# Interaction of Sodium and Calcium Salicylates with Cationic Surfactants

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**Sodium and calcium salicylates have been found to interact with surfactants of the quaternary ammonium type in much the same way as salicylic acid, as stated in a previous report. The interaction produces a marked change in viscosity which increases with salicylate concentration until the system becomes a gel. This increase in viscosity is not related to pH and is reduced with a rise in temperature. This complex interaction is probably due to attraction between the salicylate ion and the cation of the surfactant molecule leading to an increase in size of the surfactant molecule resulting in a rise in viscosity. The change in viscosity is further enhanced by an increase in the electrical charges in the system brought about by the addition of sodium salts, the order of effectiveness of the anion being as follows: citrate > phosphate > sulfate > carbonate > bromide > (except at low concentration) chloride, and by the addition of various sulfates, the order of effectiveness of the cation being as follows: sodium > potassium > ammonium > magnesium > zinc. Phenyl, ethyl, and methyl salicylates fail to show this complex interaction due to the absence of salicylate ion in aqueous solution. In addition, sodium lauryl sulfate and cetomacrogol 1000 do not demonstrate any change in viscosity in the presence of both salicylates.**

Complex interactions play an increasingly important role in pharmaceutical formulations today. Interaction of quaternary ammonium bactericides with various compounds including anionic and nonionic surfactants, dyes, and polymeric compounds have been studied by various workers (1–4). Cationic drugs have been shown to form complexes with sodium carboxymethylcellulose (5), and sodium salicylate has been reported to interact with polyvinylpyrrolidone (6) and with oxytetracycline dihydrate and tetracycline trihydrate (7) forming complexes. The factors involved in complexation and the postulations offered for the mechanisms of complexation are many and varied (8–12). As salicylic acid is the only one of the substituted benzoic acids which interact with the quaternary compounds (13), it will be interesting to discover if the salicylates behave in like manner and it is hoped to learn more of the possible mechanism of this highly specific interaction.

## EXPERIMENTAL

**Materials**—Sodium salicylate (British Drug Houses Ltd.) and calcium salicylate (E. Merck, Darmstadt) were used as supplied by the manufacturers. Phenyl salicylate, 42–43°; ethyl salicylate, density 1.140; methyl salicylate, density 1.184 (Hopkin and Williams, Ltd.); the chloride and bromide of sodium and potassium (May and Baker, Ltd.); sodium citrate, carbonate, and phosphate, and the sulfates of sodium, potassium, magnesium, zinc, and ammonium (British Drug Houses Ltd.) were used without purification. The cationic surfactants, dodecyltrimethylammonium bromide, tetradecyltrimethylammonium bromide (Glovers Chemicals Ltd.), cetyltrimethylammonium bromide, (Imperial Chemical Industries), sodium lauryl sulfate (Sipon Products Ltd.), and cetomacrogol 1000 B.P.C,[1] were the same as those described in a previous paper (13). The approximate molecular weights of dodecyltrimethylammonium, tetradecyltrimethylammonium, and cetyltrimethylammonium bromides are 314, 342, and 370, respectively.

**Apparatus**—Portable Ferranti viscometer, Pye tropical universal pH meter.

**Measurement of Viscosity**—The required amounts of salicylate were weighed into a series of 100-ml. volumetric flasks containing the required concentration of surfactant. The flasks were allowed to rotate in a thermostatically controlled water bath at 25 ± 0.1° for 24 hr. For the study of the effect of addition of salts, the required volume of a concentrated salt solution was incorporated and then equilibrated in like manner. The viscosities of the solutions were measured using the Ferranti portable viscometer placed in a thermostatically controlled water bath at 25 ± 0.5°. The shear rates employed ranged from 78.56 to 483.0 sec.$^{-1}$. An interval of 30 sec. was allowed between readings.

## RESULTS AND DISCUSSION

**Viscosity Measurements**—Figures 1 and 2 show the effect of sodium salicylate on the viscosity of cetyltrimethylammonium bromide and tetradecyltrimethylammonium bromide solutions at 25°. A marked change in viscosity is observed with increased concentration of sodium salicylate; this change is seen with all five of the different shear rates used. This viscosity effect occurs in all surfactant concentrations studied, ranging from 0.05 to 0.18 moles/L., but is much less prominent in dodecyltrimethylammonium bromide systems. Similarly, calcium salicylate exerts this viscosity effect when dispersed in the same quaternary surfactants (Figs. 3 and 4).

