Structure of Polyvinylpyrrolidone-Iodine (Povidone-Iodine)

HANS-UWE SCHENCK ˣ, PETR SIMAK, and ERICH HAEDICKE

Received April 2, 1979, from the *Plastics Laboratory, BASF Aktiengesellschaft, D 6700 Ludwigshafen, Federal Republic of Germany.* Accepted for publication June 7, 1979.

Abstract □ Hydrogen triiodide adducts were prepared from *N,N*-dimethylacetamide, *N*-alkylpyrrolidone derivatives, and polyvinylpyrrolidone, and their structures were investigated by IR spectra and X-ray structure analyses and compared with the structure of povidone-iodine USP. The results suggest that the iodine in povidone-iodine USP is complexed by the polymer such that a proton is fixed *via* a short hydrogen bond between two carbonyl groups of two pyrrolidone rings and that a triiodide anion is bound ionically to this cation.

Keyphrases □ Povidone-iodine—structure, hydrogen triiodide adducts, IR spectra, X-ray structure analysis □ Anti-infectives, topical—povidone-iodine, structure, hydrogen triiodide adducts, IR spectra, X-ray structure analysis □ Models, molecular—povidone-iodine

Povidone-iodine has been used as a multivalent, local, broad-spectrum antiseptic having bactericidal, fungicidal, sporicidal, protocidal, and virucidal properties. Based on the observation that combining iodine with polyvinylpyrrolidone (PVP) reduces iodine vapor pressure and increases iodine solubility in water (1), methods were patented that provide a polyvinylpyrrolidone-iodine adduct (povidone-iodine USP). Its aqueous solution has a higher stability in storage (smaller loss of available thiosulfate-titratable iodine) than an iodine solution in water containing polyvinylpyrrolidone.

BACKGROUND

A conventional method of preparing powdered povidone-iodine involves efficient mixing of elemental iodine with powdered polyvinylpyrrolidone[1]. The mixture is heated at an elevated temperature until the ratio of thiosulfate-titratable iodine to iodide ions is ~2:1 (2, 3). Only this ratio of iodine to iodide ions ensures adequate povidone-iodine stability. Stability is defined as: (*a*) a low iodine loss as determined in a 10% aqueous povidone-iodine solution, and (*b*) a high iodine distribution coefficient, c_{iodine} in water/c_{iodine} in *n*-heptane, between an aqueous phase and an *n*-heptane phase.

The distribution coefficient is the quotient of the iodine concentrations in water and in *n*-heptane as obtained according to a literature method (4) on extracting iodine from an aqueous povidone-iodine solution with *n*-heptane. Povidone-iodine also may be obtained without heating by mixing iodine with polyvinylpyrrolidone[1] and an iodide-containing substance at room temperature or by drying an iodide-containing polyvinylpyrrolidone[1] solution and mixing the polyvinylpyrrolidone-iodide with iodine (5).

In addition to the patent literature, numerous publications have dealt with the polyvinylpyrrolidone-iodine structure. The term polyvinylpyrrolidone-iodine has been used both for the product obtained by annealing iodine with polyvinylpyrrolidone at an elevated temperature and for the adduct formed on dissolving iodine in water containing this polymer. The papers discussed investigations into the structure of iodine adducts of natural and other synthetic polymers.

A comprehensive review article, published in 1953, dealt with numerous polyvinylpyrrolidone complexes and mentioned the adsorptivity of polyvinylpyrrolidone for iodine (6). The IR spectra were interpreted as suggesting that iodine molecules, triiodide ions, and adducts of polyvinylpyrrolidone and iodine coexist. Furthermore, strong polarization of the iodine molecules in the adduct was inferred from the direction of dissociation of the iodine molecule as discussed recently (Scheme I) (7). Disproportionation of the iodine into hypoiodite and iodide also was postulated (8–10).

$$\text{PVP}\ (i-1)\ I_2 + I_2 \rightleftarrows \text{PVP}\ (i\cdot I_2)\ \text{(outer complex)} \rightleftarrows (\text{PVP}\cdot I_{i/2})^{i/2+} \cdot (I_{3i/2})^{i/2-}\ \text{(inner complex)}$$

Scheme I

The influence of the iodide ion on iodine bonding to polyvinylpyrrolidone in chloroform and water was investigated (11–17). Molecular iodine was bonded to polyvinylpyrrolidone in chloroform (18). In aqueous solution in the presence of potassium iodide, the polymer-bonded species was triiodide, with the potassium ion complexed directly so that an insoluble product was precipitated from solution.

The literature provides few details of the solid polyvinylpyrrolidone-iodine structure. The only existing reference (19) concerns the structure of polyvinylpyrrolidone-iodine obtained by heating polyvinylpyrrolidone containing 10% water with iodine at 60° for 24 hr. According to the ratio of polyvinylpyrrolidone to iodine, some of the iodine was no longer titratable with thiosulfate. The greater the ratio, the higher was the molar polyvinylpyrrolidone excess. On extrapolation to an infinitely large polymer excess, 38.3% of the iodine was calculated to be present after complexation in a form that was not titratable with thiosulfate.

Moreover, water was involved in the reaction of iodine and polyvinylpyrrolidone; 7.4 ± 3.8 moles of water was lost per mole of nontitratable iodine and 2.33 ± 0.16 moles of acid was liberated per mole of nontitratable iodine. The UV–visible spectra revealed that triiodide ions were present.

