# Halogen- and Hydrogen Bonding in Povidone-Iodine and Related Co-phases

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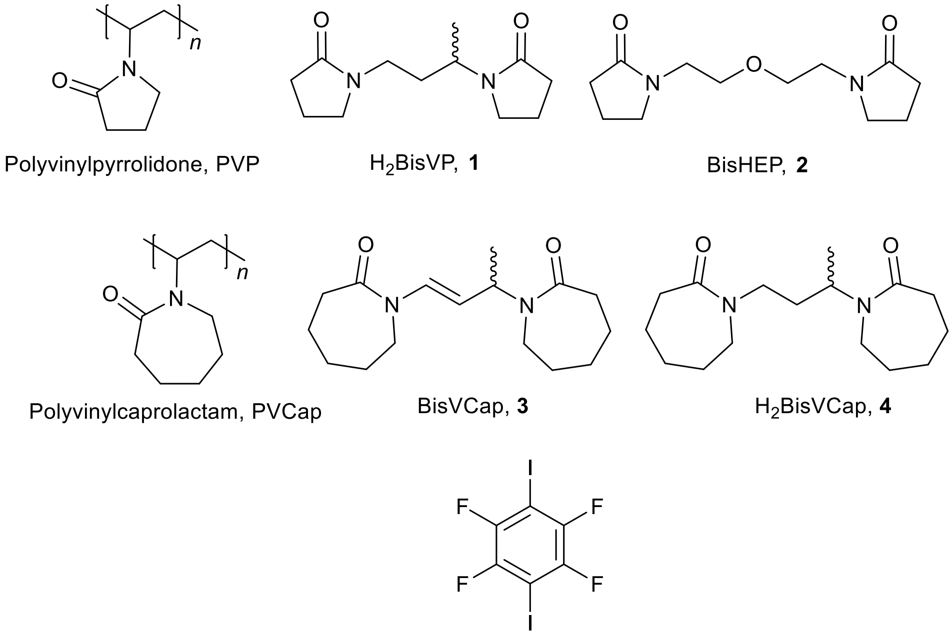
## Abstract

Povidone-iodine is a widely used antiseptic and on the WHO list of essential medicines. We report the X-ray crystal structure of a two-monomer unit model compound showing that the structure of povidone-iodine comprises protonated pyrrolidone units linked by intermolecular

hydrogen bonds along with triiodide anions. We also report an unusual example of a system exhibiting both a cocrystal and coamorphous form in a halogen bonded lactam model compound with diiodotetrafluorobenzene.

## Introduction



Polyvinylpyrrolidone, PVP

$H_2$BisVP, **1**

BisHEP, **2**

Polyvinylcaprolactam, PVCap

BisVCap, **3**

$H_2$BisVCap, **4**

*p*-Diiodotetrafluorobenzene, **5**

**Scheme 1.** Chemical structures of polyvinylpyrrolidone and analogs, and halogen bond donor p-diiodotetrafluorobenzene.

Polyvinylpyrrolidone (PVP) and its seven-membered ring analog polyvinylcaprolactam (PVCap, Scheme 1) are extremely versatile industrial materials used extensively in applications such as excipients, binders and crystallization inhibitors.[1-2] Povidone-iodine is a complex of PVP and iodine[3] that is a very commonly used antiseptic and disinfectant. It is less irritating, more slowly absorbed, more soluble and more easily applied than the more traditional tincture of iodine, and does not cause resistance in bacteria. The material was discovered in 1949[4] and is one of the World Health Organization's List of Essential Medicines.[5] The compound is prepared by milling iodine and PVP in the presence of water, followed by heating to around 90 ºC.[6] This process is thought to convert the iodine to triiodide anion. Work by Schenck *et al.* in 1979 on a series of crystalline hydrogen triiodide adducts of *N*-alkyl pyrrolidones and of a two-monomer model of PVP, 1,3-bis(2′-pyrrolidinon-1′-yl)butane ($H_2$bisVP, **1**) showed that the structure of povidone-iodine is likely to be based on an $HI_3$ complex of the polymer with the $H^+$ ions bridging between pairs of carbonyl groups, although this conclusion was based on the X-ray crystal structure of the $HI_3$ complex of monomeric *N*-methylpyrrolidone[3] (a structure that still does not appear in the Cambridge Structural Database[7]). Consistent with this picture, the hydrogen bonding of protonated pyrrolidones to a neutral pyrrolidone acceptor is typically a strong, linear interaction, as in the structure of the $HBr_3$ salt of *N*-methylpyrrolidone in which the oxygen atoms are 2.41 Å apart and the proton does not exhibit any hydrogen bonding interaction with the tribromide counter anion (CSD Refcode MIVJUW[8]). Hence the generally accepted picture of povidone iodine is one in which PVP stabilizes $HI_3$ (which does not exist in the free state) with the proton residing on the pyrrolidone carbonyl groups. Given the typical loading of 9 – 12 % free iodine by weight, there are also thought to be a significant number of free carbonyl groups.[3] Indeed povidone-iodine is so well known that it even has an extensive Wikipedia entry, Fig. 1.[9]

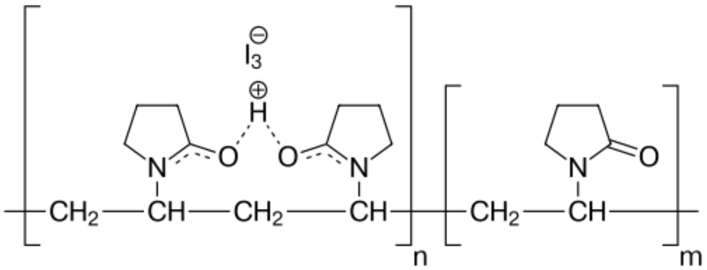


Figure 1. Generally accepted structure of povidone-iodine as represented on Wikipedia (as of 2017),[9] derived from the model proposed by Schenck in 1979.[3]