Salicylic acid has been shown to demonstrate this viscosity effect (13) but unlike the salicylates it does not gel the system even after it has become saturated with the acid. However, the salicylates produce a

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[1] Texofor A1P, Glovers Chemicals Ltd.

gel of the system at a particular concentration, probably due to the presence of the sodium or calcium ion. Gelling is taken as the state in which the viscosity cannot be determined by the Ferranti viscometer because the dial readings continually fluctuate. The molar concentration at which gelling occurs is greater for sodium salicylate than for calcium salicylate, and in addition the amount required for

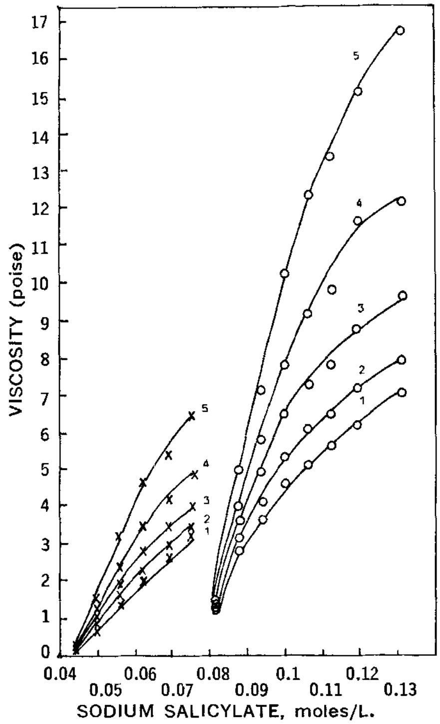


*Fig. 1—Effect of sodium salicylate on the viscosity of cetyltrimethylammonium bromide solution at 25°. Key:* ×, *0.081* M; O, *0.162* M. *Shear rate:* 1, *234.6 sec.*$^{-1}$; 2, *195.9 sec.*$^{-1}$; 3, *155.1 sec.*$^{-1}$; 4, *117.35 sec.*$^{-1}$; 5, *78.56 sec.*$^{-1}$.

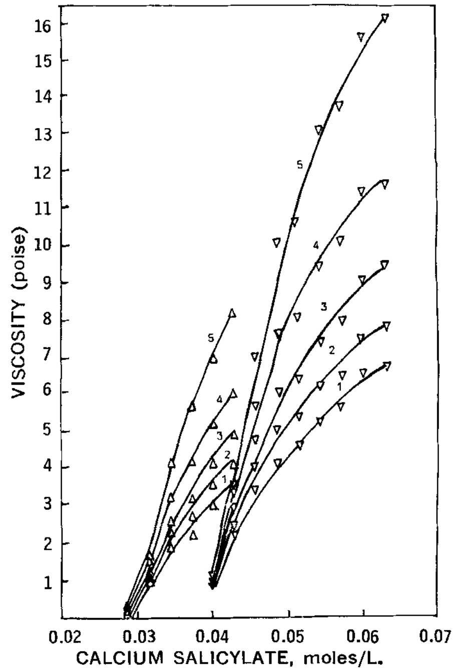


*Fig. 3—Effect of calcium salicylate on the viscosity of cetyltrimethylammonium bromide solution at 25°. Key:* Δ, *0.108* M; ∇, *0.162* M. *Shear rate:* 1, *234.6 sec.*$^{-1}$; 2, *195.9 sec.*$^{-1}$; 3, *155.1 sec.*$^{-1}$; 4, *117.35 sec.*$^{-1}$; 5, *78.56 sec.*$^{-1}$.

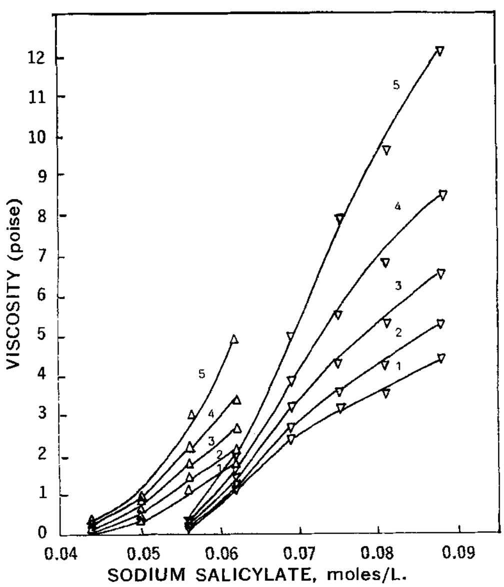


*Fig. 2—Effect of sodium salicylate on the viscosity of tetradecyltrimethylammonium bromide solution at 25°. Key:* Δ, *0.117* M; ∇, *0.1754* M. *Shear rate:* 1, *234.6 sec.*$^{-1}$; 2, *195.9 sec.*$^{-1}$; 3, *155.1 sec.*$^{-1}$; 4, *117.35 sec.*$^{-1}$; 5, *78.56 sec.*$^{-1}$.

