Interaction of Povidone with Aromatic Compounds IV: Effects of Macromolecule Molecular Weight, Solvent Dielectric Constant, and Ligand Solubility on Complex Formation

J. A. PLAIZIER-VERCAMMEN

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Abstract □ Complex formation of ligand molecules with povidone was investigated to elucidate the effect of the molecular weight of the macromolecule and the influence of the solvent dielectric constant on the complexing tendency. The higher molecular weight polymers were more effective complexing agents than those with lower degrees of polymerization. When studying complex formation as a function of the dielectric constant (D), a linear relationship was noted between D and log B/F (B/F representing the ratio of bound to free ligand); the use of solvent mixtures to achieve a range of solvent dielectric constants enabled changes of the pH of the solvent, ligand dissociation, and solubility of the ligand and macromolecule. Of the variables under investigation, only the change in ligand solubility seemed to play an important role: a linear relationship was noted between the complexing tendency (log B/F) and the logarithm of the inverse of the ligand molecule solubility in the solvent mixtures (log $1/S$). It was concluded that the change in solubility of the ligand was the predominant factor in the decrease of the complexing tendency with decreasing dielectric constant.

Keyphrases □ Povidone—complex formation with salicylic acid, influence of molecular weight, solvent dielectric constant, and ligand solubility □ Salicylic acid—complex formation with povidone, influence of polymer molecular weight, solvent dielectric constant, and solubility □ Complex formation—salicylic acid and povidone, influence of polymer molecular weight, solvent dielectric constant, and ligand solubility

The effect of the molecular weight of povidone on the complexing tendency of ligand molecules has been studied (1–4). Either a positive effect (1, 2) or no effect at all was noted (3, 4). However, no interpretative statements were given. It was also observed (5) that the complexing tendency of ligand molecules with povidone decreases with a decrease of the dielectric constant. Such dependence as a function of dielectric constant is generally attributed to hydrophobic bondings (6–8). However, varying the dielectric constant also has an effect on the solubility of the ligand molecule. It was the purpose of this report to study the influence of the molecular weight of povidone on the complexing tendency of the ligand molecule and to investigate the possible relationships between the dielectric constant of the solvent, solubility of the ligand, and complex formation with povidone.

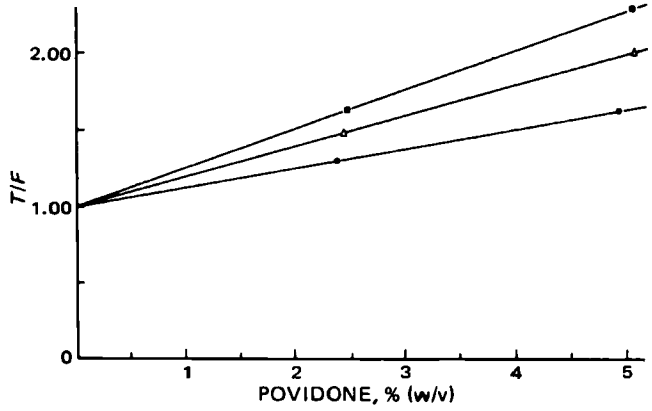

Figure 1—*Ratio of the total to free concentration of salicylic acid as a function of the concentration of povidone with molecular weights of 11,500 (●), 25,000 (△), and 700,000 (■). Initial salicylic acid concentration: 1.00 × 10⁻² M; pH 7.00; 25.0°.*

EXPERIMENTAL

Reagents—Povidone with molecular weights (weight average values) of 11,500[1] (batch I), 25,000[2] (batch II), and 700,000[3] (batch III) was used. It was oven-dried at 50° until constant weight was achieved. As ligand molecules, the following compounds were employed: salicylic acid[4], 4-hydroxysalicylic acid[5], and 5-hydroxysalicylic acid[4]. A phosphate buffer of pH 7.00 with a 0.25 ionic strength was used. The pH of the buffer was controlled with a potentiometric pH measurement[6] and adjusted as necessary. Different ethanol–water (from 0.0 to 20.0% v/v ethanol) and propylene glycol–water (from 0.0 to 50.0% v/v propylene glycol) mixtures were prepared, providing solvents with a wide range of dielectric constants.

