the spectral data of fluoro(diphenyl)-λ^6-sulfanenitrile reported by Clifford et al.[3] are doubtful because of their improper isolation and large difference from those of our sample synthesized by a new method. In recent years, we have indirectly confirmed the structure of the compound by derivation to triphenyl-[4] and diphenyl(propoxy)-λ^6-sulfanenitriles,[5] and we have also prepared other λ^6-sulfanenitriles by using the fluoro-λ^6-sulfanenitriles as starting materials.[6–8] An X-ray crystallographic analysis of the structure of fluoro(*p*-nitrophenyl)(phenyl)-λ^6-sulfanenitrile has just been carried out.[9] We have been further studying their reactivities of conversion to various other new λ^6-sulfanenitriles. It is evident that these derivatives are formed by nucleophilic substitution at the sulfur atom. At the same time, these fluoro-λ^6-sulfanenitriles were found to be readily hydrolyzed to give the corresponding sulfoximides, unlike tetracoordinated sulfonyl fluorides, which are usually unreactive toward hydrolysis under acidic or neutral conditions.[10]

Our main interest in organic λ^6-sulfanenitriles is how the SN triple bond activates other sulfur bonds. More recently, we reported that alkoxy-λ^6-sulfanenitriles undergo a facile hydrolysis through an S_N1 or S_N1-like mechanism at the alkyl carbon atom, in which the sulfoximide moiety becomes a very good leaving group upon protonation of alkoxy-λ^6-sulfanenitriles.[11] In our previous paper,[8] it was reported that alkoxy-λ^6-sulfanenitriles exceptionally undergo a facile E*i* reaction, although λ^6-sulfanenitriles are classified as tetracoordinated hexavalent sulfur compounds, such as sulfones and sulfoximides. Nucleophilic substitutions at sulfur are usually suggested to proceed with or without a hypervalent intermediate (sulfurane) via an addition–elimination mechanism or a concerted S_N2-like mechanism.[12] However, there has been no mechanistic investigation on the nucleophilic reaction at the sulfur atom of λ^6-sulfanenitriles. Since it is expected that we can find new reactions and some new information from the unusual SN bonding through a clarification of the mechanism for the hydrolysis of fluoro-λ^6-sulfanenitriles **1**, kinetic investigations on the hydrolysis were carried out in some aqueous and mixed aqueous–organic solutions by an UV spectroscopic method.

Results and Discussion

Hydrolysis Products: Product analyses were carried out for the hydrolysis of aryl(fluoro)(phenyl)-λ^6-sulfanenitriles **1a–e** in an aqueous acetonitrile solution under neutral, acidic or basic conditions. Without addition of halide salts, the reactions were found to afford the corresponding sulfoximides **2a–e** quantitatively (Scheme 1). However, in the presence of po-



a: X=H, b: X=*p*-Me, c: X=*p*-Cl, d: X=*p*-NO_2, e: X=*m*-Cl

Scheme 1.

tassium bromide, the hydrolysis of **1d** was also found to give *N*-bromo-*S*-*p*-nitrophenyl-*S*-phenylsulfimide and *p*-nitrophenyl phenyl sulfide together with the corresponding sulfoximide **2d**.

pH-Rate Profiles and Kinetic Data: The rates of the hydrolysis of fluoro-λ^6-sulfanenitriles **1** in some aqueous solutions, aqueous acetonitrile, and aqueous 2,2,2-trifluoroethanol (TFE) were determined by following the changes in the UV absorbance of the reaction mixture at a proper wavelength. In all cases, the reactions were found to follow nicely the pseudo-first-order kinetics.

Typical pH-rate profiles for the hydrolysis of **1a**, **1c**, and **1d** are shown in Fig. 1. As can be seen from the pH-rate profiles, the hydrolysis is catalyzed by both acid and base, while in the pH range of 4.57–10.96 for **1a** and **1c** and in the pH range of 4.57–9.60 for **1d**, the rate of hydrolysis is almost pH-independent. The linear dependences (Figs. 2 and 3) of k_{obs} on $[\mathrm{H}^+]$ and $[\mathrm{OH}^-]$ in the acidic and basic pH ranges afforded the second-order rate constants, k_{H} and k_{OH}, respectively, as summarized in Table 1. The intercepts in the linear plots of k_{OH} *vs.* $[\mathrm{OH}^-]$ were found to be consistent with the observed rate constants in water in Table 1.

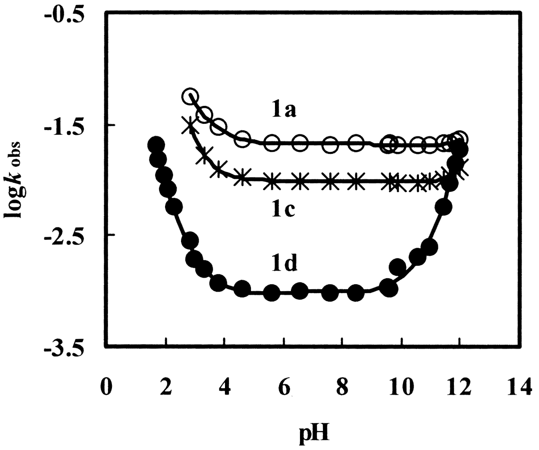


Fig. 1. pH-Rate profiles for the hydrolysis of **1a**, **1c** and **1d** at 20.4 °C. 2.81 ≤ pH ≤ 10.55: various buffer solutions at ionic strength 0.01; pH < 2.81: aqueous $\mathrm{HClO_4}$; pH > 10.55: aqueous NaOH solutions.

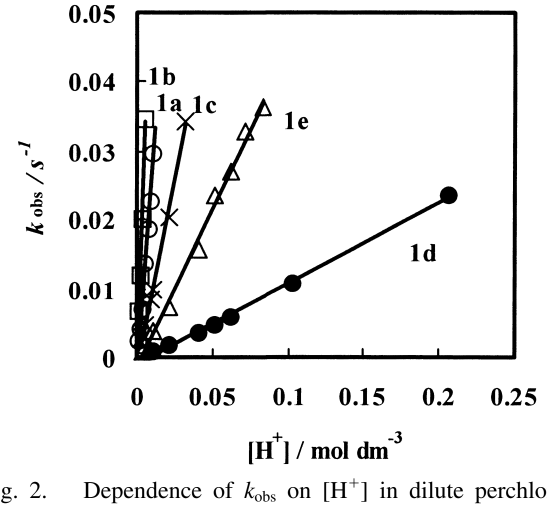


Fig. 2. Dependence of k_{obs} on $[\mathrm{H}^+]$ in dilute perchloric acid solutions containing 35.5% (v/v) of $\mathrm{CH_3CN}$ at 10.9 °C.

