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Stability of Salicylic Acid and Cetrimide System in the Presence of Additives

LUCY S. C. WAN

Abstract □ Various additives were added to the gel-like product which results from the interaction of salicylic acid with cetrimide. The additives were alcohols, acetone, water, glycerin, propylene glycol, polyethylene glycols, amyl acetate, heptane, hexadecane, dioxane, cyclohexane, benzene, methylbenzene, ethylbenzene, nitrobenzene, pyridine, tetralin, carbon tetrachloride, chloroform, liquefied phenol BP, and cresol BP. The first 10 compounds reduced the viscosity of the gel-like product to varying degrees, and the reduction generally increased with an increasing volume of the additive. The remaining 11 compounds together with the higher alcohols, from hexyl to decyl alcohol, increased the viscosity initially, followed soon after by a viscosity decrease. The instability of the system in the presence of the additives was probably due largely to their effect on the links in the network structure of the macromolecules which formed the gel-like product. The initial rise in viscosity could be due to a tendency of a small amount of the additive to bring the macromolecules closer together, thus making the system more viscous. The fall after this rise could be attributed to the breakup of the mesh with larger amounts of the additive and possibly to a change in the nature of the system.

Keyphrases □ Salicylic acid–cetrimide system—stability in presence of additives □ Cetrimide–salicylic acid interaction, stability—effect of additives □ Additives—effect on stability of salicylic acid–cetrimide system □ Viscosity—effect of additives on salicylic acid–cetrimide interaction

In previous papers (1–3), salicylic acid and its salts were found to interact with the quaternary ammonium type of surfactants in aqueous solutions, resulting in a marked increase in viscosity of the system. This viscosity was further enhanced when salts were added (2). The present report concerns the stability of the gel-like product in the presence of various compounds, many of which are commonly used as solvents. The study was undertaken to eliminate or break down the gel-like structure so as to gain an insight into the mechanism of the interaction. The results would be helpful in the investigation of the possible uses of the product.

EXPERIMENTAL

Materials—Salicylic acid was recrystallized, m.p. 158.5–159°. Cetrimide BP[1], which consisted chiefly of tetramethylammonium bromide, was used as supplied. The additives used were as follows: redistilled alcohols (methyl, ethyl, *n*-propyl, and *n*-butyl)[2], amyl alcohol[3], *n*-hexyl alcohol[3], *n*-heptyl alcohol[3], *n*-octyl alcohol[3], *n*-decyl alcohol[3], acetone[2], distilled water, glycerin BP, propylene glycol[3], polyethylene glycol 400 and 600[4], amyl acetate[3], heptane[3], hexadecane[3], dioxane[5], cyclohexane[3], benzene[3], methylbenzene[6], ethylbenzene[6], nitrobenzene[3], pyridine[7], tetralin[3], carbon tetrachloride[3], chloroform[8], liquefied phenol BP, and cresol BP.

Apparatus—A portable Ferranti viscometer[9] was used.

Measurement of Viscosity at 25°—Preliminary experiments had shown that generally the viscosity and rheological behavior of the systems produced by dissolving various amounts of salicylic acid in different concentrations of cetrimide were of the same pattern. A system containing 1.4% of the acid and 5% of the surfactant was chosen; on incorporation of additives, it would give viscosity values well within the measuring range of the viscometer. The gel-like product was formed by adding the required amount of salicylic acid to the cetrimide solution and was allowed to rotate in a thermostatically controlled water bath at 25 ± 0.5° until the acid went into solution. A sample of 50 g. (about 51 ml.) of the gel-like product so formed was equilibrated at the same temperature in a thermostatically controlled water bath, and the viscosity was determined at shear rates ranging from 78.56 to 234.6 $sec.^{-1}$.

One-tenth of a milliliter of the additive was added from a graduated pipet and mixed well, without removing the sample from the

[1] Glovers (Chemicals) Ltd., Leeds, England.
[2] Shell Company Ltd.
[3] British Drug House, Ltd., Poole, England.
[4] L. Light and Co., Colnbrook, England.
[5] May and Baker, Dagenham, England.
[6] Eastman Kodak Co., Rochester, N. Y.
[7] E. Merck, Darmstadt, Germany.
[8] Farbwerke Hoechst A.G., Frankfurt, Germany.
[9] Ferranti Ltd., Moston, Manchester 10, England.