Ultrafiltration—Ultrafiltration was used to investigate the ligand–macromolecule interactions. The equipment used was described previously (9).

Spectrophotometric Analysis—The concentration of unbound ligand was determined spectrophotometrically in the ultrafiltrate. Corrections for membrane adsorption effects were made, and the concentration of bound ligand was calculated from the difference between the concentration of total and unbound cosolute. The spectrophotometric measurements were performed with a double-beam spectrophotometer[7] at the respective λ_{max} of the ligand molecules, after appropriate dilution.

Effect of Molecular Weight of Povidone on Complex Formation—Two concentrations of the three batches of povidone were dissolved in a phosphate buffer (pH 7.00) containing 1.00×10^{-2} M salicylic acid. Ultrafiltration was carried out at 25.0°.

Effect of Dielectric Constants on Complex Formation—Salicylic acid, 4-hydroxysalicylic acid, and 5-hydroxysalicylic acid were dissolved in a range of ethanol–water mixtures (0.0 to 20.0% v/v ethanol), containing the macromolecule povidone (batch III). For 5-hydroxysalicylic acid, batch I povidone was also used. The latter ligand molecule was also dissolved in propylene glycol–water mixtures (0.0 to 50.0% v/v propylene glycol). The dielectric constants of the solvent mixtures were measured at 25.0° and 35.0°[8].

Solubility Measurements—The solubility data for salicylic acid and 4-hydroxysalicylic acid were obtained by placing amounts of the two compounds, in excess of their solubility, in 25 ml of the ethanol–water mixtures (0.0 to 20.0% v/v ethanol) in stoppered flasks. The suspensions were agitated at 25.0° and 35.0°, respectively, in a water bath. After equilibrium, the flasks were removed from the water bath, and the contents were quickly filtered through filter paper[9]. Suitable aliquots of the clear filtrate were pipetted, appropriately diluted with the respective solvent mixtures, and the absorbance of the samples was determined.

[1] Polyvinylpyrrolidone, Kollidon K_{17}, batch I, BASF, Brussels, Belgium.
[2] Polyvinylpyrrolidone, Kollidon K_{25}, batch II, BASF, Brussels, Belgium.
[3] Polyvinylpyrrolidone, Kollidon K_{90}, batch III, BASF, Brussels, Belgium.
[4] Merck, Darmstadt, West Germany.
[5] Merck-Suchardt.
[6] Radiometer Copenhagen, Denmark.
[7] Perkin-Elmer Model 124.
[8] Dekameter DK WTW Weilheim, West Germany.
[9] No. 2 Whatman.

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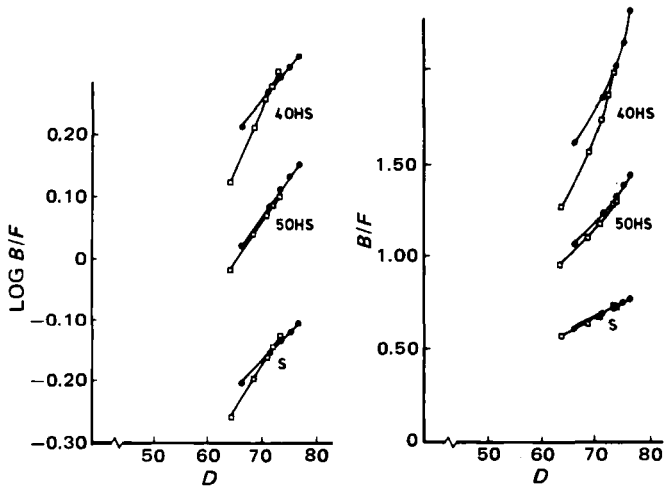