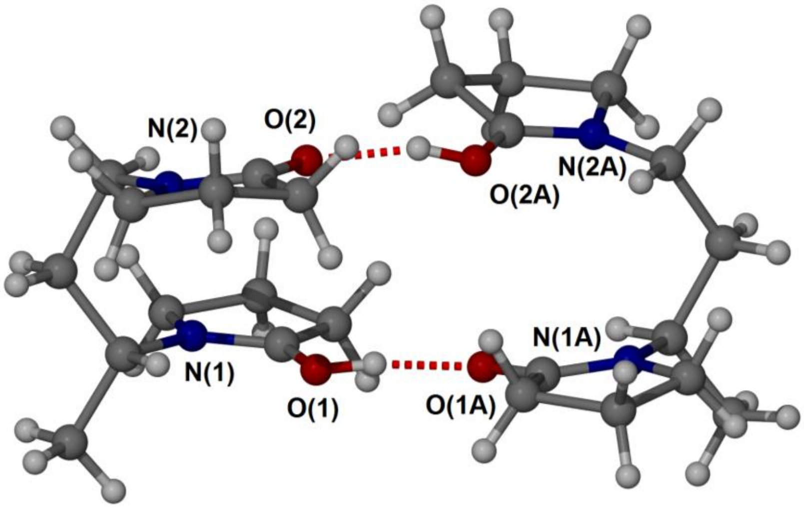
Given the relatively recent, intense interest in halogen bonding[10-14] we wondered about the rather strained-seeming geometry of the hydrogen bonded interaction in Figure 1 and whether, in the absence of hydrogen bonding, the uncomplexed lactam groups in PVP and related polymers were capable of halogen bonding interactions with residual iodine or even with $I_3^-$ (which can form weak interactions with a further iodide anion[15] to give $I_4^{2-}$), and particularly neutral activated iodo compounds such as the well-known *p*-diiodotetrafluorobenzene (**5**). Interaction of $I_3^-$ with carbonyl groups is not precedented in the CSD, however, with only one entry (a benzoyl ruthenium(II) complex, FASNUI[16]) displaying an I···O short contact, although the I···O distance of 3.48 Å is close to the sum of the van der waals radii. We now report a revised geometry for hydrogen bonding in povidone iodine and the preparation of halogen bonded co-phases of the related vinyl caprolactam dimer 1,3-bis(2′-caprolactam-1′-yl)but-1-ene, BisVCap (**3**).

## Results and Discussion

### *Analogs of Povidone-Iodine*

Reaction of bis(pyrrolidone) model compounds 1,3-bis(2′-pyrrolidinon-1′-yl)butane ($H_2$BisVP, **1**) and the bis(hydroxyethylpyrrolidone) derivative BisHEP (**2**) along with 1,3-bis(2′-caprolactam-1′-yl)butane ($H_2$BisVCap, **4**) with elemental iodine in dichloromethane resulted in an immediate color change from violet to orange suggesting an influence of the carbonyl donor on the energy of the iodine $\sigma_u^*$ antibonding LUMO.[17] Subsequent addition of hydroiodic acid and hexane antisolvent according to the procedure of Schenk[3] resulted in the formation of oils. Similarly, oils resulted from attempts to crystallize the products from the mother liquor using slow liquid or vapor antisolvent diffusion. Reaction of iodine with the unsaturated BisVCap (**3**) resulted in chemical degradation as a result of iodination of the double bond (as evidenced by $^1H$ NMR spectroscopy). In the case of **1** and **2** prolonged stirring and periodic ultrasonication of the oils resulted in the isolation of brown, crystalline solid products. Crystals suitable for single crystal X-ray diffraction were then grown by vapor diffusion of diethyl ether into dichloromethane solutions of the resulting isolated products which gave rise to well-formed orange single crystals of formula **1**$\cdot HI_3$ and **2**$\cdot HI_3$. Despite repeated attempts, however, no solid product was obtained for **4**.

Compound **1** is directly analogous to PVP in a structural sense and hence **1**$\cdot HI_3$ was characterized by single crystal X-ray crystallography. The crystals exist as an enantiotropic[18] pair of polymorphs and the phase transition at around 190 – 210 K upon cooling the high temperature $C2/c$ form to give the low temperature $P\bar{1}$ polymorph results in significant degradation of crystal quality. However, satisfactory structures of both forms were obtained at 250 K and 120 K, respectively by slow cooling of a small crystal through the phase change. Both polymorphic forms exhibit essentially the same structure features and comprise monoprotonated **1** arranged into hydrogen bonded dimers. Hydrogen bonded hydrogen atoms were located experimentally and demonstrate conclusively that the bis(pyrrolidone) molecules are arranged in pairs with very short intermolecular hydrogen bonding interactions of $O\cdots O$ distance 2.43 Å (av.) in the low temperature form, Fig. 2. The $I_3^-$ ion does not interact with the acidic proton or carbonyl oxygen atoms and its closest contacts are to a number of methylene hydrogen atoms, as shown in the Hirshfeld surface fingerprint plot,[19-20] Fig. 2b. Notably, the intramolecular $O\cdots O$ distance between the two lactam carbonyl groups is rather long at 3.05 Å (av.) implying that there is no intramolecular hydrogen bond, contrary to the literature depiction in Fig. 1. The high temperature polymorph exhibits a similar geometry, albeit with some disorder of one of the pyrrolidone rings and is *Z′* = 1 while the low temperature form is ordered, *Z′* = 2.[21] In the high temperature form the intermolecular O···O distance is the same as in the low temperature form within experimental error, while the intramolecular O···O distance is marginally longer at 3.09 Å. The polymorphic phase change appears to be related to the movement of the acidic proton which is equidistant between the two hydrogen bonded oxygen atoms at 250 K but localized at 120 K.



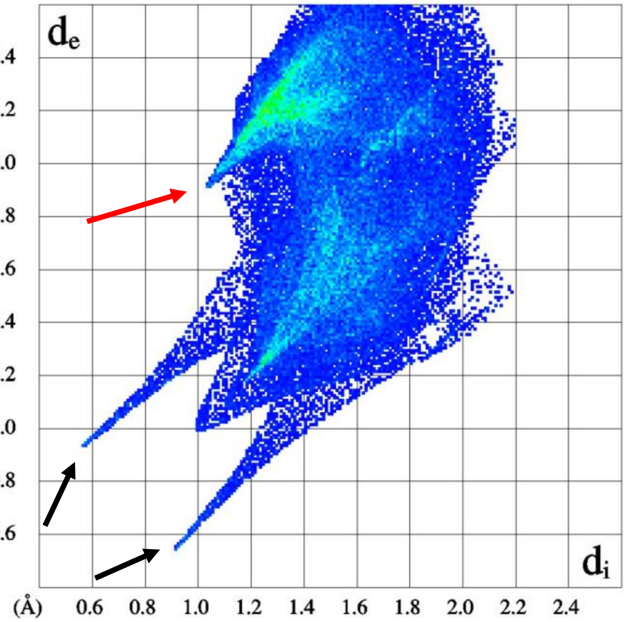


Figure 2. (a) Protonated $H_2$bisVP pairs in the low temperature form of **1**·$HI_3$. Hydrogen bonded O···O distances: 2.42(2) and 2.43(2) Å. (b) Hirshfeld surface fingerprint plot showing strong OH···O hydrogen bonding (black arrows) and CH···I interactions (red).

