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Izaskun Combarro Palacios,[1] Christoffer Olsson,[2] Christina S. Kamma-Lorger,[3] Jan Swenson,[2] and Silvina Cerveny[1,4]

AFFILIATIONS

[1] Centro de Física de Materiales (CSIC-UPV/EHU)-Material Physics Centre (MPC), Paseo Manuel de Lardizabal 5, 20018 San Sebastián, Spain
[2] Department of Physics, Chalmers University of Technology, SE-412 96 Göteborg, Sweden
[3] ALBA Synchroton—CELLS, Carrer de la Llum 2-26, 08290 Cerdanyola del Valles, Barcelona, Spain
[4] Donostia International Physics Center, Paseo Manuel de Lardizabal 4, 20018 San Sebastián, Spain

ABSTRACT

It is well-accepted that hydration water is crucial for the structure, dynamics, and function of proteins. However, the exact role of water for the motions and functions of proteins is still debated. Experiments have shown that protein and water dynamics are strongly coupled but with water motions occurring on a considerably faster time scale (the so-called slaving behavior). On the other hand, water also reduces the conformational entropy of proteins and thereby acts as a plasticizer of them. In this work, we analyze the dynamics (using broadband dielectric spectroscopy) of some specific non-biological water solutions in a broad concentration range to elucidate the role of water in the dynamics of the solutes. Our results demonstrate that at low water concentrations (less than 5 wt. %), the plasticization phenomenon prevails for all the materials analyzed. However, at higher water concentrations, two different scenarios can be observed: the slaving phenomenon or plasticization, depending on the solute analyzed. These results generalize the slaving phenomenon to some, but not all, non-biological solutions and allow us to analyze the key factors for observing the slaving behavior in protein solutions as well as to reshaping the slaving concept.

I. INTRODUCTION

Polymers are large molecules that consist of repeating units (monomers) forming long chains. In a homo-polymer, the monomers are identical, whereas in a hetero-polymer, the repeating units are two or more different (but often similar) types of monomers. Most of biomolecules (carbohydrates, proteins, and nucleic acids) are hetero-polymers synthesized in living organisms. Biopolymers have a well-defined specific structure in contrast to most synthetic polymers. In particular, proteins are the most abundant organic molecules in living systems and have a wide range of functions. Proteins in the native state (i.e., properly folded in aqueous solutions) change their conformation to perform their biological function, and therefore not only the structure but also their dynamics is connected with their functionality. Although the structure of synthetic polymers and proteins is different, their dynamical properties in solutions present some interesting similarities, which are worth exploring. Therefore and motivated by our previous studies on the dynamics of solutions of soft matter (including polymers and biopolymers),[1,2] in this work, we explore the analogies and differences of the dynamical behavior of aqueous solutions of these two types of solutes. In particular, the number of the relaxations due to the water molecules in the solutions is different for polymer and for biopolymer solutions. For polymers, a single relaxation due to water molecules was observed,[3] but for proteins[4] and other biopolymers,[5] two or even more relaxations can be distinguished related to water molecules. In this work, we will show that some particular polymeric solutions mimic the dynamical behavior of proteins.