To explain the amount of triiodide and protons formed, the decrease in the amount of water, and the residual iodine, previous investigators (19) assumed that the iodine hydrolysis reaction (Scheme II):

$$I_2 + H_2O \rightleftarrows IO^- + I^- + 2H^+$$

Scheme II

is favored greatly by the presence of polyvinylpyrrolidone so that an iodine complex, $PVP\text{-}(I_2)_x(IO^-, I^-)_y$, $y/x < 1.5$, results in which iodide and hypoiodite are present in addition to iodine. Similarly, Takikawa *et al.* (20, 21) postulated accelerated iodine hydrolysis in aqueous solution in the presence of polyvinylpyrrolidone and complexation to the polymer of the triiodide ion made up of iodide and nonhydrolyzed iodine.

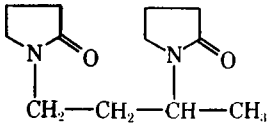
The normal iodine hydrolysis equilibrium constant is $K_{25} = 5.4 \times 10^{-13}$ (22). Such an extreme shift of the iodine hydrolysis equilibrium by polyvinylpyrrolidone seems unlikely. Rather, it was assumed that heating a mixture containing ~8.3 mole % of iodine/mole (based on monomer) of polyvinylpyrrolidone containing 1–5% (w/w) water [the ratio typical of povidone-iodine containing 10% (w/w) active iodine] reduced iodine to iodide with hydrogen iodide formation until, after reduction of one-third of the iodine amount used, a stable hydrogen triiodide–polyvinylpyrrolidone complex was present. The formation of 2 moles of acid/mole of nontitratable iodine could be explained by hydrogen iodide formation with hydrolysis of an intermediate iodized compound (Scheme III):

$$RH + I_2 + H_2O \rightarrow ROH + 2I^- + 2H^+$$

Scheme III

The iodine could have oxidized impurities or end groups (RH) in the polyvinylpyrrolidone in small amounts [~0.028 equivalent/mole (based on monomer) of polymer in commercial povidone-iodine].

To confirm this hypothesis, some well-defined crystalline adducts of the $lig_2 \cdot HI_3$ type were prepared as models of povidone-iodine materials. The ligands (lig) included *N,N*-dimethylacetamide, *N*-alkylpyrrolidones, and 1,3-bis(2′-pyrrolidinon-1′-yl)butane (1), a section of a polyvinylpyrrolidone chain with the structure:



[1] According to the USP definition for povidone.

0022-3549/79/1200-1505$01.00/0

The resultant complexes were identified structurally and compared by IR spectroscopy with the analogous hydrogen triiodide adduct of polyvinylpyrrolidone prepared from polyvinylpyrrolidone, hydrogen iodide, and iodine and with polyvinylpyrrolidone-iodine or povidone-iodine obtained by annealing polyvinylpyrrolidone or povidone with iodine. Both a low ($\overline{M}_n \sim 1000$) and a high ($\overline{M}_n \sim 10{,}000$) molecular weight product (povidone USP) were used to analyze bonding in compounds having one or two pyrrolidone rings, oligomers having about nine pyrrolidone rings (polyvinylpyrrolidone of $\overline{M}_n \sim 1000$), and polymers having ~90 pyrrolidone rings ($\overline{M}_n \sim 10{,}000$).

EXPERIMENTAL[2]

Preparation of (*N,N*-Dimethylacetamide)$_2$ · Hydrogen Triiodide (I)—To a solution of 33.84 g (133 mmoles) of iodine in 34.84 g (400 mmoles) of *N,N*-dimethylacetamide was added dropwise at room temperature 24.32 g (133 mmoles) of hydrogen iodide as a 70% aqueous solution. The mixture was well stirred and cooled throughout the addition. Then the solution was diluted with 200 ml of methylene chloride and was added to 6000 ml of *n*-hexane. A dark solid precipitated and was filtered. The residue was washed with *n*-hexane and dried *in vacuo* to give 69.7 g (94% yield) of I as a dark solid (mp 79°). Recrystallization from methanol gave 53.5 g (72% yield) of I as dark-brown crystals (mp 81°).

Anal.—Calc. for $C_8H_{19}I_3N_2O_3$: C, 17.3; H, 3.4; I^-, 22.9; I^0, 45.8; N, 5.04. Found: C, 17.4; H, 3.6; I^-, 22.6; I^0, 45.9; N, 5.1.

Other hydrogen triiodide adducts were prepared similarly.

(N-*Methylpyrrolidone*)$_2$ · *Hydrogen Triiodide* (*II*)—Compound II formed dark red-brown crystals, mp 72–74°, in a 72% yield. The IR spectrum is shown in Fig. 1. The structure was identified by X-ray structure analysis (25) (Figs. 2 and 3).

Anal.—Calc. for $C_{10}H_{19}I_3N_2O_3$:C, 20.7; H, 3.3; I_3^-, 65.6; I^0, 43.8; N, 4.8. Found: C, 20.9; H, 3.2; I_3^-, 65.7; I^0, 44.3; N, 4.8.

(N-*Isopropylpyrrolidone*)$_2$ · *Hydrogen Triiodide* (*III*)—Compound III formed dark-red-brown crystals, mp 108–110°, in a 23% yield.

Anal.—Calc. for $C_{14}H_{27}I_3N_2O_2$: C, 26.4; H, 4.3; I_3^-, 55.9; I^0, 39.9; N, 4.4. Found: C, 26.6; H, 4.1; I_3^-, 59.5; I^0, 39.8; N, 4.8.

(N-sec-*Butylpyrrolidone*)$_2$ · *Hydrogen Triiodide* (*IV*)—Compound IV formed a brown powder, mp 87–88°, in a 99% yield.

Anal.—Calc. for $C_{16}H_{31}I_3N_2O_2$: C, 28.9; H, 4.7; I_3^-, 57.3; I^0, 38.2; N, 4.2. Found: C, 29.2; H, 4.7; I_3^-, 56.8; I^0, 39.1; N, 4.2.