The exothermic phase transition from the high to low temperature forms of **1**·$HI_3$ was also studied by DSC which revealed considerable hysteresis. While the transformation to the low temperature form occurs around 190–210 K on cooling, the corresponding endothermic transformation back to the high temperature form has an onset of 261 K and the DSC trace suggests that different crystallites transform at different temperatures up to 333 K. The sample finally melts with an onset temperature of 398 K (125 °C) (supporting information, Fig. S8).

In order to examine the effect of a longer spacer between the pyrrolidone units, the ether **2**·$HI_3$ was also characterized by X-ray crystallography. This longer bis(pyrrolidone) forms 1D hydrogen bonded chains and, like **1**·$HI_3$, does not involve intramolecular hydrogen bonding (Fig. 3). The intermolecular O···O distance of 2.424(3) Å is comparable to the hydrogen bonded distance in **1**·$HI_3$ and the OH···O interaction is essentially linear with the acidic hydrogen atom predominantly localized on one oxygen atom. The triiodide anions do not exhibit any close contacts to the oxygen atoms and interact with the bis(pyrrolidone) via a number of CH···I interactions.

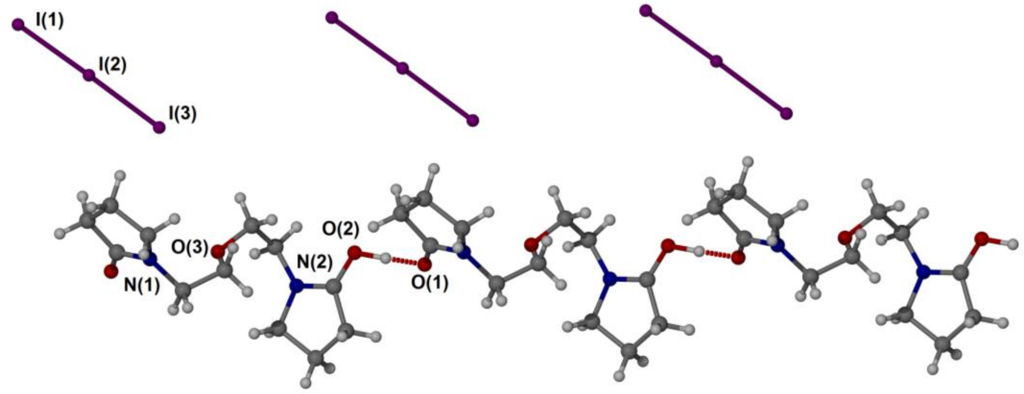


Figure 3. X-ray crystal structure of **2**·$HI_3$ showing the intermolecular hydrogen bonded chain. Hydrogen bonded O···O distance: 2.424(3) Å.

In order to assess the relevance of **1**·$HI_3$ to PVP-iodine, two samples of commercial PVP-iodine were obtained from Ashland and from Sigma. UV-Vis spectroscopy in ethanol solution of **1**·$HI_3$ and **2**·$HI_3$ confirmed the presence of the $I_3^-$ anion by its characteristic absorptions at 292 and 359 nm[22] and the absence of any features assignable to $I_2$. The UV-Vis spectrum of the commercial PVP-iodine (which is manufactured by solid state milling and subsequent heating of a PVP and iodine mixture in the presence of water[6]) proved identical, confirming the complete transformation of iodine into triiodide during preparation (Supporting information, Figure S1).[3] The commercial materials formed acid solutions when dissolved in water, confirming the presence of $H^+$ (the pH of aqueous PVP-iodine is typically around 2[23]).

The IR spectra of the two commercial samples of PVP-iodine were essentially identical to one another, however they proved quite different to the IR spectra of the hydrogen triiodide salts of **1** and **2**, Fig. 4. In particular the IR spectra of **1**·$HI_3$ and **2**·$HI_3$ showed an intense, broad feature around 760 $cm^{-1}$ attributed to the O···H···O functionality. The amide carbonyl band at 1676 $cm^{-1}$ in free **1** is almost entirely absent in the hydrogen triiodide salt **1**·$HI_3$, consistent with the weakening of the C=O bond, a phenomenon observed previously.[3] In commercial povidone-iodine, however this band is strong and present at 1653 $cm^{-1}$, slightly lower that its position in free PVP K12 (1668 $cm^{-1}$;[24] The Fikentscher K-value[6] is derived from the viscosity of a 1wt% solution of the polymer and K12 corresponds to a molecular weight of 4,000 – 6,000[25]). Interestingly, in a dry acetonitrile solution of PVP K12, this band occurs at significantly higher wavenumber, 1682 $cm^{-1}$.[24] The reduction in stretching frequency in the solid state is attributed to CH···O hydrogen bonding interactions. In PVP-iodine the presence of this band indicates the presence of a substantial number of free (non-protonated) carbonyl groups, consistent with the relatively low loading of iodine in the commercial product, which is typically produced from significantly less than 0.1 moles of iodine per pyrrolidone monomer unit.[6] Hence, while the structure of **1**·$HI_3$ is likely to be a fair reflection of the protonated part of commercial PVP-iodine, it does not speak to the role of the unprotonated carbonyl groups in the overall structure. Moreover the broadness, higher asymmetry and its lower wavenumber of the carbonyl band in PVP-iodine compared to the free polymer suggests additional interactions that slightly weaken the C=O bond. It seems unlikely that this weakening involves a contribution from C=O···$I_3^-$ halogen bonding interactions given the length of this contact in the FASNUI[16] structure and the change in carbonyl frequency is much more likely to arise from CH···O interactions and hydrogen bonding to adventitious moisture.