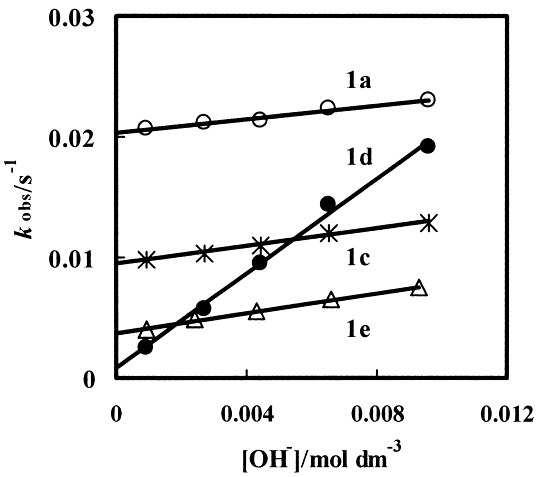


Fig. 3. Dependence of k_{obs} on $[\mathrm{OH}^-]$ in dilute NaOH solutions at 20.4 °C.

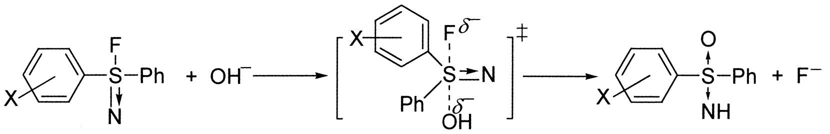
Alkaline Hydrolysis: Substituent Effect. A Hammett plot for the second-order rate constants, k_{OH}, of the alkaline hydrolysis afforded a positive ρ-value of 1.12 (Table 1), indicating that the bond formation of sulfur-nucleophile is kinetically more important than fission of the leaving group. Thus, the alkaline hydrolysis reaction is considered to proceed via a direct $\mathrm{S_N2}$ displacement (Scheme 2) or via an addition-elimination mechanism involving a hypervalent intermediate (sulfurane). The rates of typical $\mathrm{S_N2}$ reactions are not very sensitive to the substituents on the phenyl group on the displacement center atom, since there is a cancellation of electronic demands for the bond-making and bond-breaking components. Meanwhile, two-step addition-elimination reactions which proceed via rate-determining bond-making usually give larger positive Hammett ρ-values. For example, the Hammett ρ-values are around 2.2 for the alkaline hydrolysis of benzoate esters proceeding via a tetrahedral intermediate.[13] For the alkaline hydrolysis of substituted benzenesulfonyl fluorides in dioxane–water (45/55, w/w), the Hammett ρ-value is as high as 2.79.[14] On the contrary, a smaller ρ-value (1.546) was reported for the alkaline hydrolysis of substituted benzenesulfonyl chlorides,[15] in which a synchronous displacement is assumed from the fact of no $^{18}\mathrm{O}$ incorporation in the sulfonyl group in the alkaline hydrolysis of phenyl benzenesulfonate in $\mathrm{H_2{}^{18}O}$–dioxane. The ρ-value observed for the alkaline hydrolysis of **1** is even smaller than this, suggesting that there is more development of bond-breaking at the transition state, and that the present alkaline hydrolysis likely occurs via the $\mathrm{S_N2}$ mechanism.

Activation Parameters. The activation enthalpy ($\Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) for the alkaline hydrolysis of **1d** were determined to be 43 kJ $\mathrm{mol^{-1}}$ and −93 J $\mathrm{K^{-1}\,mol^{-1}}$ at 25 °C, respectively (see Table 1). The activation entropy is more negative than those of the alkaline hydrolysis of substituted benzenesulfonyl chloride and bromide,[15,16] which are in the range of $\Delta S^{\ddagger}$ values (−20–−40 J $\mathrm{K^{-1}}$ $\mathrm{mol^{-1}}$) for the usual $\mathrm{S_N2}$ reactions of neutral substrates with anion nucleophiles.[17] The

Table 1. Kinetic Data for the Hydrolysis of **1**

[**1**]	X	Temp.	$k_{obs}\times10^5/s^{-1}$			$k_H/s^{-1}\ mol^{-1}\ dm^3$		$k_{OH}$$^{a)}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
		°C	H_2O (D_2O)	CH_3CN /$H_2O$$^{b)}$	TFE/ $H_2O$$^{c)}$	CH_3CN/H_2O (D_2O)$^{d)}$	H_2O (D_2O)$^{e)}$	$s^{-1}\ mol^{-1}\ dm^3$	kJ mol^{-1}	J K^{-1} mol^{-1}
a	H	10.9		84.9	13.5	3.01 (3.39)				
a	H	20.4	2260 (1510)	202	37.0			0.278	60±1$^{f)}$	−87±1$^{f)}$
a	H	30.0		468	102				73±1$^{g)}$	−60±2$^{g)}$
a	H	39.1			244					
b	*p*-Me	10.9		249		6.61 (7.83)				
b	*p*-Me	20.4		600	130				60±1$^{f)}$	−84±4$^{f)}$
b	*p*-Me	30.0		1310						
c	*p*-Cl	10.9		33.9		1.09				
c	*p*-Cl	20.4	996	84.4	11.2			0.363	63±1$^{f)}$	−91±3$^{f)}$
c	*p*-Cl	30.0		192						
d	*p*-NO_2	10.9				0.117 (0.142)	0.371	1.09	65±1$^{f)}$	−101±5$^{f)}$
d	*p*-NO_2	20.4	101 (60.5)	10.2	0.781		0.910 (1.11)	1.97	60±1$^{h)}$	−97±2$^{h)}$
d	*p*-NO_2	30.0	225	25.1			2.31	3.66	66±2$^{i)}$	−20±6$^{i)}$
d	*p*-NO_2	39.1	471	53.0					43±1$^{j)}$	−93±4$^{j)}$
e	*m*-Cl	10.9				0.459				
e	*m*-Cl	20.4	369	31.9	3.10			0.418		
	$\rho^{k)}$		−1.76	−1.85	−2.35	−1.87		1.12		
	r		0.990	0.986	0.986	0.995		0.958		

a) In dilute NaOH of 0.001–0.01 mol dm^{-3}. b) CH_3CN/H_2O = 1/4 (v/v). c) TFE/H_2O = 1/1 (v/v). d) In dilute perchloric acid solution of 0.001–0.3 mol dm^{-3} containing 35.5% (v/v) CH_3CN. e) In dilute perchloric acid solution of 0.001–0.02 mol dm^{-3}. f) For the hydrolysis in CH_3CN/H_2O (1/4, v/v) at 25 °C. g) For the hydrolysis in TFE/H_2O (1/1, v/v) at 25 °C. h) For the hydrolysis in water at 25 °C. i) For k_H in dilute perchoric acid at 25 °C. j) For k_{OH} in dilute NaOH solution at 25 °C. k) For the rate of hydrolysis at 20.4 °C except for k_H at 10.9 °C.