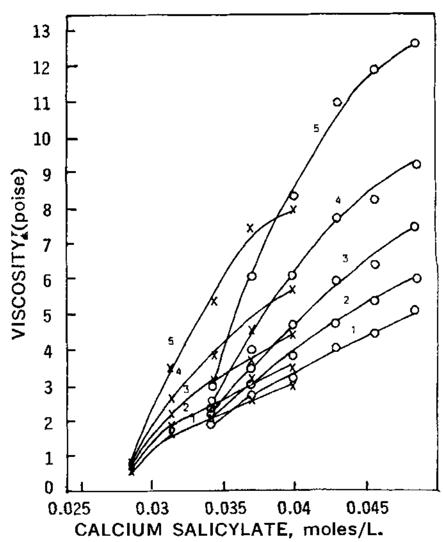


*Fig. 4—Effect of calcium salicylate on the viscosity of tetradecyltrimethylammonium bromide solution at 25°. Key:* ×, *0.1462* M; O, *0.1754* M. *Shear rate:* 1, *234.6 sec.*$^{-1}$; 2, *195.9 sec.*$^{-1}$; 3, *155.1 sec.*$^{-1}$; 4, *117.35 sec.*$^{-1}$; 5, *78.56 sec.*$^{-1}$.

gelling by sodium salicylate is approximately twice that required by calcium salicylate (Table I). This could be due to the fact that the calcium salicylate molecule produces twice as many salicylate ions as the sodium salicylate molecule. The ratios of salicylate to surfactant concentration at which the system becomes a gel decrease with increasing concentration of the quaternary compound, indicating that as the number of surfactant molecules increases following increased concentration of surfactant less salicylate molecules are required to produce a gel, and that probably at high surfactant concentration, the molecules interact less with the salicylates because of the extremely viscous nature of the system in which the surfactant molecules may find their movement restricted or are less mobile. Hence, they do not interact to the same degree as at low concentration of surfactant. From a graphical representation of the data presented in Table I, the amount of salicylate that has to be added to a given concentration of the quaternary compound to produce a gel or maximal measurable viscosity can be calculated.

TABLE I—RELATIONSHIP BETWEEN GELLING OF SURFACTANT SOLUTIONS BY SALICYLATES AND SURFACTANT CONCENTRATION

| CTAB,[a] moles/L. *A* | Na Salicylate, moles/L. Required to Gel *B* | *B/A* | Ca Salicylate, moles/L. Required to Gel *C* | *C/A* |
|---|---|---|---|---|
| 0.027 | 0.031 | 1.148 | 0.014 | 0.519 |
| 0.054 | 0.050 | 0.926 | 0.026 | 0.481 |
| 0.081 | 0.075 | 0.926 | 0.037 | 0.456 |
| 0.108 | 0.094 | 0.870 | 0.046 | 0.426 |
| 0.135 | 0.113 | 0.837 | 0.054 | 0.401 |
| 0.162 | 0.131 | 0.810 | 0.063 | 0.388 |
| TTAB,[b] moles/L. *D* | *E* | *E/D* | *F* | *F/D* |
| 0.059 | 0.044 | 0.746 | 0.020 | 0.341 |
| 0.088 | 0.056 | 0.636 | 0.029 | 0.329 |
| 0.117 | 0.069 | 0.590 | 0.037 | 0.316 |
| 0.146 | 0.081 | 0.555 | 0.043 | 0.294 |
| 0.175 | 0.094 | 0.536 | 0.049 | 0.280 |

[a] CTAB, cetyltrimethylammonium bromide. [b] TTAB, tetradecyltrimethylammonium bromide.