In order to produce a polymer more closely analogous to **1**·$HI_3$ we mechanochemically[26] mixed solid PVP K12 with iodine and aqueous hydroiodic acid in the same proportions as used in the preparation of **1**·$HI_3$ (*i.e.* one mole of HI/$I_2$ per two pyrrolidone groups – enough for every carbonyl group to form an O···H···O interaction). The result was a free-flowing, homogeneous brown product which was investigated by IR spectroscopy, Fig 5. The IR spectrum revealed a significantly shifted free carbonyl peak at 1637 $cm^{-1}$ and a very broad absorption in the 1100 – 600 $cm^{-1}$ region attributable to a range of O···H···O environments. The low wavenumber of the carbonyl band is consistent with hydrogen bonding to water[24] and reveals that not all of the PVP carbonyl groups are accessible to protonation. This observation is consistent with the intermolecular hydrogen bonded structure implied by the structure of **1**·$HI_3$ since PVP chains may not all co-align. We also prepared an analogous PVCap product by liquid-assisted grinding of a 50% butoxyethanol solution of PVCap with iodine and HI. The resulting deep brown paste was washed with water to remove the butoxyethanol to give a black, water-insoluble powder. The IR spectrum of this compound is given in the supplementary material, Fig. S2. Given its water insolubility, this PVCap-iodine product is unlikely to be commercially useful as an antiseptic.

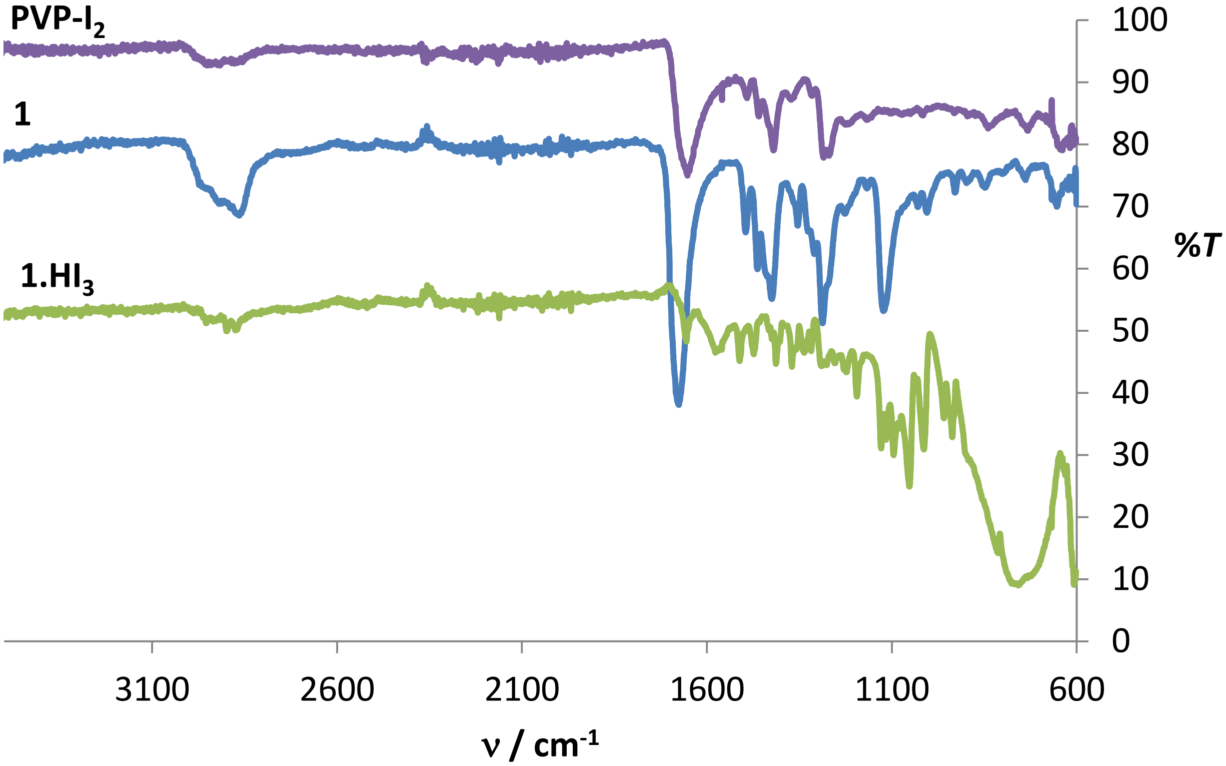


Figure 4. Solid state ATR IR spectra of commercial PVP-iodine, uncomplexed **1** (as an oil) and **1**·$HI_3$.