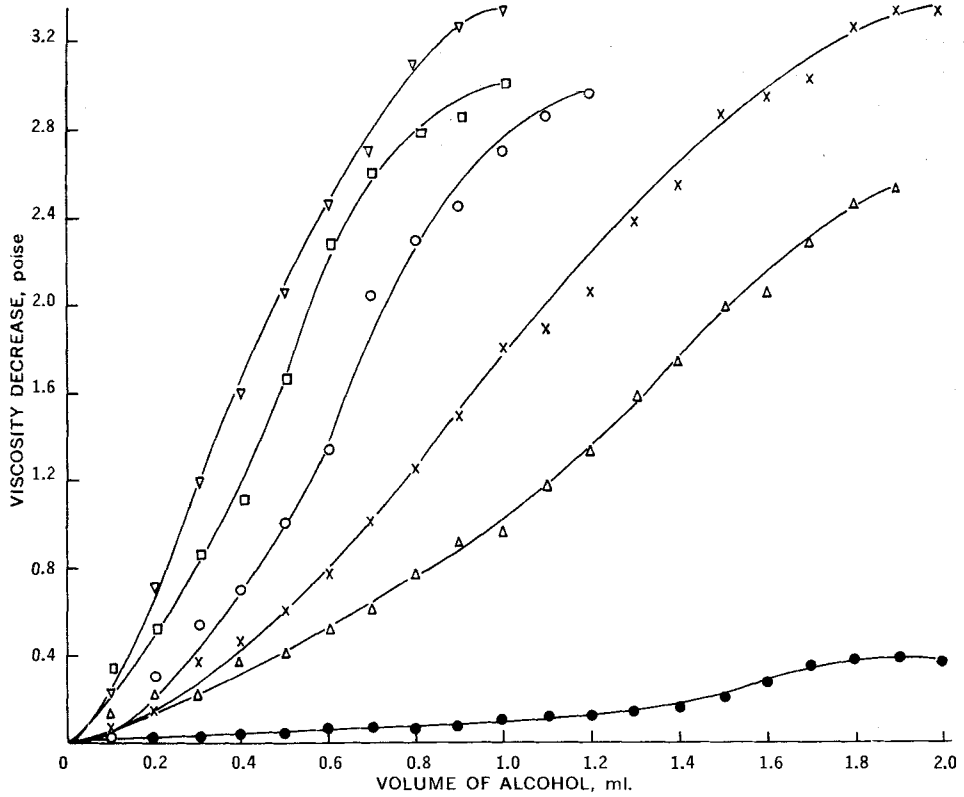

Figure 1—*Viscosity decrease of an aqueous system (50 g.) containing 5% cetrimide and 1.4% salicylic acid in the presence of various alcohols at 25°. Key: △, methyl; ×, ethyl; ○, n-propyl; □, n-butyl; ▽, n-amyl; and ●, water. Shear rate = 78.56 sec.$^{-1}$.*

viscometer. The viscosity was measured, allowing an interval of 30 sec. between readings. The shear rates were increased initially and then decreased. Successive additions of the additive to the system were continued until the viscosity was reduced to such a low value that it could not be measured accurately with the viscometer.

RESULTS AND DISCUSSION

Methyl, ethyl, *n*-propyl, *n*-butyl, and *n*-amyl alcohols were added to the gel-like product. All these alcohols reduced the viscosity (Fig. 1); the reduction increased with the volume of alcohol added. With