Figure 2—*Variation in the complexing tendency of ligand molecules with the dielectric constant of the solution (solvent: ethanol–water). Key: (●) 25.0°; (□) 35.0°; (4OHS) 4-hydroxysalicylic acid (5.00 × 10^{-3} M) plus 4.00% povidone, batch III; (5OHS) 5-hydroxysalicylic acid (5.00 × 10^{-3} M) plus 5.00% povidone, batch III; (S) salicylic acid (5.00 × 10^{-3} M) plus 4.00% povidone, batch III.*

Viscometric Analysis—Using capillary viscometers, the intrinsic viscosities of povidone dissolved in water, 20% (v/v) ethanol, and 50% (v/v) propylene glycol were determined at 25°. Temperature was controlled to ±0.05°. Povidone concentrations ranged from 0.2 to 1.0%.

RESULTS AND DISCUSSIONS

Theory of Multiple Equilibria—The principles and concepts fundamental to an understanding of macromolecular binding can be found elsewhere (10–16). In this report, the relative tendencies of several ligand molecules to form complexes are expressed as the ratio of the total ligand concentration (T) to the concentration of the free form (F) as a function of the percentage of povidone (17–19). This may be written as:

$$q = \frac{\text{concentration of total ligand}}{\text{concentration of free ligand}} = \frac{T}{F} = \frac{r}{F}[\text{PVP}] + 1 \quad \text{(Eq. 1)}$$

where r is moles of bound ligand/moles of macromolecule and [PVP] is the concentration of povidone in the solution. If r/F was constant, *i.e.*, if the same type of binding was taking place with increasing povidone concentration, T/F *versus* [PVP] plots resulted in straight lines (20).

Effect of Molecular Weight of Povidone on Complex Formation—The results expressed as T/F were plotted against the polymer concentration in Fig. 1. The higher molecular weight polymers are more efficient complexing agents than those with lower degrees of polymerization.

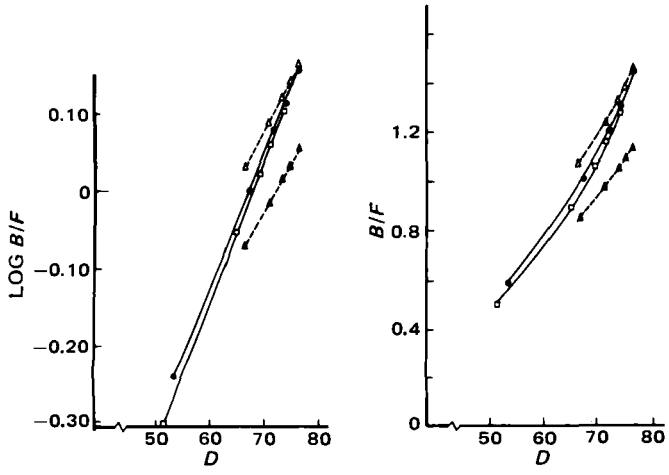

Figure 3—*Variation in the complexing tendency of 5-hydroxysalicylic acid with the dielectric constant of the solution [5-hydroxysalicylic acid (5.000 × 10^{-3} M) plus 5.00% povidone]. Key: (●) solvent propylene glycol–water, 25.0°, batch III; (□) solvent propylene glycol–water, 35.0°, batch III; (△) solvent ethanol–water, 25.0°, batch III; (▲) solvent ethanol–water, 25.0°, batch I.*

Table I—Intrinsic Viscosity of Povidone (Batch III) in Solvent Mixtures

Solvent	Intrinsic Viscosity, g/ml
Water	140
20% (v/v) Ethanol	150
50% (v/v) Propylene glycol	152

The two variables that can influence complex formation (*i.e.*, true solvation and the number of sites) are, however, independent of molecular weight for the same concentration of polymer (expressed in weight percent). On one hand, it is shown that for the same polymer, true solvation is independent of molecular weight if the active sites for solvent are equally accessible (12). On the other hand, if specific sites exist, according to the complexing theory they also will be independent of molecular weight for the same polymer percentage.