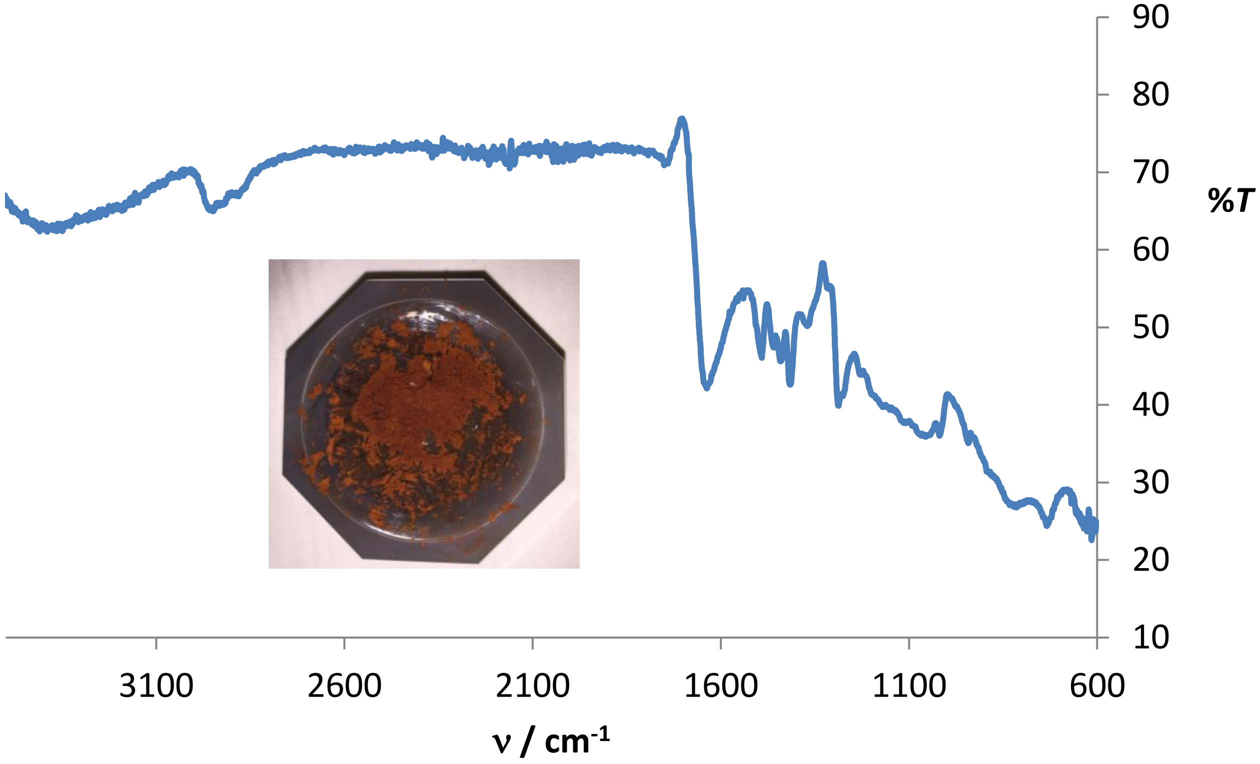


Figure 5. Mechanochemically prepared PVP·$HI_3$ and its solid state ATR IR spectrum.

*Halogen bonded co-phases*

While compound **1** is a good model for PVP-iodine, we sought to obtain an even closer model that might include free carbonyl groups as well as those that are strongly hydrogen bonded to $H^+$ in order to further explore the possibility of halogen bonding within the system. Unfortunately, no solid products were isolated from sub-stoichiometric mixtures of HI/$I_2$ and **1** with the excess lactam seeming to promote oil formation. As a result we attempted to crystallize model compounds **1** – **4** with a much stronger halogen bond donor, namely *p*-diiodotetrafluorobenzene (**5**).[10] A co-crystalline solid was isolated in only in the case of **3**. Slow evaporation of a solution containing a 1:1 molar ratio of bisVCap (**3**) and **5** in either acetone or mixed acetone / dichloromethane results in the formation of a 1:1 cocrystal of formula $C_{16}H_{26}N_2O_2 \cdot C_6F_4I_2$. Phase purity was confirmed by XRPD (see supplementary information, Fig. S3). The X-ray crystal structure of cocrystal **3·5** is shown in Fig. 6. The system exhibits halogen bonds between the oxygen atoms of the carbonyl groups and the iodo substituents of **5** with I···O distances of 2.897(6) Å and 2.916(6) Å. A search of the Cambridge Structural Database (CSD) for cocrystals of **5** with a molecule containing a carbonyl group yields 23 results, 12 of which contain no halogen bonding to the carbonyl group. Of the 11 remaining structures only 3 contain halogen bonds with a length shorter than 2.95 Å,[27-29] and hence the halogen bonding in **3·5** is a relatively short interaction.

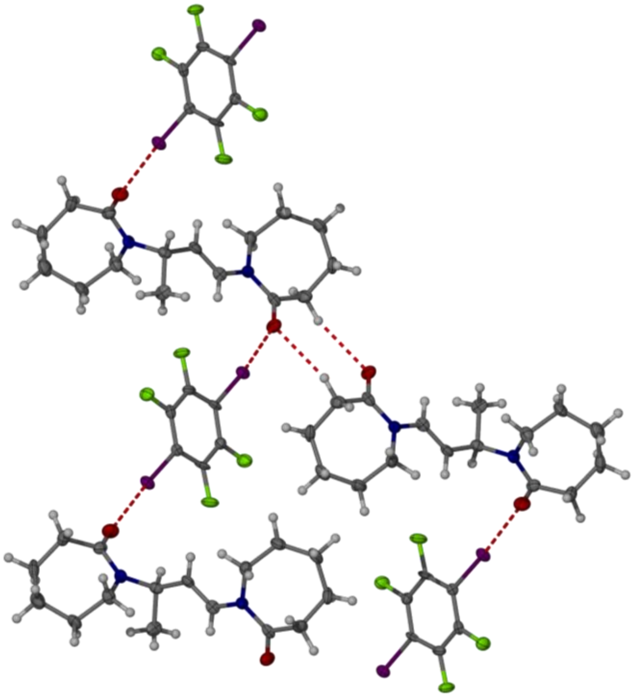


Figure 6. X-ray crystal structure of cocrystal **3·5** showing I···O halogen bonding interactions 2.897(6) Å and 2.916(6) Å, and CH···O hydrogen bonding, 3.493(9) Å.

The cocrystal **3·5** was characterized by differential scanning calorimetry (DSC) and polarized hot stage microscopy (see supplementary information for full discussion of the thermal behavior of the individual components **3** and **5**). Upon first heating cycle the cocrystal melts at 109 °C close to the melting point of pure **5** (108 ºC), and heating the melt above 150 °C leads to decomposition. Interestingly there is no recrystallization of the cocrystal on cooling from just above the melting point and a second heat cycle reveals a glass transition at 9 °C followed by a much smaller melting endotherm at 109 °C. Hot stage microscopy is consistent with the observed melting at 109 ºC. Upon cooling the melt no recrystallization occurs but the sample exhibits sudden cracking at –62 °C suggesting the formation of a super-cooled glass. During the second heating cycle the cracks disappear at 10 – 15 °C, consistent with the glass transition observed by DSC. With further heating to 77 °C the sample begins to crystallize and small crystals continue to grow as the sample is heated. By 106 °C the crystals are still growing but are also starting to melt again. The crystallization process occurs over a broad temperature range and not all of the material recrystallizes, consistent with the much smaller melting endotherm observed by DSC on the second heating cycle, Fig. 7.