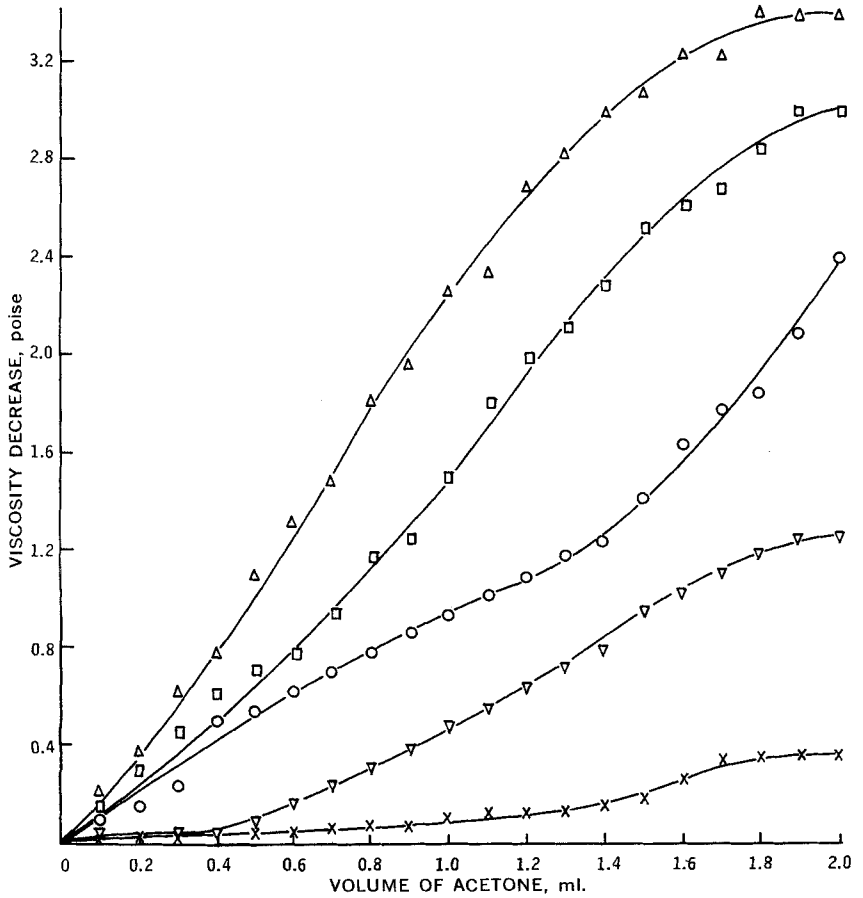

Figure 2—*Viscosity decrease of an aqueous system (50 g.) containing 5% cetrimide and 1.4% salicylic acid due to the addition of acetone of varying concentrations at 25°. Key: ×, water; ▽, 20% acetone; ○, 40% acetone; □, 60% acetone; and △, 80% acetone. Shear rate = 78.56 sec.$^{-1}$.*

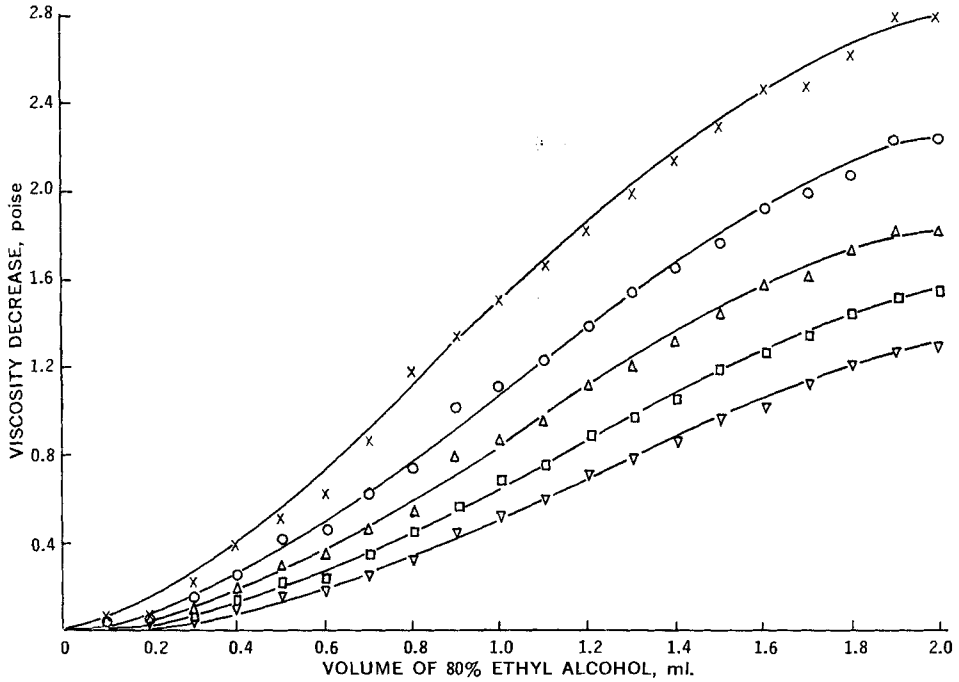

Figure 3—*Viscosity decrease of an aqueous system (50 g.) containing 5% cetrimide and 1.4% salicylic acid in the presence of 80% ethyl alcohol with different shear rates at 25°. Key: ×, 78.56 sec.$^{-1}$; ○, 117.35 sec.$^{-1}$; △, 155.1 sec.$^{-1}$; □, 195.9 sec.$^{-1}$; and ▽, 234.6 sec.$^{-1}$.*

