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Glass transition in aqueous solutions of glucose. Molecular dynamics simulation

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Abstract

We have simulated by molecular dynamics the melting and glass transition of aqueous solution of glucose in a wide concentration range. The simulated glass transition temperature (T_g) are in good agreement with experimental values but the obtained melting temperatures of relatively diluted solutions are below the experimental ones. The 'glass' branch of the temperature–concentration state diagram is quite acceptable and opens the possibility of reliable simulation of vitrification processes in carbohydrate solutions. © 1997 Elsevier Science Ltd.

Keywords: Glass transitions in carbohydrates; Simulation of phase transitions; Glucose state diagram

1. Introduction

With the interest in vitrification and its implication in cryobiology, a number of studies have been reported on melting and glass transition of carbohydrates and their aqueous solutions. A large effort has been directed at understanding the interactions of water with other molecules due to the importance of water in maintaining biological structure and function, the consequences of removing mobile water by freezing or drying being severely injurious in many cases. Many of the specialised functions of specific carbohydrates, such as their ability to modify solution viscosity or to serve as a cryoprotectants, should result from details of their interactions with water molecules [1].

Most carbohydrates form amorphous structures when rapidly cooled from the melt, dehydrated from solutions or freeze-concentrated. This amorphous state is metastable. In the aqueous solutions of many organic compounds no eutectic formation is usually observed and the ice crystals are surrounded by undercooled freeze-concentrated solution which contains all the solute in the unfrozen fraction of water. This undercooled solution undergoes a rubber–glass transition [2].

Vitrification is marked as a discontinuous change in properties which are second derivatives of the free energy, such as heat capacity and thermal expansion coefficient. This has lead to the proposal that there is a second order thermodynamic phase transition underlying the vitrification process. However, the temperature of the transition T_g is determined by kinetic factors, thus the value of T_g depends on the time scale of the observation. The glass transitions are also

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accompanied by a change in the rate of molecular translational and rotational diffusion [3].

Addition of a fluid solvent usually lowers the glass transition temperature of a substance. This effect is particularly well-known as plasticizer in amorphous polymers, where the dissolution of a small amount of water in an organic polymer substantially lowers the value of T_g [4].

In the present work we have simulated the formation of vitreous aqueous solutions of glucose and computed the corresponding values of the glass transition temperature (T_g). We also simulated the melting of a dilute frozen glucose solution and we used different criteria to characterise the transition temperature. At a very high concentration, MD presents an adequate alternative for studying the glass transition due to the experimental difficulties that appear at very high concentration of solute. We have obtained a good qualitative description of the melting and vitrification processes.

2. Experimental

Computational method.—Simulations have been carried out using the GROMOS package (Biomos n.v. Groningen) [5] where the equations of motion are solved with the leap frog algorithm. To work in the isothermal–isobaric ensemble the system was weakly coupled to a thermal bath. As our interest was to observe the melting of frozen solutions and also the glass transition, the reference temperatures were chosen for each case and the system was let to equilibrate at a pressure of 101 325 Pa (1 atm).

Time step of integration was held between 2 fs and 1 fs for the most concentrated solutions. All simulation runs were made in IBM RS/6000 32 H or 350 workstations and the analysis of results in a personal computer.

3. Results and discussion

The force field of GROMOS has been proved to be reliable for the simulation of carbohydrates in solution[6] and in pure solid, melted, and glassy states of glucose [7]. As previously we use the atomic partial charges calculated by Brady [8] using ab initio methods. In the GROMOS force field the interactions between non-bonded atoms are modelled with a 6–12 Lennard–Jones potential and through the coulombian electrostatic interaction between the atomic partial charges. These parameters for the description of β-D-glucose are shown in Tables 1 and 2.

Table 1
Lennard–Jones parameters of the potentials used for the simulation of glucose

Atom type	C_{12} (kcal nm^{12} mol^{-1})	C_6 (kcal nm^6 mol^{-1})
CH	893025	695.904
CH2	1700420	1128.960
O	177246	540.630
Ow	629325	625.500

For non-identical atom types the rule $C_{AB} = (C_A C_B)^{1/2}$ applies.