The onset of activity[6] of most proteins is around 0.2 g/g (g water/g dry protein), and therefore, it is supposed that water plays an active role in the conformational dynamics of the protein in solution.[7] However, there are some opposite views related to the motions of water in the hydration shell (traditionally defined as the first 1-2 molecular layers of water around the protein, although some THz measurements indicate up to 6 water layers[8]), the bulk water and the motions of the protein itself and how these motions are related to each other. Slaving[9] and plasticization[10] are two different concepts used to explain the role of the solvent for protein dynamics. The term "slaving" was recently introduced in the literature[11] to consider the effect of both the hydration and solvent viscosity on the protein fluctuations. In particular, it was emerged on studies of myoglobin solutions (Mb, glycerol-water, 3:1) to explain both the binding and dissociation of carbon monoxides to Mb at subzero temperatures. Considering the picture of slaving, Frauenfelder and co-workers[9,12,13] proposed that water both in the hydration shell and in the *bulk* solvent[9,13] determines the protein motions. In particular, the large-scale protein motions are controlled by the fluctuations in the *bulk* solvent, whereas the more local internal protein motions are coupled to the fluctuations in the hydration shell. In this context, it is important to remark that the expression "*bulk solvent*" refers to the quantity of the solvent required to observe the viscosity related α-like relaxation of water molecules. This amount of the solvent is not a large quantity as can be thought-out using the expression "*bulk solvent*," as we will see below. Regarding the large-scale protein motions, it was observed that the protein and solvent relaxations exhibit the same temperature dependence but occurring on different time scales.[14,15] However, the concept of solvent-slaved dynamics is still controversial and different opinions were recently published in the literature. Duboué-Dijon *et al.*[16] observed that water dynamics is very site specific at different DNA exposed sites. The water molecules confined in the minor groove were much more retarded, and therefore, it was argued that the biomolecule slaves the water, which is opposite to the slaving picture. Qin *et al.*[17] using femtosecond spectroscopy relaxation observed a coupling between the hydration water and protein side-chain dynamics of tryptophan. In this case, the hydration water was faster than the protein side-chains but with the same energy barriers, indicating a coupled dynamics. On the other hand, Demuth *et al.* by 13C CP MAS NMR[18] analyzed elastin in mixtures of water and glycerol. They showed that the water motions slave the α-like protein motions, but both water and protein motions have a mutual influence on each other.[19] Finally, we recently analyzed the dynamics of small amino acids (lysine[20] and proline[21]) as well as oligomers of *n*-lysine[5] in water solutions by broadband dielectric spectroscopy (BDS). We found that the dynamics of solutions of amino acids or short peptides show the same behavior as protein solutions.

Another point of view is that water acts as a *plasticizer* of proteins.[22] The phenomenon of plasticization was studied for several synthetic polymeric mixtures and also largely applied in food science[23,24] or in other industrial problems.[25] The term plasticization was defined as a change in the thermal and mechanical properties of a given polymer by compounding with a low molecular weight substance or with another polymer.[10] Plasticization increases the flexibility of the molecules (whether synthetic or biological polymers), allowing internal motions as well as shielding of solute-solute interactions. Because of plasticization, both the viscosity and glass transition temperature of the compounds decrease compared with those values of the dry system. Regarding the dynamical behavior, the solvent is merely an agent that moderates the energy barriers of the solute but does not determine the molecular motions of the solute as in the slaving picture. Therefore, the plasticization concept contrasts the slaving concept. In the case of plasticization, the temperature dependences of the relaxation times corresponding to the solute and solvent dynamics are independent of each other,[26] whereas for the slaving phenomenon, the relaxation times of the two components follow the same temperature dependence.[5,13]

Here, we explore the analogy between soft materials and proteins by analyzing their dynamical behavior to provide a more detailed understanding of both the slaving and plasticization phenomena. As mentioned above, we have already shown that the slaving picture is valid for oligomers of *n*-lysine, but in this case, we want to explore water solutions in which the solute has no structural similarities with proteins. From this point of view, we want to know if there is any synthetic substance that also shows the so-called slaving behavior and, in such a case, the necessary conditions to observe it. The questions we want to address are as follows: Is it possible to find a non-biological material where the surrounding water shows a similarly important role for its dynamics as water does for proteins? If this is the case, what are the differences and similarities? Is the solute really passive with motions driven by the surrounding water, as claimed in the slaving picture, or is there a mutual interference between the solute and solvent?

II. EXPERIMENTAL

Poly(vinyl pyrrolidone) (PVP, M_w = 10.000, 55.000, and 160.000 g/mol), tri-lysine (3-Lys, M_w = 402.5 g/mol), and dextran (M_w = 70.000 g/mol) were purchased from Aldrich Chemical. ε-polylysine (ε-PLL, M_w = 4.700 g/mol) was kindly supplied by the JNC Corporation (Japan).

The dry solutes (PVP, 3-Lys, ε-PLL, and dextran) were purified using an ion transfer resin (AG 501-X8, Bio-Rad Laboratories), and therefore, the polarization effects and ionic conductivity are reduced in the dielectric experiments. To prepare the solutions, water was added to the appropriated concentration (c_w). The mixtures of PVP were sealed for three months in order to achieve a good water distribution.