the addition of 1 ml. *n*-amyl alcohol or 2 ml. ethyl alcohol, the viscosity was so much reduced that the gel-like property of the system was practically eliminated and it appeared fluid and watery. Only a small amount of alcohol was sufficient to produce a substantial decrease in viscosity. Addition of 0.4 ml. of *n*-amyl alcohol or *n*-butyl alcohol resulted in the reduction of viscosity from 3.4 to 1.8 and 2.3 poises, respectively, at a shear rate of 78.56 sec.$^{-1}$. The decrease in viscosity increased with the chain length of the alcohol. The addition of water caused a small change in the viscosity, since the greatest reduction in viscosity observed was not more than 0.4 poise at a shear rate of 78.56 sec.$^{-1}$. This finding demonstrated that the viscosity decrease probably was not due to a simple dilution effect of the additive.

Figure 2 shows that the higher the concentration of acetone, the more marked the viscosity reduction. This was also true for various alcohol concentrations. Since the gel-like product was a non-Newtonian system, the apparent viscosity obtained varied with different shear rates. For the same volume of additive, the change in apparent viscosity was more pronounced when a slower shear rate was applied to the system (Fig. 3). As the volume of additive increased, the non-Newtonian behavior of the system became less apparent and there was a tendency toward a Newtonian behavior.

With the exception of amyl alcohol, which is slightly soluble in water, the other alcohols are completely miscible with water. When this series of alcohols was extended to the higher alcohols, the behavior of these additives in respect to the gel-like product was different (Fig. 4). The effect of *n*-hexyl, *n*-heptyl, *n*-octyl, and *n*-decyl

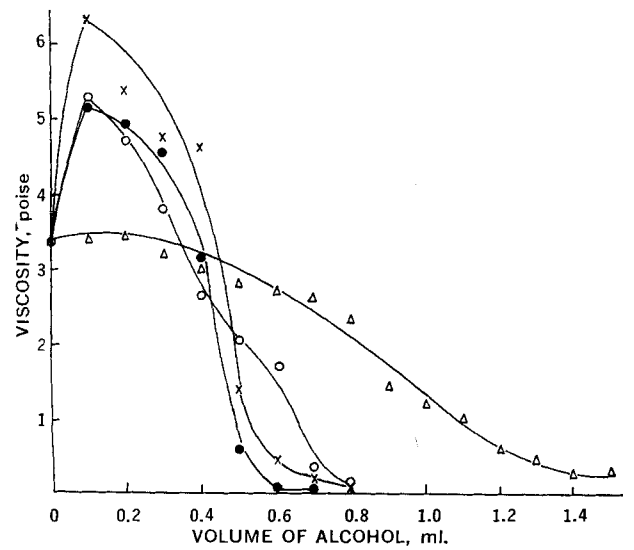

Figure 4—*Effect of water-insoluble alcohols on the viscosity of an aqueous system (50 g.) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key: △, n-hexyl; ●, n-heptyl; ×, n-octyl; and ○, n-decyl. Shear rate = 78.56 sec.$^{-1}$.*

