to CH_3OH was extinguished by compensation of the same solvent. The measurement in H_2O or H_2O-CH_3OH mixture was made in a sealed cell with CaF_2 windows of 0.025 mm. thickness. D_2O (99.5%) was used to complement the 1600 cm^{-1} region. The photochemical reactions were investigated in a sealed cell with CaF_2 windows of 0.025 mm. thickness using ca. 30% solution in CH_3OH or CH_3OH-$CHCl_3$ mixture, depending upon the solubility of the sample. The irradiation of 2536 Å ultra-violet light was directly applied into the cell, followed by subsequent spectral measurements.

The authors express their deep gratitudes to Prof. M. Hamana of Kyushu University for his kind guidance, and to Mr. M. Matsui, Director of this laboratory, and to Dr. G. Sunagawa of this laboratory for their helpful encouragements.

Summary

The infrared spectra of benzaldehyde N-methyl and N-phenyl nitrones and the corresponding imines, as well as those of the related monosubstituted benzenes, were determined and the assignment was made for most of the vibrations in the 1700~650 cm^{-1} region and the characteristic frequencies for aldonitrones were discussed.

The N-O stretching frequencies were assigned to the strong absorption at 1172 cm^{-1} in the N-methyl and the strong doublet at 1088 and 1071 cm^{-1} (1082 and 1067 cm^{-1} as solid) in the N-phenyl nitrones, respectively. From these positions, it was concluded that these aldonitrones constitute a transitory group located between heteroaromatic and aliphatic amine N-oxides with respect to the nature of the N-oxide function, the N-methyl nitrone being closer to the former and the N-phenyl nitrone to the latter. The C=N stretching frequencies showed a large shift to a lower frequency in the nitrones as compared with those in the corresponding imines. Study of the solvent effect showed that the N-O and the C=N frequencies shifted markedly to a lower and a higher frequency, respectively, in a solvent capable of hydrogen bond formation. These results were discussed in terms of resonance contribution in the electronic state of the nitrones.

Photochemical reaction of these nitrones was investigated spectrophotometrically and their conversion products on irradiation of ultraviolet light were identified and discussed.

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UDC 615.752.34-011 : 661.185

79. Hisashi Nogami, Shoji Awazu*[1], and Noriyasu Nakajima*[2] : Studies on Decomposition and Stabilization of Drugs in Solution. IX*[3] Stabilization of Acetylsalicylic Acid in Aqueous Solution by Surface-active Agents.

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The authors reported previously[1] that the hydrolysis of Methantheline Bromide, a quaternary amine, is suppressed by sodium laurylsulfate (anionic surfactant). Methantheline Bromide is positively charged in aqueous solution and therefore, the present study was instituted in order to examine the effect of cationic, anionic, and nonionic surfactants on the suppression of the hydrolysis of the drug which exists in anionic and undissociated

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*[3] Part Ⅷ : This Bulletin, **9**, 646 (1961).

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forms in aqueous solution. As the hydrolysis of acetylsalicylic acid (ASA : pKa=3.565[2]) was kinetically studied by Edwards[2] and Garrett[3] in detail, this substance was selected as the object in this study for the convenience of the discussion. The surfactants used here were sodium laurylsulfate, Emulgen 120[*5] (nonionic surfactant), cetylethyldimethylammonium bromide, as the same in the previous report, and benzalkonium chloride (cationic surfactant). The decomposition rate constants in the buffer solutions (pH value 1~7.5) were obtained with or without the surfactant and compared.

Experimental

Materials——1) ASA was recrystallized from $CHCl_3$.
2) Commercial benzalkonium chloride was used without any purification.
3) Other materials were the same as previously reported.[1]

Kinetic Procedure——Accurately weighed additive and 200 mg. ASA (solubility,[4] 1 g./300 cc. H_2O at 25°) were placed in a 100-cc. volumetric flask and made to 100 cc. with a buffer solution. The flask was immersed in a thermostatically controlled water bath (37°±0.1°). One cc. of the samples was taken from the flask at given intervals, salicylic acid was determined by the following colorimetric method, and the ammount of undecomposed ASA, was calculated from the value of salicylic acid.