Differential scanning calorimetry (DSC) measurements were performed on a DSC Q-2000 from TA Instruments, using cooling and heating rates of 10 K/min to determine the glass transition temperatures. In addition, we have used broadband dielectric spectroscopy (a technique intensively used to assess the molecular dynamics of water in solutions on various time scales[3]) to determine the temperature dependence of the relaxation times of the solutions. Broadband dielectric spectroscopy (BDS) is a broadband technique (10^{-2}–5×10^9 Hz) based on the interaction between an external electric field (1 V) and the permanent electric dipoles of the samples. The fluctuations of local electrical fields are measured, and they can be connected to the dynamics on a molecular scale. It is important to note that at physiological temperatures (~300 K), the different dynamical processes are normally very close to each other, and therefore, it is usual to analyze these types of systems at low temperatures where the different dynamical contributions are well separated in time. This makes it possible to analyze the origin and the behavior of each contribution. In addition, as BDS probes the collective behavior of the constituents of the sample (for instance, the water and the protein), it is useful to perform measurements at different water contents to be able to determine the origin of each relaxation process experimentally observed.

The dielectric data of all the systems analyzed here show similar features in terms of number of processes and their molecular origin. In our previous work on peptides[5] and amino acids,[20,21] we extensively analyzed the dielectric response of *n*-lysine and *ε*-PLL solutions. Here, we also analyze solutions of dextran and PVP. A complete analysis of the experimental data corresponding to these materials can be seen in the supplementary material section, where also the experimental methods and fitting procedures are described in detail (see Figs. S1–S8 of the supplementary material). Figure S1 in the supplementary material shows both components of the complex dielectric permittivity data for PVP solutions (M_n = 10 000 g/mol, c_w = 40 wt. %) at different temperatures.

In the rest of the paper, we only show the relaxation maps as obtained from the BDS data (see also Figs. S9–S11 in the supplementary material) considering the three main relaxations observed in these aqueous solutions (called "slow- and fast-water relaxations" and "α-relaxation," as related to the calorimetric T_g).

III. RESULTS

A. Dependence of the glass transition temperature with composition

Figure 1 shows the concentration dependence of the glass transition temperature (T_g) of different solutions measured by differential scanning calorimetry (DSC). We find two unlike scenarios for soft materials: a linear dependence of T_g with the water concentration for some polymers [Fig. 1(a)] and a much stronger and nonlinear dependence for others [Fig. 1(b)]. This type of T_g-dependence with concentration is similar to that observed in protein solutions [Fig. 1(c)], where a much broader T_g is obtained compared with non-biological solutes. This is because of the large distribution of relaxation times (i.e., highly heterogeneous) caused by the many different relaxation processes occurring on different time scales.[15,27] In contrast to proteins, other soft materials generally show a much simpler and less complex structure than proteins in solutions, which results in fewer relaxation processes (often only the so-called α-relaxation) related to the calorimetric T_g. This, in turn, results in a much narrower T_g.

The difference $|T_{g,dry} - T_{g,c_{w,max}}|$ is larger for the polymers shown in Fig. 1(b) than for those in Fig. 1(a) (where the subscript "dry" represents the dry state and "$c_{w,max}$" represents the maximum water content before crystallization occurs during cooling to T_g). For instance, the T_g difference between dry PVP and the solution with c_w = 50 wt. % is 223 K, whereas for poly(vinyl methyl ether) (PVME) ($T_{g,PVME,dry} - T_{g,PVME,50\text{wt.\%}}$), it is only 54 K. Therefore, we could say that water acts as a "better plasticizer" for some materials than for others, and this is reflected by a larger decrease in T_g.

In addition, the T_g value is higher for dry materials in (b) than for those in (a). This implies that the recovery to equilibrium is much easier for dry polymers in (a) than those in (b). This indicates that for the dry solutes in (b), more thermal energy is needed to overcome the energy barriers for the motions related to the glass transition.

A remarkable difference between polymers- and protein-solutions is that T_g is no longer observed below ~0.5 wt. % of water for proteins.[35] On the contrary, for the non-biological solutes considered here, we can access the T_g value of the dry state. This allows analyzing the molecular motions of the dry systems and comparing with those observed in the wet solutions.

