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Physical Aging of Poly(vinylpyrrolidone) under Different Humidity Conditions

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ABSTRACT: The physical aging of poly(vinylpyrrolidone) (PVP K25) was studied under different storage conditions by positron lifetime spectroscopy and scanning electron microscopy. The transition from the glassy state (at RT and 55% RH) to the completely plasticized wet rubbery state (at RT and 75% RH) is not continuous in PVP K25. It was found that not only the actual water content of the material but also its storage history determines the size distribution of free volume holes in it. At 65% RH a slow anomalous structure formation was observed. By the means of ab initio calculations on simplified model molecules, it was determined that polymer chains and water molecules are able to form a hydrogen bound "network" under certain humidity conditions.

Introduction

Water-soluble polymers are frequently used for pharmaceutical purposes as, e.g., filling agents in tablets. Most of these applications require long-term stability, but as amorphous polymers are not in equilibrium below their T_g, these polymers usually undergo spontaneous, however slow, transformations toward low-energy equilibrium states.[1] This so-called physical aging is usually manifested even in volume and enthalpy relaxation,[2,3] indicating serious structural changes in the material. Sometimes common gases[4] (as CO_2) or the natural humidity of air[5] ignite these processes, and the plasticization effects of these everyday materials are enough to change the crystallinity or the T_g of the polymer significantly. It has been repeatedly proven that the aging of amorphous polymers is controlled by the type and the rate of their characteristic molecular motion.[6] The enhanced molecular mobility, caused by the plasticization effect of absorbed water, has been proposed to be the major underlying factor in chemical and physical instability of amorphous pharmaceutical materials.[7−9]

From the pharmaceutical point of view the soluble grades of amorphous poly(vinylpyrrolidone)s possess a number of very useful properties: solubility in all conventional solvents, adhesive and binding power, film formation, ability to form complexes, availability in different molecular weights, thickening properties.[10] The authors have previously characterized the time-dependent glassy-to-rubbery phase transition of the amorphous poly(vinylpyrrolidone) (PVP K25, Kollidon-25) caused by the long-term plasticization effect of the humidity of air. The enthalpy relaxation at the glass transition temperature and the changes of the free volume were investigated, and it was found that, along with the structural changes of the poly(vinylpyrrolidone), also the tensile strength of tablets changed significantly during the storage period.[11,12] In this work we try to identify the chemical processes behind the structural changes and give an approximate image of the dynamics of these processes by combining positron annihilation spectroscopy, scanning electron microscopy, and ab initio calculations.

Positron annihilation lifetime spectroscopy (PALS) is a unique method since it is exceptionally sensitive to the free volume. It is frequently used to determine the size distribution of free volume holes in polymers.[13−15] All of these measurements are based on the interaction of the free volume holes and the so-called orthopositronium atom.[16]

When positrons are injected to an amorphous molecular material, they form three different states in the simplest case. A part of them forms positronium (Ps) atoms with the electrons of the material. This exotic atom, which is the bound state of an electron and a positron, has two ground states depending on the relative orientation of the spins of the constructing particles. The para-Ps, in which the spins are antiparallel, has a very short intrinsic lifetime (125 ps). The usual reactivity of Ps atoms is not very high, and in most of the cases the two particles bound in para-Ps (the positron and the electron) annihilate with each other by the intrinsic lifetime (τ_1). The other ground state of positronium is the ortho-Ps (o-Ps), in which the spins are parallel. This Ps state has a very long lifetime in a vacuum (141 ns), and even at very low reactivity, it interacts with the electrons of the surrounding material considerably. Usually the positron of the ortho-Ps does not annihilate with its own electron but rather with an electron of the material. This interaction decreases the intrinsic lifetime significantly, and usually a much shorter lifetime is observed (1−10 ns). Even so, this is the longest lifetime component of positron lifetime spectra (τ_3).