The molecular model of glucose was kept in the $^4C_1$ conformation since the molecule remains most of the time in this conformational state [8]. We avoided the transition between other conformations by applying improper torsion potentials. Groups CH and CH_2 were considered as united atoms, and only a centre of interactions was defined for such groups. The tetrahedral character of the carbon atom was fixed using improper torsion potentials. We used the SHAKE procedure to maintain rigid bond lengths. Bond angles were treated as having harmonic potentials. We used the model SPC/E for the water molecule [9]. The classical approach of the simulation does not allow one to compute the transition between the β (starting anomer in the solid state) and the α anomer that appears also in solution. This limitation cannot be solved within the present framework.

Table 2
Partial atom charges

Atom	Charge (e)
CH(1)	0.45
O(1)	−0.65
H(1)	0.40
CH(2)	0.25
O(2)	−0.65
H(2)	0.40
CH(3)	0.25
O(3)	−0.65
H(3)	0.40
CH(4)	0.25
O(4)	−0.65
H(4)	0.40
CH(5)	0.20
O(5)	−0.40
CH_2(6)	0.25
O(6)	−0.65
H(6)	0.40

For the simulation of the melting process of solid solutions we started by inserting a number of solute molecules (according to the desired concentration) in a crystal of ice I_h, taking off the water molecules surrounding the solute. The system was then equilibrated until we obtained a stable density. The initial box size was 3.115 nm × 2.498 nm × 2.928 nm. Table 3 shows the numbers of water and glucose molecules for each of the studied cases.

For the study of the solution melting temperature we analysed only the behaviour of the solvent molecules. For this case we worked only with solutions up to 30% (w/w) glucose. It should be noted that for pure ice it is possible to start with the experimental crystal structure. However, the solid solution produced has a considerable degree of disorder around solute molecules that may not correspond to the real state.

The simulation was started from $T = 0$ K and increased the temperature gradually. When the reference temperature was reached, the system was let to equilibrate for 100 ps. The trajectories and velocities of each atom were collected during 2 ps to compute the radial distribution function, the number of hydrogen bonds and their lifetimes, or to calculate the rotational energy of solvent molecules for the subsequent study of the system state. The reference temperature interval ranged from 0 K to 300 K or 350 K, in steps of 50 K.

The melting process.—The melting process being a first-order phase transition, one expects that a plot of the density against temperature will exhibit a discontinuity at the melting temperature. For pure glucose we found [7] that the system becomes too noisy around the transition region. Therefore a different criterion was established for computational purposes, namely the plot of the number of hydrogen bonds times its life time. As we regularly do, we have used a geometrical criterion for hydrogen bond formation in which it is considered that a donor or acceptor oxygen atom forms a hydrogen bond when the distance between acceptor and the hydrogen atom is less than 0.24 nm and the O–H–O angle lies between 145° and 180°. The order parameter now becomes the product of the number of hydrogen bonds by its own life time ($HB^*\tau$). Fig. 1 shows the corresponding plot for the glucose crystal.

Table 3
Solution concentration and number of water and glucose molecules used in the simulations

Solute concentration (% w/w)	Number of glucose molecules	Number of water molecules
0.00	0	640
9.54	6	569
19.60	12	492
29.52	18	430
40.36	27	399
50.35	36	355
69.96	48	206

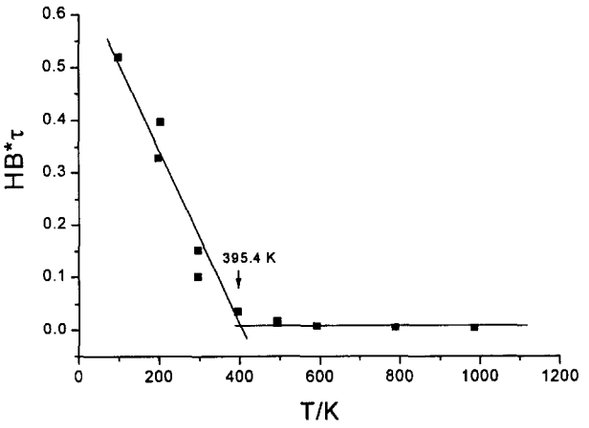

Fig. 1. Number of hydrogen bonds by its life time (order parameter $HB^*\tau$) against temperature for pure glucose. The initial structure corresponds to the crystal.