B. Dynamics of solutions of synthetic polymers at high water content

In this section, we compare the dynamical behavior of solutions in Fig. 1(a) with those in Fig. 1(b) at high c_w before crystallization occurs (i.e., c_w ~ 40 wt. %). Experimental data at different temperatures and water concentrations as well as the fitting procedures are shown in the supplementary material. Figures 2(a) and 2(b) show the temperature dependences of the relaxation times for tri(propylene glycol)[28] (3PG, with a linear T_g concentration dependence) and for poly(vinyl pyrrolidone) (PVP, with a fast decrease in T_g with increasing water concentration). Two different scenarios are observed depending on the T_g-dependence with

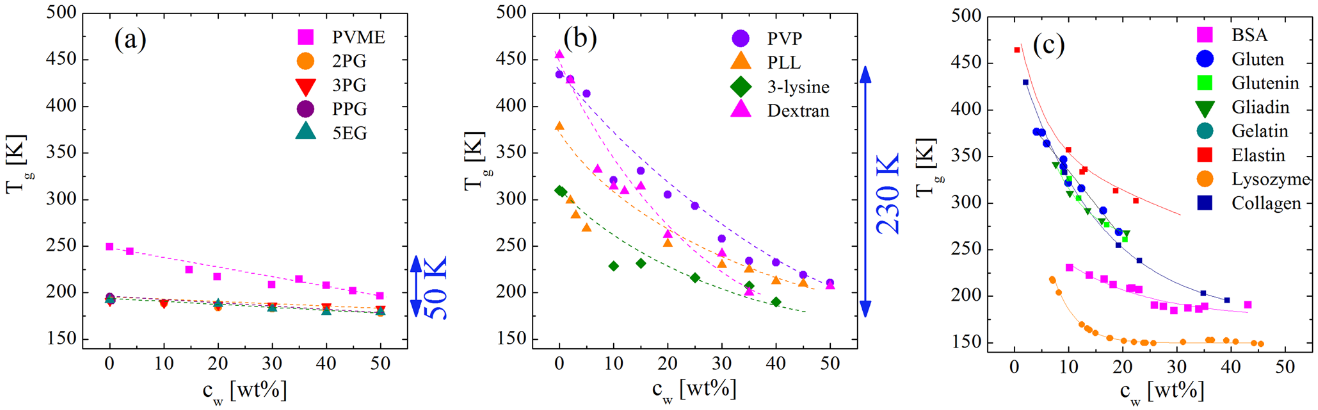

FIG. 1. Concentration dependence of the glass transition temperature (T_g) for different solutions. (a) poly(vinyl methyl ether),[26] poly(propylene glycol),[26] oligomers of propylene glycol (*n*PG),[28] and penta ethylene glycol (5EG).[29] (b) Poly(vinyl pyrrolidone), *ε*-poly(lysine), dextran, and 3-lysine.[5] (c) Proteins: Bovine Serum Albumin (BSA),[30] gluten,[31] glutenin,[32] gliadin,[32] gelatin,[32] elastin,[33] lysozyme,[34] and collagen.[33] The dashed lines are guides for eyes.

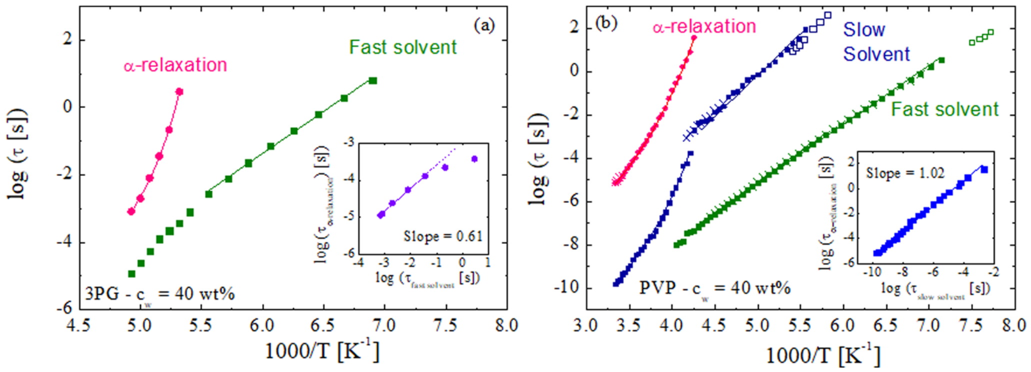

FIG. 2. Temperature dependences of the relaxation times of 3-PG (a) and PVP (b), respectively. The water content is c_W = 40 wt. %. The straight lines below T_g represent fits to the experimental data by the Arrhenius equation, whereas above T_g, full lines represent VFT-fits to the experimental data. Open points were obtained from TSDC experiments, and crosses were obtained from the derivative analysis. Insets: relaxation times of the solute as a function of the relaxation times for the solvent. An almost perfect linear dependence, with a slope of one, is found for PVP, whereas for 3PG, a substantial deviation of a linear dependence is observed.