**Effect of Temperature**—Figure 5 shows the effect of increasing temperature on the viscosity of sodium salicylate dispersed in cetyltrimethylammonium bromide solution. There is a sharp decrease in viscosity followed by a gradual fall. The viscosity decreases with increasing shear rates but approaches the same value at about 42°, after which there is practically no change with further rise of temperature, suggesting the conversion to a Newtonian liquid. At about 49° and above the viscosity is about the same as that of a solution of cetyltrimethylammonium bromide without the salicylate at 25°. With increased Brownian motion arising from high temperatures, the system offers less resistance to shear.

**Effect of pH**—Table II shows the pH of sodium salicylate and calcium salicylate dissolved in cetyltrimethylammonium bromide solutions. There is a small difference in pH for both systems and a gradual increase in pH with increasing concentration of salicylate. The effect of additives on the pH of solutions of cetyltrimethylammonium bromide containing sodium salicylate is seen in Table III. Generally a slight change in pH is observed with increased concentration of the additive. pH seems to have no effect on the viscosity change.

TABLE II—pH OF CTAB[a] SOLUTIONS CONTAINING SODIUM SALICYLATE AND CALCIUM SALICYLATE

| CTAB (0.135 *M*) + Na Salicylate (*M*) | pH | CTAB (0.135 *M*) + Ca Salicylate (*M*) | pH |
|---|---|---|---|
| 0.075 | 5.5 | 0.034 | 5.7 |
| 0.081 | 5.6 | 0.371 | 5.9 |
| 0.088 | 5.7 | 0.040 | 5.95 |
| 0.094 | 5.8 | 0.043 | 5.95 |
| 0.100 | 5.85 | 0.046 | 6.15 |
| 0.106 | 6.0 | 0.049 | 6.3 |
| 0.113 | 6.0 | 0.052 | 6.4 |

[a] CTAB, cetyltrimethylammonium bromide.

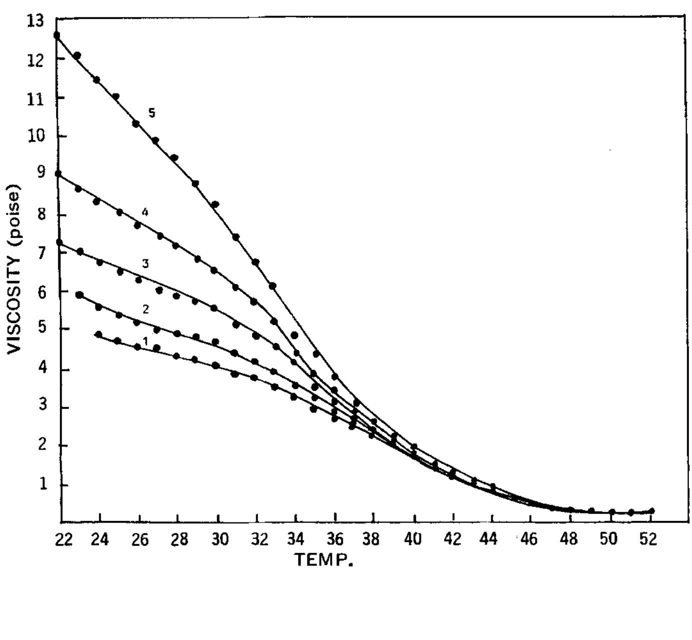


*Fig. 5—Effect of temperature on the viscosity of sodium salicylate (0.1* M*) dispersed in cetyltrimethylammonium bromide solution (0.135* M*). Shear rate: 1, 234.6 sec.*$^{-1}$*; 2, 195.9 sec.*$^{-1}$*; 3, 155.1 sec.*$^{-1}$*; 4, 117.35 sec.*$^{-1}$*; 5, 78.56 sec.*$^{-1}$*.*

TABLE III—EFFECT OF ADDITIVES ON pH OF CETYLTRIMETHYLAMMONIUM BROMIDE SOLUTIONS (0.108 *M*) CONTAINING SODIUM SALICYLATE (0.0625 *M*)