Preparation of [1,3-Bis(2′-pyrrolidinon-1′-yl)butane] · Hydrogen Triiodide (V)—To a cooled and well-stirred solution of 12.7 g (50 mmoles) of iodine and 11.2 g (50 mmoles) of 1,3-bis(2′-pyrrolidinon-1′-yl)butane in 45 ml of methylene chloride was added dropwise at room temperature 9.14 g (50 mmoles) of hydrogen iodide as a 70% aqueous solution. The solution was added to 1.5 liters of *n*-hexane, and 29.9 g of V precipitated as a red-violet powder (98.5% yield, mp 128°). Recrystallization afforded red-brown crystals (mp 136°). The IR spectrum is shown in Figs. 1 and 4.

Anal.—Calc. for $C_{12}H_{22}I_3N_2O_2$: C, 23.7; H, 3.5; I_3^-, 62.7; I^0, 41.8; N, 4.6. Found: C, 24.2; H, 3.6; I_3^-, 62.7; I^0, 42.2; N, 4.8.

Preparation of Polyvinylpyrrolidone Hydrogen Triiodide Adduct $[(C_6H_9NO)_2 \cdot HI_3]_{\sim 5}$ (VI)—The direct synthesis of VI was performed as follows. Polyvinylpyrrolidone[3] (calc. 100%), 11.1 g (0.1 mole based on monomer), was dissolved in 400 ml of analytical grade methanol, and 9.14 g of 70% aqueous hydrogen iodide solution (0.05 mole) was added. Iodine, 12.7 g (0.05 mole), dissolved in 250 ml of analytical grade methylene chloride, was dripped slowly into the solution; a homogeneous, slightly turbid solution was obtained. The solvents were distilled off *in vacuo* in a rotary evaporator (≤40°). The resultant solid was dried over phosphorus pentoxide to constant weight in a vacuum desiccator.

The product (VI), a black-brown powder, was sparingly soluble in water. Its IR spectrum is shown in Figs. 1 and 4.

Anal.—Calc. for $(C_{12}H_{19}I_3NO)_n$: C, 23.8; I_{total}, 63.0; I_3^-, 63.0; I^-, 42.0; N, 4.6. Found: C, 24.6; I_{total}, 59.5; I_3^-, 57.8; I^-, 40.7; N, 4.4.

Preparation of Polyvinylpyrrolidone Hydrogen Triiodide Adduct

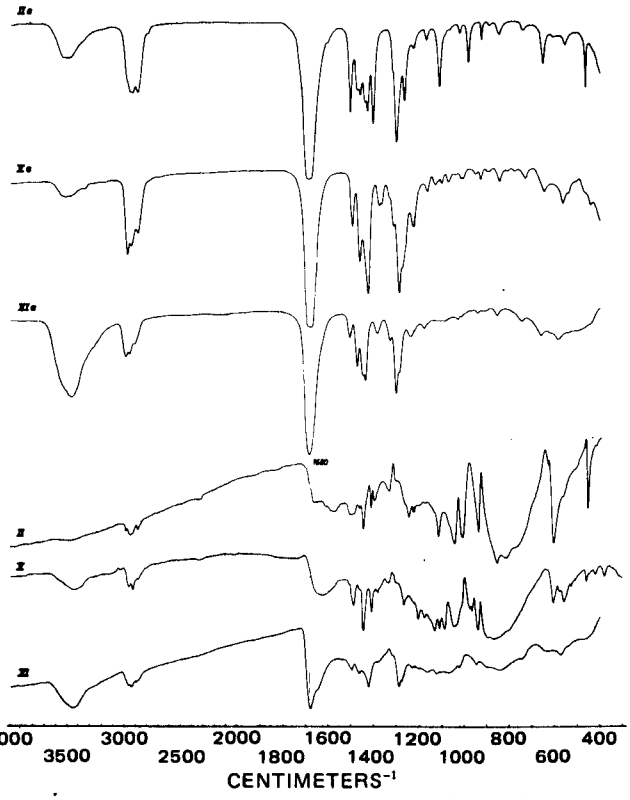


Figure 1—*IR spectra of* N-*methylpyrrolidone* (*II*a), *1,3-bis(2′-pyrrolidinon-1′-yl)butane* (*V*a), *polyvinylpyrrolidone with* $\overline{M}_n \sim 1000$ (*VI*a), (N-*methylpyrrolidone*)$_2$ · *hydrogen triiodide* (*II*), *[1,3-bis(2′-pyrrolidinon-1′-yl)butane] · hydrogen triiodide* (*V*), *and* $[(C_6H_9NO)_2 \cdot HI_3]_{\sim 5}$ (*VI*) *based on polyvinylpyrrolidone with* $\overline{M}_n \sim 1000$.

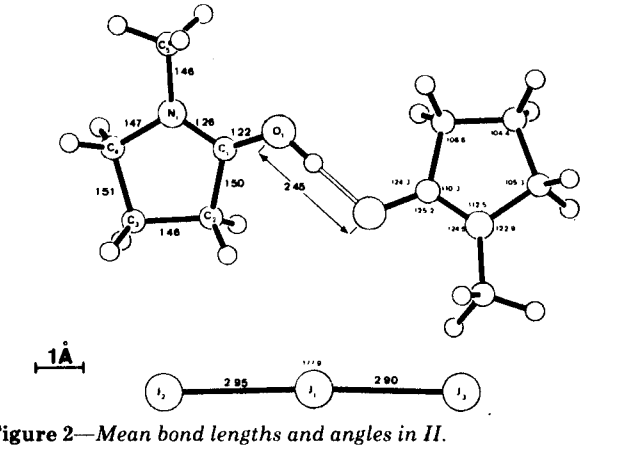


Figure 2—*Mean bond lengths and angles in II.*

[2] Melting points are uncorrected. IR spectra of the solid crystalline samples were recorded on potassium bromide pellets (1–2 mg of substance/300 mg of potassium bromide), while liquid samples were measured as thin films between potassium bromide disks or in thin cells. Spectra were taken with a Perkin-Elmer spectrometer, model 521 or 325, or a Digilab FTIR B/D-15. The absorptions discussed in the text and figures are in reciprocal centimeters. Microanalyses were run by the analytical laboratory of BASF Aktiengesellschaft.

