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Clustering of Glycine Molecules in Aqueous Solution Studied by Molecular Dynamics Simulation

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The nature of glycine−glycine interactions in aqueous solution has been studied using molecular dynamics simulations at four different concentrations and, in each case, four different temperatures. Although evidence is found for formation of small, transient hydrogen-bonded clusters of glycine molecules, the main type of interaction between glycine molecules is found to be single N−H···O−C hydrogen bonds. Double-hydrogen-bonded "dimers", which have often been cited as a significant species present in aqueous solutions of glycine, are only observed infrequently. When double-hydrogen-bonded dimers are formed, they dissociate quickly (typically within less than ca. 4 ps), although the broken hydrogen bonds have a higher than average probability of reforming. Several aspects of the clustering of glycine molecules are investigated as a function of both temperature and concentration, including the size distribution of glycine clusters, the radii of gyration of the clusters, and aspects of the lifetimes of glycine−glycine hydrogen bonding by means of hydrogen-bond correlation functions. Diffusion coefficients for the glycine clusters and water molecules are also investigated and provide results in realistic agreement with experimental results.

1. Introduction

In molecular solids, polymorphism arises when a given type of molecule is able to form different crystal structures.[1–9] Understanding the physical and chemical factors underlying the formation of different polymorphs of a given substance has become an important subject, both from a fundamental scientific viewpoint and from the perspective of optimizing industrial applications. Fundamentally, studies of polymorphic systems represent an ideal opportunity to obtain a systematic understanding of structure−property relationships for crystalline materials and competing pathways in crystallization processes. A wide variety of strategies exist for producing different polymorphic forms of a molecule, including conventional crystallization from solution using different solvents, different crystallization conditions (e.g., temperature), or crystallization in the presence of additives that promote nucleation of a specific polymorphic form. Understanding the solution chemistry is clearly an important prerequisite for rationalization of the formation of different polymorphic forms under different crystallization conditions.

Glycine ($H_2NCH_2CO_2H$) has received considerable attention in polymorphism research and has, to a large extent, assumed the status of a prototypical system in fundamental studies of polymorphism. Glycine has three known polymorphs (α, β, and γ) under ambient conditions[10] with the following order of stability: $\gamma > \alpha > \beta$.[11–13] Crystallization from neutral aqueous solution under ambient conditions generally leads to formation of the α polymorph.[14] The thermodynamically stable γ polymorph is not obtained under these conditions, presumably due to kinetic barriers inhibiting formation of this polymorph.[14] The γ polymorph, on the other hand, is obtained from aqueous solution under acidic (pH < 3.8) or basic (pH > 8.9) conditions,[10,11,14] and crystallization from deuterated aqueous solution at neutral pH has also been observed to favor formation of the γ polymorph.[15,16] Formation of the γ polymorph is also reported to be promoted by addition of sodium salts (e.g., sodium chloride, sodium fluoride, and sodium nitrate),[17] application of polarized laser radiation,[18] application of a dc electric field,[19] evaporation of microdroplets,[20] and thin-film evaporation of a neutral aqueous solution at a glass surface.[21] In neutral aqueous solution, glycine exists almost entirely in the zwitterionic form, $H_3N^+CH_2COO^-$, and it is estimated that nonzwitterionic glycine molecules NH_2CH_2COOH have a population of only ca. 4.4 ppm.[22] In the crystal structures of all three polymorphs, glycine also exists in the zwitterionic form.

The crystal structure of the α polymorph (Figure 1a; space group $P2_1/n$) comprises bilayers of glycine molecules.[23] Each glycine molecule is engaged in strong N−H···O hydrogen-bonding interactions to other molecules within a given layer and interacts through a centrosymmetric double-hydrogen-bonded motif to a molecule in the other layer of the bilayer. It has been suggested[14,20,24–28] that formation of the α polymorph is favored in neutral aqueous solution because a significant proportion of glycine molecules in these solutions exist as double-hydrogen-bonded dimers, whereas when ethanol is present in the aqueous solution, formation of such dimers is disrupted,[29] leading to preferred formation of the β polymorph. However, direct experimental observation of such double-hydrogen-bonded dimers is difficult, and the suggestion that such dimers represent a significant species in aqueous solution has been mainly inferred from results such as atomic force microscopy of cleaved glycine surfaces,[30] surface X-ray scattering of stereospecific adsorption of additives on glycine surfaces,[24] and analysis of diffusion coefficients.[31] The most direct experiments on the aggregation of glycine molecules in

