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Methanesulfonic Acid Derivative of Sulfonamide. II.[1] Successively Reversible Hydrolysis of Sulfisoxazole Derivative[2]

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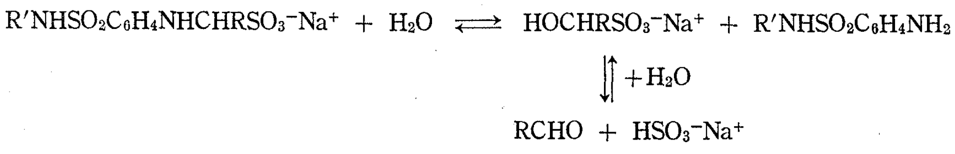
Successively reversible hydrolysis of methanesulfonic acid derivative of sulfisoxazole, $R'NHSO_2C_6H_4NHCHRSO_3Na$ ($R=CH_3$ or C_6H_5), was studied. By the sequential hydrolysis such derivative may be hydrolyzed to the extent that the precipitation of parental drug may take place. The pH-profiles of logarithm of apparent hydrolysis and reverse reaction rates and those of equilibrium constants were obtained and the effect of ionizations of the derivatives and hydrolyzates have been explained by theoretical equations. From the hydrolysis and reverse reaction rates estimated, reaction pathway of individual reactions which compose whole hydrolysis system has been discussed.

In the previous study it was concluded that methanesulfonic acid derivative (MSD)[4] of the drug such as sulfonamide needs appropriate substituent on methylene group to facilitate hydrolysis and ensure sufficient availability of parental sulfonamide.[1] However, when the hydrolysis rate of MSD is controlled purposely by the substitution on methylene group following embarrassment will possibly arise to prepare the solution of this water soluble derivative. With the substitution of electron donating R group the hydrolysis rate increases indeed, but the hydrolyzate $HOCHRSO_3^-$ also becomes liable to the hydrolysis further by R. This secondary hydrolysis retroactively promotes the 1st step hydrolysis and consequently precipitation of parental sulfonamide may take place, which conflicts with the purpose of this water soluble derivative. By the way when R=H, hence the hydrolyzate is $HOCH_2SO_3^-$, the 2nd step hydrolysis is practically negligible and the equilibrium of MSD hydrolysis is simple as has been studied previously.[5] Another purpose of the detailed study on MSD is to explore the possibility of these derivatives as the controller of the liberation rate of parental drug. Recently MSD has been used not only in medicament but also in dyeing, agricultural chemicals, hair dyeing and photography for the purpose to control the reaction rate of parental chemicals.

The 2nd step hydrolysis is known to be also reversible[6] and the total procedure may be represented as:



$$\begin{tikzcd} R'NHSO_2C_6H_4NHCHRSO_3^-Na^+ + H_2O \arrow[r, shift left] & HOCHRSO_3^-Na^+ + R'NHSO_2C_6H_4NH_2 \arrow[l, shift left] \arrow[d, shift left, "+H_2O"] \\ & RCHO + HSO_3^-Na^+ \arrow[u, shift left] \end{tikzcd}$$

These equilibria shift intricately depending upon pH, which is owing to the ionization of MSD and hydrolyzates.

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[1] Part I: K. Ikeda, Y. Kurono, and T. Tukamoto *Chem. Pharm. Bull.* (Tokyo), **20**, 863 (1972). This report consists Part III of the studies entitled "Methanesulfonic Acid Derivative of Drug."

[2] Presented at the 91st Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, April 1971.

[3] Location: *Tanabe-dori, Mizuho-ku, Nagoya.*

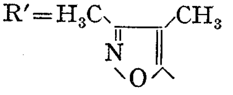
[4] MSD which is substituted R on methylene group is also represented by this abbreviation.

[5] K. Ikeda, K. Miyata, F. Kawata, and K. Kurome, *Chem. Pharm. Bull.* (Tokyo), **18**, 440 (1970).

[6] *a*) J.D. Stewart and L.H. Donnally, *J. Am. Chem. Soc.*, **54**, 3555 and 3559 (1932); *b*) K. Arai, K. Shigira, and K. Ishikawa, *Nippon Kagaku Zasshi*, **75**, 661 and 664 (1954); *c*) D.A. Blackadder and Sir C. Hinshelwood, *J. Chem. Soc.*, **1958**, 2720.