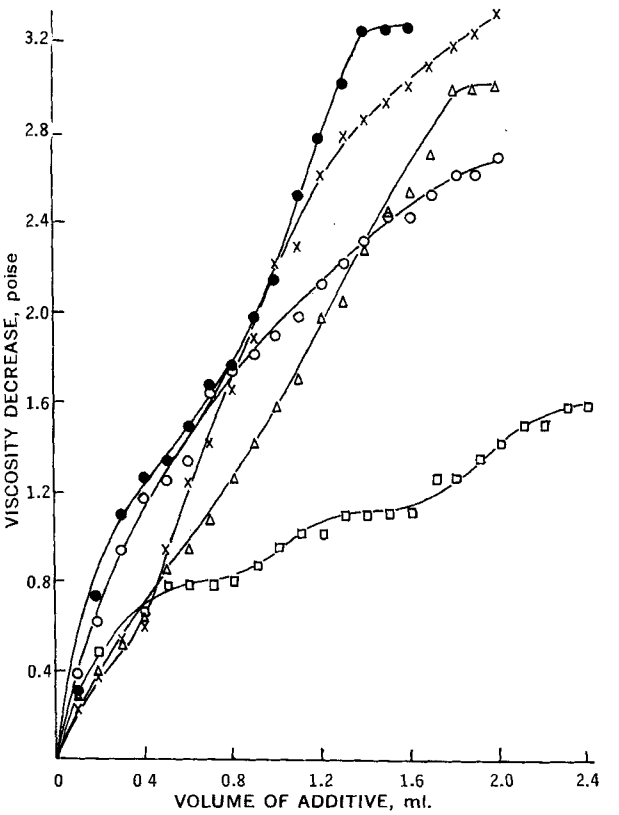

Figure 5—*Effect of polyhydric alcohols and amyl acetate on the viscosity of an aqueous system (50 g.) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key: △, polyethylene glycol 600; ○, polyethylene glycol 400; ×, propylene glycol; □, glycerin; and ●, amyl acetate. Shear rate = 78.56 sec.$^{-1}$.*

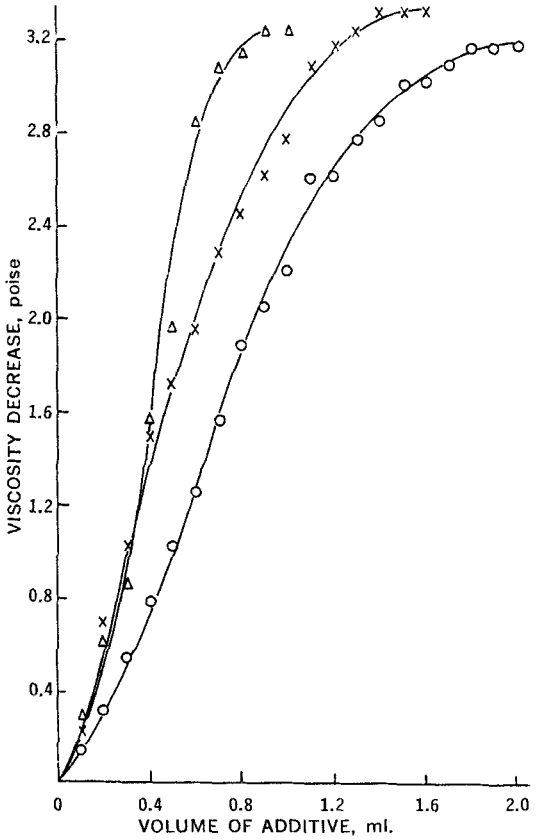

Figure 6—*Effect of hexadecane, heptane, and dioxane on the viscosity of an aqueous system (50 g.) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key: △, hexadecane; ×, heptane; and ○, dioxane. Shear rate = 78.56 sec.$^{-1}$.*

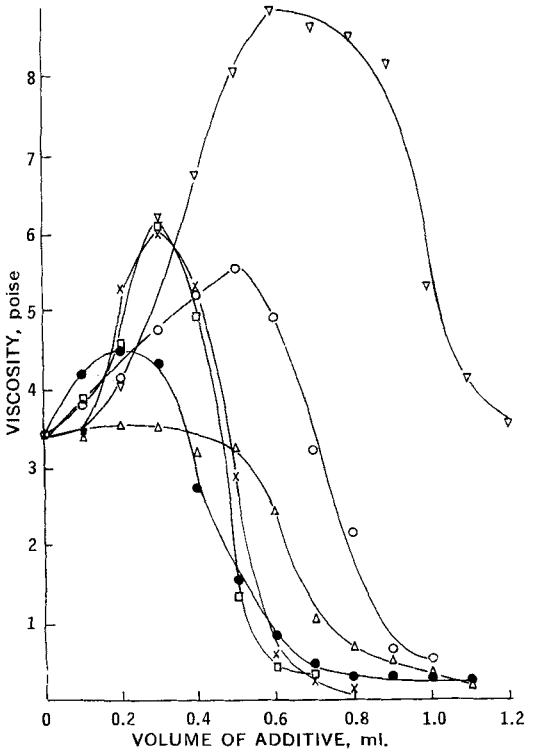

Figure 7—*Effect of benzene, substituted benzenes, pyridine, and cyclohexane on the viscosity of an aqueous system (50 g.) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key: ○, benzene; ×, methylbenzene; □, ethylbenzene; ●, nitrobenzene; ▽, pyridine; and △, cyclohexane. Shear rate = 78.56 sec.$^{-1}$.*