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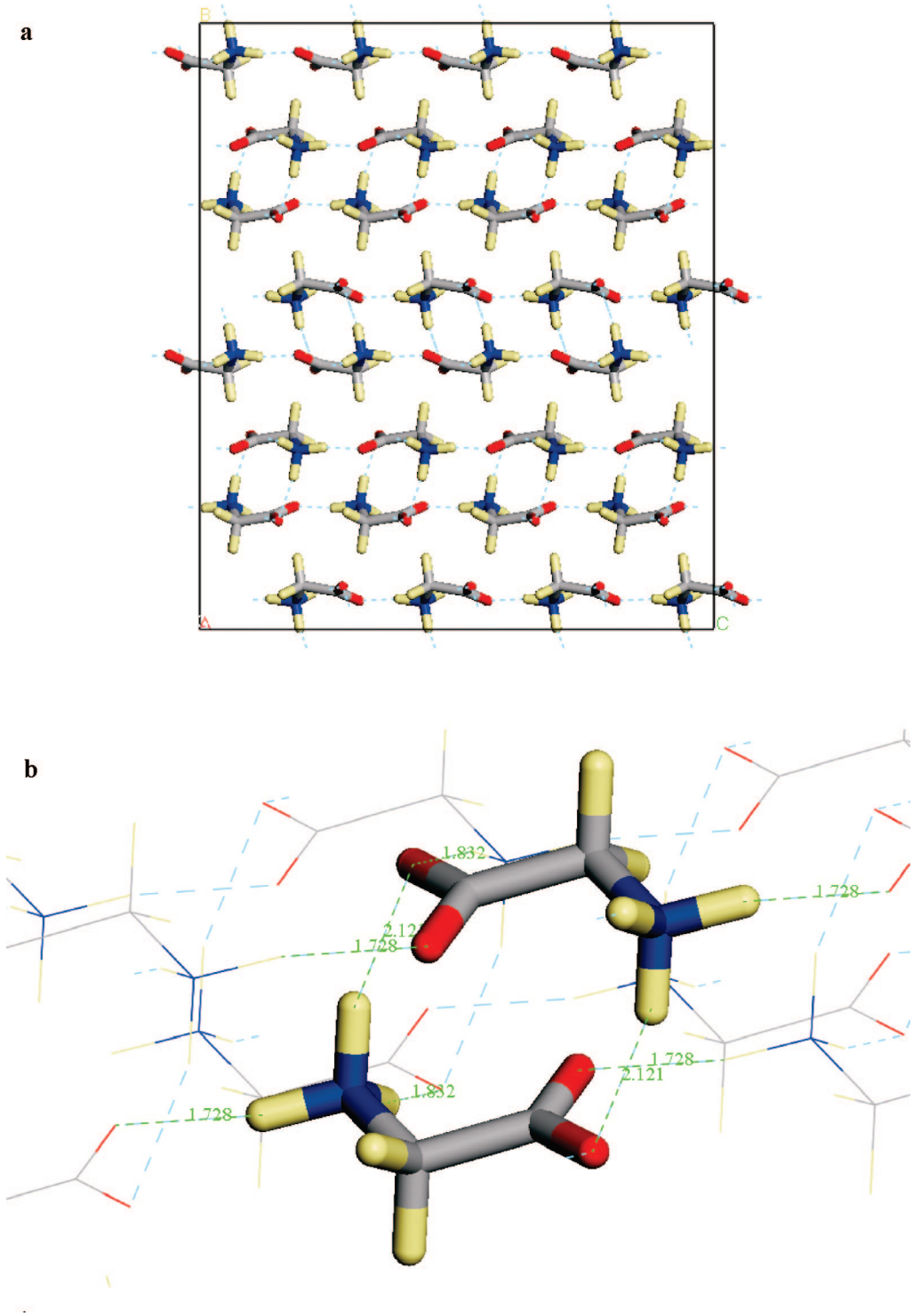

Figure 1. (a) View along the (100) direction of the crystal structure of the α polymorph of glycine. (b) The centrosymmetric, double-hydrogen-bonded dimer in the crystal structure of the α polymorph of glycine.

solution date back to the 1930s, when investigations on the depression of the freezing point of water due to glycine led to the conclusion that there is some degree of aggregation.[32–34]

Due to the challenges associated with experimental studies of molecular aggregation in solution, there is a clear opportunity to exploit computer simulation techniques to provide detailed information on this issue. Recently, Campo[35] employed classical molecular dynamics simulations to study aqueous solutions of glycine at room temperature, although the main goal was not to study glycine−glycine interactions but rather to study the influence of glycine and NaCl on the surrounding water molecules. Hence, the aims of the work of Campo were significantly different from those of the present paper.

Molecular dynamics (MD) simulations have been used widely to study the solution chemistry of a broad range of systems. For example, association of solute molecules in solution has been shown to have a major effect on the polymorphic outcome for tetrolic acid.[36,37] The influence of solvent and impurities in solution on prenucleation entities in the crystallization of 5-fluorouracil has been studied by MD simulation and provided an explanation for experimental observations on this system.[38]

In general, nucleation is very difficult to model due to the requirement for both exceedingly long simulations times and large system sizes. However, using some assumptions which allowed the problem to be simplified, Anwar and Boateng[39] successfully simulated the nucleation of a model system using MD techniques. More recently,[40] information obtained from MD simulations has been used to generate realistic models of the growth units of urea molecules in solution. The interaction between these growth units was then introduced in kinetic Monte Carlo simulations, from which very accurate descriptions of the growth process, crystal morphologies, and defect structures were obtained.

In the present paper, the aqueous solution chemistry of glycine is explored by MD simulations, carried out for four different concentrations and four different temperatures. Several aspects of the clustering of glycine molecules in these solutions are investigated and, inter alia, our results address directly the question of whether double-hydrogen-bonded dimers of glycine molecules represent a significant species in aqueous solution.

2. Computational Details

MD simulations were carried out using the DL_POLY2 program[41] for aqueous solutions of glycine at four different concentrations (0.5, 1.0, 2.0, and 3.6 mol dm^{-3}) and, in each case, four different temperatures (20, 30, 40, and 50 °C). The simulations were run on the terascale computing facility HPCx at Daresbury Laboratory. Three concentrations (0.5, 1.0, and 2.0 mol dm^{-3}) correspond to undersaturated solutions, and one concentration (3.6 mol dm^{-3}) corresponds to a supersaturated solution (the concentration of a saturated aqueous solution of glycine at 20 °C is 3.0 mol dm^{-3}). The solutions were modeled by cubic simulation cells (with lengths between 30.9 and 32.6 Å, depending on temperature and concentration) in which 1000 water molecules and 9, 18, 36, and 64 glycine molecules were included (corresponding to concentrations 0.5, 1.0, 2.0, and 3.6 mol dm^{-3}, respectively). All glycine molecules in the simulations were in the zwitterionic form. A time step of 0.6 fs was used.

A pre-equilibration run of 50 ps was performed for each concentration and temperature, with the temperature kept constant by means of the NVT Evans thermostat. MD simulations were then run in the NpT ensemble using the Nosé-Hoover barostat and thermostat in order to maintain pressure at 1 atm and temperature at one of the four values of interest (20, 30, 40, and 50 °C). Equilibration of each system in the NpT ensemble was carried out until the energies, temperatures, and cell parameters showed sufficiently small variations, which typically required between 100 and 200 ps depending on the system. Once each system had equilibrated, the final simulations were started, which included an initial period of 100 ps as additional equilibration. The length of the subsequent production run for each system was 5 ns.