It is not uncommon for a compound to exhibit a metastable amorphous form and a crystalline form, but it is much more uncommon for a cocrystal to exhibit a stable coamorphous form, as usually the mixture will stabilize one form or the other and thus not allow both. Quasi-isothermal DSC measurements can be used to calculate the heat capacity of a material and thus compare the relative stability of crystalline and amorphous forms.[30-31] These measurements showed that the crystalline bisVCap component has a higher heat capacity than cocrystal (Fig. S7). It is possible that this difference in heat capacity between **3** and cocrystal **3·5** is a major part of the driving force for the cocrystal formation, and hence cocrystal **3·5** is more thermodynamically stable than **3** alone. When considering the crystallization thermodynamics of the full system however, such comparison is not possible due to the fast rate of crystallization of **5** and subsequent inability to measure the heat capacity of its amorphous form to compare with **3** and **3**·**5** (Figure S7). The coamorphous mixture of **3** and **5** has a higher heat capacity than the cocrystalline form. After the glass transition the mixed sample has a similar heat capacity to the melt. Before the glass transition the heat capacity of the coamorphous material is very low, approaching that of the crystal, showing the coamorphous form to be particularly stable so there is little driving force for recrystallization below the glass transition.

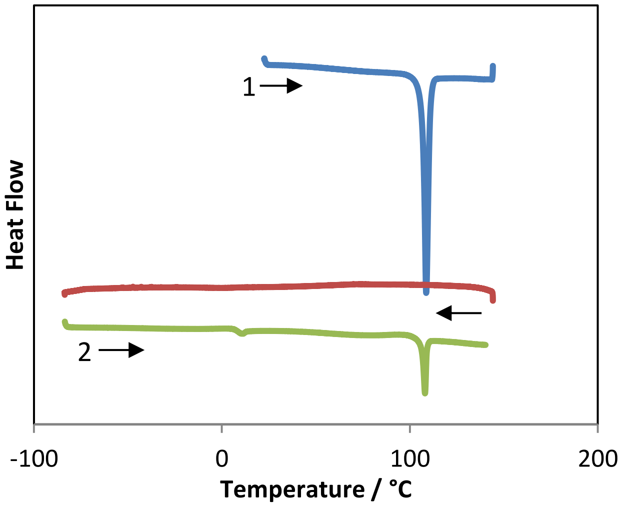


Figure 7. DSC heat (arrow 1) / cool/heat (arrow 2) experiment of cocrystal **3**·**5** at 10 °C/min. Endotherm down. The cocrystal melts at 109 ºC, supercools to give a glass and the resulting coamorphous phase undergoes a glass transition at 9 ºC on reheating. The coamorphous phase very slowly recrystallizes to give the cocrystal about 77 ºC.

## Conclusions

The structure of **1**·$HI_3$ demonstrates that the intramolecular hydrogen bonded geometry proposed for povidone-iodine in 1979 is incorrect and indeed Schenck and coworkers recognized that the pyrrolidone groups “need not be vicinal”.[3] Hence the structure of PVP-iodine is better represented as shown in Fig. 8, in which different polymer chains are hydrogen bonded together in pairs, or in a hydrogen bonded cross-linked network. The model compound **1**·$HI_3^-$ does not fully account for the IR spectrum of commercial PVP-iodine nor for the stoichiometric PVP·$HI_3$ sample prepared mechanochemically, both of which show evidence for free (non-protonated) carbonyl groups. While cocrystal **3·5** suggests that these carbonyl groups can be involved with halogen bonding, it is much more likely that they form CH···O hydrogen bonds and interact with adventitious moisture.

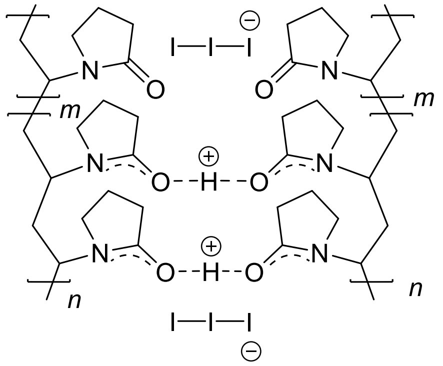


Figure 8. Revised model for the structure of Povidone-iodine showing PVP chains linked in pairs by hydrogen bonding.

## Experimental

### *Materials and Methods*

Poly(vinylcaprolactam) was supplied by Ashland Inc. as a 50 wt% mixture in 2-butoxyethanol. PVP K12 was purchased from Acros Organics. $H_2$bisVP (**1**) and bisHEP (**2**) were prepared according to the literature procedures.[24, 32] All other reagents and solvents were purchased from standard commercial sources and used without further purification.

Powder X-ray diffraction was performed using a Bruker AXS D8 Advance diffractometer, with a Lynxeye Soller PSD Detector and CuKα radiation at a wavelength of 1.5406 Å.

Crystals suitable for single crystal X-ray diffraction structure determination were immersed in perfluoropolyether oil and mounted on a micro-loop (MiTeGen Inc). Single crystal X-ray data for compounds **1**·$HI_3$ and **2**·$HI_3$ were collected on a Bruker D8 Venture diffractometer (Photon 100 CMOS detector, IμS microsource, $\lambda$MoKα, $\lambda = 0.71073$ Å) equipped with a Cryostream (Oxford Cryosystems) open-flow nitrogen cryostat at 250 or 120 K. The data for co-crystal 3·5 were collected on an Agilent XCalibur (Sapphire-3 CCD detector, fine-focus sealed tube, graphite monochromator, $\lambda$MoKα, $\lambda = 0.71073$ Å) diffractometer at 120.0 K. All structures were solved using direct methods and refined by full-matrix least squares on $F^2$ for all data using SHELXL[33] and OLEX2.[34] Diagrams were produced using X-Seed.[35-36] All non-disordered non-hydrogen atoms were refined with anisotropic displacement parameters. CH hydrogen atoms were placed in calculated positions, assigned an isotropic displacement factor that is a multiple of the parent carbon atom and allowed to ride. H-atoms attached to oxygen were located on the difference map and refined either freely (**2**·$HI_3$) or in constrained mode (the structures of **1**·$HI_3$). Crystal data and parameters of refinement are listed in the relevant experimental sections.

Fourier transform infrared spectra were recorded using a Perkin Elmer Spectrum 100 μATR spectrometer. For each solid-state spectrum, 8 scans were conducted over a spectral range 4000 to 600 $cm^{-1}$ with a resolution of 2 $cm^{-1}$.