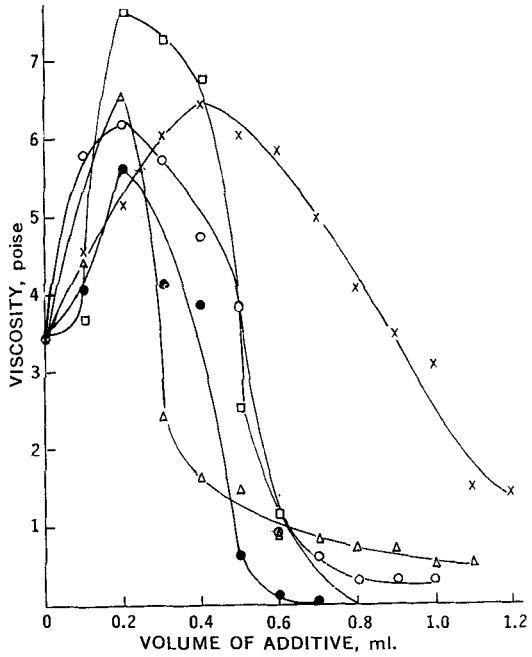

Figure 8—*Effect of various additives on the viscosity of an aqueous system (50 g.) containing 5% cetrimide and 1.4% salicylic acid at 25°. Key: ×, liquefied phenol BP; ○, carbon tetrachloride; △, chloroform; □, cresol BP; and ●, tetralin. Shear rate = 78.56 sec.$^{-1}$.*

alcohols was an initial rise in viscosity, followed by a decrease with subsequent additions of the alcohol. All these alcohols, except decyl alcohol which is water insoluble, have very limited solubilities in water. When the viscosity commenced to fall, it was generally followed by cloudiness in the system; eventually, as more of the additive was added, droplets of the alcohol could be seen dispersed in the system. At the same time, the degree of cloudiness increased also. Not more than 0.2 ml. alcohol/50 g. product was adequate to reduce viscosity after the initial rise.

The effects of the addition of other additives such as glycerin, propylene glycol, polyethylene glycol 400 and 600, amyl acetate, hexadecane, heptane, and dioxane can be seen in Figs. 5 and 6. The decrease in viscosity was similar to that exhibited by the water-miscible alcohols and acetone (Figs. 1 and 2). Several other compounds were found to behave in like manner as the higher alcohols. Thus, cyclohexane, benzene, methylbenzene, ethylbenzene, nitrobenzene, pyridine, tetralin, carbon tetrachloride, chloroform, liquefied phenol, and cresol (Figs. 7 and 8) caused an initial increase in viscosity when incorporated in the gel-like product. This increase was temporary—a decrease in viscosity was observed with further additions of the additive.

It would be unlikely that the viscosity decrease resulted from a solution of the gel-like product in the additive since the amount of additive necessary to effect a change in viscosity was relatively small. It did not seem that the water solubility or water miscibility of the additive could account for the viscosity reduction since water-soluble or water-miscible and water-insoluble or water-immiscible compounds behaved in the same way. The question of solubility of salicylic acid or cetrimide in the additive being responsible for the breakdown of the system and, hence, a lowering of the viscosity was not probable because both the acid and the surfactant are soluble in some additives and insoluble in others belonging to the same group of compounds that produced a fall in viscosity immediately when they were added. The fact that carbon tetrachloride and chloroform did not cause a viscosity reduction immediately meant that the effect was not limited to aliphatic substances only. The fall in viscosity was not associated with the polarity of the additive because both polar and nonpolar liquids were able to produce the same effect.

It is believed that the interaction of salicylic acid with aqueous cetrimide solutions led to the formation of macromolecules, enhancing the viscosity of the system. This enhancement could be brought about not only by the size of the macromolecules but also by their approaching each other to form a sort of matted matrix of high

viscosity. When an additive was added, it would penetrate the framework of the structure and weaken or disrupt the building units. It is expected that the macromolecules are joined by weak cohesive forces and not by strong bonds. Once the structural elements were affected, the system became unstable and the viscosity began to decrease. When the volume of additive present was increased, the gel-like character of the product gradually became less apparent and finally it was converted to a system of very low viscosity.