The AMBER potential[42]was used to model the glycine molecules as this potential has been shown previously[13] to be able to reproduce the crystal structures of the three polymorphs of glycine and to correctly predict their relative energy ranking. Water molecules were modeled using the TIP3P potential,[43] which has been used successfully in several previous studies. The interactions between glycine molecules and water molecules were also described using the AMBER potential. As shown in our earlier study,[16] the ability of these force fields to model aqueous solutions of glycine has been confirmed from the close comparison of calculated (from MD) and experimental radial distribution functions for glycine−water atoms.

3. Results and Discussion

3.1. Calculation of Diffusion Coefficients. Diffusion coefficients are obtained from the mean square displacement, MSD, defined as

$$\mathrm{MSD}(t) = \langle |\vec{r}(t) - \vec{r}(0)|^2 \rangle \quad (1)$$

where $\vec{r}(0)$ is the initial position of the molecule and $\vec{r}(t)$ is the position at time t via the Einstein relationship

$$D = \lim_{t\to\infty} \frac{\langle |\vec{r}(t) - \vec{r}(0)|^2 \rangle}{6t} \quad (2)$$

Typical MSD plots from our MD simulations of glycine in aqueous solution are shown in Figure 2. In Figure 3, the diffusion coefficients are compared with two independent sets of experimental results, one taken from Ma et al.[44] (employing holographic interferometry) and the other taken from our previous experimental studies using NMR.[16,45] We note that the experiments of Ma et al. used water with natural isotopic abundances, whereas our NMR experiments used deuterated water. Lower values of diffusion coefficients are obtained in deuterated water due to the higher viscosity of this solvent, which explains the difference of about 10% between the results of the two experimental studies. The only previous reported use of MD simulations to determine diffusion coefficients for glycine in aqueous solution was the study of Campo,[35] the results of which are also included in Figure 3. However, the work of Campo[35] was focused on other aspects of the aqueous solution chemistry of glycine and used a different force field (GROMOS[46]) from that employed in the present paper. Nonetheless, the results are consistent with the main findings of the present paper although somewhat further from the experimental values than our own.

Although our calculated diffusion coefficients for the glycine molecules and the experimentally determined diffusion coefficients are in agreement within 10 − 30%, it is well known that accurate values of diffusion coefficients are difficult to obtain from MD simulations.[47–50] Thus, the agreement between calculated and experimental values in the present case (which are well within an order of magnitude of each other) is considered acceptable. Although the MSD plots shown in Figure 2 have considerable fluctuations (particularly at low concentration[51]) the estimated standard errors in the diffusion coefficients are small (ca. 0.01×10^{-10} m^2 s^{-1}), partly as a consequence of the large number of data points involved in the fitting process. In the present context, comparison of calculated and experimental diffusion coefficients serves an important role in validating the potential model used to describe the aqueous glycine solutions as calculated diffusion coefficients are known to be highly sensitive to the potential model, and the level of agreement obtained in the present work provides sufficient vindication in this regard. If there were significant inadequacies in the interatomic potentials employed, the discrepancies between calculated and experimental results would be expected to be far more significant than those observed here.

Diffusion coefficients were also calculated for the water molecules in our MD simulations (Figure 4). In this case, the diffusion coefficient decreases monotonically as concentration is increased at fixed temperature or as temperature is decreased at fixed concentration (with the exception of the point corresponding to 1.0 mol dm^{-3} at 40 °C, which fails to follow this trend). At 20 °C, the calculated diffusion coefficient shows an

