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190. **Hisashi Nogami and Shoji Awazu**[*1] : Studies on Decomposition and Stabilization of Drugs in Solution. XII.[*2] Stabilization of Methantheline Bromide in Aqueous Solution by Surface-active Agents. (2).[*3]

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The authors have been studying on the stabilization of drugs in solution by surface-active agents (surfactants).[1,2] In a previous report,[1] it was found at pH 7.7 that OH$^-$ catalysed hydrolysis of methantheline bromide was suppressed markedly by sodium laurylsulfate (anionic surfactant : SLS) which has opposite charge to the drug. As methantheline bromide is hydrolysed by acid-base catalysis,[3] it will be expected that SLS may effect the hydrolysis by H$^+$ or OH$^-$ differently. In the present report, therefore, the effect of SLS was studied further on OH$^-$ catalysed hydrolysis and newly on H$^+$ catalysed one.

Experimental

All reagents used here were of extra pure grade. On OH$^-$ catalysed hydrolysis, the following buffer solutions were used, and the cation concentration in ×1, ×2 and ×4 buffer was equal to that in ×1′, ×2′, and ×4′ respectively. Ethylene dichloride, methantheline bromide and SLS were the same as those reported previously,[1] and the experimental methods were also the same.

(Na_2HPO_4	+ KH_2PO_4) M		Symbols of buffer soln.	(Na_2HPO_4	+ KH_2PO_4) M		Symbols of buffer soln.
0.0614	0.00534	×	1	0.0570	0.0144	×	1′
0.123	0.0107	×	2	0.114	0.0287	×	2′
0.246	0.0214	×	4	0.228	0.0574	×	4′

Results and Discussion

1. OH$^-$ Catalysed Hydrolysis

Here, the lower the pH, the slower the hydrolysis rate of methantheline bromide in the surfactant absent solution was. It was examined in this study whether the above tendency was also seen in the SLS solution. It was difficult to find the net effect of pH on the hydrolysis, because the hydrolysis rate varied with the buffer concentration in the SLS solution.[1] Then the half lives of methantheline bromide were compared at

Table I. Half Life of Methantheline Bromide at 70°

Buffer concn.	×4	×2	×1	×4′	×2′	×1′
Half life (min.)	193	198[a]	248	463	490	604
pH	7.69	7.76	7.78	7.27	7.32	7.38

Buffer solution contains 0.2% sodium laurylsulfate

a) obtained from the previous report.[1]

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[*2] Part XI : This Bulletin, **10**, 1017 (1962). Presented before the Kanto Local Meeting of the Pharmaceutical Society of Japan, Tokyo, June, 1961.

[*3] Part (1) : This Bulletin, **8**, 1136 (1860).

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1) H. Nogami, S. Awazu, K. Watanabe, K. Sato : This Bulletin, **8**, 1136 (1960).

2) H. Nogami, S. Awazu, N. Nakajima : This Bulletin, **10**, 503 (1962).

3) H. Nogami, M. Horioka, S. Awazu, H. Yamada : This Bulletin, **6**, 277 (1958).

pH 7.3 and 7.7 buffer solutions where the concentration of cations, i.e. gegen ions to SLS, was equal to each other. The results are shown in Table I. The effect of pH was also found in the SLS solution.

2. H^+ Catalysed Hydrolysis

All the study was carried out at pH 1 or 1.5. As SLS was hydrolysed to lauryl alcohol between pH 1 and 2,[4] the sample solution became turbid and lost homogeneity during the experiment. Unlike in OH^- catalysed hydrolysis,[1] however, the order of hydrolysis could be regarded as the pseudo-first one in the early period,[*5] and when the sample solution began to become turbid, the hydrolysis tended to deviate from the course.

As shown in Fig. 1 and Table II, SLS obviously promoted the hydrolysis of methantheline bromide. This contrasts apparently with the case in OH^- catalysed hydrolysis. This promotion may be due to the attraction of H^+ on the surface of the micelle of an anionic surfactant, SLS.

Riegelman[5] found that cetyltrimethylammonium bromide (cationic surfactant) promoted the hydrolysis of benzocain in the 0.04*N* OH^- solution and ascribed it to the attraction of OH^- on the surface of the micelle of the cationic surfactant. The results of the present study seem to correspond with the report of Riegelmen. And from the standpoint of the relation among electric charges, moreover, it may be ascribed to the repulsion between OH^- and anionic charges of SLS micelle that the OH^- catalysed hydrolysis of methantheline bromide was suppressed with SLS.