Scheme 2.

present larger negative $\Delta S^{\ddagger}$ is probably due to the strong solvation of the fluoride ion leaving group.

Solvent Effect. The solvent effect on rate was examined by using mixed CH_3CN–H_2O solvents. The *m*-values for the solvent effects obtained by the correlations (the Winstein equation) of the rate constants with Y_{OTs}-values[18] are given in Table 2. For both **1a** and **1d**, the solvent effect on k_{OH} showed a positive *m*-value (0.35) for bimolecular reactions with a hydroxide anion. Usually, the reaction of an uncharged molecule with an anion would be expected to show no change or decrease in rate

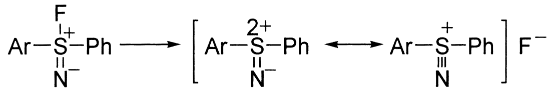
Table 2. Solvent Effect on the Hydrolysis of **1** under Neutral and Basic Conditions at 25.2 °C

Aq CH_3CN	$Y_{OTs}$$^{a)}$	$k_{obs}\times10^4/s^{-1\ b)}$		$k_{OH}/s^{-1}\ mol^{-1}\ dm^{3\ c)}$	
% v/v (w/w)$^{a)}$		**1a**	**1d**	**1a**	**1d**
40.8 (35)	1.8	3.99	0.183	0.044	0.392
35.5 (30)	1.9			0.056	
29.9 (25)	2.5	10.6	0.535	0.076	0.569
24.3 (20)	2.7	19.3	1.03	0.104	0.840
12.5 (10)	3.6	78.5	4.05	0.193	1.37
0	4.1	347	15.4	0.310	2.61
	m	0.83	0.82	0.35	0.35
	r	0.992	0.995	0.995	0.986

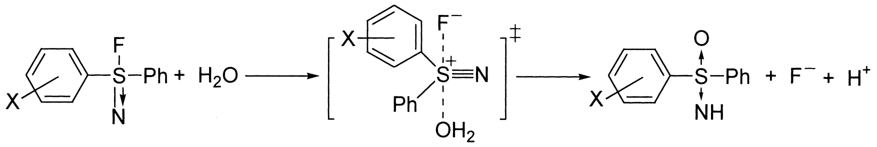
a) Ref. 18. b) Neutral. c) Dilute NaOH of 0.001–0.01 mol dm^{-3}.

with increasing the solvent polarity, since an initial charge is dispersed in the transition state.[19] The present opposite solvent effect, i.e., the 7-fold increase in rate with decreasing the acetonitrile concentration from 40.8% (v/v) to zero, reflects a relatively large degree of development of fission of the sulfur-fluorine bond in the transition state. There is an extreme example of large *m*-values (0.75–0.80), in spite of the S_N2 reaction, for the reaction of 1-phenylethyl derivatives with azide ion proceeding through an open, "exploded" transition state that closely resembles a carbocation.[20]

Neutral Hydrolysis: Substituent Effect. The rates of hydrolysis of **1** under neutral conditions were nicely correlated with σ-values and gave considerably large negative ρ-values under all three conditions ($\rho = -1.76$ (0.990) in water; $\rho = -1.85$ (0.986) in CH_3CN/H_2O (1/4, v/v); $\rho = -2.35$ (0.986) in TFE/H_2O (1/1, v/v)) (see Table 1). The behavior of the substituent effect suggests that there is a large development of positive charge on the central sulfur atom in the transition state of the nucleophilic reaction. There is an example of S_N1 hydrolysis involving a carbocation intermediate having an unsaturated carbon heteroatom bond, i.e., hydrolysis of *p*-dimethylaminobenzoyl fluoride.[21] However, the magnitude of the negative ρ-value might be too small for an S_N1 mechanism, although the standard ρ-value for S_N1 solvolysis on the sulfur atom is not established, and the ρ-value for a reaction involving an *S*-nitrilosulfonium cation may become less negative by electron movement from the nitrogen atom toward the central sulfur atom by polarization or resonance in Scheme 3. The charge on the sulfur atom in Scheme 3 shows a contribution of dication. However, the magnitude of charge is not important for the stability of the ion, as can be seen in the extreme examples of sulfonium ions; instead, the charge difference between the initial state and the transition state is rather important. There are mechanistic variations for the hydrolysis of acyl halides depending on the leaving ability. Most substituted benzoyl fluorides undergo hydrolysis in aqueous solution through an associative mechanism with $\rho = 1.7$, while most substituted benzoyl chloride through a dissociative one with nucleophilic participation by solvent with $\rho^+ = -3.12$.[21] On the other hand, the substituent effects for the neutral hydrolysis of tetracoordinated sulfur (VI) compounds, benzenesulfonyl chloride,[15] and thiophene-2-sulfonyl chloride and bromide[22] were reported to give upward curved or U-shaped Hammett plots. For this reason, the mechanism of the hydrolysis of sulfonyl halides was considered to involve a loose S_N2 transition state, which changes from the one in which the bond-breaking of sulfonyl-halogen is more advanced to the one in which the bond-making of sulfur-nucleophile is more advanced, depending on the electron-donating ability of the substituents and the ability of the leaving group. Meanwhile, a Hammett plot for the hydrolysis of benzenesulfonyl fluoride gives almost a straight line with a positive slope of 1.8,[23] suggesting an advanced bond-making transition state. All these facts reveal that the sulfonyl sulfur–fluorine bond is especially hard to be ionized. In the present case, a good linearly correlated Hammett plot with a large negative slope shows that even the sulfonyl sulfur–fluorine bond in fluoro-λ^6-sulfanenitriles has a dissociative character, as shown in Scheme 4. Though the ρ-value for the reaction in CH_3CN/H_2O (1/4, v/v) is essentially not different from that in water, the ρ-value in TFE/H_2O (1/1, v/v) is more negative than that in water, suggesting that the transition state for the reaction in less nucleophilic solvent is shifted to a



Scheme 3.



Scheme 4.