Iodine (bisublimed), hydrogen iodide, and potassium iodide were obtained from E. Merck, Darmstadt, West Germany, and were reagent grade. *N,N*-Dimethylacetamide and the *N*-alkylpyrrolidones were obtained from BASF Aktiengesellschaft, Ludwigshafen, West Germany, and distilled before use (purity > 99.0% by GLC). Reagent grade methylene chloride, methanol, and *n*-hexane were used as solvents as supplied by E. Merck.

1,3-Bis(2′-pyrrolidinon-1′-yl)butane was obtained by a literature method (23) from *N*-vinylpyrrolidone by dimerization and hydrogenation. The product was pure both analytically and by GLC (>99.0%) on distillation in a spinning band column.

The low molecular weight polyvinylpyrrolidone was obtained by free radical polymerization [$\overline{M}_n \sim 1000$, $\overline{M}_w \sim 2500$, ~2% (w/w) water] and was used as supplied by BASF Aktiengesellschaft without further purification.

The high molecular weight polyvinylpyrrolidone was obtained by free-radical polymerization [$\overline{M}_n \sim 10{,}000$, $\overline{M}_w \sim 40{,}000$, ~2.1% (w/w) water] and was used as supplied by BASF Aktiengesellschaft without further purification. It met the USP requirements for povidone.

The povidone-iodine distribution coefficient was determined by a literature method (4). The decrease in available iodine on heat storage (15 hr, 80°) of a 10% aqueous povidone-iodine solution was determined according to USP XIX by a method similar to that described in the literature (24).

[3] $\overline{M}_n \sim 1000$, $\overline{M}_w \sim 2500$, ~2% water.

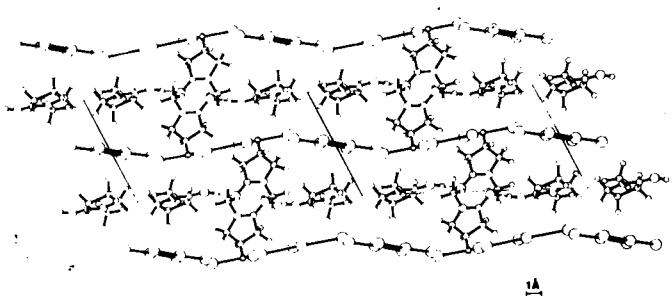


Figure 3—*Structure of II determined by X-ray structure analysis: a/b projection.*

$[(C_6H_9NO)_{19.4} \cdot HI_3]_n$ (Low Molecular Weight) (VII) According to Composition of Povidone-Iodine USP XIX—*Method A: Direct Synthesis*—Polyvinylpyrrolidone[3] (calc. 100%), 111.1 g (1 mole based on monomer), was dissolved in 105 ml of distilled water. Then 9.4 g (0.052 mole) of 70% aqueous hydrogen iodide and 13.07 g (0.052 mole) of powdered iodine were added and dissolved. The solution was freeze dried, ground, and dried over phosphorus pentoxide *in vacuo* in a desiccator. The product (VII*a*), a red-brown powder, was readily soluble in water.

The distribution coefficient was 163, and the iodine loss was 22.0%. The differential IR spectrum between VII*a* and the starting polyvinylpyrrolidone is shown in Fig. 5.

Anal.—Calc. for $[(C_6H_9NO)_{19.4} \cdot HI_3]_n$: C, 55.1; H^+, 0.38; I_{total}, 15.0; I_3^-, 15.0; I^-, 10.0; N, 10.7. Found: C, 52.5; H^+, 0.38; I_{total}, 15.0; I_3^-, 14.5; I^-, 9.7; N, 9.5.

Method B: Thermic Reaction—Polyvinylpyrrolidone[4], 121 g (1 mole based on monomer), was mixed intimately with 19.6 g (0.0772 mole) of iodine, and the mixture was heated at 90° until no further decrease in thiosulfate-titratable iodine occurred. The product (VII*b*), a red-brown powder, was readily soluble in water.

The distribution coefficient was 189, and the iodine loss was 18.2%. The differential IR spectrum between VII*b* and the starting polyvinylpyrrolidone is shown in Fig. 5.

Anal.—Calc. for $[(C_6H_9NO)_{19.4} \cdot HI_3]_n$: Found: C, 52.0; H^+, 0.40; I_{total}, 14.9; I_3^-, 14.0; I^-, 9.8; N, 9.6.

Preparation of Polyvinylpyrrolidone Hydrogen Triiodide Adduct $[(C_6H_9NO)_2 \cdot HI_3]_{\sim 45}$ (VIII)—The direct synthesis of VIII was accomplished as follows. Polyvinylpyrrolidone[5] (calc. 100%), 11.1 g (0.1 mole based on monomer), was dissolved in 800 ml of analytical grade methanol. Then 11.37 g of 55.9% (0.05 mole) aqueous hydrogen iodide solution was added with efficient stirring, and 12.7 g (0.05 mole) of iodine in 500 ml of analytical grade methanol was dripped slowly into the solution. The product was prepared as described for VI.

Compound VIII formed as a black-brown powder (30.2 g, 99.5% yield). Its IR spectrum is shown in Fig. 4.