Determination of Salicylic Acid——1) The determination in all solutions studied here except in 5% sodium laurylsulfate solution : One cc. of the sample was pipetted in 20 cc. of pH 2.35[*6] buffer solution (glycocol, NaCl-HCl buffer solution) and 1 cc. of iron test reagent (1% $Fe(NO_3)_3$ in 0.075*N* HNO_3) was added. The color which appeared was determined spectrophotometrically at 530 mμ.
2) Determination in 5% sodium laurylsulfate solution : One cc. of the sample was pipetted in 20 cc. of pH 2.35 buffer solution, which contained 3% benzalkonium chloride,[*7] and 1 cc. of the iron test reagent was added. The color was determined at 530 mμ.

Determination of Partition Coefficient——Three cc. of 0.2% ASA in CH_2ClCH_2Cl solution and 3 cc. of buffer solution containing an additive were placed in an ampoule, and shaken in a thermostatically controlled water bath (30°±0.1°) and centrifuged. Then, 1 cc. of the CH_2ClCH_2Cl layer was pipetted, and diluted adequately with CH_2ClCH_2Cl, and the optical density was read at 280 mμ.[*8]

Ultraviolet Absorption Spectra——The UV absorption of the buffer solution which contained 0.0118% ASA and 5% surfactant[*9] was determined, using the buffer solution containing 5% surfactant as blank.

In all the above experiments, Hitachi spectrophotometer Model EPU-II and Beckman-G pH meter were used.

Results and Discussion

The hydrolysis of ASA was found to follow a pseudo-first order reaction, either in a surfactant buffer solution or in a control solution. Examples are illustrated in Fig. 1. Decomposition rate constants of ASA (k) are listed in Table I and the relationship between log *k* and pH is illustrated in Fig. 2. Apparently, the hydrolysis of ASA is suppressed by surfactants and the magnitude of suppression (the magnitude of stabilization) varies with the kind of surfactants used. These phenomena may be qualitatively explained on the basis of the following assumptions.

[*5] Polyoxyethylene lauryl ether, Kao Soap Co., Ltd. product (HLB : 15.5).

[*6] This buffer was used to suppress the hydrolysis of ASA.

[*7] When the iron test reagent was added to sodium laurylsulfate solution, white turbidity appeared. The appearance of the turbidity was prevented by the addition of benzalkonium chloride.

[*8] Absorption maximum of ASA in CH_2ClCH_2Cl.

[*9] When the same concn. of ASA (0.2%) as in the kinetic study, was used, the UV absorption could not be determined (1-cm. cell was used). As the purpose of this determination was to examine the presence of the interaction between ASA and surfactants, the concn. of ASA was decreased, until the determination became possible. UV absorption of 10% Emulgen 120 solution was too high and 5% Emulgen 120 was used.

2) L. J. Edwards : Trans. Faraday Soc., **46**, 723 (1950); *ibid.*, **48**, 696 (1952).
3) E. R. Garrett : J. Am. Chem. Soc., **79**, 3401 (1957).
4) Merck index 6 th Ed.

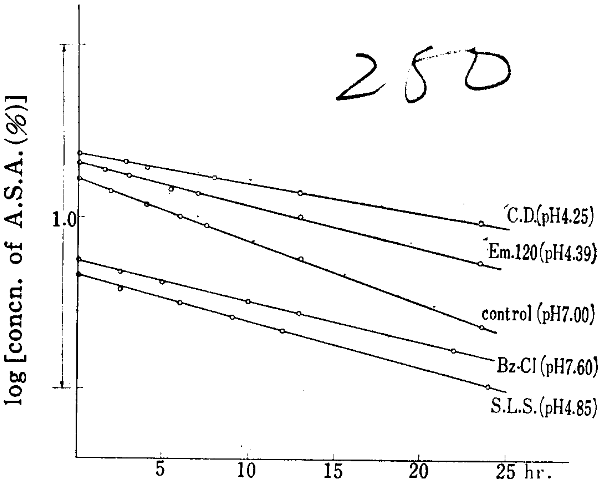

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Fig. 1. Pseudo First-order Disappearance of Acetylsalicylic Acid Solution containing Various Surfactants at 37°

To show the lines clearly, the starting points [log (100=2)] are slid on the ordinate.