The third state of positrons in materials is usually due to positrons not able to form Ps atoms. These positrons diffuse almost freely in the material, but they should also annihilate sooner or later with surrounding electrons, i.e., with the electrons of polymeric chains in our case. This provides a medium long lifetime (τ_2) that characterizes the average electron density of the mate-

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rial. This lifetime component usually reflects tiny changes of the electron structure of a material very sensitively. In our former work[12] we used this crude assumption during the evaluation of lifetime spectra, but some of the results indicated that a more detailed picture is needed to understand all the structural changes of Kollidon-25 during a long-term physical aging.

In amorphous materials as polymers the size of free volume holes is not uniformly distributed. Consequently, the simple assumption on the number and the nature of positron states is not necessarily correct. In these materials, instead of one well-defined o-Ps state, a number of similar states occur depending on the size of the free volume around the positronium. So the lifetime spectrum, $S(t)$, is not a simple sum of exponential curves, and instead of

$$S(t) = \sum_i A_i \exp(-\lambda_i t) \tag{1}$$

it can be described by a continuous distribution of lifetimes:

$$S(t) = \sum_0^\infty h(\lambda) \exp(-\lambda_i t)\, \mathrm{d}\lambda \tag{2}$$

where λ_i's are the assumed separate lifetimes, A_i's are their relative intensities, and the function $h(\lambda)$ is the lifetime distribution function which is proportional with the size distribution of free volume holes in the material.

In polymers the formed o-Ps atoms tend to be trapped in free volume holes, and as mentioned above, their annihilation is not governed by their intrinsic lifetime but by the electron density in the holes. Their lifetime is associated with the size of the free volume around them:[17]

$$\tau = \frac{1}{2}\left[1 - \frac{R}{R + \Delta R} + \frac{1}{2\pi} \sin\left(\frac{2\pi R}{R + \Delta R}\right)\right]^{-1} \tag{3}$$

where τ is the positronium lifetime, R is the radius of the free volume hole, and ΔR is a constant. Consequently, on the basis of o-Ps lifetime distributions, we gain a detailed picture on the size distribution of free volume holes.

The aim of this work is to determine the role of water molecules and hydrogen bonds in the physical aging of poly(vinylpyrrolidone). Below we try to follow the aging with positron lifetime spectroscopy through o-Ps lifetime distributions and explain the observed morphological and free volume changes on the basis of ab initio calculations.

Experimental Section

Materials. The commercial grade of poly(vinylpyrrolidone) (PVP K25/Kollidon 25, BASF, Ludwigshafen, Germany) was selected for the study. The material was a fine powder of grains of about 200 μm in diameter.

Storage Conditions. Identical amounts of Kollidon 25 were transferred into separated desiccators kept at 55%, 65%, and 75% RH and room temperature. For storage periods 1 and 4 weeks were chosen at each RH value. Because of technical reasons, we were not able to study the "unaged" sample with positron lifetime spectroscopy. Instead, we used a sample aged at 55% RH for only a day, but even this sample contained a large amount of water and had a decreased T_g (see below).

Determination of Water Content. The determination of water content of the samples was performed by Karl Fischer titration (Methrom, 736 GP Titrino). The applied reagents were Karl Fischer solution A (Merck 1.092747) and Karl Fischer solution B (Merck 9246).

Morphology of PVP Samples. The morphological examination of stored PVP powder samples was performed by scanning electron microscopy (SEM, JEOL JSM, Japan).

T_g and Physical Hardness. These data were measured and published earlier, but we think them significant in our reasoning, so we repeat some of them in this work. For technical details see ref 11.

Positron Lifetime Measurements. The positron source applied for the measurements was made of carrier-free ^{22}NaCl of activity of 4×10^5 Bq. The active sodium chloride was sealed between two very thin (5 μm) titanium foils. The source was then placed between two pieces of Kollidon 25 treated identically before.

Positron lifetime spectra were recorded by a conventional fast−fast coincidence system.[18] The system was constructed from standard ORTEC electronic units and the detectors from BaF_2 scintillator crystals and XP2020Q photomultipliers. The time resolution of the system was about 200 ps.