concentration. For 3PG solutions, we observe two relaxations: a slower one associated with the α-relaxation of the solute and a faster one related to the relaxation of water molecules in the solution.[28] By contrast, for PVP solutions [Fig. 2(b)], we observe three relaxations: the two fastest correspond to the solvent, and the slowest is related to the α-relaxation of the solute (see the supplementary material). In Fig. 2(b), it is, furthermore, evident that the relaxation times of the slow solvent process and the solute exhibit the same temperature dependence in the high temperature range above T_g. This slow solvent relaxation is not observed for 3PG [and for the other solutions

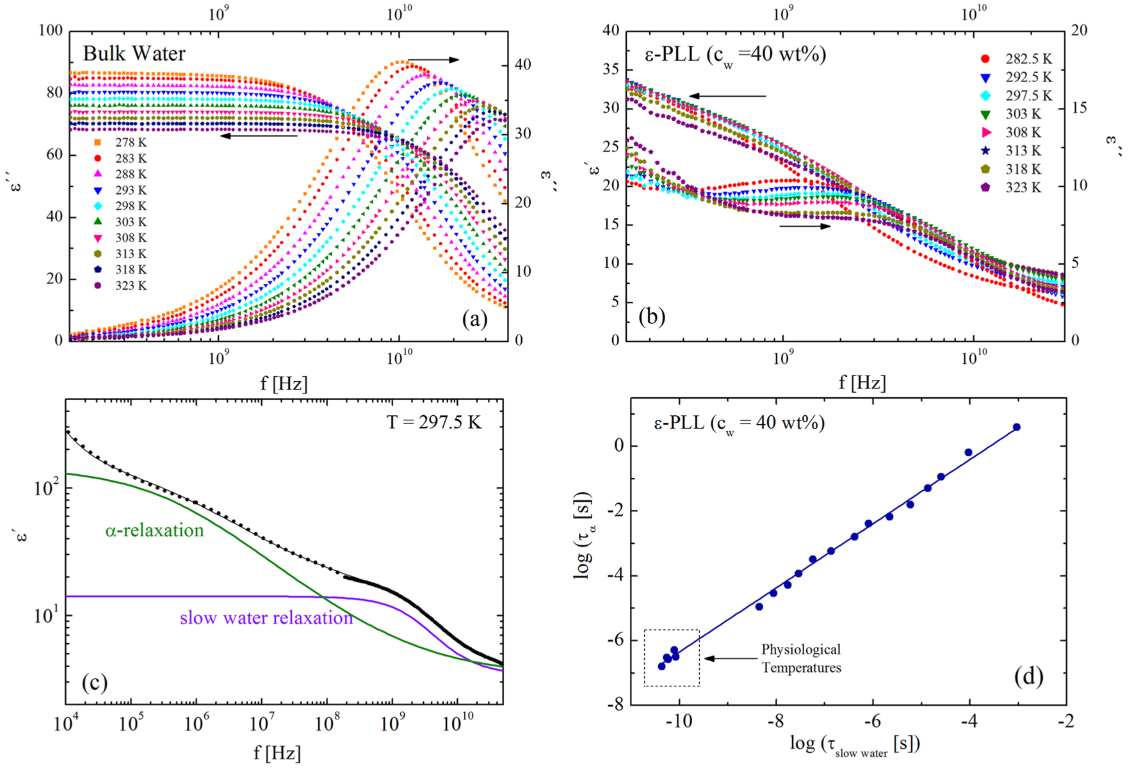

FIG. 3. [(a) and (b)] Real and imaginary parts of the complex dielectric permittivity at different temperatures for bulk water and an ε-PLL water solution. (c) An example of the fitting procedure, where both the solvent and the solute relaxation are displayed. (d) An almost perfect linear dependence, with a slope of one, is found for ε-PLL even at physiological temperatures.