C. D. : cetylethyldimethylammonium bromide
Em. 120 : Emulgen 120
Bz·Cl : benzalkonium chloride
S. L. S. : sodium laurylsulfate
A. S. A. : acetylsalicylic acid

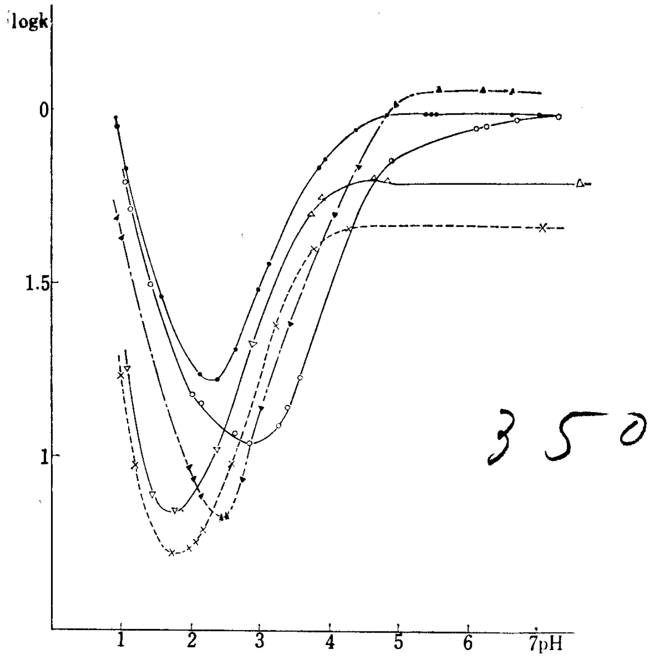

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Fig. 2. Relationship between pH and log *k* at 37°

—•— A. S. A. 2 mg./cc. —△— +Bz·Cl 10%
—▲— +Em. 10% —○— +S. L. S. 5%
--×-- +C. D. 5%

A. S. A. : acetylsalicylic acid
Em. 120 : Emulgen 120
C. D. : cetylethyldimethylammonium bromide
Bz·Cl : benzalkonium chloride
S. L. S. : sodium laurylsulfate

Table I. Decomposition Rate Constants of Acetylsalicylic Acid in the Presence and Absence of Surfactants at 37°

Buffer	A. S. A. control 2 mg./cc.		+Em. 120 10%		+C. D. 5%		+Bz·Cl 10%		+S. L. S. 5%	
	pH	k/day	pH	k/day	pH	k/day	pH	k/day	pH	k/day
Sörensen	0.92	0.893	0.88	0.485	0.97	0.169	1.08	0.182	1.04	0.629
Glycocoll-	1.07	0.688	0.98	0.428	1.20	0.0850	1.41	0.076	1.13	0.526
NaCl-HCl	1.58	0.288	1.98	0.0930	1.72	0.0521	1.75	0.069	1.42	0.310
	2.10	0.173	2.02	0.0868	2.01	0.0561	2.10	0.083	2.03	0.149
	2.39	0.166	2.14	0.0748	2.05	0.0572	2.37	0.104	2.14	0.143
	2.65	0.201	2.45	0.0653	2.16	0.0617	2.85	0.210	2.60	0.118
	2.97	0.304	2.51	0.0663	2.63	0.0951			2.83	0.109
	3.10	0.360	2.71	0.0874					3.27	0.123
			3.00	0.139						
Walpole	3.85	0.690	3.40	0.250	3.20	0.236	3.70	0.504	3.39	0.138
AcOH-AcONa	3.92	0.725	4.03	0.503	3.75	0.399	3.85	0.576	3.58	0.166
	4.35	0.902	4.39	0.685	4.25	0.458	4.62	0.661	4.85	0.724
	4.80	0.997	4.90	1.06			4.80	0.636		
	5.38	0.993	5.55	1.18						
	5.45	0.999								
	5.52	0.998								
Palitzsch	6.62	0.962	6.20	1.18	7.06	0.469	7.60	0.647	6.10	0.895
H_3BO_3-$Na_2B_4O_7$	7.00	0.986	6.60	1.14					6.25	0.902
									6.66	0.967
									7.28	0.977

A. S. A. : acetylsalicylic acid
C. D. : cetylethyldimethylammonium bromide
S. L. S. : sodium laurylsulfate
Em. 120 : Emulgen 120
Bz·Cl : benzalkonium chloride

It may be assumed that the undissociated form of ASA moves from the aqueous phase to a micellar phase (the partition law prevails between aqueous and micellar phases). In the same way, on the other hand, the anionic form of ASA may interact only with cationic surfactant. The interaction with other surfactants may be very slight or negligible.

pH 5~7.5 (the Plateau Portion)