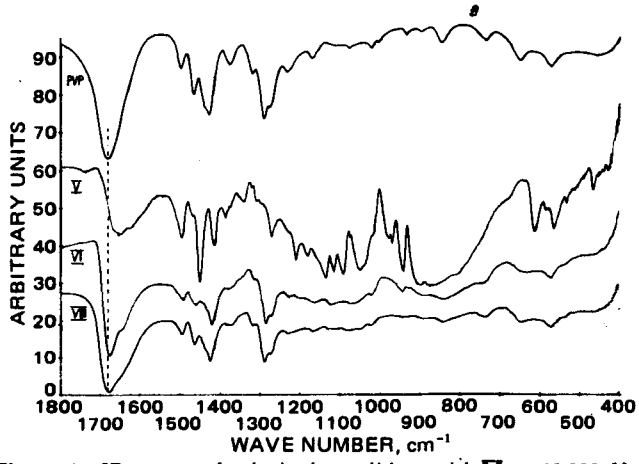


Figure 4—*IR spectra of polyvinylpyrrolidone with $\overline{M}_n \sim 10{,}000$, V, VI based on polyvinylpyrrolidone with $\overline{M}_n \sim 1000$, and $[(C_6H_9NO)_2 \cdot HI_3]_{\sim 45}$ (VIII) based on polyvinylpyrrolidone with $\overline{M}_n \sim 10{,}000$.*

[4] $\overline{M}_n \sim 1000$, $\overline{M}_w \sim 2500$, ~8% water.

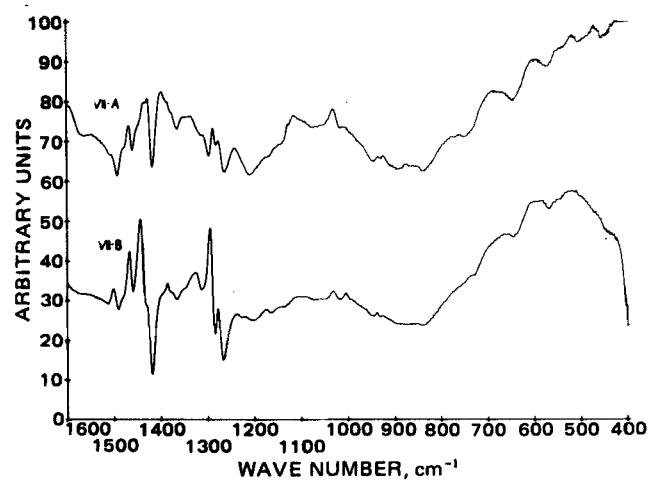


Figure 5—*Differential IR spectra between $[(C_6H_9NO)_{19.7} \cdot HI_3]_n$ based on polyvinylpyrrolidone with $\overline{M}_n \sim 1000$ (VII*a*, direct synthesis; VII*b*, heating with iodine) and the starting polyvinylpyrrolidone.*

Anal.—Calc. for $(C_{12}H_{19}I_3NO)_n$: C, 23.8; I_{total}, 63.0; I_3^-, 63.0; I^0, 42.0; N, 4.6; acid value (strongly acidic), 94.8. Found: C, 23.4; I_{total}, 62.2; I_3^-, 62.0; I^0, 45.2; N, 4.6; acid value (strongly acidic), 88.0.

Preparation of Povidone Hydrogen Triiodide Adduct $[(C_6H_9NO)_{19.4} \cdot HI_3]_n$ (High Molecular Weight) (IX) (Povidone-Iodine USP XIX)—*Method A: Direct Synthesis*—Polyvinylpyrrolidone[5] (calc. 100%), 11.1 g (0.1 mole based on monomer), was dissolved in 50 g of distilled water. Then 1.17 g of 55.9% (0.052 mole) aqueous hydrogen iodide and 1.31 g (0.052 mole) of iodine were added and dissolved by stirring for 10 hr at 50°. The solution was freeze dried, ground, and dried in a desiccator over phosphorus pentoxide. Compound IX*a* formed as a brown, water-soluble powder.

The distribution coefficient was 243, and the iodine loss was 2.4%. The differential IR spectrum between IX*a* and the starting polymer is shown in Fig. 6.

Anal.—Calc. for $[(C_6H_9NO)_{19.4} \cdot HI_3]_n$: C, 55.1; I_{total}, 15.0; I_3^-, 15.0; I^0, 10.0; I^-, 5.0; N, 10.7. Found: C, 55.0; I_{total}, 14.8; I_3^-, 13.5; I^-, 4.5; N, 11.1.

Method B: Thermic Reaction—Polyvinylpyrrolidone[5], 113.5 g (1 mole based on monomer), was mixed intimately with 21.14 g (0.0833 mole) of iodine. Then the mixture was heated at 80–100° until no further decrease in thiosulfate-titratable iodine occurred. Compound IX*b* formed as a red-brown powder and was readily soluble in water.

The distribution coefficient was 229, and the iodine loss was ~4.5%.

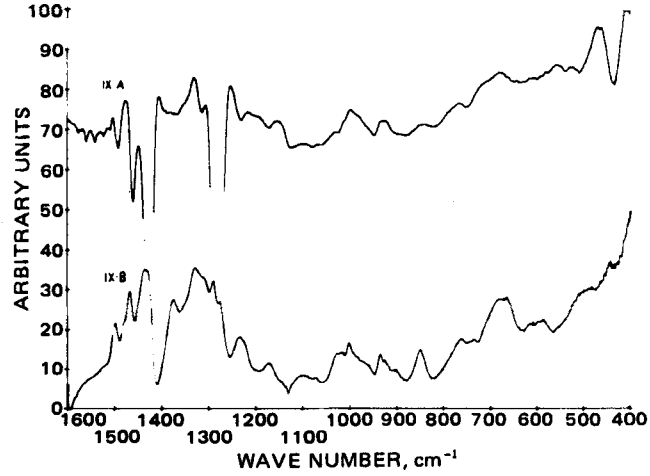


Figure 6—*Differential IR spectra between $[(C_6H_9NO)_{19.4\ (18)} \cdot HI_3]_n$ based on polyvinylpyrrolidone with $\overline{M}_n \sim 10{,}000$ (IX*a*, direct synthesis; IX*b*, heating with iodine) and the starting polyvinylpyrrolidone*

[5] $\overline{M}_n \sim 10{,}000$, $\overline{M}_w \sim 40{,}000$, ~2.1% water = povidone USP.