The spectra was first evaluated by the RESOLUTION computer code,[19] according to eq 2. From these evaluations we have determined the resolution curve of the system for each spectrum individually. After that a variation of the MELT code[20] was used to extract lifetime distributions from the spectra. These latter evaluations were used to characterize the size distribution of free volume holes in the samples through o-Ps lifetime.

Ab Initio Calculations. For the calculations the GAUSSIAN computer code[21] was used. As even the simplified model molecule was very large, we used a relatively small basis set, namely, HF/3-21G*. Consequently, the determined optimum geometries and energies are not the most exact ones but, anyhow, give some practical hints on the structure of hydrogen bound complexes formed between the polymer chains and water molecules absorbed from the humidity of air.

Results and Discussion

Morphology of the Samples. Although poly(vinylpyrrolidone) is expected to swell in water extensively, the swelling is not expected to modify the original structure of the polymer significantly. This assumption was partially confirmed by the SEM photographs which do not show any significant swelling effect at 55% RH (Figure 1A) even after a 4 week aging period. Despite the relatively large water content,[11] the sample reserved its original structure. However, it has also been shown formerly that the plasticization effect of water leads to a significant decrease of T_g[11,12] under certain conditions. Accordingly, the SEM photographs of samples stored at 75% RH show a completely swollen polymer in its rubbery phase (Figure 1C). Although the shown fibrillar structure might be artificial (due to sample preparation), the difference between the morphologies is evident: while at 55% RH the sample was a powder of well-separated grains even after a 4 week long aging, at 75% RH it formed a free film after a day of storage.

Surprisingly, the medium humidity aging has not lead to a structure that is simply a transition between the two extremes. The SEM photograph taken at 65% RH after 4 weeks (Figure 1B) indicates a structure different from both the glassy state at 55% RH and the rubbery phase at 75% RH. Although the T_g of the sample (Table 1) suggests that it should be in the glassy state, the SEM photograph contradicts this expectation and reveals a structure that is neither a free film nor a powder.

The significance of 65% RH is emphasized by the results of former physical hardness measurements[11] (Table 1). At any other relative humidity the aging leads to a decrease of the tensile strength of tablets containing

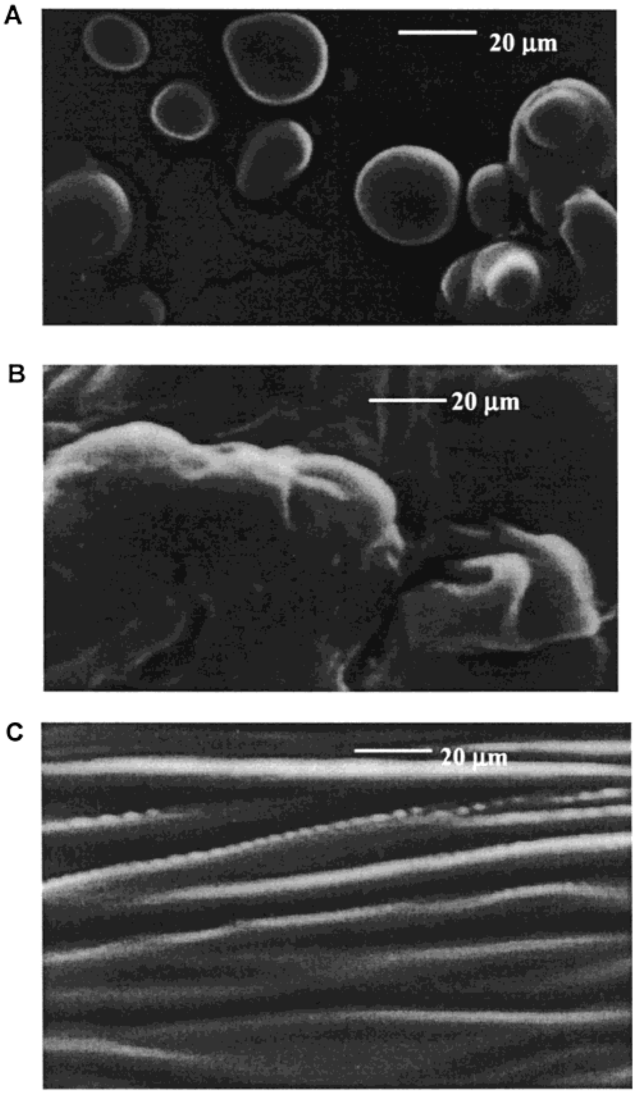

Figure 1. SEM photographs of PVP K25 powder samples under different storage conditions: (A) 55% RH, 4 weeks; (B) 65% RH, 4 weeks; (C) 75% RH, 4 weeks. Note that the fibrillar structure in (C) might be artificial, but (A) reveals a powder and (C) a film.