In the course of study on sulfonamide MSD, sulfisoxazole MSD where R is CH_3 or C_6H_5 was found to be favorable for the long duration of blood concentration and fast hydrolysis.[7] In this study, therefore, sulfisoxazol MSD substituted CH_3 or C_6H_5 on methylene group was chosen for the study on the successive hydrolysis. The abbreviations of sulfisozazole MSD and their hydrolyzates specifying their ionization are listed in Table I. When it is not necessary to specify the ionization, abbreviation such as SiMeS, Si or MeS are used as general indications of the corresponding compounds.

TABLE I. Abbreviations of Sulfisoxazole MSD and Its Hydrolyzates Specifying Their Ionizations, where R′=



Chemical formula	Abbreviation	Chemical formula	Abbreviation
$R'NHSO_2C_6H_4NHCH(CH_3)SO_3^-$	SiMeS⁻	$HOCH(CH_3)SO_3^-$	MeS⁻
$R'N^-SO_2C_6H_4NHCH(CH_3)SO_3^-$	Si⁻MeS⁻	$^-OCH(CH_3)SO_3^-$	Me⁻S⁻
$R'NHSO_2C_6H_4NHCH(C_6H_5)SO_3^-$	SiPhS⁻	$HOCH(C_6H_5)SO_3^-$	PhS⁻
$R'N^-SO_2C_6H_4NHCH(C_6H_5)SO_3^-$	Si⁻PhS⁻	$^-OCH(C_6H_5)SO_3^-$	Ph⁻S⁻
$R'NHSO_2C_6H_4NH_2$	Si	HSO_3^-	S⁻
$R'N^-SO_2C_6H_4NH_2$	Si⁻	SO_3^{2-}	S²⁻
		CH_3CHO	Me
		C_6H_5CHO	Ph

When the specification for ionization is not necessary, abbreviation such as SiMeS, Si, or Ph were used without any marking of charge.

Experimental

Material——Synthesis of sulfisoxazole MSD and material used were same to those in previous study[1] in general. MeS^-Na^+ and PhS^-Na^+ were prepared according to literature cited.[6] Buffer systems used were also same to those in previous study.

Apparent Reversible Hydrolysis Rate and Equilibrium Constants for the 1st Step Hydrolysis——All data on rate and equilibrium were obtained at 37°. To follow the hydrolysis of SiMeS and SiPhS, ultraviolet (UV) spectral changes of their 5.0×10^{-5}M solution were recorded, at which concentration the reverse reaction could be disregarded. As the 2nd step hydrolysis was found to be much faster (depending upon pH but about 100 times faster at least) than the 1st step one and its reverse reaction was also negligible at this concentration, UV spectrum at time t can be considered as the sum of spectra of unhydrolyzed MSD and completely hydrolyzed Si, Me (negligible) or Ph, and sulfite (negligible). Thus UV spectral change with time can be regarded to be proportional to Si liberated. From the plots of log (absorbance at time $t-$absorbance at ∞ time) *versus* time, which was linear, half life of the reaction was obtained and reaction rate was calculated by the relation of (1st order reaction rate constant)=0.693/(half life).

For the equilibrium constant determination 5.0×10^{-4} and 3.0×10^{-3}M for SiMeS and 3.75×10^{-3} and 7.0×10^{-3}M for SiPhS were used, at which concentrations equilibrium state could be detected quantitatively. Determination of Si liberated was carried out by diazo coupling method after the separation of unhydrolyzed MSD passing through ion exchange resin column as in previous study.[1] Equilibrium state was found to be attained in 8 hr at most. Apparent equilibrium constant for the 1st step, K_{1app}, was calculated by Eq. 1, where subscript e denotes that the concentration is the one at equilibrium.

$$K_{1app}=\frac{(\text{Si liberated})_e(\text{MeS or PhS})_e}{(\text{Si MSD unhydrolyzed})_e} \qquad (1)$$