Table 3. Salt Effect on the Hydrolysis of **1a** and **1d** in Water and TFE/H_2O at 20.4 ˚C

Solvent	[**1**]	Salt	$k_{obs}\times10^3/s^{-1}$									$k_{salt}\times10^{2\,b)}$
		[Salt]$^{a)}$	0	0.05	0.1	0.2	0.3	0.4	0.5	1	1.5	s^{-1} mol^{-1} dm^3
water	**a**	KF	22.6	22.0	22.1	23.3		25.2		33.1		1.19
	a	$LiClO_4$	22.6		23.4	24.0	24.5			27.8		0.48
	d	KF	1.01	1.04		1.16	1.26	1.33				0.08
	d	KCl	1.01		1.71	2.43	3.10	3.64				0.65
	d	KBr	1.01		2.48	3.60	5.13	6.61				1.39
	d	$LiClO_4$	1.01		0.989	0.977	0.950	0.945		0.980		0
	d	$NaClO_4$	1.01		0.953		0.950					
TFE/H_2O	**a**	KF	0.370			0.359			0.333	0.286	0.222	
(l/l, v/v)	**a**	$LiClO_4$	0.370			0.417			0.537	0.860	1.19	

a) [Salt]: mol dm^{-3}. b) k_{salt} is the slope in the plot of k_{obs} vs [salt].

more cation-like one. This is supported by the common ion effect of KF and the stronger effect of the ionic strength of $LiClO_4$ on the hydrolysis of **1a** in TFE/H_2O, shown later in Table 3.

Activation Parameters. The activation enthalpies and entropies for the neutral hydrolysis of **1a–d** in CH_3CN/H_2O (1/4, v/v) at 25 °C are in the range of 60–65 kJ mol^{-1} and -84–-101 J K^{-1} mol^{-1}, respectively, as shown in Table 1. The values of $\Delta H^\ddagger$ are found to decrease, and $\Delta S^\ddagger$ to increase slightly with increasing electron-donating ability of the substituents. This may suggest that the electron-donating substituents facilitate the dissociation of the sulfur–fluorine bond, leading to a positive contribution to $\Delta S^\ddagger$. Also, the activation enthalpy (73 kJ mol^{-1}) and entropy (-60 J K^{-1} mol^{-1}) for the hydrolysis of **1a** in TFE/H_2O (1/1, v/v) at 25 °C in Table 1 are larger than those in CH_3CN/H_2O (1/4, v/v), showing that the transition state of the reaction in the former mixed solvent is more dissociative than that in the latter. The more negative $\Delta S^\ddagger$ values than that for the usual S_N1 process are probably due to the strong solvation of the leaving fluoride ion in the transition state with water, as explained by Jencks et al.[24] Although the present values are still small, they are obviously larger than that (-171 J K^{-1} mol^{-1}) for the hydrolysis of *p*-nitrobenzenesulfonyl fluoride in dioxane/water (40/60, v/v),[23] suggesting the dissociative character in the present system.

Solvent Effect. The solvent effect using CH_3CN–H_2O afforded large *m*-values ($m = 0.83$ for **1a** and 0.82 for **1d**) for the neutral hydrolysis as given in Table 2. The large *m*-values suggest further that the dissociation of the leaving group is important for the neutral hydrolysis, although the smaller *m*-values than unity likely reflect incomplete dissociation of the fluoride anion in the transition state caused by some nucleophilic solvation of the cationic center as proposed by Bentley et al.[25] Thus, an *S*-nitrilosulfonium cation-like transition state with an advanced bond cleavage and little bond formation is the case for this reaction. In the present case, almost the same *m*-values for the compounds with very different substituents (H and *p*-NO_2) do not suggest a continuous change in the nature of the transition state upon changing the substituents to the more electron-attracting, unlike in the case of the hydrolysis of sulfonyl halides.[26] This is consistent with a linear Hammett correlation for the neutral hydrolysis in several aqueous solutions. Therefore, the present transition state is suggested to be looser than that for the sulfonyl halides.

Solvent Isotope Effect. According to the kinetic data in Table 1, the ratios of k_{H_2O}/k_{D_2O} for the neutral hydrolysis of **1a** and **1d** were found to be 1.50 and 1.67 at 20.4 °C, respectively. Song and Jencks reported that an S_N1 mechanism for the hydrolysis of *p*-dimethylaminobenzoyl fluoride had a solvent isotope effect, k_{H_2O}/k_{D_2O}, of 1.1.[21] Meanwhile, the hydrolysis of *p*-methoxybenzoyl and benzoyl fluorides was suggested to occur via an associative mechanism involving a general base catalysis, in which the solvent isotope effects are 2.3. In our case, the associative mechanism is not consistent with the large negative ρ-value for the neutral hydrolysis of fluoro-λ^6-sulfanenitriles. However, the present solvent isotope effects are larger than 1.1 for *p*-dimethylaminobenzoyl fluoride, which may be attributed to a weak nucleophilic interaction with a water molecule in the transition state having a dissociative character, as proposed by Song and Jencks for the hydrolysis of benzoyl chlorides.[21] On the other hand, the present solvent isotope effects are close to those for the hydrolysis of sulfonyl chlorides, which was suggested a looser and more ionic transition state.[26]

Salt Effect. In order to find further evidence supporting the dissociative transition state, salt effect was also examined. In the case of the reaction of either **1a** or **1d** in water, addition of potassium fluoride does not exhibit a common ion inhibition, but slightly increases the rate of hydrolysis, as shown in Table 3. Potassium chloride and bromide were found to obviously accelerate the hydrolysis of **1d**, which is attributable to an attack of the halide ion on the nitrogen atom, because the formation of *N*-bromo-*S*-*p*-nitrophenyl-*S*-phenylsulfimide was confirmed by UV and NMR spectra. The rate-enhancing effect of fluoride ion may also be due to the formation of a more easily hydrolyzable intermediate, *N*-fluorosulfimide, although the formation of any intermediate was not observed in the UV spectral change of the reaction mixture in the presence of potassium fluoride. The rate of hydrolysis of *N*-fluorosulfimide may be estimated as being sufficiently faster than other *N*-halosulfimides from our previous results concerning the halide effect on the alkaline hydrolysis of *N*-halosulfimides,[27] but it is difficult to discuss the rate of the unknown *N*-fluorosulfimide. Furthermore, there is another possibility of a general base catalysis of fluoride ion toward the attacking water molecule.

On the other hand, the salt effect in Table 3 shows that perchlorate salts slightly accelerate the hydrolysis of **1a** in water, but not the hydrolysis of **1d**. The small positive salt effect of perchlorate for **1a** and the almost no salt effect for **1d** are consistent with those reported by Manege et al. for S_N1–S_N2 intermediates, isopropyl bromide and benzyl chloride.[28]

It is interesting that the addition of potassium fluoride to TFE/H_2O (1/1, v/v) exhibited an obvious common ion inhibition, and lithium perchlorate more strongly accelerated the hydrolysis of **1a** in the mixed solvent than in water, suggesting a substantial or complete dissociation of fluoride anion in the transition state. The results show that the hydrolysis of **1a** in a less nucleophilic solvent, TFE/H_2O (1/1, v/v), leads to S_N1 or more S_N1-like transition state than in water. The close ρ-value for the hydrolysis in water to the one in TFE–H_2O suggests that the transition state in the reaction in water is also loose enough.