The interactions in the water network are of the H-bond type, so that the inclusion of a certain number of glucose molecules will break the H-bonds between water molecules and consequently new bonds will be set between solvent and solute, bearing in mind that glucose molecules have a high probability to form H-bonds with water and among themselves. Following the positive results used to determine the melting and glass transition temperatures of glucose in the anhydrous state, we expect the same approach to work for aqueous solutions. We have applied this analysis to investigate the water–water hydrogen bonds.

Fig. 2 shows the order parameter $HB^*\tau$ for pure water and some aqueous solutions of glucose plotted against the temperature. As we can see the very sharp transition observed for pure glucose does not appear. However, it is possible to obtain the melting temperature by fitting the points with a sigmoidal curve and taking the temperature at the inflexion point of the curve as the melting temperature. This gives a good agreement for pure water. However, when the concentration of glucose is increased the curves become flatter and the transition temperature less defined. Moreover, the cryoscopic decrease of the melting temperature obtained in this way is much larger than the experimental data.

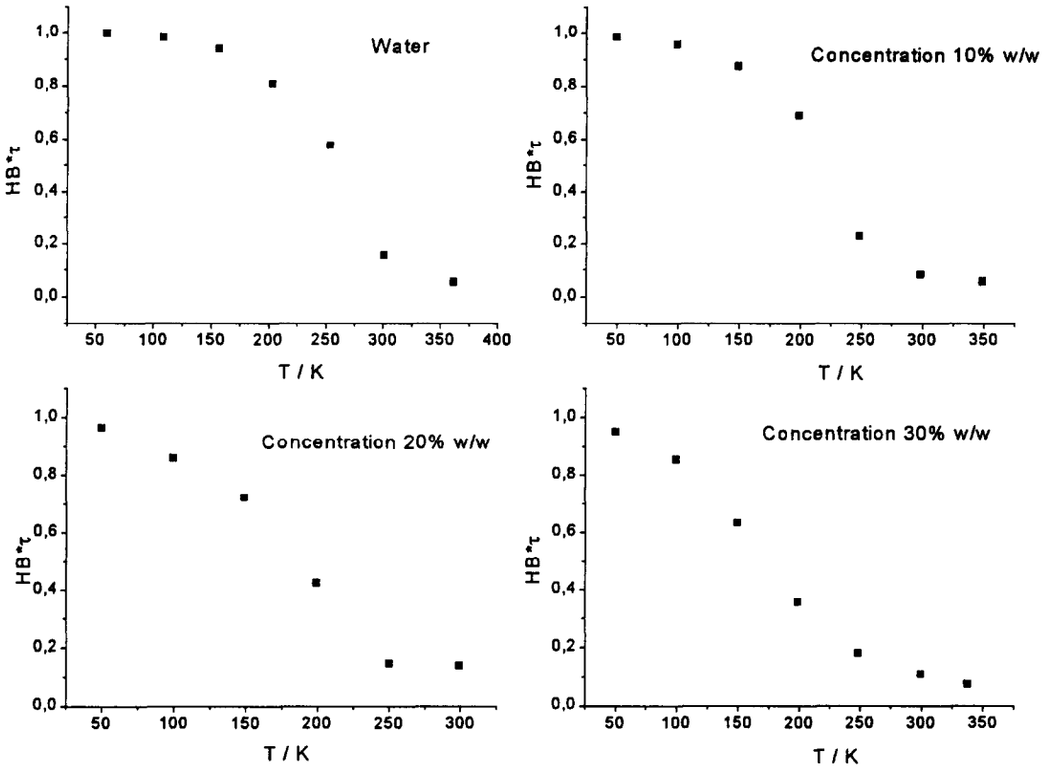

Fig. 2. Order parameter $HB^{*}\tau$ plotted against temperature for different aqueous solutions of glucose at 0, 10, 20, and 30% w/w.