$(\text{Si liberated})_e$ and $(\text{Si MSD unhydrolyzed})_e$ can be estimated by above method but MeS or PhS can not be directly estimated because of the 2nd step hydrolysis. When equilibrium constant of the 2nd step hydrolysis, K_{2app}, is obtained as will be described, $(\text{MeS or PhS})_e$ can be estimated by Eq. 2.[8]

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7) Unpublished data.

$$(\text{MeS or PhS})_e = (\text{Si liberated})_e + \frac{K_{2\text{app}} - \sqrt{K_{2\text{app}}^2 + 4(\text{Si liberated})_e K_{2\text{app}}}}{2} \qquad (2)$$

On SiMeS, however, the correction for the 2nd step hydrolysis can be disregarded, because the value $K_{2\text{app}}$ for MeS is reported to be very small, in the order of 10^{-6},[9] which will be discussed later.

Apparent Reversible Hydrolysis Rate and Equilibrium Constants for MeS and PhS——To follow MeS formation from Me and S, equal volumes of S and Me solutions, both of them have equal concentration of 1.2×10^{-2} M, were mixed and the recording of UV spectral change at 280 mμ in 10 cm cell was started immediately. UV spectrum of Me disappears with the formation of MeS. The second order reaction rate of MeS formation was calculated from the slope of $1/a(a-x)$ *versus* time t, where a and x are absorbances at the beginning and time t. The hydrolysis and equilibrium constants on MeS could not be obtained accurately which will be dicussed later.

On the other hand for the reaction of $\text{PhS} \rightleftharpoons \text{Ph} + \text{S}$, hydrolysis rate constant could be determined from the recording of UV spectral change at 250 mμ. PhS was taken in 1 cm spectrophotometer cell which was mounted on thermostatic cell holder and buffer solution was injected with syringe to dissolve PhS. The recording was started immediately after the injection. Calculation of hydrolysis rate constant was as that of SiMeS described above. The hydrolysis of PhS could be followed at lower concentration, about 4×10^{-5} M, where the reverse reaction was found to be negligible. Apparent equilibrium constant can not be calculated directly from spectral change because intact absorbance of PhS can not be determined owing to the rapid hydrolysis. Therefore estimation of equilibrium constant was carried out by a special procedure as follows. Two solutions were prepared, one of which contained a M Ph and b_1M S and the other a M Ph and b_2M S, and these were attained to equilibrium state in a thermostat. The decreases of absorbance at 250 mμ from the sum of intact absorbances of Ph and S, which are represented by ΔE_1 and ΔE_2 for two solutions respectively, are proportional to the concentration of PhS formed at equilibrium. This relationship is represented as $(\text{PhS})_e = \alpha\Delta E_1$, and the coefficient α can be estimated by Eq. 3.[10]

$$\alpha = \frac{\Delta E_1 \Delta E_2 (b_2 - b_1) - \sqrt{\Delta E_1 \Delta E_2 \{\Delta E_1 \Delta E_2 (b_2 - b_1)^2 - 4a(\Delta E_2 - \Delta E_1)(\Delta E_1 b_2 - \Delta E_2 b_1)\}}}{2\Delta E_1 \Delta E_2 (\Delta E_2 - \Delta E_1)} \qquad (3)$$

Equilibrium constant calculated from α thus obtained was proved to be reproducible in another couple of solutions equilibrated from different concentrations of Ph and S.

Result and Discussion

To see the reaction pathway of successive hydrolysis equilibria, pH-plofile of logarithum of fraction rates and equilibrium constants were obtained. Considering the ionizations of hydrolytes and hydrolyzates which compose complexed equilibria, whole reaction system can be represented as in Chart 1, which is for SiMeS. Essentially similar scheme can be written for SiPhS. The explanations of rate and equilibrium constants used in Chart 1 are listed in Table II.