In the solution of pH value about 5, ASA dissociates in anionic form beyond 95%. The decomposition of ASA is attributed primarily to that of the anionic form according to Edwards[2] and Garrett.[3] Then, due to electrostatic attraction the anion may form a complex with a cationic surfactant and the complex will move to micelle which is composed of excess surfactant. Consequently, a cationic surfactant will suppress the hydrolysis of ASA in this pH region. This contrasts markedly with the fact that the hydrolysis of methantheline bromide, which has a opposite charge to ASA, was suppressed by sodium laurylsulfate, an anionic surfactant, as reported previously.[1] In fact, as shown in Fig. 2, benzalkonium chloride and cetylethyldimethylammonium bromide which are cationic surfactants suppress the hydrolysis of ASA in this pH region.

More strictly, the dissociation of ASA in the surfactant solution may be considered as follows.

Dissociation of ASA in the Surfactant Solution

According to the preceding assumption, the following equations may be given for the dissociation of ASA in nonionic or anionic surfactant solution.

$$\frac{[\mathrm{ASA}^-][\mathrm{H}^+]}{[\mathrm{ASAH}]}=\mathrm{K} \tag{1}$$

$$\frac{[\mathrm{ASAH}]}{[(\mathrm{ASAH})_m]}=\mathrm{K}_m{}^{*10} \tag{2}$$

From Eqs. (1) and (2)

$$[\mathrm{ASA}^-]=\frac{[\text{total ASA}]}{1+\dfrac{[\mathrm{H}^+]}{\mathrm{K}}+\dfrac{[\mathrm{H}^+]}{\mathrm{K}\cdot\mathrm{K}_m}} \tag{3}$$

$$[\mathrm{ASAH}]=\frac{[\mathrm{H}^+]}{\mathrm{K}}\,\frac{[\text{total ASA}]}{1+\dfrac{[\mathrm{H}^+]}{\mathrm{K}}+\dfrac{[\mathrm{H}^+]}{\mathrm{K}\cdot\mathrm{K}_m}} \tag{4}$$

$$[(\mathrm{ASAH})_m]=\frac{[\mathrm{H}^+]}{\mathrm{K}\cdot\mathrm{K}_m}\,\frac{[\text{total ASA}]}{1+\dfrac{[\mathrm{H}^+]}{\mathrm{K}}+\dfrac{[\mathrm{H}^+]}{\mathrm{K}\cdot\mathrm{K}_m}} \tag{5}$$

On the other hand, only Eq. (1) is given for the solution which does not contain any surfactant,

$$[\mathrm{ASA}^-]=\frac{[\text{total ASA}]}{1+\dfrac{[\mathrm{H}^+]}{\mathrm{K}}} \tag{6}$$

where ASAH is the undissociated ASA, ASA^- is the ASA anion, $(\mathrm{ASAH})_m$ is the undissociated ASA in micelle, K is the dissociation constant of ASA, and K_m the partition coefficient of ASA between an aqueous and micellar phase. Comparing Eq. (3) with Eq.

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*10 Strictly speaking, Km may vary with the pH value, added electrolytes, buffer components, etc. of the solution, but these effects are neglected here.

(6), at the same pH value, it is predicted that the solution where a nonionic or an anionic surfactant is added will contain a smaller amount of the ASA anion and a larger amount of the undissociated ASA in aqueous and micellar phases than the solution without a surfactant.

Thus, in the sodium laurylsulfate solution, the undissociated ASA will still exist at pH 5, and hydrolysis will be suppressed slightly, and above pH 6.5, ASA may dissociate almost completely, and the hydrolysis should not be suppressed, as shown in Fig. 2 and Table I.

In order to examine the presence of an interaction between ASA and a surfactant, and the prediction that, at the same pH value, there are smaller amount of the ASA anion and larger amount of the undissociated form in the anionic or nonionic surfactant solution than in the control, ultraviolet spectra were examined. As illustrated in Fig. 3, at pH 7, the spectrum of ASA in the cetylethyldimethylammonium bromide solution distinctly differs from that in the control solution and, on the other hand, the spectra in sodium laurylsulfate and in Emulgen 120 solution coincide with that in the control. It shows that the ASA anion interacts with cetylethyldimethylammonium bromide. In the lower pH region, as illustrated Figs. 4 and 5, the spectra in the sodium laurylsulfate and Emulgen 120 solution are more like that of the undissociated form (Fig. 6) than that

