to give 121 mg. (52%) of product, m.p. 330–333° dec. Recrystallization from aqueous *N,N*-dimethylformamide gave white crystals, m.p. 327–330° dec.; $\nu_{max.}$ 3300 (NH); 1700–1650 (broad C=O); 755–720 cm.$^{-1}$ (C_6H_5—). (See Table I for analytical data.)

Other compounds prepared by this method are listed in Table I under *Method D*.

p-Nitrophenyl Uracil-1-acetate (XXVII).—To a solution of 680 mg. (4 mmoles) of XIIg and 612 mg. (4.4 mmoles) of *p*-nitrophenol in 13 ml. of *N,N*-dimethylformamide was added a solution of 912 mg. (4.4 mmoles) of dicyclohexylcarbodiimide in 3 ml. of the same solvent. After standing at room temperature for 20 hours protected from moisture, the separated *N,N'*-dicyclohexylurea was removed by filtration. The filtrate was spin-evaporated to residue *in vacuo* and crystallized from acetone; yield, 803 mg. (69%) of product, m.p. 191–194°, which was slightly contaminated with the urea. Recrystallization from *N,N*-dimethylformamide–ethanol gave 547 mg. (47%) of white needles, m.p. 213°; the analytical sample obtained in one more recrystallization had the same melting point and $\nu_{max.}$ 1750 (ester C=O); 1670 (broad C=O, C=C); 1520, 1335 cm.$^{-1}$ (NO_2).

Anal.—Calcd. for $C_{12}H_9N_3O_6$: C, 49.5; H, 3.11; N, 14.4. Found: C, 49.7; H, 3.30; N, 14.3.

Uracil-1-acetyl-β-alanine (XXVIII).—To a solution of 45 mg. (0.5 mmole) of β-alanine in 6 ml. of water containing 0.55 mmole of sodium hydroxide was added a suspension of 155 mg. (0.53 mmole) of XXVII in 10 ml. of chloroform. The three-phase system was stirred magnetically in a stoppered flask for 24 hours during which time the *p*-nitrophenyl ester (XXVII) had dissolved. The separated aqueous phase was adjusted to pH 3 with 5% hydrochloric acid, then spin-evaporated to dryness *in vacuo*. The residue was extracted with a large volume of hot 95% ethanol to remove sodium chloride. The insoluble residual product weighed 69 mg. (57%), m.p. 250–255°. Recrystallization from *N,N*-dimethylformamide–acetone gave the pure product, m.p. 254–256°; $\nu_{max.}$ 3300 (NH); 2600–2500 (broad acidic H); 1700 (carboxyl C=O); 1650 cm.$^{-1}$ (uracil C=O). (See Table I for analytical data.)

This reaction failed with *p*-aminosalicylic acid in place of β-alanine.

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Interaction Between Poly-*N*-vinyl-5-methyl-2-oxazolidinone and Certain Pharmaceuticals in Aqueous Solution

By SEYMOUR M. BLAUG and ARTHUR G. RICH

The interaction between certain pharmaceuticals and poly-*N*-vinyl-5-methyl-2-oxazolidinone is reported. Compounds studied include aromatic hydroxyl compounds, aromatic amino compounds, *p*-hydroxybenzoic acid esters, barbiturates, plant growth hormones, and sulfonamides. A dialysis method is used to study the complexing reaction. Data indicate that, in general, *p*-substituted compounds exhibit a degree of binding greater than their *m*-isomers. The *o*-substituted compounds appear to interact less than the *p*- or *m*-substituted compounds with poly-*N*-vinyl-5-methyl-2-oxazolidinone. 5,5-Substitution of barbituric acid greatly reduces its ability to associate with the polymer. Data are reported to show the value *K*, the ratio of the total drug concentration in solution to the concentration of the unbound drug as a function of the polymer concentration.

CONTINUING advances in the areas of pharmaceutical product development and research have shown that some organic polymeric substances are suitable for incorporation in medicinal preparations as auxiliary agents and/or as vehicles. Observations of the nonionic polymers in the presence of certain drug molecules showed that there was a tendency for some medicinals to form molecular association complexes with several different macromolecules (1–3, 6–20). In some cases the solubility of the medicinal was

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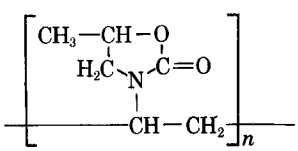
increased through the formation of a soluble complex. Other systems gave rise to insoluble complexes, which can be either desirable or undesirable. Insoluble complexes themselves can permit the slow release of the drug molecule from the complex. Advantageous use of such a fact would include the use of solid implants in muscle tissue or incorporation into a sustained-release medication.