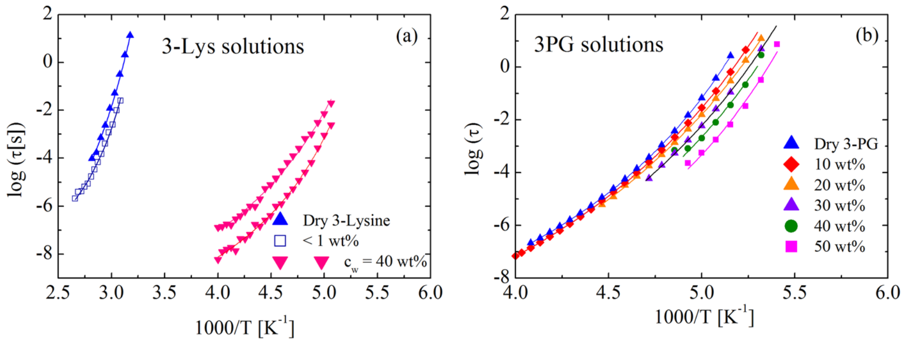

FIG. 4. (a) Temperature dependences of α-related relaxation times of 3-lysine from the dry state to c_w = 40 wt. %. At very low water content, plasticization is observed, and at high water content, a slaving behavior is observed. (b) Temperature dependences of α-related relaxation times of 3PG from the dry state to c_w = 50 wt. %. Plasticization is observed in the whole concentration range analyzed. In both plots, the full lines represent VFT-fits to the experimental data.

in Fig. 1(a)]. In addition, for these solutions, the fast solvent relaxation shows a completely different temperature dependence than the solute relaxation [Fig. 2(a)]. Therefore, the observation of the slaving phenomenon is linked to the appearance of the slow solvent relaxation.

The same dynamical features as shown here for PVP are seen for the rest of the polymers in Fig. 1(b). New and revised data[36,37] of poly(vinyl pyrrolidone), ε-PPL, dextran (a polysaccharide), and oligomers of n-lysine[5] show that their dynamics follow the same characteristics as PVP. The relaxation maps for these systems are shown in Figs. S9–S11 of the supplementary material.

As mentioned above, the main difference between solutions in Figs. 1(a) and 1(b) is that the solvent relaxation splits into two relaxations in Fig. 1(b), where the slower one slaves the α-relaxation of the solute. Although at concentrations between 15 and 20 wt. %, there are indications of a splitting of the water relaxation, until a water content of 30 wt. % is reached it cannot be clearly observed. This indicates that a minimum hydration level is necessary to observe this behavior. However, for 3PG and the group of materials in Fig. 1(a), only a single solvent relaxation is observed even at the highest water content.

C. Dynamics at physiological temperatures

In this section, we discuss the slaving behavior between the water and the solute relaxations at physiological temperatures. Figure 3 shows the dielectric relaxations of bulk water (a) and an ε-PLL solution (b) at temperatures between and 280 and 323 K. As shown in Figs. 3(a) and 3(b), the bulk water relaxation is much faster than the corresponding water relaxation in ε-PLL. Figure 3(c) shows an example of the fitting of the dielectric permittivity at T = 297.5 K, where both the α-relaxation and the slow water relaxation are observed. The extrapolation of the line to high temperatures in Fig 3(d) confirms that the same dependence between the relaxation time of solvent and solute remains, even at physiological temperatures.

D. Segmental dynamics from the dry to wet state—Slaving vs plasticization phenomena

Unlike proteins, for oligomers of lysine, PVP, and dextran, it is possible to observe a glass transition even in the absence of water. For these types of materials, the pure solute (no solvent) displays different types of relaxations which can be related to molecular motions, as typically observed in the literature of soft materials.[38] Here, we focus on the α-relaxation (or segmental dynamics) of the dry solute, and how this relaxation is affected by the presence of water for both 3-Lys and 3PG.