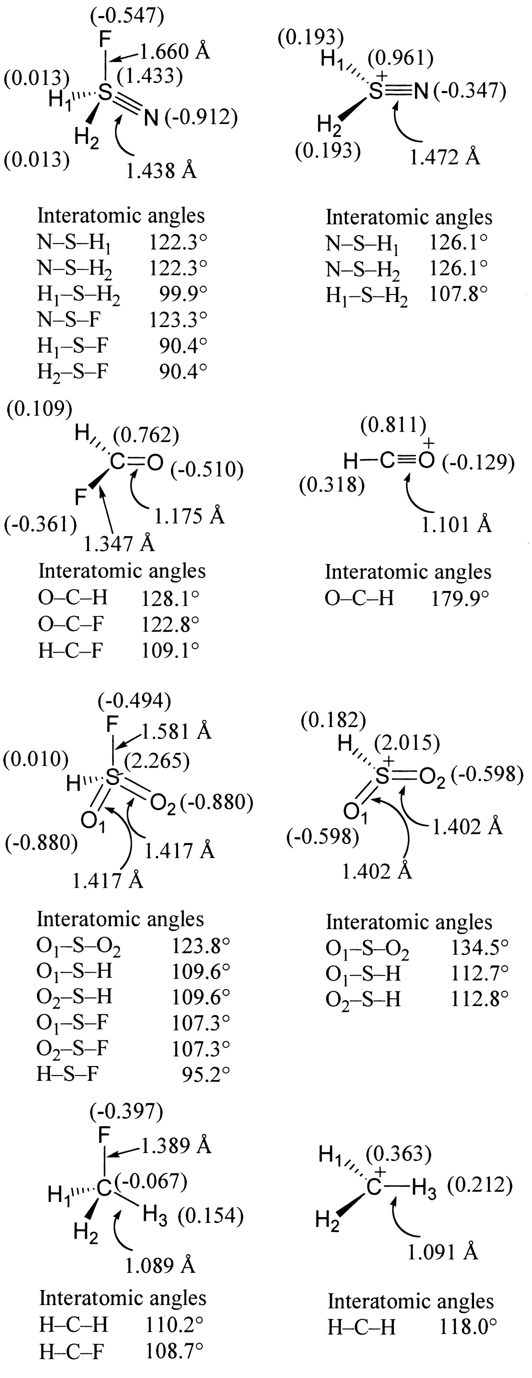
Density Function Theory Calculation of *S*-Nitrilosulfonium Cation. In order to confirm the ease of ionic dissociation of fluoro-λ^6-sulfanenitriles, the heterolytic dissociation energy of a model compound of fluoro-λ^6-sulfanenitriles was calculated and compared with that of formyl fluoride, methyl fluoride, and sulfonyl fluoride at the B3LYP/6-311++G (3df, 2pd) level. A zero-point energy correction was performed at the B3LYP/6-31G*//B3LYP/6-31G* level using the scaling factor 0.9804.[29] The results are compiled in Table 4. The heterolytic bond dissociation energies include information about both the bond energy and the stabilization energy of the cation by substituents. The large positive endothermic dissociation energies are actually compensated by solvation to make ionization possible. The heterolytic dissociation energy of formyl fluoride is expectedly smaller than that of methyl fluoride, but the energy for the fluoro-λ^6-sulfanenitriles is further 105 kJ

Table 4. Heterolytic Dissociation Energies (ΔE) of R–F Bond in Various Model Compounds[a)]

$$\mathrm{R{-}F} \xrightarrow{\Delta E} \mathrm{R^+ + F^-}$$

R	E_m[b)]	E_{m0}[c)]	E_c[b)]	E_{c0}[c)]	ΔE[d)]
CH_3	−367046	102	−103693	81	1074
HC(=O)	−561475	54	−298233	37	967
$H_2S(\equiv N)$	−1454371	66	−1191236	51	862
$\underset{\underset{\mathrm{O}}{\|}}{\mathrm{HS}}(=O)$	−1704430	57	−1441134	43	1024

a) The total energies (kJ mol^{-1}) were calculated at the B3LYP/6-311++G (3df, 2pd) level. The zeropoint energies were calculated at the B3LYP/6-31G*//B3LYP/6-31G* level and corrected by the scaling factor 0.9804 (Ref. 29). b) E_m, E_c are the total energies of molecule and cation, respectively. c) E_{m0}, E_{c0} are the zero-point energies of the molecule and the cation, respectively. d) The total energy (E_f) of fluoride ion is −262258 kJ mol^{-1}. c) $\Delta E = (E_c + E_{c0}) + E_f - (E_m + E_{m0})$.

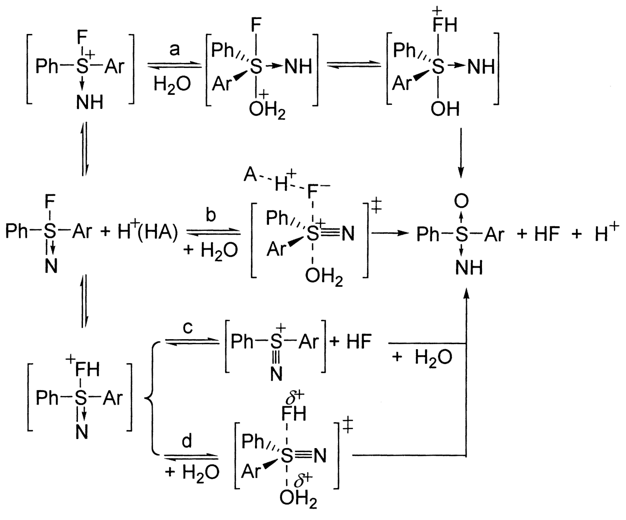


Optimized geometry by B3LYP/6-311++G (3df, 2pd)

Scheme 5.