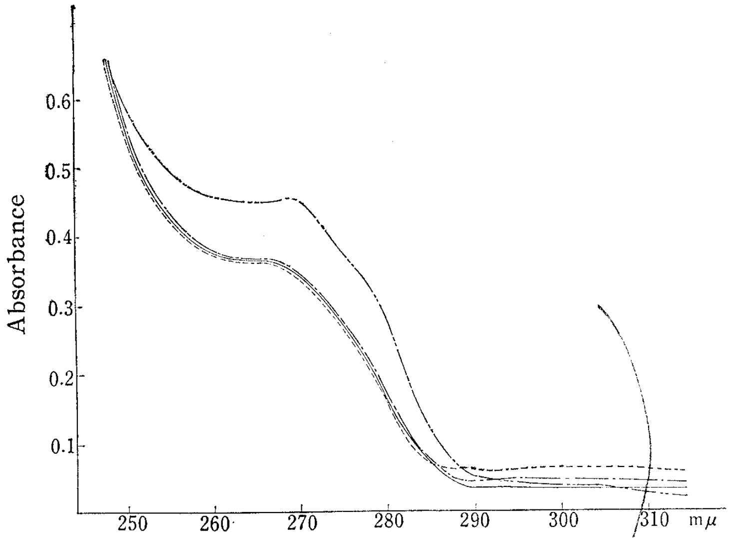

Fig. 3. Ultraviolet Absorption Spectra of Acetylsalicylic Acid in Buffer Solution containing Various Surfactants

———— A. S. A. (pH 7.17)
-·-·-·- 5% S. L. S. (pH 7.12)
··········· 5% Em. 120 (pH 2.19)
- - - - - 5% C. D. (pH 7.20)

S. L. S. : sodium laurylsulfate
Em. 120 : Emulgen 120
C. D. : cetylethyldimethylammonium bromide
A. S. A. : acetylsalicylic acid

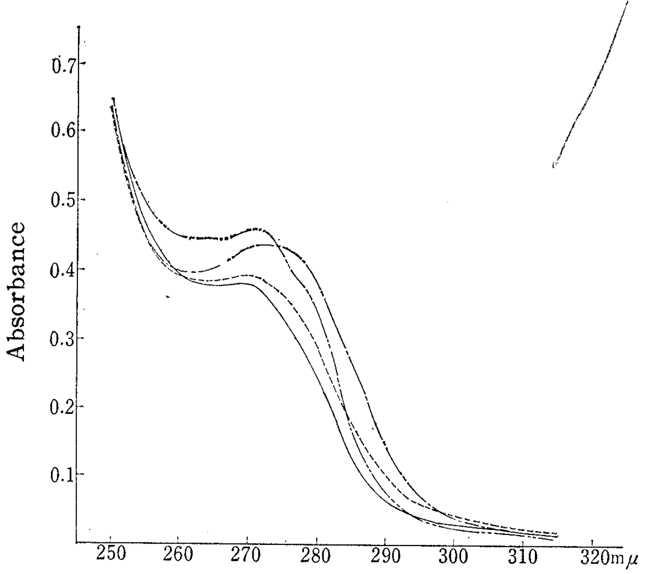

Fig. 4. Ultraviolet Absorption Spectra of Acetylsalicylic Acid Solution containing Various Surfactants

———— control (pH 4.66)
-·-·-·- S. L. S. (pH 4.69)
··········· Em. 120 (pH 4.78)
- - - - - C. D. (pH 4.65)