The differential IR spectrum between IX*b* and the starting polyvinylpyrrolidone is shown in Fig. 6.

Anal.—Calc. for $[(C_6H_9NO)_{18.0} \cdot HI_3]_n$: C, 54.4; I_{total}, 16.0; I_3^-, 16.0; I^0, 10.7; I^-, 5.3; N, 10.6; acid value (strongly acidic), 23.5. Found: C, 51.4; I_3^-, 15.9; I^-, 5.5; N, 10.2; acid value (strongly acidic), 30.

RESULTS AND DISCUSSION

Well-defined crystalline ligand$_2$ · hydrogen triiodide or ligand · hydrogen triiodide adducts were obtained by reaction of low molecular weight model substances for povidone-iodine [*N,N*-dimethylacetamide, *N*-alkylpyrrolidones, and 1,2-bis(2′-pyrrolidinon-1′-yl)butane, a section of a polyvinylpyrrolidone chain] with iodine and hydrogen iodide. The compounds had characteristic IR spectra different from those of the free ligands (Fig. 1). The elemental analyses were consistent with the indicated structures.

The hydrogen triiodide adducts prepared usually were soluble in strongly polar organic solvents such as methanol. They were only sparingly water soluble and hydrolyzed with the release of iodine (iodine flakes, heavy iodine odor). The aqueous solutions showed a strong mineral acid reaction due to the hydrogen iodide. The adducts may be regarded as ligand-stabilized forms of hydrogen triiodide acid, which does not exist in the free form.

As iodophores, the compounds had a high thiosulfate-titratable iodine content (45.6% in I). The adducts were stable for months at room temperature without iodine loss. Dark-red single crystals of II of ≤2 cm in edge length were grown.

On reaction with hydrogen iodide and iodine, 1,3-bis(2′-pyrrolidinon-1′-yl)butane yielded an adduct of the stoichiometry [1,3-bis(2′-pyrrolidinon-1′-yl)butane]·hydrogen triiodide and not a [1,3-bis(2′-pyrrolidinon-1′-yl)butane]$_2$ · hydrogen triiodide adduct. The same adduct was obtained when using excess ligand. The ligand$_2$ · hydrogen triiodide adduct was not obtained with this ligand in any experiment.

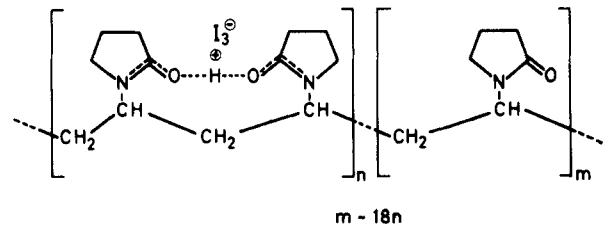
An attempt to prepare a $[(C_6H_9NO)_2 \cdot HI_3]_n$ adduct based on polyvinylpyrrolidone of different molecular weights ($\overline{M}_n \sim 1000$ or 10,000) by reacting 2 moles (based on monomer) of polymer with 1 mole of iodine and 1 mole of hydrogen iodide resulted in the loss of minor portions of the iodine and iodide and yielded products in which the pyrrolidone rings could not all have taken part in the complexation. Based on steric and statistical considerations, participation of all pyrrolidone rings had not been expected.

Polyvinylpyrrolidone-iodine or commercial povidone-iodine, which USP XIX requires to contain ≤6.6% iodide ions and 9.0–12.0% (w/w) thiosulfate-titratable iodine (I^0), can be prepared by reacting 1 mole (based on monomer) of polyvinylpyrrolidone[6] or povidone[7] with 0.052 mole of hydrogen iodide and 0.052 mole of iodine (VII or IX, Method A) or by heating 1 mole (monomer based) of polyvinylpyrrolidone[6] or povidone[7] with 0.083 mole of iodine (VII or IX, Method B). The two methods gave products with identical color, solubility, distribution coefficient, iodine loss, elemental analysis, and IR spectrum (Figs. 5 and 6).

The iodine loss of the aqueous solutions of the polyvinylpyrrolidone-iodines was ~18–20% (polymer of $\overline{M}_n \sim 1000$) or ~2–4% (polymer of $\overline{M}_n \sim 10{,}000$) and was independent of the preparation method. Apparently, every proton introduced (Method A) or formed during heating (Method B) readily found the pyrrolidone carbonyl groups needed for complexation due to the large molar excess of polyvinylpyrrolidone monomer units.

Unequivocal proof of the structure of the hydrogen triiodide adducts of the model substances was provided by the complete X-ray structure analysis of II (25). The compound crystallized in the triclinic space group $P\bar{1}$ with two triiodide units and four *N*-methylpyrrolidone molecules per asymmetric unit. The result is shown in Figs. 2 and 3. A proton was fixed *via* a short hydrogen bond between two carbonyl oxygen atoms of two pyrrolidone rings. The large triiodide anion was coordinated ionically to this large complex cation. Similar bonds were found (26) for adducts of *N,N*-dimethylacetamide and hexafluoroarsenic acid or hexafluorophosphoric acid. A short hydrogen bond (2.40–2.45 Å) links the two carbonyl oxygen atoms of two *N,N*-dimethylacetamide molecules (26).