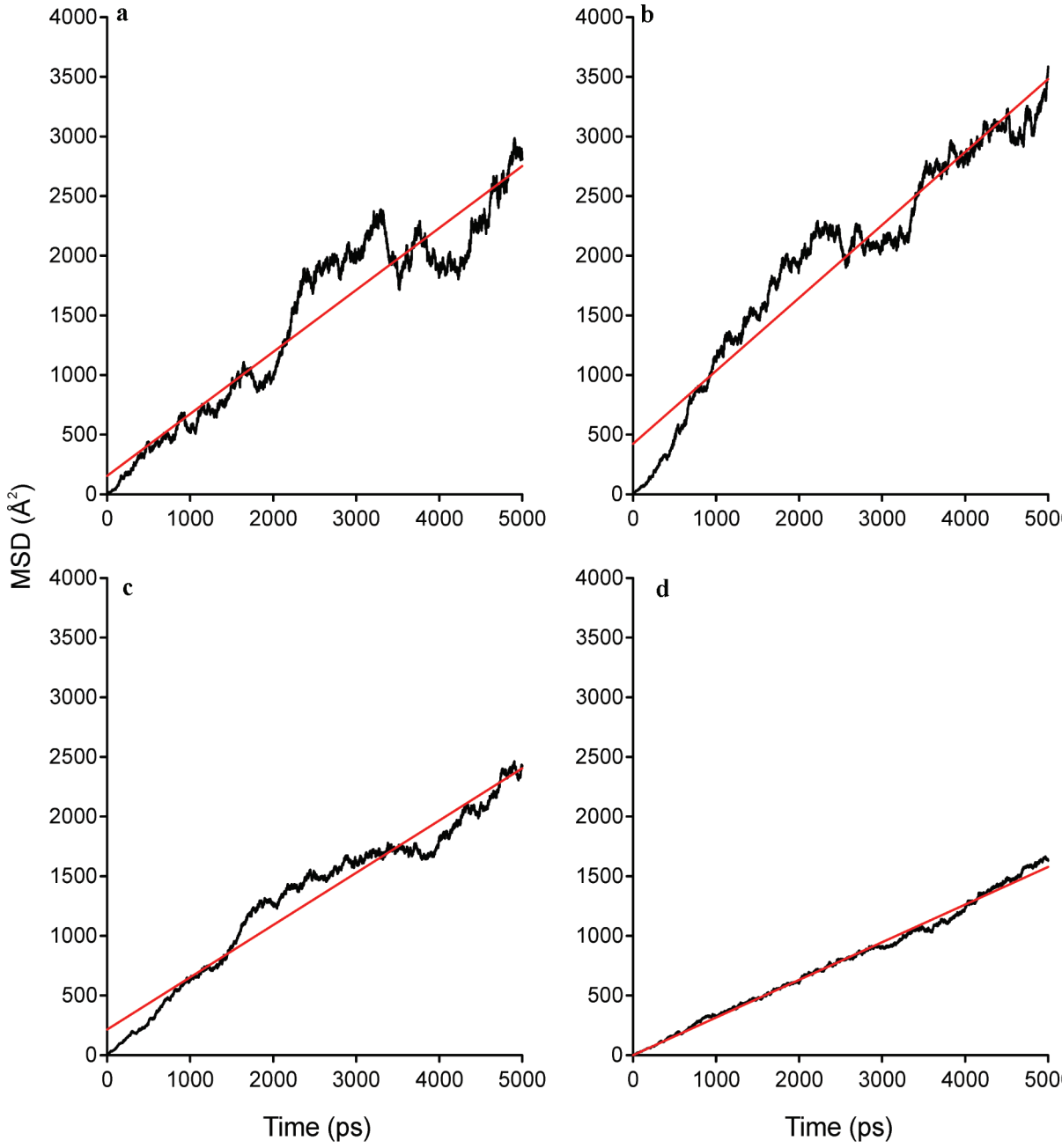

Figure 2. MSD plots for glycine molecules in the MD simulations under the following conditions: (a) 0.5 mol dm^{-3}, 30 °C; (b) 1 mol dm^{-3}, 50 °C; (c) 2 mol dm^{-3}, 40 °C; and (d) 3.6 mol dm^{-3}, 30 °C. The red lines represent a linear fit of the data, the gradient of which gives the diffusion coefficient.

approximately linear dependence on concentration, allowing the value of the diffusion coefficient at infinite dilution (24.9×10^{-10} m^2 s^{-1}) to be obtained by extrapolation. For comparison, the diffusion coefficient calculated from MD simulations of pure water at 25 °C using a modified TIP3P potential[52] is 40×10^{-10} m^2 s^{-1}, whereas two experimental determinations (using the diaphragm-cell[53] and PGSE NMR[54] techniques) both led to a value of 23×10^{-10} m^2 s^{-1}.

3.2. Analysis of Hydrogen-Bonded Glycine Clusters. We now consider the properties of the hydrogen-bonded clusters of glycine molecules formed in the MD simulations. In our previous study,[16] formation of an N—H···O hydrogen bond between two glycine molecules was defined on the basis of a maximum H···O distance of 2.2 Å and a minimum N—H···O angle of 140°. These criteria were chosen because all the hydrogen bonds present in the crystal structures of the three polymorphs of glycine fall within these limits. We now assess further, on the basis of experimental data and the results of our MD simulations, the most appropriate criteria to define N—H···O hydrogen bonding between glycine molecules. In the 1930s, three experimental studies of the freezing point depression of aqueous solutions of glycine[32–34] provided estimates of the average particle mass (APM) as a function of concentration. Clearly, APM values can also be determined directly from our MD simulations given a specific criterion to define N—H···O hydrogen bonding between glycine molecules (and hence to define formation of glycine clusters), and here we use the comparison with the experimental results as a means of guiding our assessment of suitable hydrogen-bonding criteria to be used in the analysis of the results from our MD simulations. In Figure 5, our calculated (at 20 °C) APM values (for different hydrogen-bond definitions) and the

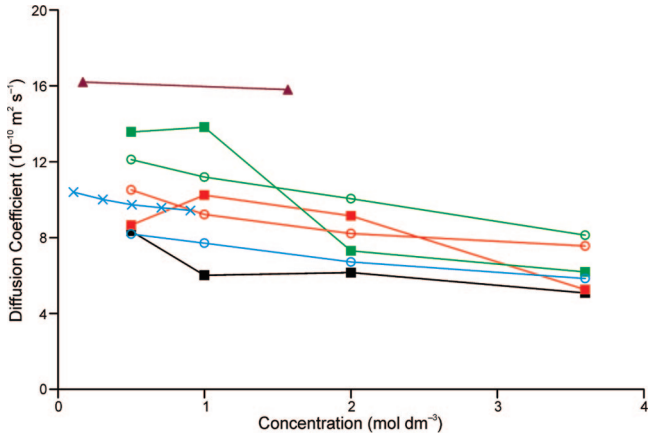

Figure 3. Comparison of experimental and calculated diffusion coefficients for glycine molecules. Experimental values in H_2O (Ma et al.[44]) at 25 °C are shown with blue crosses. Experimental values in D_2O (Hughes et al.[16]) are shown with open circles (blue, 25 °C; red, 30 °C; green, 40 °C). The data from the present work are shown with filled squares (black, 20 °C; red, 30 °C; green, 40 °C). Results from the previous MD simulations of Campo[35] at 27 °C are shown with purple filled triangles.

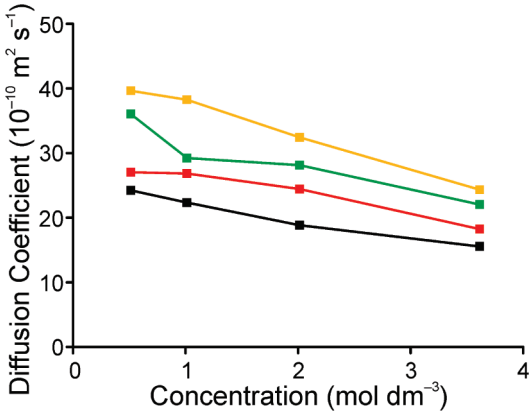

Figure 4. Diffusion coefficients of water molecules obtained from the MD simulations (black, 20 °C; red, 30 °C; green, 40 °C; yellow, 50 °C).

experimental APM values are plotted as a function of concentration. The molar mass of glycine is 75 g mol^{-1}, which represents the minimum value of APM that our simulations can predict. Nine different sets of hydrogen-bond criteria were considered in our analysis of the results of the MD simulations (Figure 5), and the definition giving rise to the best agreement with the experimental APM values corresponds to a maximum H···O distance of 2.2 Å and a minimum N—H···O angle of 160°. The fact that good agreement is obtained between experimental and calculated APMs gives further confidence in the validity of our simulations and the reliability of the description of glycine−glycine and glycine−water interactions in our simulations.