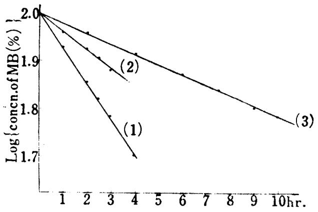

Fig. 1. Decomposition of Methantheline Bromide in Sodium Laurylsulfate at 70°

(1): 0.2% SLS Soln. at pH 1.07
(2): 0.1% SLS Soln. at pH 1.07
(3): 0.2% SLS + M/10 NaCl Soln. at pH 1.57

Table II. Half Life of Methantheline Bromide at 70°

Surfactant	Concn. (%)	Electrolyte (*M*)	Half life (min.)	pH	Concn. of HCl (*N*)
Control	0	0	1230[a]	1	
SLS	0.2	0	246	1.07	0.10
〃	0.2	0	406	1.57	0.0311
〃	0.2	0.0689 NaCl	691	1.57	0.0311
〃	0.2	0.1 KCl	864	1.57	0.0311
〃	0.2	0.1 NaCl	813	1.57	0.0311
〃	0.2	0.1 LiCl	801	1.57	0.0311

a) Calculated from the experimental equation reported in the previous report.[3]

Effect of Added Electrolyte——The effect of added electrolyte was examined at pH 1.57. As shown in Table II, electrolytes decreased the rate of the hydrolysis in the SLS solution. The rate proceeded in the following order : $Li^+ > Na^+ > K^+$ solution. It

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[*5] The period varied with the experimental condition. In 0.1% SLS solution, the hydrolysis tended to deviate from the pseudo-first order course in a short time. In 0.2% SLS solution (without added salt), the order of the hydrolysis could be regarded as the pseudo-first one till the half life. In the solution at pH 1.57 with added salt, the half life was longer than 10 hr., therefore, the experiment was carried out till the time when 40% of the drug decomposed, when the order could be regarded as the pseudo-first one. The half lives in Table II were calculated from these linear portions.

4) Part XIII. H. Nogami, S. Awazu, Y. Kanakubo : This Bulletin, (1963) to be published.

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

is interesting that the order is same as that of the degree of the cation hydration. The exchange of cation with hydrogen ion on the micelle surface may one of the causes to decrease the hydrolysis rate.

Effect of pH——As methantheline bromide is hydrolysed by H^+ in the pH region, the larger the pH, the slower the hydrolysis rate in the surfactant absent solution was. It was examined whether the above tendency was seen in the SLS solution. As already described, in the SLS solution the electrolyte influenced the rate of the hydrolysis, so it was impossible to examine the effect of pH only with the change of hydrochloric acid concentration. Methantheline bromide was hydrolysed in 0.0311*N* hydrochloric acid and 0.0689*N* sodium chloride solution (the total cation concentration was 0.1*M*) and the rate was compared with that in 0.1*N* hydrochloric acid solution. Apparently, the rate in the pH 1.57 solution was slower than that in the pH 1.07 solution (Table II).

3. Test of the Pharmaceutical Effect

Not relating to the hydrolysis, the pharmaceutical effect of methantheline bromide was studied in the SLS solution. The control solution having 0.5% methantheline bromide only, and the test solution, having 0.5% methantheline bromide and 0.5% SLS, were made. Both solutions were adequately diluted and antispasmodic actions were compared by Magnus' method using $10^{-7} \sim 5 \times 10^{-5}$ g./cc. acetylcholine. The difference was not found.

Summarizing the above with the previous report,[1] SLS, an anionic surfactant, remarkably influenced the hydrolysis of methantheline bromide, a cationic drug. SLS suppressed the OH^- catalysed hydrolysis, and on the other hand, promoted the H^+ catalysed one. It may be explained with the repulsion and attraction between the electric charges of the SLS micelle and those of catalytic species.

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Summary

Sodium laurylsulfate, an anionic surfactant, promoted the H^+ catalysed hydrolysis of methantheline bromide, quaternary amine ester. This contrasts with the phenomenon that sodium laurylsulfate suppressed the OH^- catalysed hydrolysis of methantheline bromide. This difference may be explained with the attraction and repulsion between the electric charges of the sodium laurylsulfate micelle and those of catalytic species.

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