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164. **Hisashi Nogami**[*1] **and Yoshio Kanakubo**[*2] : Studies on Decomposition and Stabilization of Drugs in Solution. XV.[*3] Hydrolysis of Sodium Octyl, Myristyl,[*4] Cetyl,[*5] and Pentadecane-8-sulfates.

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There have been several reports on the effects of surfactants on the reaction rates. Kolthoff and Johnson[1] reported that the reaction rate between iodine and acetone was accelerated by the presence of dodecanesulfonic acid, and Llopis and Davies[2] showed that the hydrolysis of the monolayer of cholesterol formate was accelerated by the addition of sodium docosyl sulfate and retarded by octadecyltrimethylammonium chloride in hydrochloric acid solution.

The stabilization of drugs by surfactants has been investigated in this series of study and it was found that sodium lauryl sulfate (SLS) promoted the hydrogen ion catalyzed hydrolysis and suppressed the hydroxyl ion catalyzed hydrolysis of methantheline bromide.[3,4]

Since the system, in which the stabilization of drugs was observed, was not simple, the stability of surfactants themselves was investigated.

The stability of SLS was studied and it was found that the hydrolysis rate of SLS was dependent on not only hydrogen ion concentration but also SLS concentration in the part XIII.[5] SLS was stable below its critical micelle concentration (CMC) and less stable above its CMC in hydrochloric acid solution.

It is apparent, from the above studies, that the micelle and gegen-ion around the micelle participate with the reaction rate of substrate.

Therefore, it was the authors' purpose to study the stability of sodium octyl (SOS), myristyl (SMS), and cetyl sulfate (SCS) as SLS homologue and sodium pentadecane-8-sulfate (SPS) as secondary alcohol sulfate, respectively.

Hitherto, the hydrolysis of sodium alkyl sulfate has been reported on non-micellar esters[6~8] but scarcely on micellar esters[9~11] in detail.

During the progress of this study, the effects of micellization on the hydrolysis of monoalkyl sulfates was reported by Kurz,[12] who pointed out that the value of CMC could be calculated from the variation in the hydrolysis rate of sodium decyl sulfate with concentration. The authors' result that the hydrolysis rate of SLS increased markedly near its CMC agreed with his result.

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[*3] Part XIV. H. Nogami, S. Awazu, M. Iwatsuru : This Bulletin, to be published in near future (1963).

[*4] Presented at the Kanto Local Meeting of the Pharmaceutical Society of Japan, November 24, 1962.

[*5] Presented at the 15th Annual Meeting of the Pharmaceutical Society of Japan, April 7, 1962.

1) I.M. Kolthoff, W.F. Johnson : J. Am. Chem. Soc., **73**, 4563 (1951).
2) "Surface Phenomena in Chemistry and Biology" edited by J.F. Danielli : 65 (1958).
3) H. Nogami, S. Awazu, K. Watanabe, K. Sato : This Bulletin, 8, 1136 (1960).
4) *Ibem* : *Ibid.*, **10**, 1158 (1962).
5) H. Nogami, S. Awazu, Y. Kanakubo : *Ibid.*, **11**, 13 (1963).
6) G.H. Green, J. Kenyon : J. Chem. Soc., **1950**, 1389.
7) R.L. Burwell, Jr. : J. Am. Chem. Soc., **74**, 1462 (1952).
8) G.M. Calhoun, R.L. Burwell, Jr. : *Ibid.*, **77.**, 6441 (1955).
9) R.R. Read, W.G. Fredell : Drug & Cosmetic Ind., **84**, 178 (1959).
10) M. Aoki, Y. Iwayama : Yakugaku Zasshi, **80**, 1749 (1960).
11) E.W. Maurer, A.J. Stirton, J.K. Weil : J. Am. Oil Chemists' Soc., **37**, 34 (1960).
12) J.L. Kurz : J. Phys. Chem., **66**, 2239 (1962).