mol^{-1} lower than that of formyl fluoride and 162 kJ mol^{-1} lower than that of sulfonyl fluoride. This means that the ionization of fluoro-λ⁶-sulfanenitriles is essentially easier than that of acyl fluoride, although the stabilization energies by substituted phenyl groups of the present system cannot be compared with those of the *p*-dimethylaminobenzoyl fluoride and *p*-methoxybenzoyl fluoride.[21] The optimized geometry of the *S*-nitrilosulfonium cation is planar with a longer SN bond length of 1.472 Å than that of 1.438 Å of the fluoro-λ⁶-sulfanenitrile, as shown in Scheme 5, which is in contrast to the results for the C–O bond length in formyl fluoride, although the change in the S–O bond length is very small in sulfonyl fluoride. NBO natural population analyses were performed[30] at the B3LYP/6-311++G (3df, 2pd)//B3LYP/6-311++G (3df, 2pd) level. The change in the natural charge on the central atoms and some other atoms and fluorine are shown in Scheme 5. The increase in the positive natural charge on the sulfur atom is more negative in fluoro-λ⁶-sulfanenitrile than that in sulfonyl fluoride, although the opposite change does not match to the reaction image and cannot be compared with the change on the different atoms. The electron movement from the nitrogen to the sulfur atom in the dissociation process is found to be very large. The negative charge on the fluorine atom of fluoro-λ⁶-sulfanenitrile is the largest of the four. The NBO analysis for fluoro-λ⁶-sulfanenitrile shows a strong ionic character for the S–F bond, which is characterized as lone-pair occupancies (1.996, 1.972, 1.958, 1.616), suggesting that the negative hyperconjugation[31] from the lone electron-pair on the nitrogen atom to the S–F σ* bond activates the S–F bond to make easier the S–F ionization. The relatively small change in the charge on the sulfur atom is the result of resonance stabilization of the cation. It is therefore probable that the strong stabilization by resonance between the nitrogen and the cationic sulfur atom makes it possible to dissociate even the poorly leaving fluoride ion, so that the substitution reaction of **1** with a weak nucleophile, such as a water molecule, takes place via a loose transition state having a dissociative character, and with a further weak nucleophilic solvent, TFE–H_2O, via an S_N1 process.

Acidic Hydrolysis: Substituent Effect. The acidic hydrolysis is also facilitated by electron-donating substituents. The Hammett plot of k_H for the hydrolysis of **1** in dilute perchloric acid containing 35.5% (v/v) CH_3CN at 10.9 °C afforded a large negative ρ-value of −1.87, close to those for the neutral hydrolysis (see Table 1), indicating that the positive charge at the central sulfur atom in the transition state is simi-



Scheme 6.

lar to, or a little larger than, that in the neutral hydrolysis. The acidic hydrolysis may be considered to take place by several possible pathways, as shown in Scheme 6. Path a is an acid-catalyzed addition–elimination mechanism involving an initial protonation on the nitrogen atom, followed by a rate-determining addition of a water molecule on the sulfur atom to form a hypervalent intermediate, resembling acid-catalyzed carboxylic ester hydrolysis. The initial protonation cannot be the rate-determining step, because proton transfer between heteroatoms without other concerted bond cleavage or bond formation is commonly very fast. Paths c and d involve an initial pre-equilibrium protonation on the fluorine atom, followed by a rate-determining cleavage of the sulfur–fluorine bond unassisted and assisted by a nucleophilic attack of a water molecule on the sulfur atom, respectively. Path b involves a general acid-catalyzed cleavage of the sulfur–fluorine bond. Of these, path a is not expected to afford a large negative ρ-value due to the result of a cancellation of the negative ρ-value for the pre-equilibrium protonation by a positive one for the rate-determining nucleophilic reaction, as is the case for ester hydrolysis.[32] Path c would give a large negative ρ-value (probably -2.35 estimated from the S_N1 solvolysis in TFE–H_2O) due to the net positive charge on the sulfur atom of the intermediate. Paths b and d would give a moderate ρ-value, depending on the degree of the S–F bond cleavage and the nucleophilic O–S bond formation. The protonated fluorine atom in path d is a much better leaving group than the fluoride ion in the neutral hydrolysis, and thus the transition state in path d should be more cation-like to give a more negative ρ-value than that in the neutral hydrolysis. The present ρ-value is too close to that in the neutral hydrolysis to consider path d, and is therefore most consistent with path b.

Activation Parameters. The activation enthalpy and entropy for k_H of the hydrolysis of **1d** in dilute perchloric acid solutions ([H^+]: 0.001–0.02 mol dm^{-3}) are 66 kJ mol^{-1} and -20 J $K^{-1}mol^{-1}$ at 25 °C, respectively (see Table 1). Path c of an A1 mechanism is not compatible to the present system, because it should afford a large positive activation entropy.[33] Meanwhile, the activation entropy for path b may be a moderate value, considering a positive contribution by the proton transfer from hydronium ion to the fluoride ion leaving group relative to $\Delta S^{\ddagger}$ (-97 J $K^{-1}mol^{-1}$) for the neutral hydrolysis, and for paths a and d, the initial protonation should make a further positive contribution.

Solvent Isotope Effect. The solvent isotope effects, k_H/k_D, for **1a**, **1b**, and **1d** in dilute perchloric acid containing 35.5% (v/v) CH_3CN at 10.9 °C were found to be smaller than those in the neutral hydrolysis, and even a little smaller than unity (0.89 for **1a**, 0.84 for **1b**, and 0.82 for **1d**, respectively, see Table 1). The hydrolysis of **1d** in aqueous perchloric acid at 20.4 °C also afforded the same isotope effect (0.82) as in the aqueous acetonitrile solution at 10.9 °C. The values are not in the range of 0.3–0.45 for typical A1 mechanisms,[34] nor in the range of 0.5–0.6 for acid-catalyzed ester hydrolyses,[35] showing paths c and a to be unlikely. These specific acid-catalyzed mechanisms contribute largely to the reverse isotope effect, and are not consistent with the present results. For path d, the large reverse isotope effect is cancelled by some secondary nomal effect due to the attack of water, depending on the position of the transition state. Meanwhile, a general acid-catalyzed mechanism shows a large normal isotope effect, depending on the position of the transition state. However, the present results show that some contribution of protonation should be involved in the mechanism of the neutral hydrolysis. There are examples of reverse isotope effect (0.5–1) for the general acid-catalyzed hydrolysis of ortho esters in which the Brønsted α-values are large.[36]

Buffer Effect. In order to further clarify the acid-catalyzed mechanism, the buffer effect was examined, as shown in Table 5. Typical buffer dependences of the hydrolysis of **1d** in several buffers are shown in Fig. 4. In almost all cases, the observed rate constants, k_{obs}, are linearly dependent on the total buffer concentration, $[B]_t$: $k_{obs} = k_0 + k_B[B]_t$. k_0 is the rate constant extrapolated to zero buffer concentration, and k_B is the second-order rate constant calculated from the buffer-dependent term. The k_0 values are almost equal to the values in neutral hydrolysis or in acidic hydrolysis without a buffer. In the range of neutral pH, phosphate and imidazole buffers have some buffer effects, but MES, MOPS, and MOPSO buffers do not show any buffer effects, likely suggesting a nucleophilic catalysis by a conjugate base of a buffer, depending on the possibility of bond formation between the sulfur atom in the substrate and the buffer base. In the low-pH range, plots of the buffer-catalyzed constant, k_B, vs. acid fraction of buffer gave straight lines with intercepts, as shown in Fig. 5, suggesting that both the conjugate acid of the buffer and the base component catalyze this hydrolysis. Since there is no tendency to curve involving second-order dependency of the buffer concentration at the present range in Fig. 4, the two kinds of catalysis take place in two parallel reaction processes.