Nonionic macromolecules have been shown (1) to interact with various preservatives. Pisano and Kostenbauder (2) and Blaug and Ahsan (3) have shown that such interactions inhibited preservative activity.

A new nonionic macromolecule, reputed to function well as an adjunct to certain pharmaceutical dosage forms, has become available (4). Chemically, the structure can be described as poly-*N*-vinyl-5-methyl-2-oxazolidinone (PVOM).[1]



This polymer is highly water soluble and only slightly hygroscopic. Its solutions possess a viscosity lower than would be expected normally from a polymer having a molecular weight of 165,000. It has been suggested for incorporation into tablet formulations, either as a tablet coating or as a granulating agent. Because of its attraction for protein materials like hair and skin, its use as a hair wave-setting agent has been proposed (5). Reference is also made to the possibility of producing a sustained-release medication by complexing the polymer with certain medicinal agents (4). Formation of an association compound with some phytochemicals opens a field whereby control of plant growth hormones may be undertaken.

The objective of this study was to investigate the interaction between PVOM, and a number of pharmaceutical agents. It was hoped that through this investigation suitable comparison of the binding ability of the PVOM polymer could be made to binding data reported in the literature for other nonionic macromolecules.

EXPERIMENTAL

To determine the complexing ability of the PVOM macromolecule, it was decided first to utilize the solubility method referred to in an earlier work (6). This procedure was discarded after visual examination showed that the insoluble complex, formed with some of the pharmaceuticals, entrapped part of the excess undissolved drug, thereby producing erroneous results. The dialysis method described earlier (7–9) provided satisfactory results, and was adopted for the remainder of the study. Visking cellulose casing (Union Carbide Corp., New York, N. Y.) was chosen because it permitted the free passage of low molecular weight drug in aqueous solution; but it acted as an impermeable barrier toward the high molecular weight PVOM polymer. The concentration of the monomer, as reported by the manufacturer (4), was deemed insignificant for this study. Also, experimental control solutions run in this study showed that the semipermeable membrane did not bind the drugs used. The casings were soaked first in distilled water for 60 minutes to prepare them for the experiment. Solutions of PVOM were then placed inside of sacs prepared from the casings. The sacs were tied and placed in solutions of the drugs under study, then allowed to equilibrate. If no complex formation occurred with the PVOM, the concentration of the drug on each side of the semipermeable membrane was the same. If molecular association did occur, then the drug concentration in the external solution decreased. If the drug molecule is bound to the polymer, it is no longer free to traverse the semipermeable membrane and must remain within the sac. Analysis of the internal solution will show a corresponding increase in drug concentration.

Reagents.—All materials not classified as reagent grade or as reference standard were recrystallized from an appropriate solvent.

The following compounds were employed in this study: *p*-hydroxybenzoic acid, m.p. 214°; *m*-hydroxybenzoic acid, m.p. 201°; salicylic acid, m.p. 158°; acetylsalicylic acid, m.p. 135°; benzoic acid, m.p. 121°; *p*-aminobenzoic acid, m.p. 184°; anthranilic acid, m.p. 144°; *p*-aminosalicylic acid, m.p. 151°; benzocaine, m.p. 89°; procaine hydrochloride, m.p. 154°; sulfadiazine, m.p. 247°; sulfathiazole, m.p. 172°; indoleacetic acid, m.p. 165°; indolebutyric acid, m.p. 125°; caffeine, m.p. 232°; theobromine, m.p. 337° (subl.); theophylline, m.p. 267°; barbituric acid, m.p. 247° dec.; barbital, m.p. 188°; phenobarbital, m.p. 173°; thiopental sodium[2]; methyl *p*-hydroxybenzoate, m.p. 126°; ethyl *p*-hydroxybenzoate, m.p. 116°; propyl *p*-hydroxybenzoate, m.p. 96°; butyl *p*-hydroxybenzoate, m.p. 69°; PVOM.