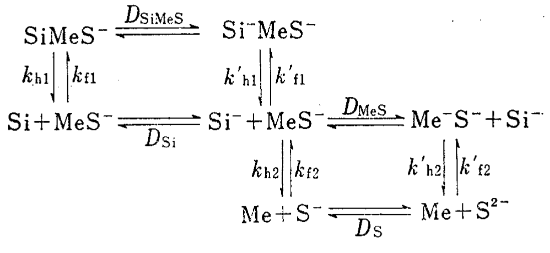

Chart 1

Hydrolysis of SiMeS

The 1st step hydrolysis of SiMeS could be followed by UV spectral method. UV spectral change of SiMeS solution (5.0×10^{-5} M) at pH 5.4 is shown in Fig. 1 as an example, which

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8) The definition of $K_{2\text{app}} = (\text{Me or Ph})_e(\text{S})_e/(\text{MeS or PhS})_e$ can be rewritten as $\{(\text{Si liberated})_e - (\text{MeS or PhS})_e\}^2/(\text{MeS or PhS})_e$ because $(\text{Me or Ph})_e = (\text{S})_e = (\text{Si liberated})_e - (\text{MeS or PhS})_e$. This relation gives an equation quadratic with respect to $(\text{Me or Ph})_e$ and the solution of which gives Eq. 2.

9) *a*) A.E. Parkinson and E.C. Wagner, *Ind. Anal. Chem.*, **6**, 433 (1934); *b*) L.C. Schroeter, "Sulfur Dioxide," Pergamon Press, London, 1966, p. 198.

10) The constancy of $K_{2\text{app}}$ for the two solutions can be represented as

$$K_{2\text{app}} = \frac{(\text{Ph})_e(\text{S})_e}{(\text{PhS})_e} = \frac{(a - \alpha\Delta E_1)(b_1 - \alpha\Delta E_1)}{\alpha\Delta E_1} = \frac{(a - \alpha\Delta E_2)(b_2 - \alpha\Delta E_2)}{\alpha\Delta E_2} \qquad (4)$$

From Eq. 4 an equation quadratic concerning to α is obtained, and one of the solution with respect to α, which has $-$sign before root, is Eq. 3.

Table II. Explanation of Rate and Dissociation Constant Noted in Scheme 1

Contstant	Explantion
k_{h_1}	1st order hydrolysis rate of SiMeS$^-$ (or SiPhS$^-$), min^{-1}
k'_{h_1}	1st order hydrolysis rate constant of Si$^-$MeS$^-$ (or Si$^-$Ph$^-$), min^{-1}
k_{f_1}	2nd order formation rate constant of SiMeS$^-$ (or SiPhS$^-$) from MeS$^-$ (or PhS$^-$) and Si, M^{-1} min^{-1}
k'_{f_1}	2nd order formation rate constant of Si$^-$MeS$^-$ (or Si$^-$Ph$^-$S$^-$) from MeS$^-$ (or PhS$^-$) and Si$^-$, M^{-1} min^{-1}
k_{h_2}	1st order hydrolysis rate constant of MeS$^-$ (or PhS$^-$), min^{-1}
k'_{h_2}	1st order hydrolysis rate constant of Me$^-$S$^-$ (or Ph$^-$S$^-$), min^{-1}
k_{f_2}	2nd order formation rate constant of MeS$^-$ (or PhS$^-$) from Me (or Ph) and S$^-$, M^{-1} min^{-1}
k'_{f_2}	2nd order formation rate constant of Me$^-$S$^-$ (or Ph$^-$S$^-$) from Me (or Ph), and S^{2-} M^{-1} min^{-1}
D_{SiMeS}	dissociation constant of (H$^+$) (Si$^-$MeS$^-$)/(SiMeS$^-$).
D_{SiPhS}	dissociation constant of (H$^+$) (Si$^-$PhS$^-$)/(SiPhS$^-$).
D_{Si}	dissociation constant of sulfisoxazole, (H$^+$)(Si$^-$)/(Si), 2.50×10^{-5} [10]
D_{MeS}	secondary dissociation constant of (H$^+$)(Me$^-$S$^-$)/(MeS$^-$), 6.44×10^{-7} [6c]
D_{PhS}	secondary dissociation constant of (H$^+$) (Ph$^-$S$^-$)/(PhS$^-$), 6.95×10^{-10} [6]
D_S	secondary dissociation constant of (H$^+$)(S^{2-})/(S$^-$), 6.24×10^{-8} [9b]