Two specific hydrogen-bond criteria, 2.2 Å/140° (which encompasses all hydrogen bonds in the crystal structures of the three polymorphs of glycine, as discussed previously[16]) and 2.2 Å/160° (which better fits the freezing point depression data, as discussed above), have been used in our further analysis of the clustering of glycine molecules from our MD simulations. First, the percentage of glycine molecules that exist as monomers (i.e., with no hydrogen bonding to any other glycine molecule), dimers (i.e., pairs of glycine molecules hydrogen bonded to each other but not to any other glycine molecule), and trimers (i.e., groups of three glycine

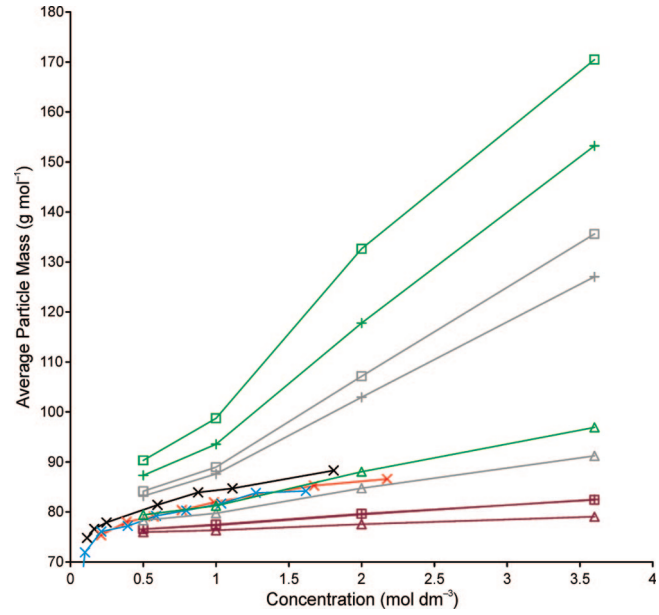

Figure 5. Average particle masses in glycine solutions determined from our MD simulations and previous freezing point depression experiments. The experimental data are from Frankel[33] (black crosses), Lewis[34] (red crosses), and Anslow[32] (blue crosses). Data from the present work are shown for several different hydrogen-bond definitions, based on the minimum N—H···O angle [120° (□), 140° (+), 160° (△)] and the maximum H···O distance [1.8 Å (purple), 2.0 Å (grey), 2.2 Å (green)].

molecules hydrogen bonded to each other but not to any other glycine molecule) were calculated from the simulations carried out for each concentration at 20 °C. The results are shown in Figure 6. For both hydrogen-bond criteria, monomers are the predominant species present at all concentrations considered, although the proportion of monomers decreases steadily as concentration is increased. However, even for the supersaturated solution (3.6 mol dm^{-3}), as many as 80% of the glycine molecules exist as monomers with the more restrictive (2.2 Å/160°) hydrogen-bond definition and 50% of the glycine molecules exist as monomers with the less restrictive (2.2 Å/140°) hydrogen-bond definition. For both hydrogen-bond definitions, the results suggest that glycine molecules do not have a strong tendency to form clusters in aqueous solution. This observation is also consistent with other results from MD simulations[35] and recent results from dielectric relaxation spectroscopy.[55]

Nevertheless, our results reflect the expected tendency for the distribution of cluster sizes to shift toward clusters of increasing size as concentration is increased. For the highest concentration (3.6 mol dm^{-3}) studied, a small number of clusters comprising more than six molecules are observed, although the predominant species are still monomers and smaller clusters (dimers and trimers). It is also clear from our MD simulations that there is a continuous process of formation and breakage of hydrogen bonds in glycine clusters in aqueous solution and that the majority of the clusters are short-lived (with hydrogen bonds usually broken in less than ca. 4 ps). Aspects of the time dependence of cluster formation are now discussed in more detail.

3.3. Analysis of Glycine−Glycine Hydrogen Bonding Using Correlation Functions. Our analysis of hydrogen-bond formation discussed in section 3.2 considered the time-averaged distribution of cluster sizes and did not consider the time-dependence of hydrogen-bond formation. In particular, breaking

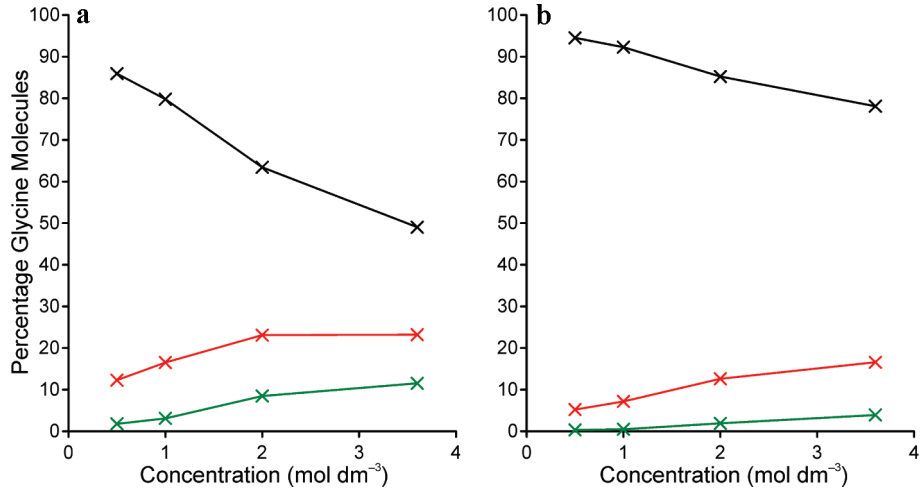

Figure 6. Average percentages of glycine molecules present in monomers (black), dimers (red), and trimers (green), as a function of concentration, in the MD simulations at 20 °C. The results are shown for two different hydrogen-bond definitions: (a) 2.2 Å/140° and (b) 2.2 Å/160°.

and reforming of hydrogen bonds between a given pair of molecules contributes to the time-averaged description in exactly the same way as the same number of breakage and reformation events for different pairs of molecules. The physics of these two situations is clearly different, and we therefore analyzed the probability of reforming a given hydrogen bond once it has been broken.