The difference in complexing tendency is in accordance with the existence of carboxylic end groups on the polymer (2, 21), as shown by IR spectroscopy. The end groups per unity weight polymer will be largest for the lower molecular weight, accompanied by an increase of solvation; this will result in a lower complexing tendency, as dehydration has a positive effect on the binding of ligand molecules onto povidone (22).

Effect of Dielectric Constant on Complex Formation—The results expressed as log B/F and B/F (the ratio of bound to free ligand concentration) were plotted in Figs. 2 and 3 as a function of the dielectric constant of the solvent, measured at the same temperatures as the ultrafiltration experiments. For all the derivatives, complex formation was diminished with decreasing dielectric constant (or increasing ethanol or propylene glycol concentration). Furthermore, the complexing tendency was diminished at higher temperatures. Comparing complex formation of 5-hydroxysalicylic acid onto povidone batch III and batch I (Fig. 3), the higher molecular weight macromolecule was the most effective complexing agent.

Figures 2 and 3 corresponded to the following equations:

$$\log \frac{B}{F} = b_1 + a_1 \cdot D \quad \text{(Eq. 2)}$$

where D is the dielectric constant and b_1 and a_1 are two constants, or:

$$\frac{B}{F} = 10^{b_1 + a_1 \cdot D} \quad \text{(Eq. 3)}$$

Using Eq. 2, it was noted that log B/F increased linearly with the dielectric constant of the solvent or diminished linearly with the percentage ethanol or propylene glycol.

In addition to the dielectric constant, temperature also played a role: for salicylic acid and 4-hydroxysalicylic acid (Fig. 2), the lines at 25.0° crossed those at 35.0°; for 5-hydroxysalicylic acid, the two lines are nearly parallel. That complex formation is not only dependent on dielectric constants could be observed from the results obtained with 5-hydroxysalicylic acid in ethanol–water and propylene glycol–water (Figs. 2 and 3, respectively). For the same dielectric constant, complex formation was

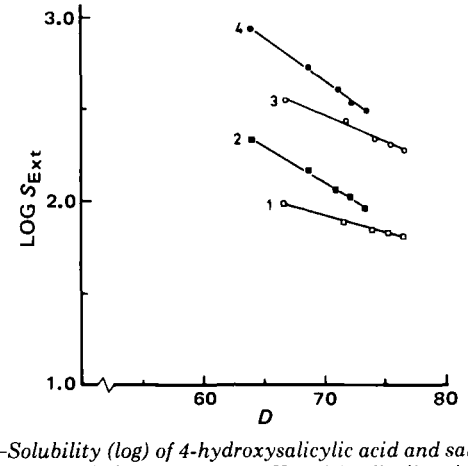

Figure 4—*Solubility (log) of 4-hydroxysalicylic acid and salicylic acid as a function of the dielectric constant. Key: (1) salicylic acid, 25.0°; (2) salicylic acid, 35.0°; (3) 4-hydroxysalicylic acid, 25.0°; (4) 4-hydroxysalicylic acid, 35.0°.*

lowest in the propylene glycol–water mixture. Thus, the nature of the solvent must also play a role.

A diminishing complexing tendency with lower dielectric constants is generally attributed to hydrophobic bonds (6–8). However, the use of ethanol–water mixtures in differing proportions to achieve a range of solvent dielectric constants changed the ionization of the ligand (23), the pH of the solution, and the solubility (hydration) (24) of the macro- and ligand molecules (23–25). These factors, which also could influence complex formation, were investigated.

Ionization and dissociation of ligand molecules are depressed under conditions of low dielectric constant of the medium (23). This factor cannot be very important, in view of experimental observations (22) where a decrease in the dissociation of ligand molecules enhanced complex formation; this is not observed for the ligand molecules under investigation.