Table 1. Glass Transition Temperature of Stored PVP K25 Powder Samples and the Tensile Strength Values of Tablets Containing PVP K25 at Different Relative Humidity

rel humidity (%)	glass transition temp[a] (°C)	tablet tensile strength (MPa)	
		1 week	4 weeks
sample as-received	164.8		
45	58.4	0.82 ± 0.11	0.66 ± 0.09
55	52.6	0.82 ± 0.10	0.58 ± 0.06
65	39.1	0.23 ± 0.03	0.36 ± 0.06
75	17.0	0.06 ± 0.01	0.06 ± 0.02

[a] The given T_g's were reached after a day of storage, and they remained mostly constant through the whole aging period.

Kollidon 25. On the other hand, at 65% RH the aging, after a significant initial decrease, increases the hardness of tablets. This and the SEM photographs might suggest that a very slow process takes place at 65% RH which forms a structure different from both the normal glassy and the rubbery states of poly(vinylpyrrolidone).

According to the above results, the unusual structure formation takes place only in a limited humidity range.

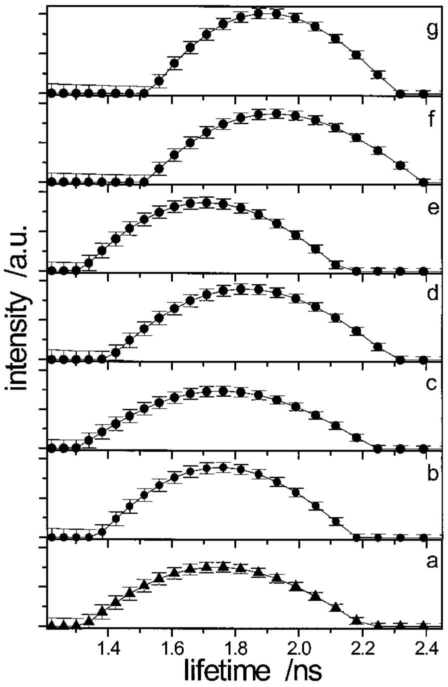

Figure 2. o-Ps lifetime distributions of samples stored at different relative humidities. For the exact characterization of (a)–(g) distributions, see Table 2.

Moreover, it is definitely due to the swelling. In the swelling of hydrophilic materials such as PVP the formation of hydrogen bonds between water molecules and polymeric chains plays a determining role. Sometimes even hydrogen bound complexes of well-defined structures are formed[10,14] at the beginning of the swelling process. Let us assume at this point, without further evidence, that a unique hydrogen bound structure is formed at 65% RH in Kollidon 25 as well. Below this range the absorbed water is not enough to form all the necessary hydrogen bonds, and above the range, on the other hand, the polymeric chains are departed too far from each other by the large amount of absorbed water molecules.

o-Ps Lifetime Distributions. The "structure formation" has a serious effect on the aging of tablets, which is revealed by o-Ps lifetime distributions (Figure 2). It is clear from the figure that the lifetime distributions do not show any dramatic changes in the size distribution of free volume holes. However, the area of the peaks increases slightly with the increasing water content; the width of the peaks does not change significantly except the expected random scattering (Table 2). The only parameter showing significant variation with water content is the peak position, i.e., the average size of free volumes around the annihilating o-Ps atoms. The peak shifts toward longer lifetimes as the water content increases, indicating the increase of free volume holes. This is what someone expects from polymers: as the swelling ratio increases, also the size of free volume holes increases.