The most commonly used function to study the processes of hydrogen-bond formation and breakage is the hydrogen-bond correlation function, $c(t)$,[56,57] which represents the probability that a hydrogen bond in existence at time $t = 0$ is also in existence at a later time t, and is defined as

$$c(t) = \frac{\langle h(0)h(t)\rangle}{\langle h(t)\rangle} \tag{3}$$

where $h(t) = 1$ if a particular pair of glycine molecules is hydrogen bonded at time t and $h(t) = 0$ otherwise. The angular brackets represent an ensemble average over all pairs of glycine molecules. For a system with N glycine molecules, the number of pairs is

$$N_p = \frac{N(N-1)}{2} \tag{4}$$

The clustering of the system can be described entirely by the N_p values of $h(t)$. By definition, $c(0) = 1$ and $c(\infty) = 0$, because any two molecules will become uncorrelated after a sufficiently long time.

Figure 7 shows a comparison of the results for two different rates of sampling $c(t)$, 0.6 and 24 fs, and demonstrates that $c(t)$ falls very rapidly from $c(0) = 1$ within the first few hundred femtoseconds. The hydrogen-bond correlation functions obtained for the four concentrations at 20 °C are shown in Figure 8, demonstrating that, at a given temperature, $c(t)$ decreases slightly faster at higher concentration. As shown in Figure 9, the dependence of $c(t)$ on temperature (at a given concentration) is more significant, with the value of $c(t)$ at long values of time decreasing by ca. 4 % as temperature is increased from 20 to 50 °C.

3.4. Distribution of Cluster Sizes. So far, we have discussed the size of glycine clusters formed in aqueous solution in terms of the number of molecules involved in the cluster. In this section, we discuss aspects of the size and shape of the clusters using the radius of gyration R_g, which is used widely in

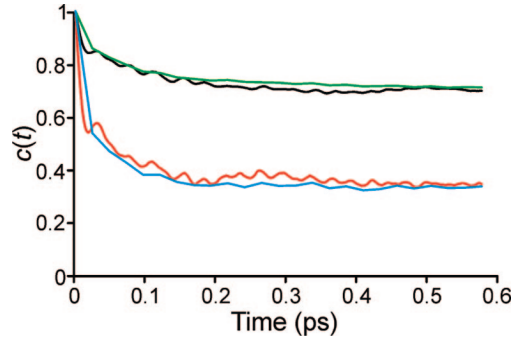

Figure 7. Hydrogen-bond correlation functions, $c(t)$, determined from the MD simulation for the 3.6 mol dm^{-3} glycine solution at 20 °C. The trajectories were stored in steps of 0.6 (black and red) and 24 fs (green and blue). Hydrogen bonds are defined for a maximum H···O distance of 2.2 Å and minimum N—H···O angles of 160° (black and green) and 140° (red and blue).

experimental studies of cluster formation in solution. For a cluster formed by N atoms labeled i ($i = 1, 2, \ldots, N$), R_g is defined as

$$R_g = \sqrt{\frac{\sum_i^N m_i |\vec{r}_i|^2}{\sum_i^N m_i}} \tag{5}$$

where m_i is the mass of atom i and $|\vec{r}_i|$ is the distance of atom i from the center of mass of the cluster.

The value of R_g was calculated for each class of cluster (i.e., monomers, dimers, trimers, etc.) present in our MD simulations, and the distribution of R_g values for a given class of cluster is shown in Figure 10. As most glycine molecules exist as monomers, the largest peak corresponds to the value of R_g for a single molecule and has a maximum at 1.51 Å (the distribution of values of R_g in this case is caused by fluctuations in the molecular conformation). For dimers, the value of R_g ranges from 2.0 to 3.6 Å, with a maximum in the distribution at 2.8 Å and a clear "shoulder" at around 3.1 Å. A similar shape of distribution is observed for trimers, ranging from 2.6 to 5.0 Å with a maximum at 3.4 Å and a shoulder at around 4.1 Å. Clearly, clusters involving a greater number of molecules (tetramers and pentamers) correspond to larger values of R_g, up to ca. 7.5 Å, although these species are extremely rare.

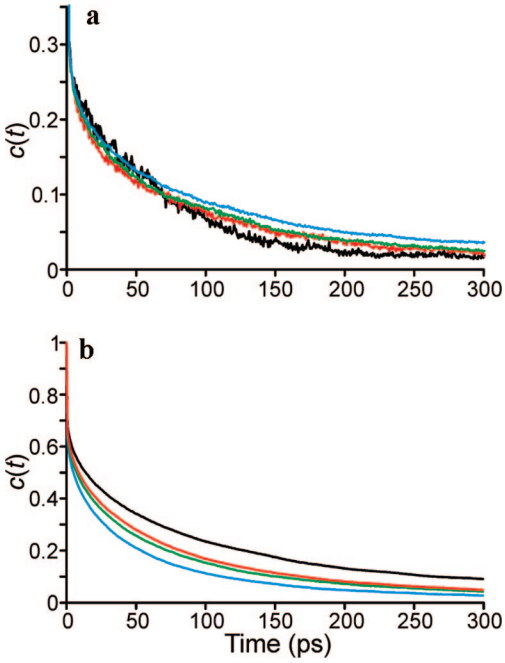

Figure 8. Hydrogen-bond correlation functions, $c(t)$, determined from the MD simulations for the 0.5 (black), 1.0 (red), 2.0 (green), and 3.6 mol dm^{-3} (blue) glycine solutions at 20 °C. Hydrogen bonds are defined for a maximum H···O distance of 2.2 Å and a minimum N—H···O angle of (a) 160° and (b) 140°.