The difference in hydration of povidone in water, ethanol, and propylene glycol solutions was investigated with viscometric measurements. The intrinsic viscosities are given in Table I. No attempts were made to interpret changes in the Huggins constant (26), since no good interpretation in small deviations of these constants exists (27, 28).

From Table I, it was observed that the parameters are not significantly affected by change in solvent composition; this may possibly indicate that the total solvation of povidone was not affected much by changes in solvent composition. After all, povidone is not only soluble in water, but also in alcohol and even in chloroform, and hence, presumably in propylene glycol as well. Therefore, alcohol and propylene glycol will also be bound to povidone, in addition to water.

From pH measurements, it is noted that the pH of the solutions is almost unaffected by changing the solvent composition from zero to 20.0% (v/v) ethanol. At constant pH, ethanol enhances the solubility of weak electrolytes, by lowering the polarity of the solvent (23). For povidone batches I and III, the solubility of the ligand molecule is not changed in the same solvent composition; therefore, the difference in complex formation must be due to the macromolecule. The difference in complex formation of 5-hydroxysalicylic acid onto the two povidone batches also is attributed to the lower hydration of povidone batch III, enhancing the complexing tendency.

The solubility of two ligand molecules, *i.e.*, salicylic acid and 4-hydroxysalicylic acid, as a function of solvent composition and dielectric constant was investigated. The results obtained at 25.0° and 35.0° are represented in Fig. 4. The values of the ordinate are extinction values.

The solubility (log) of the two ligand molecules is linearly decreasing with increasing dielectric constant of the solvent medium; the decrease is faster at 35.0° than at 25.0°. This can be written as:

$$\log S = b_2 - a_2 \cdot D \qquad \text{(Eq. 4)}$$

where S is the solubility of the compounds and b_2 and a_2 are two constants or:

$$\log \frac{1}{S} + b_2 = a_2 \cdot D \qquad \text{(Eq. 5)}$$

The relationship between the solubility of the ligand and the complexing tendency onto povidone can be obtained from Eqs. 2 and 5. Dividing the two equations results in:

$$\log \frac{B}{F} = \frac{a_1}{a_2} \log \frac{1}{S} + b_2 \frac{a_1}{a_2} + b_1 \qquad \text{(Eq. 6)}$$

or:

$$\log \frac{B}{F} = a_3 \log \frac{1}{S} + b_3 \qquad \text{(Eq. 7)}$$

with $a_1/a_2 = a_3$ and $b_3 = (b_2 \cdot a_1/a_2) + b_1$.

The correctness of Eq. 7 was checked with the experimental results: the data obtained for 4-hydroxysalicylic acid and salicylic acid (Fig. 2) expressed as log B/F were plotted as a function of log $1/S$. The deduced linear relationship between log B/F and log $1/S$ in Eq. 7 was confirmed experimentally. The corresponding values of a_3 and b_3 for salicylic acid are 0.492 and 0.823 at 25.0° and 0.534 and 0.612 at 35.0°; for 4-hydroxysalicylic acid these values are 0.435 and 1.35 at 25.0° and 0.365 and 1.23 at 35.0°. A similar relationship was obtained for the interaction of anilines to nylon (29).

Log $1/S$ is a partitioning term, as it is an equilibrium constant between drug (pure) $\rightleftarrows$ drug (H_2O) (30) and is correlated with another partitioning function. Indeed, B/F may also be considered a partitioning term expressing the partition of ligand between the macromolecule and the solvent; it is directly analogous to an organic solvent–water partition coefficient.

From our experiments, it can be concluded that the predominant effect of the decrease in complex formation in the solvent mixtures was caused by the increasing solubility of the ligand molecules. Correlation between complex formation to povidone and solubilities for the two derivatives provide additional support for the occurrence of complex formation by hydrophobic interactions.

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