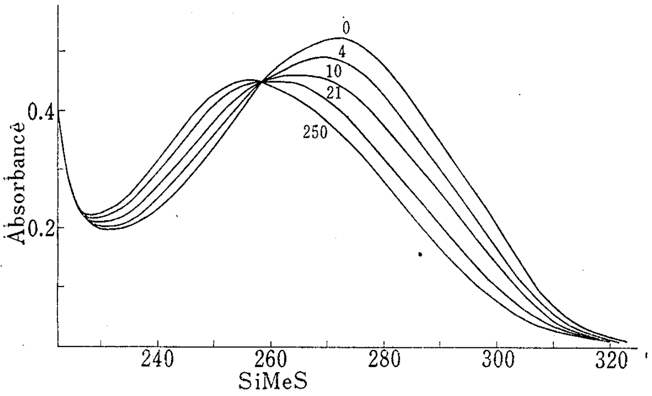

Fig. 1. UV Spectra of 5.0×10^{-5}M SiMeS Solution Changing with Time at pH 5.4 and 37° (1 cm cell)

Recording was started at indicated minutes after the dissolution.

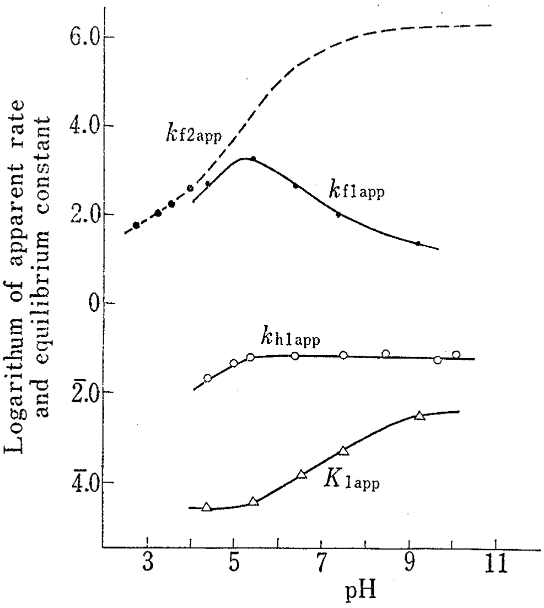

Fig. 2. The pH-profiles of log (Apparent Reaction Rate or Equilibrium Constant) Determind for SiMeS

holds isobestic point through the change and the spectrum obtained at 250 minutes lasted unchanged thereafter. The pH-profile of logarithum of apparent rate constant of the 1st step hydrolysis, log k_{h1app}, is shown in Fig. 2. The rate is pH-independent from 6 to 10. Below pH 6 the reaction rate decreases, which may be explained by the undissociation of sulfonamide group in acidic region. As was generally observed on MSD of various sulfonamides,[1] Si$^-$MeS$^-$ has hydrolysis rate constant higher than that of SiMeS$^-$. The pH-independent rate constant can be considered as the rate constant for Si$^-$MeS$^-$, k'_{h1}, refering to D_{Si} (2.5×10^{-5}).[11] From this supposition, k_{h1} can be estimated using following relation on the apparent hydrolysis rate at any (H$^+$), which is represented by (Rate)$_{h1app}$.

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[11] T. Struller, *Drug Res.*, **12**, 389 (1968).

$$(\mathrm{Rate})_{\mathrm{h1app}} = k_{\mathrm{h1}}(\mathrm{SiMeS}^-)+k'_{\mathrm{h1}}(\mathrm{Si}^-\mathrm{MeS}^-) = (\mathrm{SiMeS})_{\mathrm{total}}\left\{\frac{k_{\mathrm{h1}}(\mathrm{H}^+)+k'_{\mathrm{h1}}D_{\mathrm{SiMeS}}}{D_{\mathrm{SiMeS}}+(\mathrm{H}^+)}\right\} \qquad (5)$$

In this equation $(\mathrm{SiMeS})_{\mathrm{total}}=(\mathrm{SiMeS}^-)+(\mathrm{Si}^-\mathrm{MeS}^-)$, and the bracketted term is k_{h1app} which can be experimentally determined. From values k_{h1app} determined at two different (H^+), unknown k_{h1} and D_{SiMeS} (not equal to D_{Si} but probably not so far from it) can be estimated. The rate constants thus estimated are listed in Table III. Value D_{SiMeS} estimated is 1.79×10^{-5}, which is near to D_{Si} as was supposed.