The other hydrogen triiodide adducts of the model substances (I–V) and the corresponding complexes prepared using polyvinylpyrrolidone ($\overline{M}_n \sim 1000$, $\overline{M}_n \sim 10{,}000$) are believed to be analogous in structure, with



m - 18n

Figure 7—*Proposed structure of povidone-iodine.*

their IR spectra undergoing similar changes on transition from the free ligand to the hydrogen triiodide adduct. Reference is made to the IR spectra (Figs. 1 and 4) of the free model substances polyvinylpyrrolidone and the hydrogen triiodide adducts. The structural analogy is particularly evident in the complex based on polyvinylpyrrolidone of $\overline{M}_n \sim 1000$. It is less evident, although still detectable by differential spectroscopy, in the complex based on polyvinylpyrrolidone of $\overline{M}_n \sim 10{,}000$[7] due to the broad bands (Figs. 5 and 6).

Even without detailed knowledge of the origin of the absorptions, it is apparent that the IR spectra of the model substances agree with the polyvinylpyrrolidone spectrum. The differences between individual spectra are due almost exclusively to different alkyl groups (and methyl groups in particular). Therefore, the frequency and intensity of the vibrations of the CN–, NC=O, and carbonyl groups and the ring are largely independent of the *N*-alkyl side chain. The bonds in the complexes of the model substances and in the corresponding polyvinylpyrrolidone adducts must be at least very similar. This view may be confirmed by comparing IR spectra of model substances with those of the polyvinylpyrrolidone hydrogen triiodide adducts.

While there have been numerous IR spectroscopic investigations into polyamides and the corresponding low molecular weight compounds, few publications have dealt with the IR spectra of alkylpyrrolidones. Therefore, bands were assigned on the basis of the known spectra of *N,N*-dimethylacetamide (27), *N,N*-dimethylacetamide-d_9 (28), tetramethylurea (29), dialkylurea (30), monoalkylurea (31), δ-valerolactam (32), and cyclopentanol (33). Further comparisons made it possible to assign the bands of the hydrogen triiodide adducts.

Notable features in the IR spectra of the hydrogen triiodide adducts were a very broad and intense absorption at about 815 cm^{-1} and the high intensity of the band at about 560 cm^{-1}. Compared with the spectra of the starting compounds, which absorbed intensely due to the carbonyl groups at about 1685 cm^{-1}, the stretching vibration of the carbonyl groups of the adducts was hardly detectable. It appeared as a weak, very broad band at 1650–1600 cm^{-1}. Such a change in the IR spectra was attributed to the bonding changes in the region of the carbonyl and O=CN groups. The shift in position with a simultaneous intensity decrease can be explained easily by assuming a C=OH bond, including the hydrogen atom of hydrogen triiodide, as detected for II by X-ray structure analysis (25). The hydrogen bonds shift the position of the carbonyl band toward smaller wave numbers because the double bond of the group is weakened. Strong C–O···H···O–C bonds were found in other classes of compounds and were investigated spectroscopically. For example, the IR and Raman spectra of compounds of the metal-$H(CH_3COO)_2$ type were investigated and given the following assignments of the bands for $(CH_3COO\cdots H\cdots OOCCH_3)Na$ (34):

	vibration				
	$\overline{\nu_{as}O—H—O}$	$\overline{OH}$	$\overline{OH}$	$\overline{\nu_{sym}O—H—O}$	$\overline{C{=}O}$
frequency	720	1540	1285	IR inactive	1710
intensity	vs, b	m	s	—	s

The very broad and intense absorption at 850 cm^{-1} in the potassium hydrogen oxalate spectrum, obtained by IR measurements on single crystals using polarized light, was described as another hydroxyl stretching vibration (35). The IR spectra of the hydrogen triiodide adducts of polyvinylpyrrolidone (VI, VII*a*, VII*b*, VIII, IX*a*, and IX*b*) (Figs. 4–6) showed that the carbonyl groups did not all participate in the adduct formation (this was expected in view of the elemental analysis of VI and VIII and because of the large excess of pyrrolidone rings in the VII and IX mixture). The absorptions at ~800 and 1020 cm^{-1}, characteristic of the adduct structure, occurred.

In adducts VI and VIII, these characteristic absorptions were clearly visible. In VII*a*, IX*a*, VII*b*, and IX*b*, which have the composition of

[6] $\overline{M}_n \sim 1000$, $\overline{M}_w \sim 2500$.
[7] $\overline{M}_n \sim 10{,}000$, $\overline{M}_w \sim 40{,}000$ = povidone USP.

commercial povidone-iodine with an approximately 10-fold molar excess of pyrrolidone rings, these characteristic absorptions showed up in the differential spectra between the starting polyvinylpyrrolidone and the adducts.

Contrary to conventional assumptions on the structure of polyvinylpyrrolidone-iodine prepared by heating polyvinylpyrrolidone[8] with iodine, the compound probably is an adduct of the polymer and hydrogen triiodide in which a proton is fixed between two carbonyl groups of two pyrrolidone rings (*cf.*, Fig. 7) and the triiodide anion is bound ionically to this complex cation. Incidentally, the pyrrolidone rings participating in the complexation need not be vicinal in the polymer chain as shown in Fig. 7. Due to an appreciable excess of free pyrrolidone rings in povidone-iodine USP XIX, the product was readily soluble in water.

SUMMARY

N,N-Dimethylacetamide and *N*-alkylpyrrolidones are capable of forming stable ligand$_2$ · hydrogen triiodide adducts. This finding coincides neatly with the complex chemistry of these organic compounds discussed in the literature. The bonding is similar in all adducts of this type, where a proton is fixed between two carbonyl groups of two ligands *via* a short hydrogen bond. This bonding manifests itself in similar IR spectra of the complexes, which all show a strong shift of the carbonyl band toward lower wave numbers. For II, this structure could be unequivocally verified (25).