Experimental

Materials——SOS, SMS and SCS were purified samples of Nikko Co., Ltd. and SPS was a purified sample of Nippon Soda Co., Ltd. Their values[*6] of CMC were approximately consistent with the literature values.[13~16)]

HCl, H_2SO_4, $CHCl_3$, NaCl and Methylene blue were of G.R.

Na_2SO_4 was of E.P.

Sudan III was a commercial product (Tokushu Chemical Co., Ltd.).

Determination of Sodium Alkyl Sulfate——The sodium alkyl sulfates were determined by the colorimetric method using methylene blue as the part XIII,[5)] except 4 cc. of methylene blue solution for SOS. The $CHCl_3$ layer was assayed spectrophotometrically at 650 mμ with a Shimadzu QB-50 spectrophotometer in this study. The linear relationship was found between absorbancy and concentration within the range of 0.02～0.20 m*M* of the sodium alkyl sulfates.

Kinetic Procedure——SOS and SPS in 0.1*N* HCl solution and SMS and SCS in 0.01*N* HCl solution were used. The sampling procedure at 70° was similar to the part XIII.[5)] The procedure at the boiling water temperature was as follows. Twenty cc. of the test solution (SOS and SLS in 0.1*N* HCl solution) was placed in a test tube. The test tubes were immersed in a vigorously boiling water bath. After 5 minutes' heating (zero time), one of them was withdrawn from the water bath at given intervals and immediately cooled in running cold water.

Determination of CMC (Solubilization Method with Dye (Sudan III))——The procedure was similar to the part XIII.[5)] The solubilized dye was assayed spectrophotometrically at 490 mμ with a Shimadzu QB-50 spectrophotometer.

Results and Discussion

Hydrolysis and CMC——The hydrolysis of the sodium alkyl sulfates did not follow the pseudo-first order course as well as SLS in long time observation. The linear relationship, however, was recognized at the initial stage and the hydrolysis rate was calculated from the initial linear region (SOS : 24 hr., SMS : 10 hr., SCS : 8 hr., and SPS : 10 hr.) assuming the pseudo-first order reaction. The relationships between the rates and the concentration are shown in Figs. 1～4. The hydrolysis rates increased

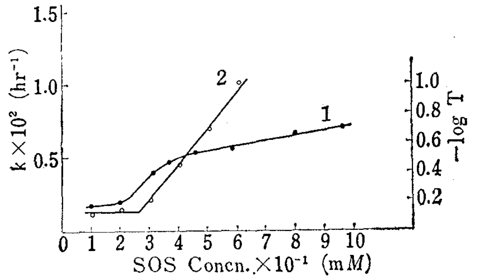

Fig. 1. Relationship between the Reaction Rate and SOS Concentration in 0.1*N* HCl Solution (1) and Solubilization Curve in 0.1*M* NaCl Solution (2) at 70°

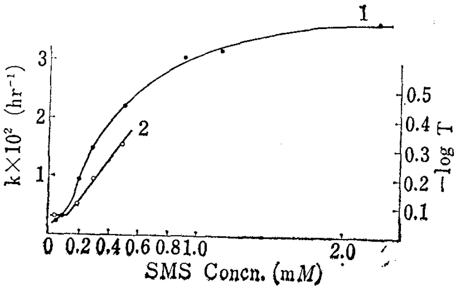

Fig. 2. Relationship between the Reaction Rate and SMS Concentration in 0.01*N* HCl Solution (1) and Solubilization Curve in 0.01*M* NaCl Solution (2) at 70°

[*6] The value of CMC was as follows.