According to the above experimental results, the total rate equation is as follows, considering an equilibrium protonation at the nitrogen atom in terms of the basicity of the nitrogen atom of λ^6-sulfanenitrile:[4,6]

$$k_{obs} = \frac{K_{aSN}(k_{H_2O} + k_H[H^+])}{K_{aSN} + [H^+]} + \frac{K_{aSN}}{K_{aSN} + [H^+]}(k_{HA}[HA] + k_A[A^-]), \quad (1)$$

where k_{H_2O} is the pseudo first-order rate constant for the reac-

Table 5. Buffer Effect on the Hydrolysis of **1d**[a)]

Buffer[b)]	Fraction of buffer acid[c)]	Temp °C	pH	$k_0\times10^3$ s^{-1}	$k_B\times10^2$ $s^{-1}\,mol^{-1}\,dm^3$	$k_{HA}\times10^2$ $s^{-1}\,mol^{-1}\,dm^3$	$k_A\times10^2$ $s^{-1}\,mol^{-1}\,dm^3$
Phosphate	0.67	10.9	1.72	8.32±0.08	2.0±0.1		
Phosphate	0.50	10.9	2.12	3.75±0.28	1.5±0.2	3.0	0
Phosphate	0.33	10.9	2.35	2.09±0.02	0.92±0.03		
Glycine	0.50	10.9	2.66	1.22±0.03	0.18±0.03		
Chloroacetate	0.67	10.9	2.42	1.77±0.08	0.41±0.04		
Chloroacetate	0.50	10.9	2.78	1.13±0.07	0.43±0.05	0.48	0.33
Chloroacetate	0.33	10.9	3.01	0.71±0.07	0.36±0.08		
Formate	0.67	10.9	3.31	0.59±0.04	0.40±0.02		
Formate	0.50	10.9	3.62	0.48±0.03	0.47±0.02	0.27	0.68
Formate	0.33	10.9	3.92	0.42±0.04	0.54±0.04		
Acetate	0.50	25.2	4.66	1.51±0.01	0.56±0.01		
Acetate	0.33	25.2	4.98	1.50±0.02	0.65±0.02	0.29	0.82
MES	0.83	25.2	5.40	1.51±0.01	0		
MES	0.50	25.2	6.12	1.50±0.01	0		
MOPSO	0.50	25.2	6.93	1.44±0.02	0		
MOPS	0.50	25.2	7.20	1.43±0.03	0		
Phosphate	0.50	25.2	6.87	1.48±0.01	0.39±0.02		
Imidazole	0.50	10.9	7.50	0.42±0.02	0.32±0.01		

a) The buffers at the ionic strength 0.10 maintained with $LiClO_4$ were used. b) MES: 2-morpholinoethanesulfonate (pK_a 6.15, 20 °C), MOPSO: 2-hydroxy-3-morpholinopropanesulfonate (pK_a 6.90), MOPS: 3-morpholinopropanesulfonate (pK_a 7.20, 20 °C). c) [Buffer acid]/total buffer concentration.

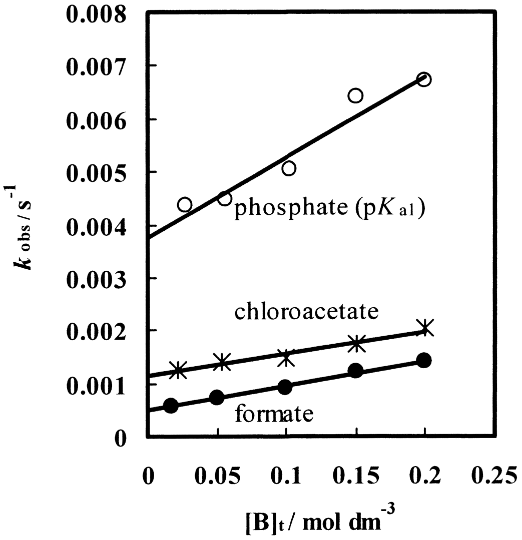


Fig. 4. Buffer effect on the hydrolysis of **1d** in phosphate (pH = 2.12), chloroacetate (pH = 2.78), and formate (pH = 3.62) buffer solutions with ionic strength 0.1 maintained with $LiClO_4$ at 10.9 °C.

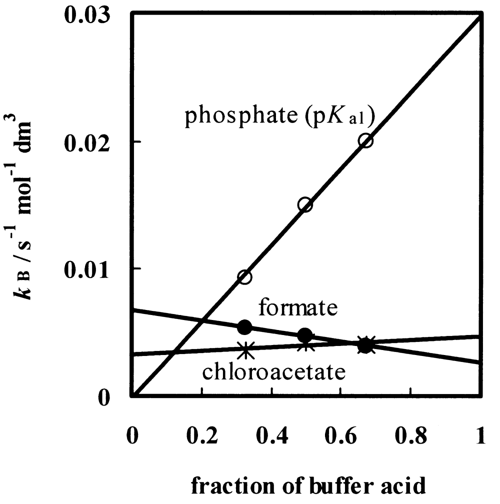


Fig. 5. Plots of k_B for the hydrolysis of **1d** vs. fraction of buffer acid in buffer at ionic strength 0.1 maintained with $LiClO_4$ at 10.9 °C.

tion with a water molecule, and k_H, k_{HA}, and k_A are the second-order rate constants, depending on the concentration of proton, buffer acid, and buffer base, respectively. K_{aSN} is the dissociation constant of the *N*-protonated λ^6-sulfanenitrile. [HA] and [A^-] represent the concentration of the buffer acid and base, respectively. The protonation on the nitrogen atom is considered to depress the dissociation of fluoride anion. Since no saturation was observed at low pH in the pH-rate profile, no significant protonation on the nitrogen atom is considered to occur in the present pH-range, suggesting that pK_a of fluoro-λ^6-sulfanenitrile is smaller than 1 for **1d** and 2 for **1a**. Thus, the buffer-dependent second-order rate constant, k_B, can be described as follows from the second term of Eq. 1:

$$k_B = k_{HA}\frac{[HA]}{[B]_t} + k_A\frac{[A]}{[B]_t}, \tag{2}$$

where $[B]_t$ is the total buffer concentration. Since $[HA] + [A^-] = [B]_t$, the equation can be rearranged as

$$k_B = k_A + (k_{HA} - k_A)\frac{[HA]}{[B]_t}, \tag{3}$$

and the catalytic rate constants, k_A and k_{HA}, are determined from the intercepts extrapolated at that buffer acid fraction is zero and unity, respectively, in the plot of k_B vs. acid fraction of buffer (Fig. 5). There is an apparent tendency that the stronger is the acidity of the buffer acid, the larger is the k_{HA} value, though the α-value cannot be estimated because of large experimental errors and too few data. The observation of general acid catalysis is consistent with the small reverse isotope effect, and thus path b. The buffer effect is attributable to the ease of ionic dissociation of the sulfur-fluorine bond in fluoro-λ^6-sulfanenitriles.