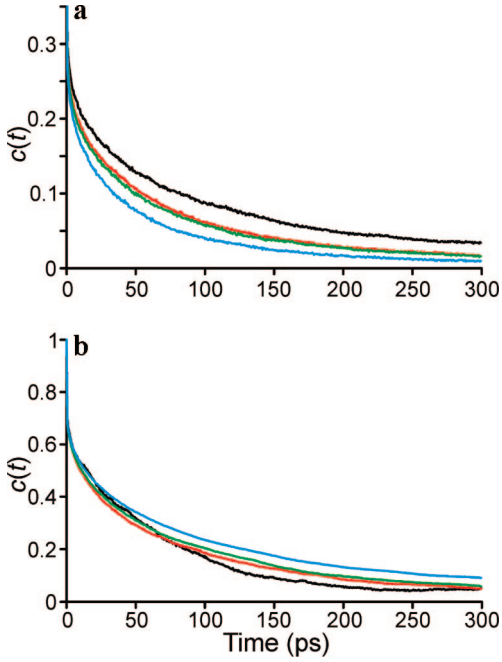

Figure 9. Hydrogen-bond correlation functions, $c(t)$, determined from MD simulations for the 3.6 mol dm^{-3} glycine solution at 20 (black), 30 (red), 40 (green), and 50 °C (blue). Hydrogen bonds are defined for a maximum H···O distance of 2.2 Å and a minimum N—H···O angle of (a) 160° and (b) 140°.

3.5. Do Double-Hydrogen-Bonded Dimers of Glycine Represent a Significant Species in Aqueous Solution? It has often been implied[14,20,24–28] that, for glycine molecules in aqueous solution, there is a significant population of double-hydrogen-bonded dimers and that these species play an important role in directing crystallization toward the α polymorph under these conditions. This view has been accepted mainly because such double-hydrogen-bonded dimers (as shown in Figure 1b) are known to exist in the crystal structure of the α polymorph of glycine, which is the polymorph formed preferentially from neutral aqueous solution.

Figure 1b shows the hydrogen-bond distances for the double-hydrogen-bonded dimer in the crystal structure of the α polymorph (determined from neutron diffraction data[23]) involving two N—H···O hydrogen bonds with an H···O distance of 2.10 Å and N—H···O angle of 154.3°. However, each glycine molecule also forms stronger (as assessed from geometric criteria) N—H···O hydrogen bonds to other glycine molecules in the same layer. Indeed, the oxygen atom that is involved in the double-hydrogen-bonded dimer is also involved in a stronger hydrogen bond to another molecule in the same layer with an H···O distance of 1.82 Å and a more linear N—H···O angle of 168.8°. The other oxygen atom (not involved in the double-hydrogen-bonded dimer) is engaged in an N—H···O hydrogen bond to another neighboring molecule, which is even shorter and more linear, with an H···O distance of 1.73 Å and N—H···O angle of 169.2°. The two oxygen atoms in each molecule therefore connect to three different neighboring molecules, and the NH_3^+ group forms two strong N—H···O hydrogen bonds to two other molecules and one weaker N—H···O hydrogen bond to the other molecule in the double-hydrogen-bonded dimer. Thus, the bilayer structure comprises strong N—H···O hydrogen bonding within each constituent layer and only weaker N—H···O hydrogen bonding (i.e., the double-hydrogen-bonded dimer) between the two layers of the bilayer. Clearly, a detailed analysis of the crystal structure of the α polymorph does not support the suggestion that the double-hydrogen-bonded dimer is the most fundamental building block of this structure.

The article by Gidalevitz et al.[30] is often cited as providing experimental evidence for the existence of double-hydrogen-bonded dimers in solution, based on data from atomic force microscopy and grazing incidence X-ray diffraction of cleaved glycine surfaces. Although these two techniques can provide valuable information on the growth processes on the surfaces of glycine crystals, they do not provide any direct information on the equilibrium populations of the clusters of glycine molecules that exist in aqueous solution.

The results of small-angle X-ray scattering (SAXS) studies[26,28] of glycine in aqueous solution have also been discussed in the context of supporting the notion that glycine dimers represent a significant species in neutral aqueous solutions. In the more recent study[28] (published after completion of the current work), the radius of gyration, R_g, of glycine clusters was reported to be 3.2 Å for a 4.05 mol dm^{-3} aqueous solution at 6.5 °C. This value of R_g was constant for a period of 40 min at this temperature (the solution had earlier been cooled from 65 to 6.5 °C over 15 min with the radius of gyration increasing from 2.7 to 3.2 Å during this period). The value of $R_g = 3.2$ Å was ascribed as representing "the progressive dimerization of glycine molecules and formation of multimers". It is relevant to make a number of comments regarding this statement in relation to the results of the present work. First, we note that the SAXS study was focused on conditions of temperature and concentration (6.5 °C and 4.05 mol dm^{-3}) that lie outside the range of conditions of the MD simulations carried out in the present work, representing lower temperature and higher concentration than any of the conditions studied in our MD simulations. As a consequence, a higher degree of aggregation of glycine molecules would be anticipated in the SAXS study, as reflected in the higher (average) value of R_g reported.[28] Second, our MD simulation study provides access to knowledge of the distribu-