In order to check if the departure from experimental values was due to the method of analysis or to an intrinsic problem with the simulation, we also used other methods for determining the melting temperature such as the geometric criteria defined by Uttomark et al. [10], which is based on the departure of oxygen–oxygen angles form the tetrahedral angle for the ideal lattice (109°), and that proposed by Wendt and Abraham [11], which is a parameter defined as the ratio of the position of the first minimum to the first maximum of the radial distribution functions ($g(r)$) for the water in the solution.

In all cases the cryoscopic decrease is much larger than the experimental value, as shown in Table 4. As all methods give the wrong answer we can conclude that this is due to the structures obtained from the simulation. When we form the initial solid solution, we are producing, as mentioned, a local disorder around the glucose molecules that seems to exceed the natural one. If the system is correctly designed and the simulation time is sufficient, it should allow for re-crystallisation of the water molecules that have been misplaced. It seems that some conditions are not fulfilled, and that we are working with a system with extra disorder.

The glass transition.—The search for the glass transition temperature starts from the higher glucose content, i.e. pure glucose after defining the procedure to produce the glassy state. Such an amorphous systems were produced by first heating the system to a certain temperature in which we have a molten state, and then the temperature instantaneously lowered to a defined level. This process is equivalent to a very fast quenching. In fact we are working at infinite cooling rate, and as we showed previously [7] the radial distribution functions, for instance, have the signature of the glass state after the quenching. After attaining

Table 4
Melting temperature obtained by molecular dynamics according to different criteria and experimental data (dielectric measurements)

Solute concentration (% w/w)	$g(r)$	$HB^{*}\tau$	Geometric	Energetic	Experimental
0.00	251	258	285	265	272.96
9.54	211	217	228	240	270.75
19.60	166	180	167	221	267.76
29.52	160	166	158	179	266.58

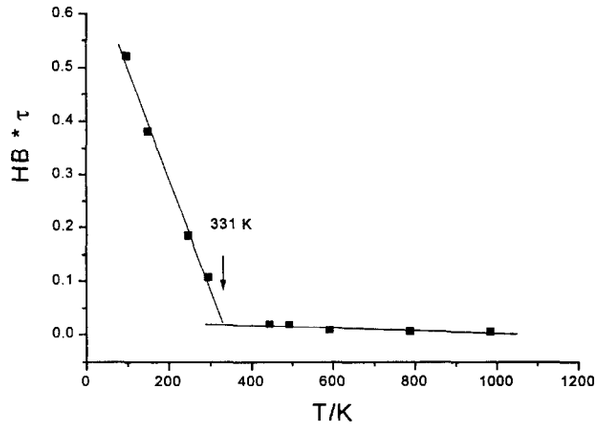

Fig. 3. Dependence of HB $^*\tau$ with the temperature for amorphous glucose.

the amorphous state, the system was slowly heated to different temperatures. During the heating procedure we pass through the transition temperature, defined then as the glass transition. To follow the transition for the pure glucose the hydrogen bonds properties (HB $^*\tau$) were also used. Fig. 3 shows the dependence of HB $^*\tau$ on temperature for amorphous glucose. We observe a well defined transition at $T = 331$ K, which is in good agreement with the experimental values reported for the glass transition [12].

For aqueous solutions, decreasing the solute concentration decreases the number of hydrogen bonds between the glucose molecules and thus in this case the hydrogen bond criterion is useless. As discussed by several authors the key of glass transition is an abrupt change in the mobility of molecules and the translational diffusion coefficient can be to search for the transition temperature.