Procedure.—A 500-ml. solution of the drug was prepared at such a concentration that a 50-ml. aliquot would contain the following amounts of material: *p*-hydroxybenzoic acid, 0.10 Gm.; *m*-hydroxybenzoic acid, 0.25 Gm.; salicylic acid, 0.05 Gm.; acetylsalicylic acid, 0.075 Gm.; benzoic acid, 0.10 Gm.; *p*-aminobenzoic acid, 0.15 Gm.; anthranilic acid, 0.10 Gm.; *p*-aminosalicylic acid, 0.075 Gm.; benzocaine, 0.025 Gm.; procaine hydrochloride, 0.10 Gm.; sulfadiazine, 0.005 Gm.; sulfathiazole, 0.20 Gm.; indoleacetic acid, 0.0025, 0.005, and 0.010 Gm.; indolebutyric acid, 0.0025, 0.005, and 0.010 Gm.; caffeine, 0.50 Gm.; theobromine, 0.01 Gm.; theophylline, 0.20 Gm.; barbituric acid, 0.02 Gm.; barbital, 0.20 Gm.; phenobarbital, 0.04 Gm.; thiopental sodium, 0.01 Gm.;

[1] Available as Devlex 130 from the Dow Chemical Co., Midland, Mich.

[2] Marketed as Pentothal Sodium by Abbott Laboratories, North Chicago, Ill.

methyl *p*-hydroxybenzoate, 0.085 Gm.; ethyl *p*-hydroxybenzoate, 0.05 Gm.; propyl *p*-hydroxybenzoate, 0.015 Gm.; butyl *p*-hydroxybenzoate, 0.005 Gm. All carboxylic acids and esters were dissolved in 0.005 *N* sulfuric acid to suppress ionization and hydrolysis. The thiopental sodium was placed in 0.1 *N* sodium hydroxide to maintain solubility.

From a 10% solution of PVOM, 20-ml. solutions of varying concentrations of the polymer were prepared. These concentrations included: 0.0% as a control, 0.125, 0.250, 0.50, 1.0, 2.0, 3.0, 4.0, and 5.0%. The polymer solutions were placed in individual Visking sacs. The tied sacs were then immersed in 50 ml. of drug solution which had been placed previously in 125-ml. wide mouth glass-stoppered bottles. The bottles were then placed in a constant temperature water bath shaker at 30 ± 0.1°. The solutions were equilibrated for 22 to 26 hours.

After equilibration had been achieved, a suitable aliquot of the external solution was removed and diluted with the same solvent used to prepare the original solution. The only exception was barbital, where the dilution of the aliquot with 0.1 *N* sodium hydroxide provided a resolution of the ultraviolet spectrum of the solution better than deionized water. Aliquots were assayed spectrophotometrically using a Beckman model DU spectrophotometer with 1-cm. cells. A blank for each analysis consisted of the diluting solvent, since diluted aqueous solutions of PVOM do not absorb in the ultraviolet range. The drugs were studied at the following wavelengths: *p*-hydroxybenzoic acid, 255 mμ; *m*-hydroxybenzoic acid, 290 mμ; salicylic acid, 300 mμ; acetylsalicylic acid, 275 mμ; benzoic acid, 274 mμ; *p*-aminobenzoic acid, 280 mμ; anthranilic acid, 328 mμ; *p*-aminosalicylic acid, 267 mμ; benzocaine, 286 mμ; procaine hydrochloride, 291 mμ; sulfadiazine, 266 mμ; sulfathiazole, 260 mμ; indoleacetic acid, 278 mμ; indolebutyric acid, 280 mμ; caffeine, 272 mμ; theobromine, 272 mμ; theophylline, 273 mμ; barbituric acid, 257 mμ; barbital, 245 mμ; phenobarbital, 240 mμ; thiopental sodium, 306 mμ; methyl *p*-hydroxybenzoate, 256 mμ; ethyl *p*-hydroxybenzoate, 256 mμ; propyl *p*-hydroxybenzoate, 255 mμ; butyl *p*-hydroxybenzoate, 256 mμ.

RESULTS AND DISCUSSION

Examination of the structure of PVOM may well give an explanation of its ability to form molecular complexes readily with many types of aromatic nuclei. Structurally, the polymer is classified as poly-*N*-vinyl-5-methyl-2-oxazolidinone. There are three electronegative centers, which contribute heavily to the polarization of the PVOM, in the oxazolidinone portion of the molecule. The oxygen atom in the 1-position and the nitrogen atom in the 3-position are both strong electron acceptors. The carbonyl function in the 2-position forms a dipole, resulting in a partial positive charge on the carbon atom and a partial negative charge on the oxygen atom. There is also a π electron cloud associated with the carbonyl configuration. Resonant structures will also be associated with the carbonyl double bond. These result in partial positive charges at either the 1- or 3-position.