Apparent rate constant of SiMeS formation from Si and MeS, k_{f1app}, could not be directly determined because the solubility of Si is very small and the formation of SiMeS was very small in a definite time. Therefore, k_{f1app} was estimated from the apparent equilibrium constant, K_{1app}, and k_{h1app} assuming the following relationship.

$$K_{\mathrm{1app}} = \frac{(\mathrm{MeS})_{\mathrm{e}}(\mathrm{Si})_{\mathrm{e}}}{(\mathrm{SiMeS})_{\mathrm{e}}} = \frac{k_{\mathrm{h1app}}}{k_{\mathrm{f1app}}} \qquad (6)$$

Estimation of K_{1app} was carried out as described in experimental section, but the correction for the hydrolysis of MeS was disregarded because K_{2app} for MeS has been reported to be in the order of 10^{-6} and the effect of the 2nd step hydrolysis could be supposed to be negligible. The pH-profile of log k_{f1app} for SiMeS calculated by equation 6 is also shown in Fig. 2 which has a maximum at around pH 5. The increasing in acid side may be attributed to the ionization of Si, which means that k'_{f1} is larger than k_{f1}. That Si^- has reactivity higher than Si may be explained from the decrease of electron attracting activity of sulfonamide group owing to ionization, which is in accord with the results in previous studies.[1,5] The decreasing of k_{f1app} above pH 5 may be attributed to the secondary dissociation of MeS^- to $\mathrm{Me}^-\mathrm{S}^-$, *i.e.* the latter has lower reactivity with amine, which is agreealbe to the fact that the reaction of MeS on amine is electrophilic.[1]

On the reactions of $\mathrm{MeS}\rightleftharpoons\mathrm{Me}+\mathrm{S}$ and related reactions a number of investigators have reported,[6,9] but accurate rate and equilibrium constants concerning with MeS are not reported. Effort to obtain accurate value of K_{2app} at various pH was attempted but failed. The most sensitive method to follow these changes has been spectral method according to literature. However, because of the low spectral absorbance of Me, at least 1.0×10^{-2}M is necessary for spectral method using 10 cm cell. Above 1.0×10^{-3}M, however, dimerization of bisulfite ion and related complexity arise.[9b] Probably because of these circumstances no reproducible result was obtaind varying the concentrations of MeS or Me and S.

Rate constant of MeS formation from Me and S, k_{f2app}, could be determined by the recording of UV spectral change after the mixing of Me and S solutions, which could be carried out restrictively below pH 4. Above this pH the reaction was too fast to follow. The pH-profile of log k_{f2app}, which can be considered as a part of sigmoid curve specific to the change due to dissociation, indicates that MeS formation rate, $(\mathrm{Rate})_{\mathrm{f2app}}$, can be represented as;

$$\begin{aligned}(\mathrm{Rate})_{\mathrm{f2app}} &= k_{\mathrm{f2}}(\mathrm{Me})(\mathrm{S}^-)+k'_{\mathrm{f2}}(\mathrm{Me})(\mathrm{S}^{2-})\\ &= (\mathrm{Me})(\mathrm{S})_{\mathrm{total}}\left\{\frac{k_{\mathrm{f2}}(\mathrm{H}^+)+k'_{\mathrm{f2}}D_{\mathrm{S}}}{D_{\mathrm{S}}+(\mathrm{H}^+)}\right\} \qquad (7)\end{aligned}$$

The bracketted term is k_{f2app} which can be experimentally determined and $(\mathrm{S})_{\mathrm{total}}=(\mathrm{S}^-)+(\mathrm{S}^{2-})$. Using D_{S} value in literature, 6.24×10^{-8} [9b] k_{f2} and k'_{f2} were estimated from k_{f2app} determined at two different (H^+). In Fig. 2 the dotted line extended from the plots of experimental result is based on the calculation by equation 7.

From these results and literature value for MeS[9] mentioned in the experimental section it may be said that in the case of MSD substituted with CH_3 on methylene group the effect of the 2nd step hydrolysis of MeS would not be a serious problem in the preparation of MSD solution.