The only exception from this smooth tendency is, again, observed at 65% relative humidity. In this case the peak position is shifted toward shorter lifetimes, indicating that the aging for 4 weeks at 65% RH decreases the average size of free volume holes in the sample significantly (Table 2). The decrease is so dramatic that this is the shortest lifetime observed, shorter even than in the case of the lowest amount of

Table 2. Characteristic Parameters for the Lifetime Distributions of PVP K25 Samples Stored under Distinct Relative Humidity Conditions

sample	water content (% w/w)	humidity (%)	aging[a] (weeks)	peak position (ns)	width (ns)	area
a	15.5	55, 65[b]	"unaged"	1.754 ± 0.010	0.448 ± 0.018	0.180 ± 0.007
b	15.6	55	1	1.760 ± 0.008	0.408 ± 0.015	0.195 ± 0.006
c	17.6	55	4	1.763 ± 0.010	0.470 ± 0.019	0.185 ± 0.007
d	18.9	65	1	1.841 ± 0.009	0.454 ± 0.017	0.218 ± 0.007
e	19.6	65	4	1.716 ± 0.008	0.418 ± 0.016	0.194 ± 0.007
f	23	75	1	1.937 ± 0.008	0.442 ± 0.016	0.207 ± 0.006
g	23.7	75	4	1.908 ± 0.007	0.394 ± 0.013	0.215 ± 0.006

[a] Because of technical reasons we were not able to measure the dry sample by positron lifetime spectroscopy. So, we consider samples aged for a day as "unaged" because they contained the smallest amount of water. [b] There was no significant difference observed after a day.

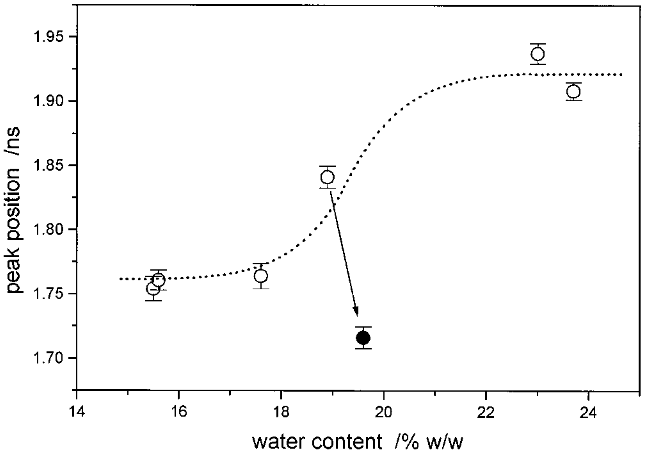

Figure 3. Peak position as a function of water content of samples. The closed circle marked by an arrow represents the anomalous sample stored under 65% RH for 4 weeks.

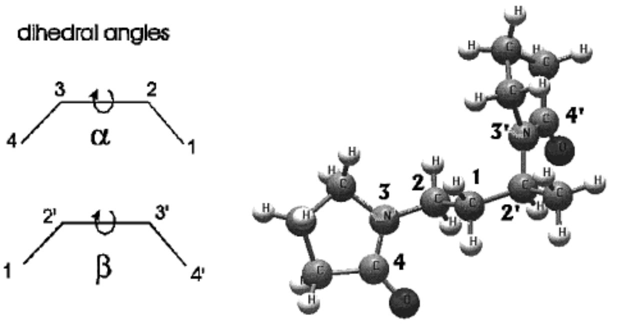

Figure 4. Optimum geometry of the trans isomer of the dimer vinylpyrrolidone. The geometry was determined using a 3-21G* basis set in a HF calculation. Dihedral (torsion) angles are given for explaining the abbreviations of Figure 5.

absorbed water (55% RH, 1 day). It is also interesting that 65% relative humidity is the case where, during the aging period, o-Ps lifetimes reveal a change at all. At other relative humidities the observed lifetime distributions remained constant after the first week of storage.