Aside from these areas of high electron density in the molecule, which will be receptive to electron donor groups from other nuclei, there are also hydrogen bonding reactions with other compounds. The points of bonding can be through the oxygen atom on the ring at the 1-position and the oxygen atom of the carbonyl group in the 2-position. Van der Waals attractive forces, among other factors, must also be considered to aid and abet formation of a stable complex molecule but would be of secondary importance to the electron transfer concepts just described.

In Figs. 1–8, the phase diagrams were plotted to show that the value *K*, a ratio of the total drug concentration in solution to the concentration of the unbound drug, is a function of the concentration of the PVOM. This *K* value may be used to compare the binding ability of PVOM to the binding ability of other polymers in other published reports. (For example, see the comparison in Table I.) It can also be used as an approximation of the excess of drug that must be added to the system to insure the presence of sufficient unbound drug when the PVOM polymer is present.

The interaction of PVOM with benzoic acid and with some hydroxybenzoic acids is shown in Fig. 1. As would be expected from considerations of electronic resonance through an aromatic nucleus, the *p*-hydroxybenzoic acid interacts to an extent greater than any of the other positional isomers. The hydroxyl substituent in the position *para* to the carboxylic acid group is able to donate electrons through the nucleus to the acid function, thereby creating a definite dipolar molecule. The *o*-hydroxyl compound should produce a dipole moment as strong, if not stronger, assuming that there are only resonant and inductive forces determining the electron shifts in the molecule. However, because of the proximity of the two substituent groups on the benzene nucleus, a strong intramolecular attraction exists. The hydroxyl group shows a tendency to form a hydrogen bond with the carbonyl oxygen of the acid group. This greatly reduces the possibility of the *o*-hydroxybenzoic acid combining with other molecules, such as the PVOM polymer. The experimental results support this theory. The salicylic acid is bound by

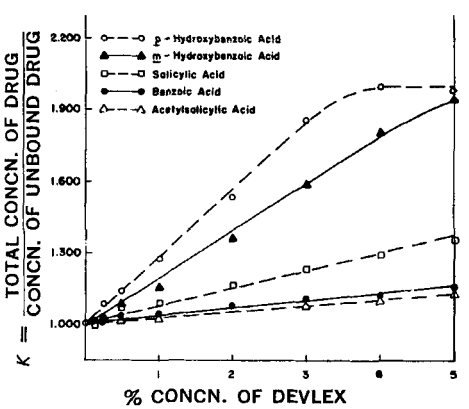


Fig. 1.—Binding of benzoic acid, *p*-hydroxybenzoic acid, *m*-hydroxybenzoic acid, salicylic acid, and acetylsalicylic acid by Devlex 130 resin at 30°C.

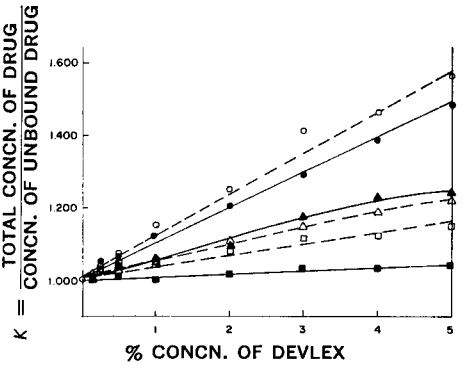


Fig. 2.—Binding of benzoic acid, several amino benzoic acids, and their derivatives by Devlex 130 resin at 30°C. Key: O———O, *p*-aminobenzoic acid; ▲———▲, anthranilic acid; □———□, benzoic acid; ●———●, *p*-aminosalicylic acid; △———△, benzocaine; ■———■, procaine hydrochloride.

the complexing agent only slightly more than the benzoic acid itself. Acetylation of the *o*-hydroxyl group reduces the molecule's binding capacity even further. This observation would seem to confirm theoretical conclusions that there is some hydrogen bonding between the hydroxyl groups and the PVOM molecule.