Figure 4(a) shows the relaxation times of the α-relaxation of dry (c_w = 0 wt. %) and wet (c_w = 1 and 40 wt. %) 3-Lys, whereas Fig. 4(b) shows how the α-relaxation of 3PG varies with the water content.[28] The temperature dependence of the α-relaxation times of dry 3-Lys shows a Vogel-Fulcher-Tammann (VFT) behavior, which extrapolates to the calorimetric T_g at 100 s. When adding some water (less than 1 wt. %), the relaxation time becomes slightly faster and the T_g value lower (see Table S1 in the supplementary material) compatible with plasticization. However, at high water contents, the dynamics above T_g deeply change since there is a splitting of the α-relaxation into two different relaxations. The situation for 3PG solutions[28] is drastically different compared to the 3-Lysine solutions. For the whole water concentration range (0–50 wt. %), we can only observe a single α-relaxation and the T_g value decreases from 191 to 183 K, i.e., only 8 K (see Table S2 in the supplementary material).

IV. DISCUSSION

In this study, we found that certain molecules (ε-PLL, 3-Lys, PVP, and dextran) exhibit analogous water concentration dependences of their T_g's as protein solutions. For these solutions, the T_g value is dramatically affected by the water content (the differences between the T_g values of the dry and wet states are, in some cases, more than 200 K). For all these types of systems, two independent water relaxations can be detected in the experiments (one fast and one slow) at high water contents. Above T_g, the slower water relaxation is coupled to the solute relaxation as previously observed for protein solutions.

The advantage to study soft materials instead of proteins lies in the possibility to analyze a broad concentration range including the dry polymer. Thus, for these solutions, we can observe how the dynamical behavior progressively changes from a single water relaxation (at low c_w) to a double water relaxation (at high c_w). When two water relaxations are observed, the solute and the slow solvent dynamics follow the same temperature dependence but with the slow solvent relaxation on a faster time scale. Therefore, we can define a threshold where the slaving behavior is detected. This threshold is about c_w = 15-20 wt. %, which corresponds to 0.17-0.25 g solvent/g solute. The onset of activity of most proteins is around 0.2 g/g, and we believe that these values are not a mere chance. This coincidence of the onset of the functionality with the onset

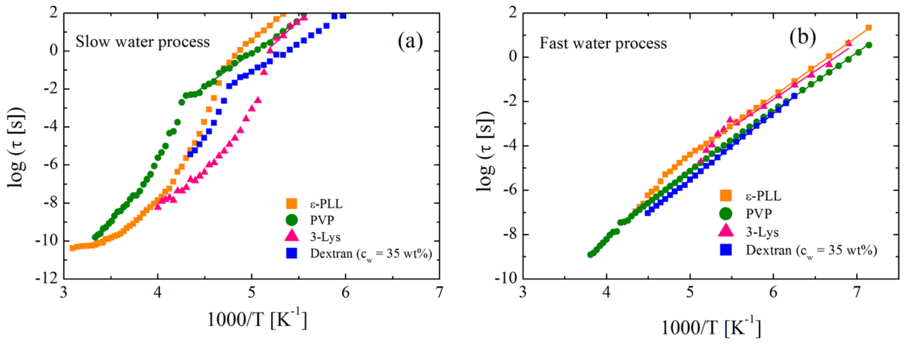

FIG. 5. Temperature dependences of the relaxation times of slow (a) and fast (b) water relaxations for 3-lysine, e-PLL, PVP, and dextran. The water content is 40 wt. %.

of a slaving behavior suggests that the slaving behavior is directly related to the protein functionality. At lower water concentrations (where only plasticization of protein motions due to the presence of water molecules is observed), there are no sufficiently α-like solvent motions to "drive" the dynamics and functions of the proteins. Our results from BDS spectroscopy indicate that a minimum hydration level of 15-20 wt. % is needed to activate the collective water motions that are responsible for the global protein motions. The present results are therefore in line with other results, suggesting that the activation of water motions is a key step in the activation of the protein functionality.

At very low water contents (lower than ~5 wt. %), the results concerning the α-relaxation of all the solutes analyzed (biological or synthetic) are compatible with the effects observed by plasticizers in other materials, i.e., the barriers to overcome to produce the α-relaxation are modulated by the water, and therefore, the glass transition temperature decreases with increasing hydration level. By contrast, at high water contents (c_W > 15-20 wt. %), some soft materials show a splitting of the water relaxation and a slower and more α-like water relaxation appears. The reason for why this slower water relaxation only appears in the solvents of some types of solutes is not evident, but, as discussed below, it seems as this process is a coupled water-solute relaxation where also the dynamical nature of the solute molecules plays a key role. Here it should, furthermore, be noted that no clusters of water or solutes are evidently formed in these samples (see Fig. S13 in the supplementary material), and in the investigated concentration ranges, there is no crystallization to ice, which also excludes the possibility to have water clusters larger than 2 nm.[39,40]