| Additives Concn., moles/L. | pH | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $Na_2SO_4$ | $K_2SO_4$ | $(NH)_2SO_4$ | $MgSO_4$ | $ZnSO_4$ (moles/L.) | $Na_3C_6H_5O_7$ | $Na_2HPO_4$ | $Na_2CO_3$ | NaBr | NaCl |
| 0.1 | 6.35 | 5.8 | 5.7 | 5.7 | 5.55 | 7.8 | 8.7 | 9.9 | 5.9 | ... |
| 0.2 | 6.3 | 5.9 | 5.65 | 5.8 | 5.4 | 7.8 | 8.75 | 9.95 | 6.0 | 6.05 |
| 0.3 | 6.25 | 5.95 | 5.55 | 5.8 | 5.3 | 7.85 | 8.8 | 10.1 | ... | ... |
| 0.4 | 6.25 | 6.0 | 5.5 | 5.85 | 5.25 | 7.85 | 8.85 | 10.1 | ... | ... |
| 0.5 | 6.2 | 6.0 | 5.5 | 5.85 | 5.25 | 7.9 | 8.85 | 10.15 | 6.2 | 6.1 |
| 0.6 | 6.2 | ... | 5.45 | 5.9 | 5.2 | 7.9 | 8.9 | 10.3 | ... | ... |
| 0.7 | 6.1 | ... | 5.45 | 5.9 | 5.1 | 8.0 | 8.9 | 10.3 | ... | ... |
| 0.75 | 6.0 | ... | 5.45 | 5.95 | 5.1 | 8.1 | 8.95 | 10.35 | 6.25 | 6.45 |

**Effect of Anion**—The addition of sodium chloride, bromide, citrate, phosphate, sulfate, and carbonate to a cetyltrimethylammonium bromide solution containing sodium salicylate further enhances the viscosity effect as seen in Fig. 6. This is true for different shear rates used. The order of effectiveness of the anion is: citrate > phosphate > sulfate > carbonate > bromide > (except at low concentration) > chloride. The valency of the charge on the anion appears to determine the effectiveness on the enhancement as the higher the valency the greater is the additional increase in viscosity. For the sodium halides the effect is different in that a much higher concentration of the corresponding salt is required to effect an additional increase in viscosity in which case the increase is also gradual. In addition, up to a concentration of 1.8 moles/L. of the salt the system does not become a gel, in contrast to the other sodium compounds, all of which form a gel at about 0.7 to 0.75 moles/L. of the salt concentration. Sodium iodide has been included in the investigation but it forms a white precipitate and the viscosity of the system decreases because the surfactant has been removed by precipitation and thus is not available for interaction with the salicylate. Potassium chloride and bromide also show an enhanced viscosity effect similar to that produced by the corresponding sodium compounds, the potassium salts exerting a relatively larger effect on the viscosity. Since the above-mentioned salts form insoluble compounds with calcium salicylate, only sodium citrate, chloride, bromide, and potassium chloride and bromide were added to aqueous solutions of cetyltrimethylammonium bromide containing calcium salicylate. The additives also increase the viscosity of the system similar to that in the systems containing sodium salicylate (Fig. 7). Here again the concentration of sodium citrate required to gel the system is the same as that containing sodium salicylate. The viscosity of cetyltrimethylammonium bromide solutions containing the sodium or potassium compound in the absence of the salicylate remains unaffected.

**Effect of Cation**—Figure 8 shows the effect of adding the sulfates of ammonium, sodium, potassium, magnesium, and zinc to a solution of cetyltrimethylammonium bromide containing sodium salicylate. The order of enhanced viscosity effect is sodium > potassium > ammonium > magnesium > zinc. This order seems to be related to the valency of the charge on the cation and is the reverse of that observed with the effect of anions in that the smaller the valency of the charge of the cation, the greater the enhancement. A higher concentration of potassium sulfate could not be used since it became insoluble in the system at above 0.5 moles/L.

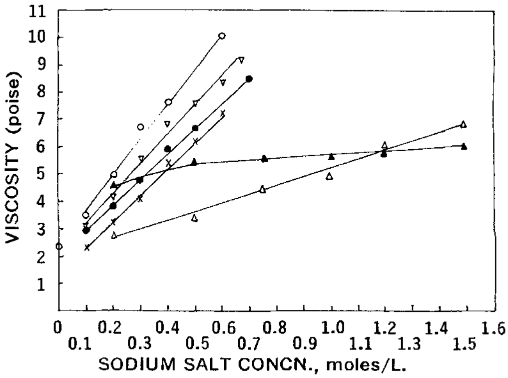


*Fig. 6—Effect of various anions of a series of sodium salts on the viscosity of cetyltrimethylammonium bromide solution (0.108* M*) containing sodium salicylate (0.0561* M*) at 25°. Key:* ⦶, *without salt;* O, $C_6H_5O_7Na_3$; ∇, $Na_2HPO_4$; ●, $Na_2SO_4$; ×, $Na_2CO_3$; ▲, *NaBr;* Δ, *NaCl; shear rate, 78.56 sec.*$^{-1}$.