Although the question whether the acid-catalyzed hydrolysis of fluoro-λ^6-sulfanenitrile is S_N1 or not is hard to answer, the ρ-value of -1.87 is too small a negative value compared to that of -2.35 for the neutral hydrolysis in TFE–H_2O, suggesting that some nucleophilic assistance of water cannot be neglected in the transition state.

Conclusion

The S–F bond in aryl(fluoro)(phenyl)-λ^6-sulfanenitriles **1** easily undergoes heterolytic dissociation, probably due to strong resonance stabilization between the nitrogen and the sulfur atom. It results in that the neutral hydrolysis of aryl(fluoro)(phenyl)-λ^6-sulfanenitriles **1** proceeds via an *S*-nitrilosulfonium cation intermediate or cation-like transition state with a large amount of dissociative character, even the sulfone-type compounds, and even having a poorer leaving group fluoride ion than other halide ions. The alkaline hydrolysis takes place more possibly via an S_N2 mechanism. The acid-catalyzed hydrolysis may involve a concerted proton transfer to the fluorine atom and breaking of the sulfur-fluorine bond in the λ^6-sulfanenitrile. All three mechanisms under the respective conditions reflect the ease of the ionic cleavage of the S–F bond of fluoro-λ^6-sulfanenitriles.

Experimental

General: All reagents and solvents were obtained commercially, and were further purified by general methods when necessary. The pH value of a buffer solution was determined by a Horiba F-13 pH meter. UV spectra were measured by a HITACHI U-3000 spectrophotometer. Density function theory calculations and natural bond orbital calculations were performed using the GAUSSIAN 94[37] program package in an IBM RS/6000-SP2 computer at Toyama University Computing and Network Services Center.

Aryl(fluoro)(phenyl)-λ^6-sulfanenitriles: The aryl(fluoro)(phenyl)-λ^6-sulfanenitriles **1a–e** were prepared according to the methods reported in our previous papers.[2,8]

***m*-Chlorophenyl(fluoro)(phenyl)-λ^6-sulfanenitrile (1e).** Yield 55%; mp 118–120 °C (decomp); IR (KBr) 1366 cm^{-1} (ν_{SN}); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.51 (m, 1H), 7.55–7.59 (m, 3H), 7.63–7.67 (m, 1H), 7.78–7.81 (m, 1H), 7.90–7.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.0, 127.0, 127.1, 129.5, 130.6, 133.3, 133.6, 135.6, 143.0, 143.2, 145.2, 145.4. Found: C, 56.72; H, 3.62; N, 5.17%. Calcd for $C_{12}H_9ClFNS$: C, 56.81; H, 3.58, N, 5.52%.

Hydrolysis Product Analysis: To an CD_3CN solution of **1** (0.023 mmol, 0.19 mL) in an NMR tube was added 0.37 mL of D_2O and NMR spectrum was immediately taken. After two days at room temperature, the mixture was analyzed by NMR again. Besides the corresponding sulfoximides being formed, no other products were found.

On the other hand, an acetonitrile solution of **1** (0.14 mmol, 0.5 mL) was pipetted into 4 mL of CH_3CN/H_2O (1/4, v/v) under neutral, acidic (0.02 mol dm^{-3} of $HClO_4$) or basic (0.01 mol dm^{-3} of NaOH) conditions and stirred rapidly to start the reaction at room temperature. When the reaction finished, to the mixture solution was added 50 mL of 0.05 mol dm^{-3} of NaOH; it was then extracted with $CHCl_3$. The obtained organic layer was dried over anhydrous magnesium sulfate. After the solvent was evaporated, the residue was identified by NMR as corresponding sulfoximides only.

The hydrolysis products of **1** in TFE/H_2O (1/1, v/v) mixed solvent were analyzed in the similar experimental procedure in CH_3CN/H_2O (1/4, v/v) under neutral conditions. Besides the corresponding sulfoximide, no other products were found by NMR.

The Hydrolysis of Fluoro(*p*-nitrophenyl)(phenyl)-λ^6-sulfanenitrile (1d) in the Presence of KBr. To a 12.2% (v/v) acetonitrile aqueous solution (114 mL) of 2 mol dm^{-3} of KBr was gradually added 1 mL of an acetonitrile solution of fluoro(*p*-nitrophenyl)(phenyl)-λ^6-sulfanenitrile (21.3 mg). After 30 min, the solution was diluted with an $NaHCO_3$ solution and extracted by $CHCl_3$. The organic layer was dried over anhydrous magnesium sulfate. After the solvent was evaporated, the residue was identified by NMR to contain *N*-bromo-*S*-*p*-nitrophenyl-*S*-phenylsulfimide (40%), *p*-nitrophenyl phenyl sulfide (20%), besides the corresponding hydrolysis product, *S*-*p*-nitrophenyl-*S*-phenylsulfoximide (**2d**) (40%).

Kinetic Measurement: The hydrolysis reaction was started by adding a 2 μL sample of the acetonitrile solution of **1** (0.14 mol dm^{-3}) to 3.0 mL of a reaction solution in a 10 mm quartz cell equilibrated at 20.4 ± 0.1 °C in a cell compartment of a spectrophotometer. The variation of the UV absorbance of λ^6-sulfanenitriles at a given wavelength (220 nm for **1a**, 225 nm for **1b** and **1c**, 240 nm for **1d**, and 229 nm for **1e**) was automatically recorded at 10-second intervals. The reactions were followed over 10 half-lives. The pseudo-first-order rate constants were calculated by a least-squares method using more than 8 points accumulated during the first 70% of the reaction.

An examination of the solvent effect was carried out by measuring the rates of hydrolysis of **1a** and **1d** in mixed solvents of several compositions of CH_3CN/H_2O under neutral and basic conditions. The *m*-values of the solvent effects, as shown in Table 2, were obtained from plots of the logarithms of various rate constants against the solvent ionizing power, Y_{OTs},[18] of 2-adamantyl tosylate.

The salt effect was examined by measuring the rate constants of hydrolysis in several concentrations of salt solutions. The solvent isotope effect was determined by using the corresponding deuterium solvent or reagent.

The buffer effect was examined by measuring the rates of hydrolysis in five concentrations of buffer solutions with the same pH and the same ionic strength, which were prepared by diluting a stock concentrated buffer solution with a $LiClO_4$ solution.

The activation parameters were obtained from a least-squares treatment of ln k against T^{-1} at three or four temperatures of 10–40 °C.

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