	CMC (m*M*)	Temp. (°C)	Method
SOS	110	30	Solubilization method with dye (sudan III)
SMS	1.9	40	Solubilization method with dye
SCS	0.5	50	〃
SPS	7.6	60	〃

13) I. Nishi, T. Imai, M. Kasai : "Kaimenkasseizai Binran," 128 (1960).
14) K. Meguro, T. Kondō : Kagaku no Ryōiki, **12**, 701 (1958).
15) H.C. Evans : J. Chem. Soc., **1956**, 579.
16) K. Shimokai, M. Fukushima : Yukagaku Zasshi, to be published (1963).

markedly in 18.5~30.5 mM (SOS), 0.21~0.30 mM (SMS), 0.05~0.10 mM (SCS), and 1.50~1.96 mM (SPS), respectively. The CMC of SOS and SPS in 0.1 M sodium chloride solution and that of SMS and SCS in 0.01M sodium chloride solution were determined respectively by the solubilization method with dye. The results are shown in Figs. 1~4. The CMC obtained from the solubilization method agreed approximately with the flection point where the reaction rate increased.

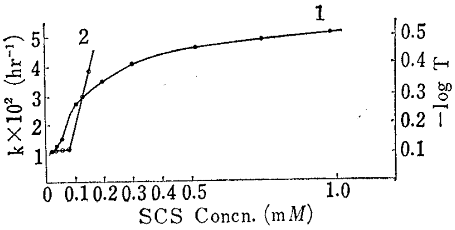

Fig. 3. Relationship between the Reaction Rate and SCS Concentration in 0.01N HCl Solution (1) and Solubilization Curve in 0.01M NaCl Solution (2) at 70°

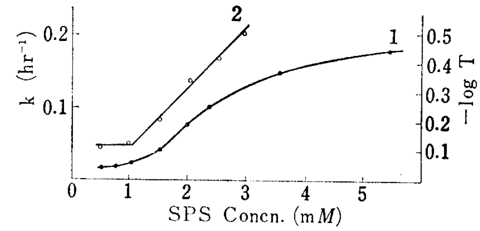

Fig. 4. Relationship between the Reaction Rate and SPS Concentration in 0.1N HCl Solution (1) and Solubilization Curve in 0.1M NaCl Solution (2) at 70°

Sodium chloride was used instead of hydrochloric acid in this experiment, to prevent*[7] the hydrolysis by acid at high temperature as the part XIII.[5]

The Stability of Sodium Alkyl Sulfates with the Different Alkyl Chain Length—— Desseigne[17] studied the hydrolysis rates of alkyl sulfates, from sodium ethyl to lauryl sulfate, in N hydrochloric acid solution at boiling temperature and found a minimum at sodium amyl sulfate. According to Bauer and Poethke,[18] the hydrolysis rate of sodium amyl sulfate was about 75% that of sodium ethyl sulfate in hydrochloric acid solution and sodium octadecyl sulfate was far less stable. The formation of micelle was not recognized at sodium alkyl sulfates with short alkyl chain length, from sodium ethyl to hexyl sulfate.[19] But they did not discuss the relationship between the rate and the concentration of the sodium alkyl sulfate.

Table I. The Comparison of the Hydrolysis Rates of SOS and SLS in 0.1N HCl Solution

Concn. (mM)	k (hr^{-1})	k_{SLS}/k_{SOS}
Below the CMC:		
0.92 (SLS)	0.0019	1.12 (at 70°)
9.6 (SOS)	0.0017	
1.07 (SLS)	0.0617	1.08 (at boiling water temperature)
11.4 (SOS)	0.0570	
Above the CMC:		
5.53 (SLS)	0.0326	5.93 (at 70°)
57.9 (SOS)	0.0055	
6.12 (SLS)	0.5403	6.54 (at boiling water temperature)
66.3 (SOS)	0.0826	

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*[7] The hydrolysis of SOS and SPS in 0.1M NaCl solution and that of SMS and SCS in 0 NaCl solution at 70° were as follows.

	Initial concn. (mM)	Final concn. (mM)
SOS	53.5	53.0 (after 24 hr.)
SPS	6.84	6.61 (after 10 hr.)
SMS	2.13	2.06 (after 24 hr.)
SCS	1.01	1.00 (after 10 hr.)