Hydrolysis of SiPhS

The reaction pathway assumed for the hydrolysis of SiPhS is essentially the same as that of SiMeS. The logarithum of the 1st step hydrolysis rate of SiPhS, log k_{h1app}, is plotted in Fig. 3. Determinations of reaction rate and equilibrium constants were restricted below pH 8 because above this pH the 2nd hydrolysis equilibrium showed unexplanable result which will be described below. As is seen in Fig. 3, k_{h1app}, is also pH-independent above pH 5 and in acid region it decreases which may be explained by the unionization of sulfonamide group in acid range as was so on SiMeS. Direct determination of k_{f1app} could not be carried out as was mentioned for SiMeS. K_{1app} was calculated by equation 1 correcting the effect due to hydrolysis of PhS using K_{2app} determined as will be described. Contrarly to SiMeS, the pH-profile of log K_{1app} is almost pH-independent with slight deviation. The plots of log k_{f1app} which were estimated by equation 6 have also a pattern different from that of SiMeS. The decrease of k_{f1app} in acid range is not so evident as that of SiMeS, which indicates that the difference between k_{f1} and k'_{f1} is small. The plots of log k_{f1app} is almost pH-independent from pH 4 to 6, and somewhat increase at higher pH. As D_{PhS} (6.95×10^{-10})[6b] is 10^3 times smaller than D_{MeS} (6.44×10^{-7})[6c], that k_{f1app} is not decreased from around pH 5 as is for SiMeS is understandable. On the slight increase above pH 7 further study has not be done and unaccountable from the result obtained. D_{SiPhS} estimated similarily to D_{SiMeS} is 3.57×10^{-5}, which is also not so far from D_{Si} as was supposed.

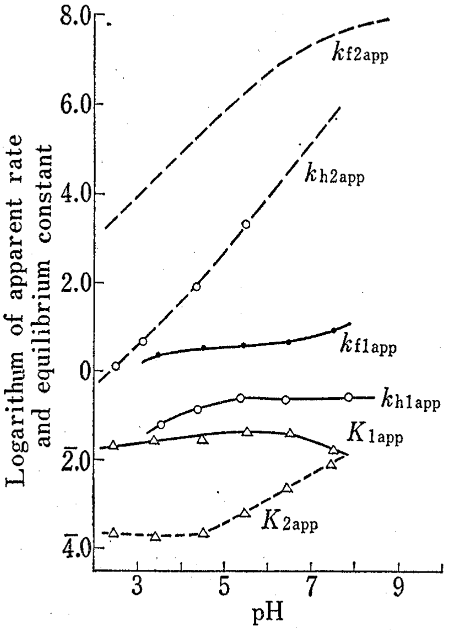

Fig. 3. The pH-profiles of log (Apparent Reaction Rate or Equilibrium Constant) Determined for SiPhS

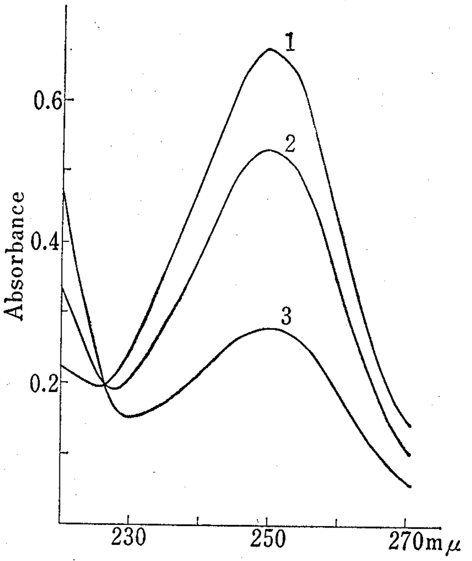

Fig. 4. UV Spectra of Solutions Equilibrated in Ph+S⇌PhS at 37° (1 cm cell)

initial concentrations
1: 7.92×10^{-5}M Ph and 1.60×10^{-4}M S
2: 7.92×10^{-5}M Ph and 4.00×10^{-4}M S
3: 7.92×10^{-5}M Ph and 1.60×10^{-3}M S