The fact that the solute and water dynamics are coupled is independent of the type of solute (biological or non-biological), provided that the slower water relaxation can be observed. Thus, the slaving phenomenon is not dependent on the structure or conformation of the solute molecules. In fact, oligomers of n-lysine have a defined structure [α-helix (10-Lysine) or β-sheet (ε-PLL)], but PVP and dextran are disordered amorphous materials without any 3D structure. Moreover, details of hydrogen bonds between the water and solute molecules are not likely to be of importance for this behavior since the hydrogen bonding to the solutes shown in Fig. 1(a) is not expected to be systematically different compared to the systems in Figs. 1(b) and 1(c).

We now discuss the presence of two water relaxations (fast and slow processes) in some of the systems analyzed. Figure 5 shows the relaxation times of both relaxations in the four different systems (PVP, ε-PLL, dextran, and 3-lysine).

The dynamics corresponding to the fast process [Fig. 5(b), observed below T_g] corresponds to a local process of water molecules. This conclusion is based on the facts that the time scale is independent of the solute type (i.e., the environment), its temperature dependence is Arrhenius, and the relaxation is symmetric. Even more, at high water contents, the relaxation times of the faster process are also similar to those found in water solutions where a single water relaxation is observed (see Fig. S12 in the supplementary material). This relaxation is therefore classified as the Johari-Goldstein[41] relaxation of "water in solutions."[42]

Contrary to the fast relaxation, the dynamics of the slow water process is dependent on the type of solute [Fig. 5(a)]. The temperature dependence of this relaxation shows a crossover from non-Arrhenius above T_g to Arrhenius at lower temperatures, and both the time scale and the crossover temperature are dependent on the solute. This water relaxation therefore contains cross-terms, which involves both water and solute molecules. This may further explain why this slow water relaxation can be so much slower compared to the bulk water at room temperature[43] and that observed in hard confinements, such as MCM-41.[44] The involvement of the solute in this cooperative process implies also that these more local solute motions play a role in the slaving behavior of the large-scale protein motions.

This new evidence allows us to reshape the concept of slaving. The so-called slaving between the solvent and the solute is observed for solutions with a strong concentration dependence of T_g. This strong dependence implies differences in T_g up to 230 K between the dry and wet solutes [Figs. 1(b) and 1(c)]. In addition, the T_g value of the dry solute is very high (as it would be for proteins) compared with other materials (in which the slaving is not observed) and this implies that they have to overcome very high enthalpy barriers to perform the (conformational) transitions. We can also define a threshold where the slaving behavior is produced (above c_w = 15-20 wt. %) not only in biological solutions, but probably in every solution where the glass transition of the dry solute is very high.

V. CONCLUSION

For the first time, we are able to make a direct correspondence of the role of surrounding water for the dynamical behavior of proteins and some synthetic polymers, respectively. It is demonstrated here that the so-called slaving behavior, developed to describe the role of solvent motions for protein motions, is also observed for non-biological solutions with the condition that these solutes show a strong concentration dependence of T_g with water concentration (up to 230 K between the dry and wet solutes). In addition, it is also possible to define a threshold where the slaving behavior is produced (above c_w = 15-20 wt. %) in every solution where the glass transition of the dry solute is very high. In the case of proteins, this fact further suggests that the onset of the slaving behavior is directly related to the onset of the protein functionality.

Finally, we consider that these types of experiments, to some extent, eliminate a distinction between synthetic polymers and proteins in solutions, which permits us to analyze protein dynamics from a new perspective and to reach a more fundamental physical understanding of how proteins are activated.

SUPPLEMENTARY MATERIAL

See supplementary material which includes isothermal and isochronal dielectric data of PVP solutions; derivative analysis of PVP of different molecular weights, thermal stimulated depolarization current (TSDC) experiments, examples of fitting procedure of the isothermal dielectric data, PVP dielectric data at different water contents, additional relaxation maps for PVP, ε-PLL, and dextran at different water contents, comparison of relaxation times of some aqueous solutions, glass transition temperatures of 3PG and 3-Lys at different water contents, and SAXS data of n-lysine solutions.

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