Very little hydrolysis was observed.

17) G. Desseigne: Industries corps gras, **1**, 136 (1945). Through C. A., **40**, 4901¹(1946).
18) K.H. Bauer, W. Poethke: J. prakt. Chem., **126**, 296 (1930).
19) M. Raison: Oléagineux, **13**, 189 (1958).

The stability of SOS, SLS,[5)] SMS and SCS are shown in Figs. 5 and 6 at 70°. Further, the stability of SOS and SLS was compared below and above their CMC in Table I at 70° and the boiling water temperature.

It was recognized that the longer the alkyl chain length, the less the stability became.

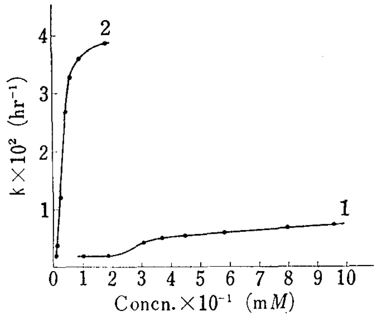

Fig. 5. The Reaction Rate of SOS and SLS in 0.1*N* HCl Solution at 70°

1: SOS 2: SLS

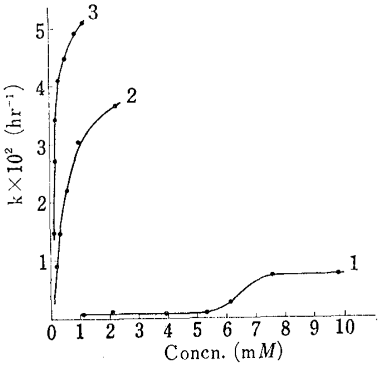

Fig. 6. The Reaction Rate of SLS, SMS and SCS in 0.01*N* HCl Solution at 70°

1: SLS 2: SMS 3: SCS

However, the difference of rates was not so remarkable below the CMC, but evident above the CMC. The similar tendency was recognized at 70° and the boiling water temperature, respectively.

Tartar[20,21)] studied the CMC, the micellar molecular weight, and the association number per micelle etc. on several series of surfactants and showed that the longer the alkyl chain length, the larger the micellar molecular weight became.

Debye[22)] found that the effect of a given amount of added salt in increasing the micellar molecular weight was more pronounced at the longer the hydrocarbon tail of the surfactant molecule.

From the above studies, the authors thought that the micelle with the longer alkyl chain length was more affected by gegen-ion than the shorter chain length.

Accordingly, in this study, it was considered that the micelle of the sodium alkyl sulfate with the longer alkyl chain length was more subject to the catalytic effect by the hydrogen ion than the shorter chain length.

When the stability of sodium alkyl sulfates is compared, this result suggests that it is necessary to consider the effect of the concentration of the sodium alkyl sulfate (below or above the CMC) and that the stability of drugs is affected by their dispersion states, such as association and micellization.

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Summary

The hydrolysis of sodium octyl (SOS), myristyl (SMS) and cetyl sulfate (SCS) as sodium lauryl sulfate (SLS) homologue and that of sodium pentadecane-8-sulfate (SPS) as secondary alcohol sulfate in hydrochloric acid solution were studied.

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20) H. V. Tartar: J. Phys. Chem., **59**, 1195 (1955).
21) *Idem*: J. Colloid Sci., **14**, 115 (1959).
22) P. Debye: J. Phys. & Colloid Chem., **53**, 1 (1949).

1) It was recognized that the sodium alkyl sulfates were relatively stable below their critical micelle concentration (CMC) and less stable above their CMC as well as SLS. Accordingly, this phenomenon was ascribed to the micellization and the ionic atmosphere around the micelle of the sodium alkyl sulfate.

2) The sodium normal alkyl sulfate with the longer alkyl chain length was less stable than the shorter chain length. It was thought that the micelle with the longer alkyl chain length was more affected by gegen-ion than the shorter chain length.

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