S. L. S. : sodium laurylsulfate
Em. 120 : Emulgen 120
C. D. : cetylethyldimethylammonium bromide

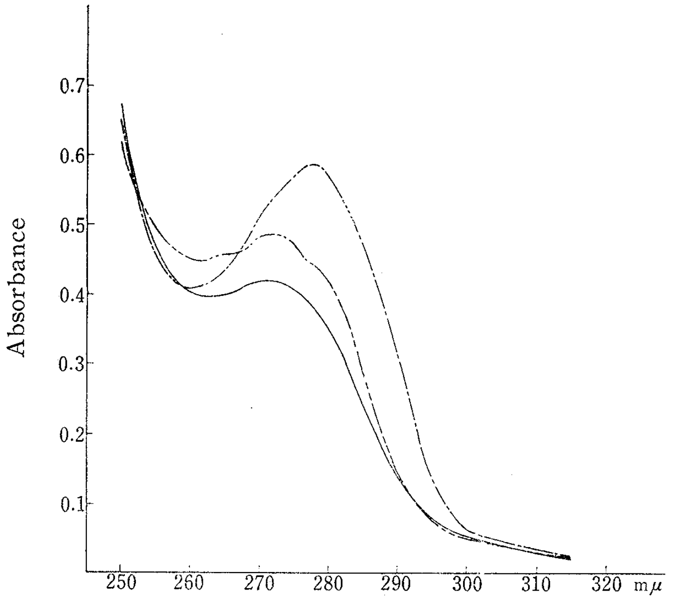

Fig. 5. Ultraviolet Absorption Spectra of Acetylsalicylic Acid Solution containing Various Surfactants

——— control (pH 4.03)
–·–·–·– S. L. S. (pH 4.02)
– – – – C. D. (pH 4.00)

S. L. S. : sodium laurylsulfate
C. D. : cetylethyldimethylammonium bromide

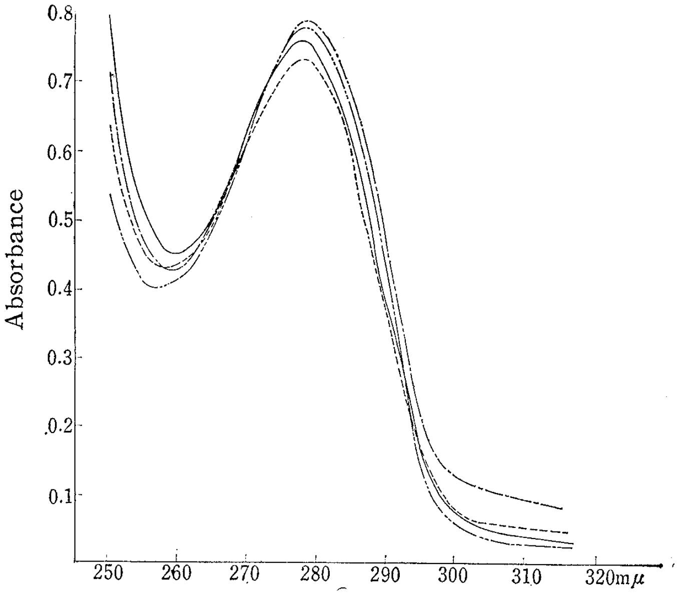

Fig. 6. Ultraviolet Absorption Spectra of Acetylsalicylic Acid Solution containing Various Surfactants

——— control (pH 1.16)
–·–·–·– S. L. S. (pH 1.20)
··········· Em. 120 (pH 1.11)
– – – – C. D. (pH 1.19)

S. L. S. : sodium laurylsulfate
Em. 120 : Emulgen 120
C. D. : cetylethyldimethylammonium bromide

in the control at the same pH. It shows that there are larger amount of the undissociated ASA in the sodium laurylsulfate and Emulgen 120 solutions than in the control.

To ascertain further that a cationic surfactant interacts with the ASA anion and forms a comlex, which is solubilized, by the excess surfactant, the effect of surfactants was examined on the partition of ASA between water and dichloroethylene. As shown in Table II, at pH 7, the lower organic solvent layer (dichloroethylene) does not contain ASA at all when the upper layer is a buffer or 5% sodium laurylsulfate solution. On the other hand, the organic solvent layer contains ASA when the upper layer is cetylethyldimethylammonium bromide solution, and in lower concentrations (0.042% and 0.42%) a larger amount of ASA exists than in the 5% sytstem. This may be due to the formation of a complex of ASA with cetylethyldimethylammonium bromide and transition of the complex into aqueous layer by the excess surfactant. By this experiment, the above mentioned interaction was further ascertained.

Table II. Apparent Partition Coefficient of Acetylsalicylic Acid between Dichloroethylene and Water

Soln.	Partition coeff.	pH	Soln.	Partition coeff.	pH
control	0	7	control	2.6	1
5% S.L.S.	0	7	5% NaCl	3.6	1
0.042% C.D.	0.066	7	5% S.L.S.	0.36	1
0.42% C.D.	0.080	7	5% C.D.	0.58	1
5% C.D.	0.016	7			

$$\text{Apparent partition coeff.} = \frac{\varepsilon_1}{\varepsilon_0 - \varepsilon_1}$$

Where ε_0 = UV absorption at 280 mμ in the initial acetylsalicylic acid-dichloroethylene soln.
ε_1 = UV absorption at 280 mμ in the dichloroethylene layer after shaking.