The initial rise in viscosity could not be attributed to solubilization of the additive by the surfactant to cause a swelling of the gel-like product, because most of the cetrimide molecules would have interacted with salicylic acid already, the latter being present in sufficient quantities to saturate practically the system. In support of this, it was observed that heptane and hexadecane, which are water insoluble, and amyl acetate, which is slightly water soluble, did not produce a rise in viscosity initially, although they could be solubilized. In addition, pyridine and liquefied phenol, both of which are miscible with water and could not be solubilized, also caused an initial increase in viscosity. Apparently the additives that increased the viscosity when first added were not able to disrupt the links at once, but they instead probably tended to attract the macromolecules closer together and thereby made the system more viscous. However, this situation did not remain for long; as soon as more of the additive was present, the bridges were unable to prevent a rupture of the framework and instability of the system was produced.

The decrease in viscosity after the initial increase was also associated with the change of the nature of the system, from a gel-like product to a cloudy dispersion or emulsion containing droplets of the immiscible additive. Generally the viscosity commenced to fall when the additive present had already exceeded its solubility or miscibility limits. However, this was not always the case. Pyridine and liquefied phenol, which did not produce cloudiness in the system, showed the same rise and fall in viscosity.

The findings of this investigation showed that two effects are possible when additives, many of which are simple solvents, are added to the system. One is the effect of immediate reduction in viscosity with a small volume of the additive; the other is an initial increase with very small amounts of the additive, followed by a decrease when a larger volume is included. These results will be of value in determining the usefulness of the gel-like product when incorporated in suspension formulation.

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Spectrophotometric Determination of Organic Cations by Solvent Extraction with Tetrabromophenolphthalein Ethyl Ester

MASAHIRO TSUBOUCHI

Abstract □ Spectrophotometric methods are proposed for the determination of organic cations such as neostigmine, benzethonium, tetraethylammonium, sparteine, and diphenhydramine. The methods are based on solvent extraction into dichloroethane of the ion-pairs or addition compounds formed between colored tetrabromophenolphthalein ethyl ester and the cations. Calibration graphs were linear in the range 8.0×10^{-7}–4.0×10^{-6} *M* for neostigmine, benzethonium, tetraethylammonium, and sparteine, and in the range 2.0×10^{-6}–1.0×10^{-5} *M* for diphenhydramine in aqueous solution. Optimum conditions for the extraction and the composition of the extracted species were also investigated.

Keyphrases □ Organic cations—spectrophotometric determination by solvent extraction with tetrabromophenolphthalein ethyl ester □ Tetrabromophenolphthalein ethyl ester, solvent extraction—spectrophotometric determination of organic cations □ Spectrophotometric determination—organic cations–tetrabromophenolphthalein ethyl ester, solvent extraction

In general, acid dye is known to react with amine or quaternary ammonium salt to form a colored compound (1, 2). Bromthymol blue (3), bromcresol green (4), or bromphenol blue (5) was used for the determination of thiamine, quaternary compound, or quinine.

Tetrabromophenolphthalein ethyl ester has been used as a pH indicator. Various amines and organic cations were extracted with tetrabromophenolphthalein ethyl ester into 1,2-dichloroethane. During this study, the colors of the extracts were found to be classified into three categories: (*a*) red-violet, which is developed by the presence of diphenhydramine, pilocarpine, eserine, *N,N*-dimethylpiperazine, papaverine, or triethanolamine; (*b*) blue, which is extracted by the presence of neostigmine, benzethonium, sparteine, tetraethylammonium, acetylcholine, or thiamine; and (*c*) yellow, which is the same color as the reagent blank for the presence of aniline, 3-aminoquinoline, *N,N*-dimethylformamide, ethylenediaminetetraacetic acid, or nitrilotriacetic acid.

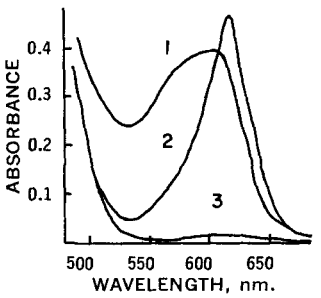

Figure 1—*Absorption spectra. Key: 1, extract with 5.0 × 10⁻⁶ M diphenhydramine; 2, extract with 2.0 × 10⁻⁶ M neostigmine; and 3, extract without neostigmine and diphenhydramine. Reference = water.*

This paper deals mainly with the determination of neostigmine with tetrabromophenolphthalein ethyl ester based on such a phenomenon; the results are then summarized for the determination of diphenhydramine, benzethonium, sparteine, or tetraethylammonium, which are on the market as medicines or disinfectants. The proposed methods have a very good reproducibility and a high sensitivity.