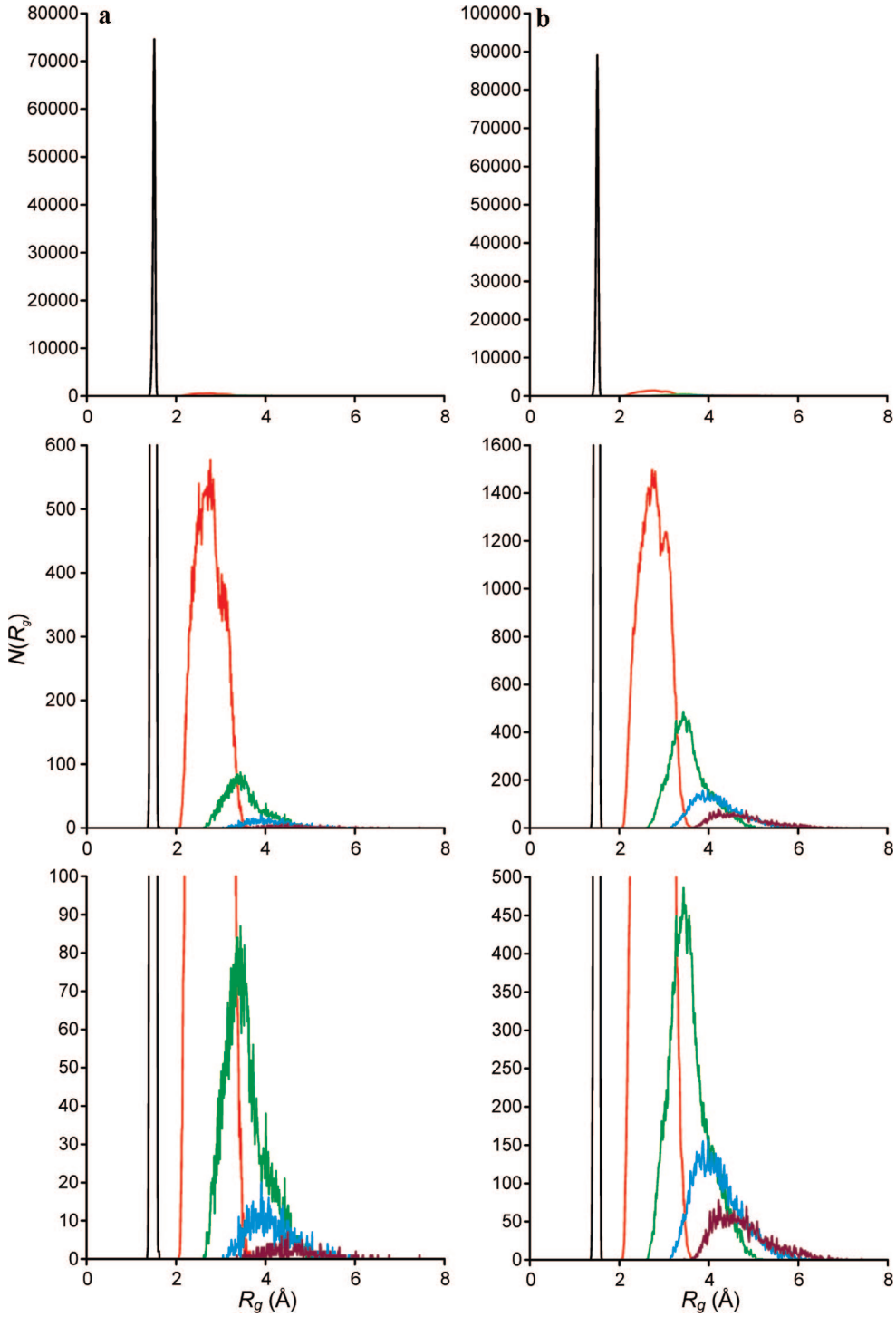

Figure 10. Distribution of R_g values determined from the MD simulation for the 3.6 mol dm^{-3} glycine solution at 20 °C. The data are separated according to the number of glycine molecules in the cluster: 1 (black), 2 (red), 3 (green), 4 (blue), and 5 (purple). Hydrogen bonds are defined for a maximum H···O distance of 2.2 Å and a minimum N—H···O angle of (a) 160° and (b) 140°.

tion of R_g values present in the system, in contrast to the single (average) value of R_g extracted from the SAXS data. Thus, while the single value of R_g reported from the SAXS studies may provide an indication of the average size of the glycine clusters present, details of the actual *distribution* of cluster sizes that exists in solution cannot be extrapolated from this value.

A strong inference of ref 28 is that dimeric entities make a significant contribution to the distribution of glycine clusters that give rise to the average R_g value of 3.2 Å, although clearly the actual proportion of glycine molecules present as dimers cannot be assessed quantitatively from such data. The radius of gyration of a double-hydrogen-bonded dimer (taking the geometry as that of the double-hydrogen-bonded dimer in the crystal structure of the α polymorph of glycine) is 2.18 Å. Thus, while such dimers may contribute to the distribution of glycine clusters observed in the SAXS study, it is unlikely that they represent the predominant species present. Such a conclusion (although not stated as such by the authors of ref 28) would be consistent with the results from the MD simulations reported here. Clearly dimeric entities should exist at some stage during the nucleation process as the system evolves from single (isolated but solvated) glycine molecules through to the critical

nucleation entity, but any assertion that dimeric entities represent the predominant species in such solutions is certainly not supported by the results of the present work (at least within the range of conditions of temperature and concentration covered by our MD simulation studies).

4. Concluding Remarks

In this paper, MD simulations have been used to probe the aqueous solution chemistry of glycine over a range of conditions of temperature and concentration. Evidence is found for the formation of small, transient hydrogen-bonded clusters of glycine molecules, but there is no evidence from our results for the extensive formation of double-hydrogen-bonded dimers. Of course, even though the concentrations of such clusters observed in our simulations are very low, we cannot rule out the possibility that they might still be important entities on the pathway toward nucleation of the α polymorph of glycine (which is observed experimentally as the final outcome of the crystallization of glycine from neutral aqueous solution). Nevertheless, it is important to emphasize that the cluster sizes probed in the types of MD simulation reported here are significantly smaller than the clusters that represent the critical nucleation events in the formation of organic molecular crystals from solution. As a consequence, it is important to exert considerable caution before extrapolating from the structural properties of the small clusters observed in such simulations in order to rationalize the final outcome of crystallization processes carried out under the corresponding experimental conditions. Even if some of the small clusters observed in the simulations in the present work may participate on the pathway toward crystallization of glycine from aqueous solution, it is not necessarily valid to assume that the structures of these small clusters should be retained within the structures of the larger crystalline aggregates that they subsequently evolve into at more advanced stages of the pathway toward crystal nucleation.

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