In the plateau portion, Emulgen 120 promotes the hydrolysis of ASA slightly. This could not be expected. In order to study whether it is the specific effect of a nonionic surfactant or not, the decomposition rate of ASA was obtained in the buffer solution containing polyethylene glycol 400 or Carbowax 4000. As shown in Table III, the hydrolysis of ASA was promoted in these solutions. Garrett[3] had already reported that in this pH region ethanol promotes the hydrolysis of ASA. Considering these phenomena, it may not be the specific effect of a nonionic surfactant to promote the hydrolysis of ASA.

Table III. Decomposition Rate Constants of Acetylsalicylic Acid Solution Containing Polyethylene glycol or Ethanol at 37°

Additive	Concn. (%)	pH	Rate constant (day^{-1})
Control	0	0.92	0.893
EtOH[a]	10	1.00	0.822
P.E.G. 400	10	1.01	0.814
Carbowax 4000	10	1.01	0.818
Control	0	7.00	0.986
P.E.G. 400	10	7.53	1.16
Carbowax 4000	10	7.49	1.12

a) percentage by volume was used.
P.E.G. = polyethylene glycol

pH 1~5

Below pH 5, all surfactants used here suppressed the hydrolysis of ASA. As the undissociated ASA exists in this region, it may be explainable with the assumption that a part of the undissociated ASA moves in micelle and becomes less hydrolyzable. Moreover, it is of interest that the pH value where the hydrolysis rate is minimum, is lower in the cetylethyldimethylammonium bromide or benzalkonium chloride solution and higher in the sodium laurylsulfate than in the control, and not so different in the Emulgen 120 as in the control (Fig. 2).

Near pH 1

Near pH 1, sodium laurylsulfate loses the effect of suppressing the hydrolysis of ASA. According to Edwards[2] and Garrett,[3] in this pH region the predominant catalyst for the hydrolysis of ASA is H^+. Riegelman[5] found that, in 0.04 OH^- solution, a small amount of cetyltrimethylammonium bromide promotes the hydrolysis of benzocaine and a large amount of it suppresses the hydrolysis. The phenomenon was explained that in the dilute surfactant solution which contains the micelle of a loose arrangement of hydrocarbon chains, the attracted OH^- on the environment of the micelle easily approaches the solubilized benzocaine, so the hydrolysis is promoted and in the more concentrated

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[5] S. Riegelman: J. Am. Pharm. Assoc., Sci. Ed., **49**, 339 (1960).

surfactant solution where surfactant molecules aggregate more closely to form a micelle, it is difficult for OH^- to approach the solubilized benzocaine, and the hydrolysis is suppressed. Considering the above phenomenon, the relationship between sodium laurylsulfate micelle and H^+ may be assumed as follows. The promoting effect of sodium laurylsulfate on the hydrolysis of ASA due to the attracted H^+ on the micelle environment competes with the suppressing effect of the solubilization. And therefore, it may be explained with the above assumption that sodium laurylsulfate loses gradually the stabilization effect on ASA solution. If it is true, in a more dilute surfactant solution where hydrocarbon chains of micelle is loosely arranged, the attracted H^+ will easily approach the solubilized ASA and consequently, the hydrolysis will be promoted. This prediction was proved in 0.2% and 0.5% sodium laurylsulfate solutions. As shown in Table IV, the hydrolysis is evidently promoted. When sodium chloride is added to the solution, the hydrolysis rate constant of ASA decreases a little. It is probable that the decrease is partly due to the substitution of Na^+ for H^+ on the environment of micelles.

Table IV. Decomposition Rate Constants of Acetylsalicylic Acid Solution Containing 0.2~0.5% Sodium Laurylsulfate and 0.1*M* NaCl at 37°

Concn. of S.L.S.(%)	Concn. of NaCl	k/day (at pH 0.99)	Concn. of S.L.S.(%)	Concn. of NaCl	k/day (at pH 0.99)
0	0	0.777[a]	0.5	0	1.51
0.2	0	1.14	0.5	0.1*M*	1.25
0.2	0.1*M*	1.02			

a) obtained graphically from Fig. 2.