According to the order of interaction between PVOM and the benzoic acid or the unsubstituted hydroxybenzoic acid isomers, hydrogen bonding appears to play a substantial role in this complexing reaction. Thus, the *o*-hydroxybenzoic acid shows less interaction with the PVOM because its hydrogen bonding ability has been decreased.

The *m*-hydroxybenzoic acid is complexed only slightly less than the *p*-isomer. The dipole moment of the *m*-hydroxyl compound is smaller than that of the *p*-compound due to resonant factors. Resonant structures cannot be drawn showing a shift of electrons from the *m*-position to the carboxylic acid group. This helps to explain the diminished ability to form a complex. Therefore, it is assumed that there is a dipole–dipole interaction between the PVOM and the hydroxybenzoic acids as well as the hydrogen bonding concept discussed above.

The phase diagram shows that the slope of the linear plot for *p*-hydroxybenzoic acid decreases at the higher concentrations of the complexing agent used in this study. Visual examination of the sac at the time of analysis of the sample showed that an insoluble complex was produced within the dialysis membrane. As this precipitate clung to the walls of the sac, it interfered with the transfer of the drug from one side of the membrane to the other. The other isomers showed a smaller degree of precipitation. However, the *m*-hydroxyl compound also shows a slight deviation from linearity of the slope at higher concentrations of the PVOM. The same reasoning discussed for the *p*-isomer can be applied to the *m*-compound.

Figure 2 is a phase diagram of the aminobenzoic acids and their binding tendencies with PVOM. The results appear to be analogous to those obtained for the hydroxyl acids, and indeed they should be. The amino substituent exhibits electronic properties that are similar to those obtained from the compounds shown in Fig. 1. The extent of complex formation is decreased with the nitrogen-containing compounds because the amino hydrogen is less acidic than a corresponding hydroxyl hydrogen atom. This would also account for a decrease in the hydrogen bonding ability of the aminobenzoic acid compounds. *p*-Aminosalicylic acid shows a lowering of its complexing tendencies compared to the *p*-aminobenzoic acid. Again, the proximity of the *o*-substituent to the acid function permits the formation of an intramolecular hydrogen bond. The *o*-aminobenzoic acid also has its functional groups associated, so that a decrease in the ratio of total drug to unbound drug is evident. Esterification of the carboxylic acid, as in benzocaine, reduces the ability of the molecule to engage in complex formation by elimination of the acidic hydrogen atom from the carboxylic acid. This compound is still more reactive than the benzoic acid itself because of the presence of the amino grouping in the *p*-position. Procaine hydrochloride, in an acidic solution, is present as an undissociated salt. It binds only slightly with the PVOM polymer, even though the amino group is in the position *para* to the carboxylic ester. The length of the ester chain produces steric hinderance.

Barbituric acid and its derivatives show great variations in their binding abilities (see Fig. 3). The unsubstituted barbituric acid itself complexes with the PVOM probably as a result of enolization at the 1-, 2-positions of the drug. Disubstitution at the 5-position completely eliminates molecular association. Both 5,5-diethyl and 5-phenyl-5-ethyl substitution produce barbiturates that will not interact with the PVOM polymer. Since the substituents do not influence the keto-enol tautomerization of the nucleus, it appears safe to assume that steric factors must be considered. Both phenobarbital and barbital (diethyl barbituric acid) contain substituents that are replacing hydrogen atoms of the barbituric acid. These bulkier substituents are probably interfered with by neighboring monomer units in the polymer chain.

Thiopental sodium, in solution as the ionic species, combines with the PVOM molecule. The value for the slope of the plot is lower than for the

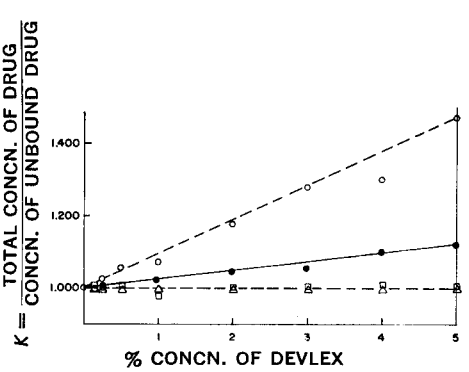


Fig. 3.—Binding of barbituric acid and several derivatives by Devlex 130 resin at 30°C. Key: O———O, barbituric acid; △———△, phenobarbital; □———□, barbital; ●———●, thiopental sodium.