If we draw the peak position as a function of water content of the samples, the effects of aging become even clearer (Figure 3). The obtained curve is S-like, indicating the water-induced phase transition from a glassy to rubbery state.[11] The samples stored at 65% relative humidity are located just at the transition range. Consequently, one should expect that a longer storage at this humidity leads to the slow transition of the polymer to the rubbery phase. On the other hand, due to the mentioned "structure formation", the end stage is far from the normal rubbery phase. Instead of large free volume holes, the sample stored at 65% relative humidity contains smaller ones. This serious anomaly emphasizes the role of the mentioned structure formation in the swelling process.

Ab Initio Calculations. At this point we have already demonstrated the anomalous aging of Kollidon 25 at 65% RH by three independent methods. Now we should determine the structure of the formed hydrogen bound complex that might be responsible for the observed anomalies at 65% RH. The complex should possess a structure that is stable at 65% RH and explain the increased tensile strength of tablets, but on the other hand, a small amount of excess water is able to destroy it.

To achieve endurable calculation times, we have used a small model molecule; i.e., all the calculations was performed on dimers of vinylpyrrolidone instead of long polymer backbones. Although, we have lost the effects of long chains but gained the perfection of ab initio calculations by this method. The results, however, are only crude approximations, but we think that they are exact enough to determine the structure responsible for the anomalous aging of Kollidon 25 at 65% RH.

The dimer vinylpyrrolidone has two optimum geometries distinguished by the relative positions of the two pyrrolidone rings. Figure 4 shows the trans isomer. The energy difference between the cis and trans isomer is very small (Table 3), and the relative position of the rings is almost insignificant because at least one of them can spin almost freely around the "backbone" (Figure 5). Although they provided very similar results in further calculations, we should distinguish these two isomers because their geometrical structure is different.

The absorbed water molecules can form hydrogen bonds with any of the oxygens, and the total energies of the two hydrogen bound isomers are still the same (Table 3). As the calculations revealed, the nitrogens are insignificant for hydrogen bonds in the case of the dimer vinylpyrrolidone.

The simple complex formation, i.e., one water molecule on each pyrrolidone ring, does not explain the anomalous behavior of Kollidon 25 at 65% RH. On the other hand, it proposes a continuous transition from the dry to the completely swollen state, so we need a more "sophisticated" complex. Some earlier results showed that, under certain conditions, two neighboring pyrrolidone rings get bound "through" a water molecule[10] (Figure 6a). The formation of this "bridgelike" complex changes the "rigidity" of the polymer backbone definitely and, thus, might explain the observed experimental results. This complex can even decay (or not form at all) in the presence of excess water as two separate hydrogen bonds mean less tension for the complex than

Table 3. Total Energies for the Isomers of the Dimer Vinylpyrrolidone and Its Hydrogen Bound Complexes Formed with Water Molecules

molecule/complex	energy/hartrees	comparable energy[a]/hartrees[b]	note
cis isomer	−720.707		
trans isomer	−720.710		Figure 4
simple cis complex	−871.924	−1743.848	one water molecule
simple trans complex	−871.923	−1743.846	on each oxygen
intramolecular bridge	−871.921	−1743.843	Figure 6a
intermolecular cross-link		−1743.861	Figure 6b

[a] To compare the total energies of hydrogen bound complexes, we should count two of the simple and the "bridgelike" complexes each and only one of the cross-linked complex. [b] For a more familiar gauge, 1 hartree ≈ 2623 kJ/mol.