To ascertain the assumption that the undissociated ASA is solubilized by surfactants, the effect of surfactants on the partition of Aspirin between water and dichloroethylene was examined only with sodium laurylsulfate and cetylethyldimethylammonium bromide at pH 1. As shown in Table II, both surfactants distinctly solubilize the undissociated form, and moreover, the solubilizing power of 5% cetylethyldimethylammonium bromide solution and that of 5% sodium laurylsulfate solution are not so different from each other. In spite of this, however, the aqueous solution of ASA is well stabilized by cationic surfactants. This may be due to the difficulty for H^+ to approach the cationic surfactant micelle by repulsion.

At pH 1, the decomposition rate constants of ASA was obtained in the solution of 10% Carbowax 4000, polyethylene glycol 400, or ethanol (Table III). As ASA solution is not stabilized in any solution, it is found that the suppressing effect of Emulgen 120 on the hydrolysis of Aspirin is specific to a nonionic surfactant.

Effect of Buffer Concentration and Added Electrolyte on the Stabilization

It was reported previously[1] that the hydrolysis of methantheline bromide in sodium laurylsulfate was affected by buffer concentration. It was studied here whether the effect was also observed on the hydrolysis of ASA. To examine the effect both on the undissociated and anionic forms of ASA the hydrolysis rates were obtained at two pH values, as shown in Table V. As the pH values varied with buffer concentration near pH 1, sodium chloride was added instead of increasing the concentration. In 5% sodium laurylsulfate solution where sodium chloride was added, white turbidity appeared during the course of the experiment at pH 1, and the hydrolysis rate was obtained at pH 2. The effect of buffer concentration and of added electrolyte was not observed so markedly in the ASA solution as in the methantheline bromide solution. This may be due to the difference in the type of solubilization, and in the degree of stabilization of ASA and methantheline bromide, and due to the 10 times larger concentration of surfactants used here than that used previously.[1]

Form the above experiments, it was found that the hydrolysis of the undissociated form of ASA is suppressed by three kinds of surfactants and that of the anionic form

TABLE V. Effect of Neutral Salt and Buffer Concentration

Surfactant	k(day^{-1}) in buffer	k(day^{-1}) in buffer contg. 0.1M NaCl	k(day^{-1}) in buffer concn. × 2	pH
Em. 120 10%	0.428	0.434	—	0.99
	1.14	—	1.13	5.57
C.D. 5%	0.200	0.190	—	0.90
	0.478	—	0.450	6.50
S.L.S. 5%	0.143	—	0.136	2.08
	0.977	—	0.974	7.28

Temp.: 37°

is suppressed only by cationic surfactants (cetylethyldimethylammonium bromide and benzalkonium chloride). This relationship between charges contrasts with the results of the previous work.$^{1)}$

The present study was supported partly by a Grant-in-Aid for Fundamental Scientific Research from the Ministry of Education, to which the authors are grateful.

Summary

1) Attempt was made to suppress the hydrolysis of acetylsalicylic acid with anionic (sodium laurylsulfate), cationic (cetylethyldimethylammonium bromide and benzalkonium chloride), and nonionic (Emulgen 120) surfactants. The hydrolysis of the undissociated form of acetylsalicylic acid is suppressed by the three kinds of surfactants and that of the anionic form is suppressed by cetylethyldimethylammonium bromide and benzalkonium chloride.

2) Through the ultraviolet spectra and the partition coefficient, it was ascertained that the undissociated form of acetylsalicylic acid is solubilized with the above three kinds of surfactants and the anionic form interacts with only a cationic surfactant.

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80. **Hiroshi Mitsuhashi and Tsuneo Itoh**: Studies on the Constituents of Umbelliferae Plants. V. Studies on the Constituents of *Angelica edulis* MIYABE. (1). Isolation of Edultin.

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Angelica edulis MIYABE (Japanese name "Amanyu" or "Marubaezonyu"-Umbelliferae) is widely distributed in the northern part of Japan, especially in Hokkaido, and is said to be used in the vegetable diet or as an antiseptic by mixing it with fishoil among the people of the Ainu race. Although it is well assumed by its flavor the root contains some essential oils, the presence of any other constituents in the root has not been reported so far.

The authors have investigated the constituents of the root as a part of the studies on the constituents of Umbelliferae$^{2)}$ to see whether any biological active principle could

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1) A preliminary communication appeared in this Bulletin, **9**, 170 (1961).

2) H. Mitsuhashi, *et al.*: This Bulletin, 8, 245 (1960).