### *Synthesis*

*1,3-bis(2'-pyrrolidinon-1'-yl)butane hydrogen triiodide* (**1**·$HI_3$). This compound was prepared as described in the literature.[3] Compound **1** (0.098g, 0.44 mmol), was dissolved in dichloromethane (3 mL) and a dichloromethane solution of iodine (2 mL, 0.116 g, 0.46 mmol) was added producing a color change from purple to brown. Aqueous hydroiodic acid (56.5%, 0.100 g, 0.44 mmol) was added and the mixture allowed to stand for 5 minutes. To the resulting stirred mixture was added excess *n*-hexane (50 mL) resulting in the formation of a brown oil. Prolonged stirring with a magnetic follower and periodic ultrasonication resulted in the formation of a brown precipitate which was isolated by filtration, washed with *n*-hexane and air dried. Yield 0.148 g, 0.24 mmol, 56 %. A sample for X-ray diffraction was recrystallized by slow diffusion of diethyl ether vapor into a dichloromethane solution of the target compound resulting in orange-brown plates. Anal. calc. for $C_{12}H_{21}N_2O_2I_3$: C, 23.78; H, 3.49; N, 4.62 %. Found: C, 23.73; H, 3.32; N, 4.41 %.

*Crystal data for* ***1***$\cdot$*HI*$_3$ *(high temperature form)*: $C_{12}H_{21}N_2O_2I_3$, $M$ = 606.01, monoclinic, space group $C2/c$, $a$ = 12.2571(6), $b$ = 29.5216(14), $c$ = 11.3842(5) Å, $\beta$ = 113.746(2)°, $V$ = 3770.6(3) Å$^3$, $F(000)$ = 2256, $Z$ = 8, $D_c$ = 2.135 mg m$^{-3}$, $\mu$ = 4.974 mm$^{-1}$, $T$ = 250(1)K. 35327 reflections were collected, yielding 4544 unique data ($R_{merg}$ = 0.0674). Final $wR_2(F^2)$ = 0.1297 for all data (173 refined parameters), conventional $R_1(F)$ = 0.0546 for 2684 reflections with $I \geq 2\sigma(I)$, $GOF$ = 1.061.

*Crystal data for* ***1***$\cdot$*HI*$_3$ *(low temperature form)*: $C_{12}H_{21}N_2O_2I_3$, M = 606.01, triclinic, space group $P\bar{1}$, $a$ = 11.2761(13), $b$ = 12.1616(14), $c$ = 15.4719(18) Å, $\alpha$ = 69.543(4), $\beta$ = 79.646(4), $\gamma$ = 66.800(3)°, $V$ = 1825.0(4) Å$^3$, $F(000)$ = 1128, $Z$ = 4, $D_c$ = 2.206 mg m$^{-3}$, $\mu$ = 5.139 mm$^{-1}$, $T$ =

120.0(1)K. The twinned data were indexed using CELL_NOW procedure, processed with TWINABS program and refined as non-merohedral twin against HKLF 5 data. 31392 reflections were collected, yielding 10565 unique data ($R_{\mathrm{merg}}$ = 0.0756). Final $wR_2(F^2)$ = 0.2151 for all data (347 refined parameters), conventional $R_1(F)$ = 0.0800 for 8354 reflections with $I \geq 2\sigma(I)$, *GOF* = 1.026.

*1-{2-[2-(2-oxo-pyrrolid-1-yl)-ethoxy]-ethyl}-pyrrolid-2-one hydrogen triiodide* (**2**·$HI_3$). Compound **2** (0.099g, 0.41 mmol), was dissolved in dichloromethane (3 mL) and a dichloromethane solution of iodine (2 mL, 0.106 g, 0.42 mmol) was added producing a color change from purple to brown. Aqueous hydroiodic acid (56.5%, 0.097 g, 0.43 mmol) was added and the mixture allowed to stand for 5 minutes. To the resulting stirred mixture was added excess *n*-hexane (50 mL) resulting in the formation of a brown oil. Prolonged stirring with a magnetic follower and periodic ultrasonication resulted in the formation of a brown precipitate which was isolated by filtration, washed with *n*-hexane and air dried. Yield 0.077 g, 0.12 mmol, 30 %. A sample for X-ray diffraction was recrystallized by slow diffusion of diethyl ether vapor into a dichloromethane solution of the target compound resulting in orange-brown plates. Anal. calc. for $C_{12}H_{21}N_2O_3I_3$: C, 23.17; H, 3.40; N, 4.50 %. Found: C, 23.14; H, 3.29; N, 4.40 %.

*Crystal data for* ***2**·$HI_3$*: $C_{12}H_{21}N_2O_3I_3$, M = 622.01, monoclinic, space group $P2_1/n$, $a$ = 9.8888(7), $b$ = 11.1703(8), $c$ = 17.4138(12) Å, $\beta$ = 105.943(2)°, $V$ = 1849.6(2) Å$^3$, $F(000)$ = 1160, $Z$ = 4, $D_c$ = 2.234 mg m$^{-3}$, $\mu$ = 5.078 mm$^{-1}$, $T$ = 120.0(1)K. 39644 reflections were collected, yielding 5635 unique data ($R_{\mathrm{merg}}$ = 0.0603). Final $wR_2(F^2)$ = 0.0812 for all data (185 refined parameters), conventional $R_1(F)$ = 0.0325 for 4676 reflections with $I \geq 2\sigma(I)$, $GOF$ = 1.059.

Cocrystal **3**·**5**. Crystallization was performed in 2 cm$^3$ glass vials with loosely fitting plastic screw lids. Compound **3** (0.047 g) and compound **5** (0.50 g) were dissolved in acetone/$CH_2Cl_2$ mixed solvent (1.5 mL) and the solution allowed to evaporate at room temperature.

*Crystal data for* ***3·5***: $C_{16}H_{26}N_2O_2 \cdot C_6F_4I_2$, M = 680.25, monoclinic, space group $P2_1/n$, $a$ = 21.8250(12), $b$ = 5.2275(3), $c$ = 23.0386(15) Å, $\beta$ = 114.280(7)°, $V$ = 2396.0(2) Å$^3$, $F(000)$ = 1320, $Z$ = 4, $D_c$ = 1.886 mg m$^{-3}$, $\mu$ = 2.678 mm$^{-1}$, $T$ = 120.0(1)K. 33512 reflections were collected, yielding 4716 unique data ($R_{merg}$ = 0.1420). Final $wR_2(F^2)$ = 0.1006 for all data (290 refined parameters), conventional $R_1(F)$ = 0.0505 for 3202 reflections with $I \geq 2\sigma(I)$, $GOF$ = 1.005.