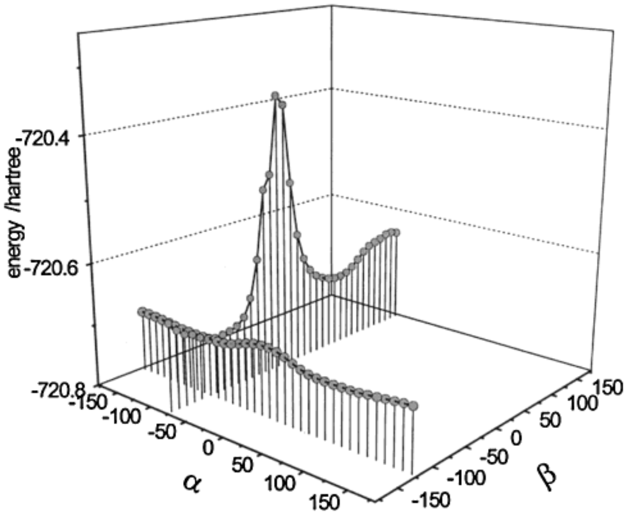

Figure 5. Total energy of the trans isomer of the dimer vinylpyrrolidone molecule at different relative positions of the pyrrolidone rings. The sharp high energy peak is due to an impossible configuration in which two hydrogen atoms are too close to each other. The angles α and β are given in Figure 4.

a "bridge" between the rings. Unfortunately, the total energy of such a complex, although it contains an excess hydrogen bond, is not smaller than that of the simple complex (Table 3). Since the formation of an intramolecular bridge does not provide any energy gain, we cannot consider it as a real explanation for the observed anomalies.

The only remaining possibility is that water molecules are able to form hydrogen bound "cross-links" between separate poly(vinylpyrrolidone) chains (Figure 6b). The energy gain supported by the formation of this complex can be enough to initiate the creation of such "cross-links" at a certain water concentration. As this process requires a certain position of the neighboring polymeric chains, below a certain water concentration separate hydrogen bonds are preferred. Similarly, in the presence of excess water the chains depart from each other and the possibility of "cross-link" formation vanishes. Moreover, although these "cross-links" are weaker than real ones, they explain the increase of the tensile strength since the polymer/water complex forms a networked structure.

Conclusions

We have studied the physical aging of poly(vinylpyrrolidone) under different humidity conditions. Tensile strength, SEM, and positron lifetime measurements revealed that the structure of the polymer does not change significantly at 55% RH. On the other hand, at 75% RH the material suffers a phase transition from a glassy to rubbery state due to the plasticization effect of water.

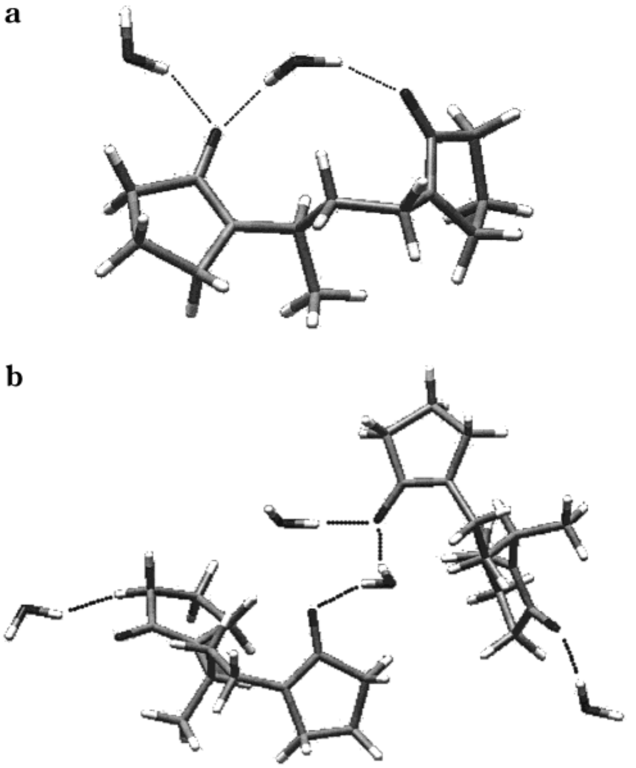

Figure 6. Optimum geometries for two possible hydrogen bound complexes of the dimer. The top structure (a) is unlikely due to its high energy, but the other might explain the anomalies observed at 65% RH (Table 3).

At 65% RH an anomalous aging was observed. Ab initio calculations revealed that a networked structure can be formed under this condition, where "cross-links" are formed by water molecules between different polymeric chains via hydrogen bonds.

These results raise very serious questions about the use of poly(vinylpyrrolidone) as binding material in tablets. According to our study, not only the actual water content of the tablets but also their storage history determines the size distribution of free volume holes in them.

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