On the reaction of PhS⇌Ph+S, the result obtained approved the mechanism suggested by Stewart, *et al.*[6a] Fig. 4 shows some examples of UV spectral changes according to the concentrations of Ph and S, which retain an isobestic point. Above pH 8 UV spectral change showed a pattern different from that at lower pH and at higher alkaline condition the solution was colored yellow. The plots of log k_{h2app} obtained for PhS, which is shown in Fig. 3, indicates that the apparent hydrolysis rate of PhS, $(\text{Rate})_{h2app}$, can be represented as:

$$(\text{Rate})_{h2app} = k_{h2}(\text{PhS}^-) + k'_{h2}(\text{Ph}^-\text{S}^-)$$
$$= (\text{PhS})_{total}\left\{\frac{k_{h2}(\text{H}^+) + k'_{h2}D_{PhS}}{D_{PhS} + (\text{H}^+)}\right\} \qquad (8)$$

Apparent equilibrium constant, K_{2app}, determined is also shown in Fig. 3. PhS formation rate constant, k_{f2app}, which was too fast to follow, was calculated from k_{h2app} and K_{2app} assuming the relation expressed by equation 6 and shown in Fig. 3. As the slope of log k_{f2apq} versus pH is estimable to be 1, $(\mathrm{Rate})_{f2app}$ for PhS may be also represented in the form of equation 7. From equation 7 and 8 k_{2app} may be represented as follows.

$$K_{2app}=\frac{(\mathrm{Ph})_e(\mathrm{S})_e}{(\mathrm{PhS})_e}=\frac{k_{h2app}}{k_{f2app}}$$

$$=\left\{\frac{k_{h2}(\mathrm{H}^+)+k'_{h2}D_{\mathrm{PhS}}}{D_{\mathrm{PhS}}+(\mathrm{H}^+)}\right\}\left\{\frac{D_{\mathrm{S}}+(\mathrm{H}^+)}{k_{f2}(\mathrm{H}^+)+k'_{f2}D_{\mathrm{S}}}\right\} \qquad (9)$$

Table III. Rate Constants Obtained for SiMeS and SiPhS

	1st step hydrolysis				2nd step hydrolysis			
	Forward		Reverse		Forward		Reverse	
	k_{h1}	k'_{h1}	k_{f1}	k'_{f1}	k_{h2}	k'_{h2}	k_{f2}	k'_{f2}
	(min^{-1})		($\mathrm{M}^{-1}\,\mathrm{min}^{-1}$)		(min^{-1})		($\mathrm{M}^{-1}\,\mathrm{min}^{-1}$)	
SiMeS	5.93×10^{-4}	6.93×10^{-2}	8.10×10	1.83×10^{3}	–	–	1.44×10	1.58×10^{6}
SiPhS	5.65×10^{-2}	2.31×10^{-1}	2.19	8.50	8.57×10^{-1}	4.59×10^{6}	3.05×10^{3}	7.48×10^{7}

The comparison of rate constants shown in Table III offers the following remarks on the 1st step hydrolysis. 1) Dissociation of sulfonamide group facilitates both of hydrolysis and formation reaction, *i.e.* $k_{h1}<k'_{h1}$ and $k_{f1}<k'_{f1}$, which was explained above. 2) The effect of dissociation of sulfonamide group is evident for SiMeS more than for SiPhS. 3) Substitution of C_6H_5 facilitates the hydrolysis evidently more than that of CH_3 does, *i.e.* k_{h1} or k'_{h1} of SiMeS$<k_{h1}$ or k'_{h1} of SiPhS, which may be explained by the resonance effect of benzene ring as was pointed out in previous report.[1] 4) Contrary to above, C_6H_5 substitution is not favorable for formation reaction comparing to CH_3 substitution, *i.e.* k_{f1} or k'_{f1} of SiMeS$>k_{f1}$ or k'_{f1} of SiPhS. The resonance effect seems in this case to effect to lessen the electrophilic activity of PhS on amine.

Following remarks are obtained for the 2nd step hydrolysis, which are in accordance with the literature concerning with aldehydebisulfite addition compounds.[6,9] 1) Doubly ionized aldehydebisulfite addition compound is much labile comparing to mono valent ion as was reported by Blackadder, *et al.*[6c] 2) S^{2-} is reactive with aldehyde more than S^{-}. 3) C_6H_5 is reactive with sulfite ion more than CH_3.