## ASSOCIATED CONTENT

**Supporting Information**. Supporting information comprising crystallographic information in CIF format has been deposited with the Cambridge Structural Database deposition numbers CCDC 1557771-1557774. IR and UV-Vis Spectra are also available as supplementary information. This material is available free of charge via the Internet at http://pubs.acs.org. Underlying research data is available from doi: 10.15128/r1qr46r0813 in accordance with the UK research councils' open data policy.

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## Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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## REFERENCES

(1) Haaf, F.; Sanner, A.; Straub, F., *Polym. J.* **1985**, *17*, 143.
(2) Perrin, A.; Musa, O. M.; Steed, J. W., *Chem. Soc. Rev.* **2013**, *42*, 1996.
(3) Schenck, H.-U.; Simak, P.; Haedicke, E., *J. Pharm. Sci.* **1979**, *68*, 1505.
(4) Beller, H.; Hosmer, W. A. Process for the Preparation of Iodine-Polyvinylpyrrolidone by Dry Mixing. US Patent 2706701, 1955.
(5) *WHO Model List of Essential Medicines (19th List)*. World Health Organization: 2015.
(6) Siggia, S. Preparation of Iodine Polyvinylpyrrolidone Adducts. US Patent 2,900,305, 1959.
(7) Groom, C. R.; Allen, F. H., *Angew. Chem., Int. Ed.* **2014**, *53*, 662.

(8) Bekaert, A.; Barberan, O.; Kaloun, E. B.; Danan, A.; Brion, J. D.; Lemoine, P.; Viossat, B., *Z. Kristallog. New Cryst. Str.* **2001**, *216*, 479.
(9) Povidone-iodine. https://en.wikipedia.org/wiki/Povidone-iodine (accessed 13 June 2017).
(10) Metrangolo, P.; Meyer, F.; Pilati, T.; Resnati, G.; Terraneo, G., *Angew. Chem., Int. Ed.* **2008**, *47*, 6114.
(11) Gilday, L. C.; Robinson, S. W.; Barendt, T. A.; Langton, M. J.; Mullaney, B. R.; Beer, P. D., *Chem. Rev.* **2015**, *115*, 7118.
(12) Metrangolo, P.; Resnati, G., *Cryst. Growth Des.* **2012**, *12*, 5835.
(13) Cavallo, G.; Metrangolo, P.; Milani, R.; Pilati, T.; Priimagi, A.; Resnati, G.; Terraneo, G., *Chem. Rev.* **2016**, *116*, 2478.
(14) Desiraju, G. R.; Ho, P. S.; Kloo, L.; Legon, A. C.; Marquardt, R.; Metrangolo, P.; Politzer, P.; Resnati, G.; Rissanen, K., *Pure Appl. Chem.* **2013**, *85*, 1711.
(15) Ilioudis, C. A.; Steed, J. W., *CrystEngComm* **2004**, *6*, 239.
(16) Dauter, Z.; Mawby, R. J.; Reynolds, C. D.; Saunders, D. R.; Hansen, L. K., *J. Chem. Soc., Dalton Trans.* **1987**, 27.
(17) Greenwood, N. N.; Earnshaw, A., Chemistry of the Elements. 1st ed.; Pergamon: Oxford, 1984; pp 941.
(18) Desiraju, G. R.; Vittal, J. J.; Ramanan, A., *Crystal Engineering: A Textbook*. IISc Press/World Scientific: New Jersey, 2011.
(19) Spackman, M. A.; McKinnon, J. J., *CrystEngComm* **2002**, *4*, 378.
(20) Wood, P. A.; McKinnon, J. J.; Parsons, S.; Pidcock, E.; Spackman, M. A., *CrystEngComm* **2008**, *10*, 368.
(21) Steed, K. M.; Steed, J. W., *Chem. Rev.* **2015**, *115*, 2895.
(22) Afrooz, M.; Dehghani, H., *RSC Adv.* **2015**, *5*, 50483.
(23) The Merck Index. O'Neil, M. J., Ed. Royal Society of Chemistry: Cambridge, 2013; p 1425.
(24) Perrin, A.; Goodwin, M. J.; Musa, O. M.; Berry, D. J.; Corner, P.; Edkins, K.; Yufit, D. S.; Steed, J. W., *Cryst. Growth Des.* **2017**, *17*, 3236.
(25) Ashland Product Data Sheet 4845 PVP K-12 Polymer. 2013.
(26) James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C., *Chem. Soc. Rev.* **2012**, *41*, 413.
(27) Aakeroy, C. B.; Desper, J.; Fasulo, M.; Hussain, I.; Levin, B.; Schultheiss, N., *CrystEngComm* **2008**, *10*, 1816.
(28) Hursthouse, M. B.; Gelbrich, T.; Plater, M. J., *Private Communication* **2003**, CCDC 223298.
(29) Takemura, A.; McAllister, L. J.; Hart, S.; Pridmore, N. E.; Karadakov, P. B.; Whitwood, A. C.; Bruce, D. W., *Chem Eur. J.* **2014**, *20*, 6721.
(30) Nurzyńska, K.; Booth, J.; Roberts, C. J.; McCabe, J.; Dryden, I.; Fischer, P. M., *Mol. Pharm.* **2015**, *12*, 3389.
(31) Wunderlich, B., *Pure Appl. Chem.* **2009**, *81*, 1931.
(32) Musa, O. M.; Narayanan, K. S. N-Alkyl Lactam Ethers, and Compositions and Uses Thereof. US Patent 2012/0148514 A1, 2012.
(33) Sheldrick, G. M., *Acta Crystallogr. Sect. C* **2015**, *71*, 3.

(34) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H., *J. Appl. Crystallogr.* **2009**, *42*, 339.
(35) Barbour, L. J., *J. Supramol. Chem.* **2001**, *1*, 189.
(36) Atwood, J. L.; Barbour, L. J., *Cryst. Growth Des.* **2003**, *3*, 3.

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# Halogen- and Hydrogen Bonding in Povidone-Iodine and Related Co-crystals

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We demonstrate a revised structure of the well-known antiseptic povidone-iodine and report interesting cocrystalline and coamorphous phases of a related halogen bonded tetrafluorodiiodobenzene-lactam system.