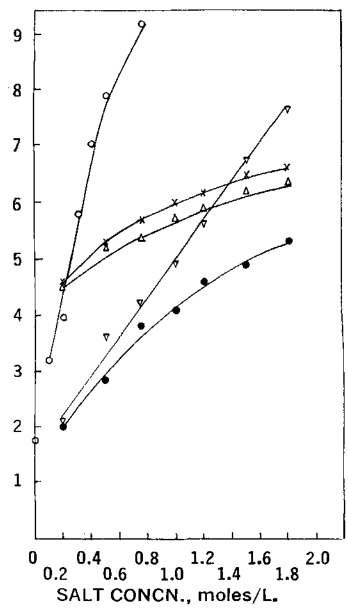


*Fig. 7—Effect of sodium and potassium salts on the viscosity of cetyltrimethylammonium bromide solution (0.108* M*) containing calcium salicylate (0.0314* M*) at 25°. Key:* ⦶, *without salt;* O, $C_6H_5O_7Na_3$; ×, *KBr;* Δ, *NaBr;* ∇, *KCl;* ●, *NaCl; shear rate, 78.56 sec.*$^{-1}$.

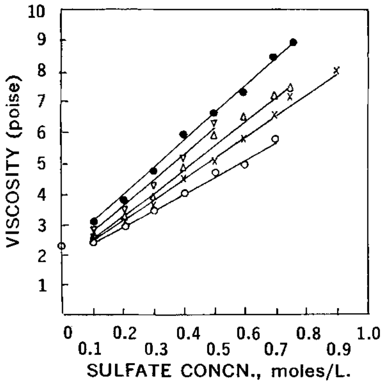


*Fig. 8—Effect of various cations of a series of sulfates on the viscosity of cetyltrimethylammonium bromide solution (0.108 M) at 25°. Key:* ⊕, *without sulfate;* ●, $Na_2SO_4$; ▽, $K_2SO_4$; Δ, $(NH_4)_2SO_4$; ×, $MgSO_4$; ○, $ZnSO_4$; *shear rate, 78.56 sec.*$^{-1}$.

The results of this investigation indicate that sodium and calcium salicylates interact with the quaternary surfactants in much the same way as salicylic acid itself. They further confirm that the salicylate ion is of prime importance in the interaction, since phenyl, ethyl, and methyl salicylates do not demonstrate any viscosity effect. The complex interaction of salicylates with the quaternary surfactants may be due to a strong attraction between the salicylate ion and the bulky cation of the surfactant, thus enlarging its size and leading to an increase in viscosity. The attraction is enhanced by the addition of anions such as chloride, bromide, citrate, phosphate, sulfate, and carbonate and also by the addition of cations such as sodium, potassium, magnesium, ammonium, and zinc since they reinforce the electrical charges in the system. No change in viscosity is observed either with dispersions containing any of the salts investigated and a salicylate in the absence of the surfactant or with dispersions containing any of the salts studied and the surfactant in the absence of the salicylate. Hence the anions and cations only affect the viscosity in the presence of the complex formed by the interaction of salicylate and the surfactant.

## REFERENCES

(1) Walter, G. R., and Gump, W. S., *J. Pharm. Sci.*, **51**, 770(1962).
(2) DeLuca, P. P., and Kostenbauder, H. B., *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 430(1960).
(3) Lachman, L., Kuramoto, R., and Cooper, J., *ibid.*, **47**, 87(1958).
(4) Lawrence, C. A., "Surface Active Quaternary Ammonium Germicides," Academic Press Inc., New York, N.Y., 1950.
(5) Kennon, L., and Higuchi, T., *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 157(1956).
(6) Higuchi, T., and Kuramoto, R., *ibid.*, **43**, 393(1954).
(7) Gans, E. H., and Higuchi, T., *ibid.*, **46**, 458(1957).
(8) Cohen, J., and Lach, J. L., *J. Pharm. Sci.*, **52**, 132 (1963).
(9) Schlenk, H., and Sand, D., *J. Am. Chem. Soc.*, **83**, 2312(1961).
(10) Lach, J. L., and Chin, T. F., *J. Pharm. Sci.*, **53**, 69 (1964).
(11) Higuchi, T., and Drubulis, A., *ibid.*, **50**, 905(1961).
(12) Goudah, M. W., and Guth, E. P., *ibid.*, **54**, 298(1965).
(13) Wan, L. S. C., *ibid.*, **55**, 1395(1966).