The diffusion coefficient of the water was computed as 1/6 of the slope of the mean square displacement versus time. [13]. The simulation time used for computing the diffusion coefficient was 20 ps after equilibrium. Due to the long time scale needed to observe diffusion phenomena in the glassy state, the quantitative values of the diffusion coeffi-

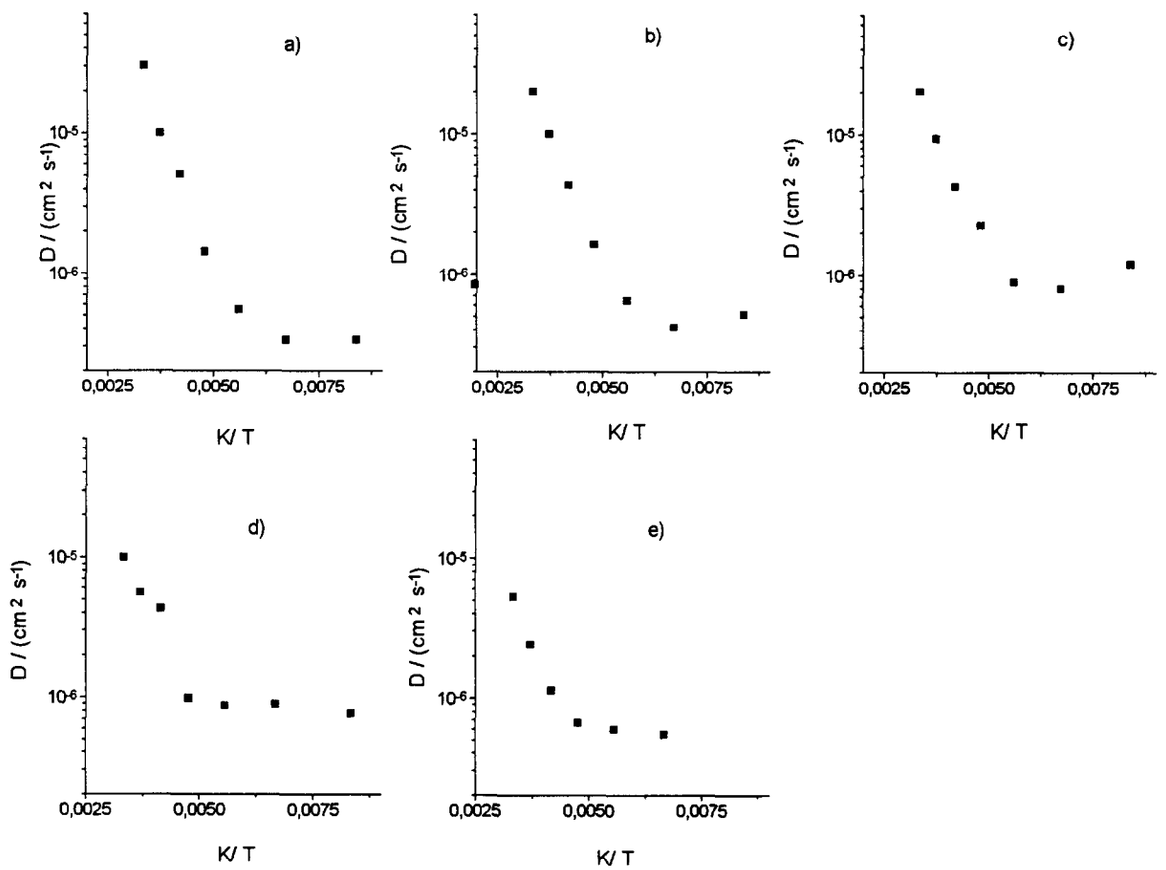

Fig. 4. Water diffusion coefficient plotted against the inverse temperature for different aqueous solutions of glucose: (a) 0% (w/w) glucose; (b) 9.54% (w/w) glucose; (c) 29.52% (w/w) glucose; (d) 50.35% (w/w) glucose; and (e) 69.96% (w/w) glucose.