By analogy with the model compounds, polyvinylpyrrolidone[8] can be reacted with hydrogen iodide and iodine to form adducts whose spectroscopic properties are analogous to those of the low molecular weight complexes, which suggests identical bonding. However, for steric reasons, it seems impossible for all pyrrolidone rings to take part in adduct formation. If there is more halogen, halogen losses occur on drying. If there are ≤20 pyrrolidone rings for every hydrogen triiodide, as in commercial povidone-iodine, complexation is good and the excess pyrrolidone rings not taking part in the complexation provide the desired water solubility.

The structure of povidone-iodine USP XIX prepared by heating polyvinylpyrrolidone[7] with iodine agrees with that of a product obtained by the direct synthesis of polyvinylpyrrolidone[7], hydrogen iodide, and iodine. Previous assumptions regarding the structure of polyvinylpyrrolidone-iodine (18–20) are not consistent with the results discussed in this paper.

REFERENCES

(1) H. A. Shelanski, U.S. pat. 2,739,922 (1956); through *Chem. Abstr.*, **50**, 11623g (1956).

(2) H. Beller and W. A. Hosmer (General Aniline & Film Corp.), U.S. pat. 2,706,701 (1955); through *Chem. Abstr.*, **49**, 12788a (1955).

(3) S. Siggia (General Aniline & Film Corp.), U.S. pat. 2,900,305 (1956).

(4) A. Cantor and M. W. Winicov (West Laboratories Inc.), U.S. pat. 3,028,300 (1960).

(5) A. Cantor and M. W. Winicov (West Laboratories Inc.), German pat. 2,422,767 (1974); through *Chem. Abstr.*, **82**, 103138y (1975).

(6) W. Scholtan, *Makromol. Chem.*, **11**, 131 (1954).

(7) I. Moriguchi, Y. Araki, and N. Kaneniwa, *Chem. Pharm. Bull.*, **17**, 2088 (1969).

(8) V. O. Mokhnach and L. N. Propp, *Dokl. Akad. Nauk SSR*, **170**, 103 (1966); through *Chem. Abstr.*, **66**, 60485j (1967).

(9) V. O. Mokhnach and I. P. Zueva, *Zh. Neorgan. Khim.*, **8**, 668 (1963); through *Chem. Abstr.*, **58**, 13304h (1963).

(10) W. W. Korshak, L. B. Zubakova, L. Y. Nikiforova, and N. V. Kachurina, *Tr. Mosk. Khim.-Tekhnol. Inst.*, **1972**, No. 70, 201; through *Chem. Abstr.*, **79**, 23822q (1973).

(11) S. M. Barkin, H. P. Frank, and F. R. Eirich, *Ric. Sci.*, **25**, *Suppl. Simp. Int. Chim. Macromol., Milan-Turin*, **1954**, 844; through *Chem. Abstr.*, **54**, 11554a (1960).

(12) J. Neél and B. Sébille, *C. R. Hebd. Seances Acad. Sci. Ser. C*, **252**, 405 (1961).

(13) J. Neél and B. Sébille, *J. Chim. Phys.-Chim. Biol.*, **58**, 738 (1961).

(14) G. Oster and E. H. Immergut, *J. Am. Chem. Soc.*, **76**, 1393 (1954).

(15) N. Kaneniwa and A. Ikekawa, *Chem. Pharm. Bull.*, **22**, 2990 (1974).

(16) F. Eirich, *Chem. Eng. News*, **32**, 2768 (1954).

(17) J. Neél and B. Sébille, *C. R. Hebd. Seances Acad. Sci. Ser. C*, **252**, 867 (1961).

(18) J. Eliassaf, *Eur. Polym. J.*, **2**, 269 (1966).

(19) R. F. Cournoyer and S. Siggia, *J. Polym. Sci. Polym. Chem.*, **12**, 603 (1974).

(20) K. Takikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **26**, 874 (1978).

(21) *Ibid.*, **26**, 1370 (1978).

(22) T. L. Allen and R. M. Keefer, *J. Am. Chem. Soc.*, **77**, 2957 (1955).

(23) J. W. Breitenbach, F. Galinovsky, H. Nesvadba, and E. Wolf, *Monatsh. Chem.*, **87**, 580 (1956).

(24) Defense Medical Purchase Description No. 4, Jan. 4, 1972, p. 4, 6505-491-7557 and 6505-994-7224.

(25) H. U. Schenck, P. Simak, and E. Haedicke, *Makromol. Chem.*, in press.

(26) D. Cook, *Can. J. Chem.*, **42**, 2721 (1964).

(27) G. Durgaprasad, D. N. Sathyanarayana, C. C. Patel, H. S. Randhawa, A. Goel, and C. N. R. Rao, *Spectrochim. Acta, Part A*, **28**, 2311 (1972).

(28) K. L. Dorris, T. H. Sidall, W. E. Stewart, and M. L. Good, *ibid.*, **23**, 1657 (1967).

(29) H. Spell and J. Laane, *ibid.*, **28**, 295 (1972).

(30) Y. Mido, *ibid.*, **28**, 1503 (1972).

(31) C. I. Jose, *ibid.*, **25**, 111 (1969).

(32) M. Rey-Lafon and M. T. Forel, *ibid.*, **29**, 471 (1973).

(33) J. Durig, J. M. Karriker, and W. C. Harris, *ibid.*, **27**, 1955 (1971).

(34) D. Hadži, B. Orel, and A. Novak, *ibid.*, **29**, 1745 (1973).

(35) B. Orel, thesis, University of Ljubljana, Yugoslavia, 1972.

[8] $\overline{M}_n \sim 1000$, $\overline{M}_w \sim 2500$ or $\overline{M}_n \sim 10{,}000$, $\overline{M}_w \sim 40{,}000$.