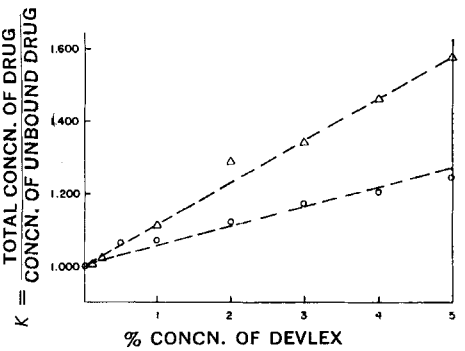


Fig. 4.—Binding of sulfadiazine and sulfathiazole by Devlex 130 resin at 30°C. Key: O———O, sulfadiazine; Δ———Δ, sulfathiazole.

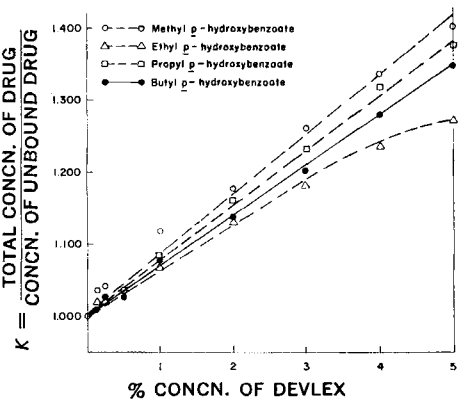


Fig. 5.—Binding of esters of *p*-hydroxybenzoic acid by Devlex 130 resin at 30°C.

barbituric acid. This lends support to the supposition that both alkyl and aryl substitution at the 5-position will interfere with any interaction of the barbiturates with the PVOM macromolecule.

Both sulfathiazole and sulfadiazine undergo complex formation with the PVOM. The phase diagrams in Fig. 4 graphically represent this fact. The only structural difference between the sulfathiazole and the sulfadiazine is the thiazole ring in the former and the diazine ring in the latter compound. The sulfur atom in the thiazole nucleus will show an ability to accept electrons because of the vacant antibonding pd^2 orbital present. Since the PVOM molecule is polar, as previously discussed, it has the ability to form a complex molecule with the sulfa drug at the thiazole ring. The diazine nucleus of sulfadiazine will show less electron accepting ability; therefore, it has a lower capacity for interaction. The difference in binding ability can be observed in Fig. 4.

The alkyl esters of *p*-hydroxybenzoic acid have their preservative activity reduced when combined with a number of nonionic macromolecules (1, 2, 13, 15). Formation of a molecular association compound is considered the chief factor for the decrease in antimicrobial activity. In solutions of the PVOM polymer, the esters are observed to undergo complex formation. The results of these experiments are depicted in the phase diagrams of Fig. 5. The methyl ester shows the greatest binding tendency, followed by the propyl, butyl, and the ethyl esters, respectively. If a squeezing out effect is exerted by the water molecules on the hydrophobic moieties to produce binding between the polymer and the ester, then the order of the complexing tendency would be reversed essentially from the observations in Fig. 5, and the plot for the butyl ester would show the greatest slope. It would appear that increasing the length of the alkyl group produces an inhibition of complex formation. The longer chain length must, therefore, produce steric effects which prevent the ester molecule from aligning itself in a position relative to the polymer that can afford optimum binding between the two molecules. The deviation of the ethyl ester from the order of decreasing complexing capacities must be accounted for by other means. The decrease in the slope of the plot at higher concentrations of the macromolecule shows that an equilibrium situation is being established. Since this is the only plot in the series producing this equilibrium within the range of concentrations used in this study, it would seem likely that the stability constant is much lower than that of other esters. This would produce a lower slope for the K ratio *versus* polymer concentration plot.

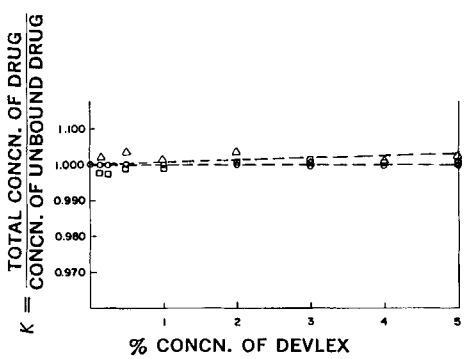


Fig. 6.—Binding of caffeine, theophylline, and theobromine by Devlex 130 resin at 30°C. Key: O———O, caffeine; Δ———Δ, theophylline; □———□, theobromine.