Table 5
Glass transition temperatures obtained by simulation for solutions of different concentrations

Solute concentration (% w/w)	T_g (K)
0.00	161
9.54	172
29.52	173
50.35	205
69.96	226
100.00	302–331

cient obtained in this way are unreliable. However, the transition between glassy and melted state should be clearly defined. The total simulation time was the same for all studied concentrations.

To improve the statistics of the of mean square displacement line we considered the different configurations successively as they evolved with time. In this way we have a larger number of data to average and the quality of the lines is improved.

In Fig. 4 we can observe the behaviour of diffusion coefficients for the different concentration solutions plotted against their inverse temperature.

It is assumed that the temperature behaviour of the diffusion coefficient of the glassy state follows an Arrhenius law. Departure from this law should be an indication of a transition. Following this rule we can obtain the glass transition temperature (T_g) for each of the studied solutions (Table 5).

The state diagram.—All the above mentioned results are collected in Fig. 5 representing the concentration–temperature state diagram for β-D-glucopyranose together with the experimental values obtained with calorimetric techniques [14,15]. The values obtained with molecular dynamics simulation of the glass transition temperatures agree fairly well with the experimental data, acknowledging the experimental difficulties. The simulated values obtained for melting temperatures are good for pure water but the agreement fails as the concentration of glucose increases. As we discussed earlier another approach must be used to handle those solutions.

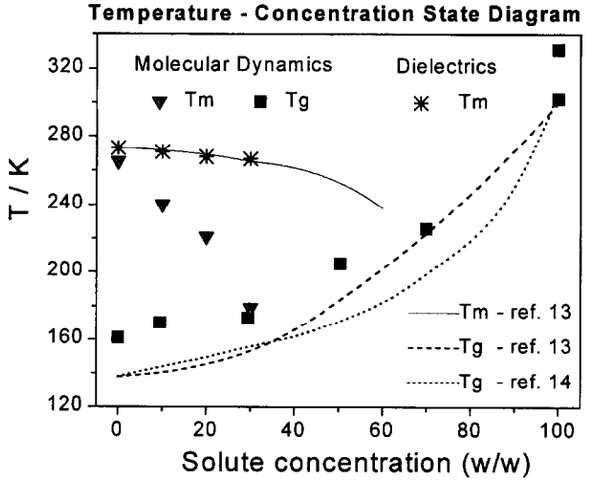

Fig. 5. Concentration–temperature state diagram for aqueous glucose solutions. Experimental data are of Refs. [13,14] and dielectrics form Bolzicco, Caffarena and Grigera, unpublished.

4. Conclusions

Addition of water to a carbohydrate matrix produces a depression in T_g. In the same way, addition of solute to the water produces a depression in the melting temperature. Both effects are observed in a qualitative way with MD.

The computed melting temperatures are lower than experimental ones. This may be due to the fact that in preparing the initial configurations, molecules that surround the solute molecule are much more disordered than the real systems. As the simulation conditions do not allow recrystallisation, the configuration 'melts' at lower temperature.

For the case of glass transitions, the agreement between the computed values and the experimental results is very good. Translational diffusion seems to be a good indicator of the mobility of molecules in order to detect the transition from the glass to molten state. The change of diffusion properties of the solvent molecules with temperature is well defined at the transition, so it allows us to compute the T_g temperature. The agreement is better for high concentrations of solute. We can see that the glucose model used is quite reliable even considering that it does not allow for the anomerization effect. Since the melting branch of the state diagram is unreliable we were unable to estimate the T_g'.

Considering the results obtained we believe that glass transitions of complex systems involved in vital processes, or with interest to the pharmaceutical and foodstuff industries, can be determined by molecular dynamics simulations. The GROMOS force field seems suitable for this task. The molecular dynamics technique can be applied to the study of interactions in high concentration carbohydrate matrices.

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