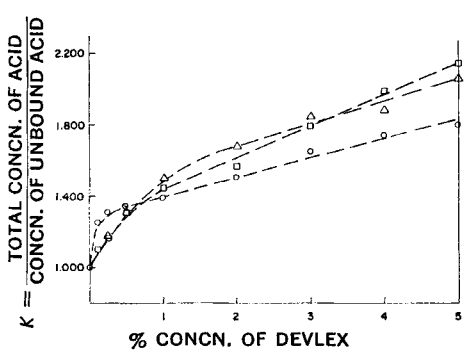


Fig. 7.—Effect of variation in the concentration of indoleacetic acid on the binding by Devlex 130 resin at 30°C. Key: O———O, $3.00 \times 10^{-4} M$ indoleacetic acid; Δ———Δ, 5.69×10^{-4} *M* indoleacetic acid; □———□, 11.09×10^{-4} *M* indoleacetic acid.

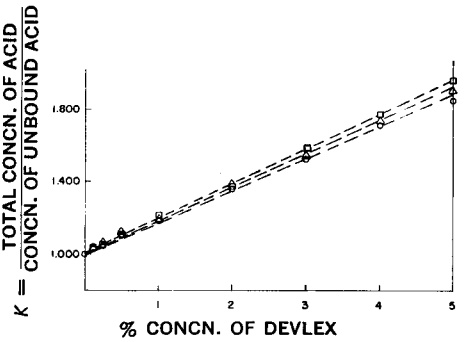


Fig. 8.—Effect of variation in the concentration of indolebutyric acid on the binding by Devlex 130 resin at 30°C. Key: O———O, 2.53×10^{-4} *M* indolebutyric acid; △———△, 4.99×10^{-4} *M* indolebutyric acid; □———□, 10.11×10^{-4} *M* indolebutyric acid.

TABLE I.—COMPARISON OF THE COMPLEXING TENDENCIES OF SEVERAL DRUGS WITH PVOM AND PVP IN 1% CONCENTRATION

Drug	Drug in Complex, % PVOM	PVP[a]
Sulfathiazole	10.2	31.0
Benzoic acid	4.9	11.5
Salicylic acid	8.0	18.5
m-Hydroxybenzoic acid	13.1	30.0
p-Hydroxybenzoic acid	23.9	30.0
p-Aminobenzoic acid	13.1	18.7
Phenobarbital	0.0	10.0
Procaine hydrochloride	0.0	0.0

[a] Obtained from Higuchi, T., and Kuramoto, R., THIS JOURNAL, **43**, 393, 398(1954).

Experiments combining caffeine, theophylline, and theobromine with the PVOM show that little or no association takes place. The results are plotted in Fig. 6. The apparent lack of interaction is not surprising since these xanthine molecules will also maintain centers of high electron density. Theophylline shows a slight almost negligible binding tendency. Only the 7-position of the xanthine nucleus is demethylated in theophylline, and weak attractive forces can be extended from this position to the nonionic macromolecule.

The plant growth hormones, indoleacetic acid and indolebutyric acid, are shown to undergo complex formation with the PVOM. The results, shown in Figs. 7 and 8, agree with other reports (4). The indoleacetic acid appears to form a weaker complex because a decrease in the slope of the plot is observed at low concentrations of the nonionic macromolecule. The change in slope is due to attainment of equilibrium between the free and complexed form of the acid molecule. Variation in the concentration of both carboxylic acids produces only slight changes in the plot of the indoleacetic acid (Fig. 7) and virtually none for the indolebutyric acid (Fig. 8). This confirms the fact that complex formation is essentially independent of the drug concentration but strongly influenced by alterations in the concentration of the complexing agent.

Because of the similarity in structure between PVOM and polyvinylpyrrolidone (PVP), both being five-membered rings with *N*-vinyl groupings, a comparison of the amount of drug bound by each complexing agent was made in Table I. The results are expressed as a percentage of the total drug present in its complexed form. The data relating to the PVP were obtained from reports of Higuchi and Kuramoto (7, 10). Less complex formation is obtained when the PVOM is used in combination with these drug molecules. The methyl group in the 5-position of the oxazolidinone nucleus must present a steric blocking factor which affects the ability of the PVOM molecule to interact freely with the molecules used in this study.

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