

Phase changes and chemical reactions in solid aqueous solutions: Science and technology

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Abstract: In recent years supersaturated solutions, especially those of carbohydrates, have been receiving increasing interest, because of their importance in natural environmental resistance mechanisms and in diverse branches of technology. The structures, dynamics and reactions in amorphous, water soluble solids are largely unexplored. Being thermodynamically unstable, such mixtures rely for their real-time stability on their high viscosities, in excess of 10^{12} Pa s. Like other amorphous materials, they exhibit the phenomenon of glass transitions, with the residual moisture, typically less than 5%, acting as plasticiser. Although thermomechanically such mixtures can be classified as solids, their molecular dynamics are complex; small molecules are able to diffuse within the glassy substrates and participate in chemical reactions, such as hydrolysis and oxidation. There is also increasing evidence that intramolecular, conformational processes, such as protein inactivation and sugar inversion, can occur in such "solids". The thermochemical properties of amorphous, water sensitive materials are important determinants of long-term stability and quality in many pharmaceutical and food products. They also play a dominant role in seasonal acclimation processes of living organisms to environmental stresses, such as drought, freezing and saline conditions.

The peculiar physical properties of water as a solvent first became a subject of study in the 1940s, following the pioneering work of Frank and Evans (1) whose theory of the intermolecular and unique nature of aqueous solutions laid the foundation for most subsequent advances in the field. The subject was reviewed in all its aspects in the seven-volume work *Water - A Comprehensive Treatise* (2). Implicit in all these studies of aqueous solutions was the assumption of "well-behaved" potential wells, shown in Fig. 1a, causing a system to adapt more or less rapidly to a perturbation and achieving its equilibrium state of minimum free energy.

Until quite recently, water was considered, explicitly or implicitly, as the 'solvent', i.e. the solution component present in excess, even in saturated solutions of most chemical species. Since the early 1980s, however, metastable, highly supersaturated, even solid, aqueous solutions have become subjects of interest. They can be represented by irregular potential wells (Fig. 1b), where the system is trapped in an

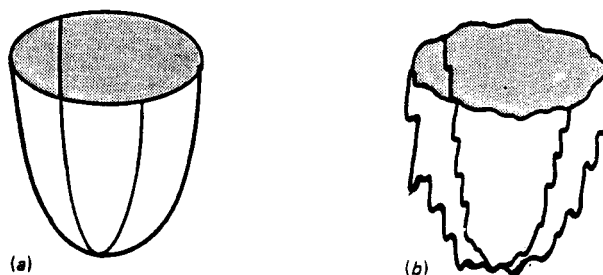


Fig. 1 Energy diagrams of (a) a well-behaved system with a single minimum, corresponding to equilibrium and (b) a system with several subsidiary minima which give rise to a corresponding number of metastable states.

intermediate free energy minimum, separated from the global, equilibrium state by one or more potential barriers. Such solutions can generally only be prepared by the removal of water from an initially unsaturated solution, specifically of substances that do not immediately precipitate from their saturated solutions.

In a binary solid/liquid phase diagram the systems of interest occupy the area (shown stippled in Fig. 2) that lies beyond the equilibrium domain bounded by the liquidus and solidus curves, specifically between the saturation solubility, denoted by S, and the glass transition profile (3). Thus, an unsaturated, dilute solution A can be dried by freezing to the notional eutectic T_e and beyond, or by isothermal evaporation to S and beyond. In either case the system has to traverse the region of supersaturation and be subject to thermodynamic instability for long enough to reach the vitreous state of 'kinetic stability' at B. The mixture then takes on the form of a homogeneous, solid solution (glass), possibly still containing a few percent of residual water.

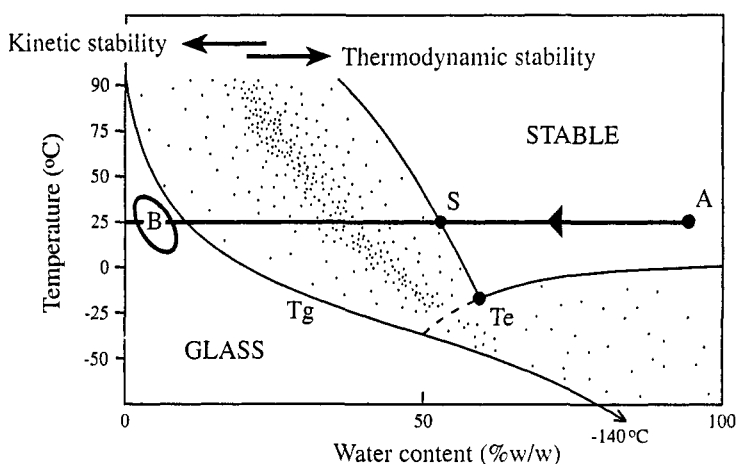


Fig. 2 Regions of stability and instability (stippled area) traversed during the drying of a dilute solution (A) to an amorphous glassy solid (B). T_e is the eutectic point and S denotes the saturation solubility at the drying temperature. The density of stippling corresponds to the degree of instability of the supersaturated mixture. Reproduced, with permission, from ref. 3.

In this context, polyhydroxy compounds (PHCs) have received most attention (4). With few exceptions, they fulfil the requirements of very slow crystallisation, coupled with an 'interesting' rheology and chemistry. As water is removed from their dilute solutions, either by freezing or by evaporation at ambient or elevated temperature, the viscosity of the supersaturated residue increases to the point, usually 10^{12} - 10^{14} Pa s, where the mixture undergoes vitrification, although it may then still contain up to 50% w/w of water, depending on the temperature at which the drying is performed and the chemical nature of the solute(s).

Inorganic amorphous solids, more correctly termed "solid liquids", have been studied for many years, because of their useful mechanical properties as materials of construction (5). There remain, however, large gaps in our understanding of the phenomenon of the glass transition, especially at the molecular level.

Luyet and his colleagues were probably the first to realise the importance of vitrification (of water), as applied to aqueous solutions. In a series of pioneering publications, unfortunately in an obscure journal, they catalogued their observations on frozen aqueous mixtures that could undergo vitrification, depending on the cooling rate (6), and they described the qualitative nature of amorphous aqueous solids. Their studies had a major influence on the development of cryobiology as a scientific discipline, but they led to an obsession of later workers with the phenomenon of freezing and its circumvention, rather than to any general advances in studies of the effects of freezing on the solutes, i.e. freeze concentration.

It was left largely to Slade and Levine to emphasise the importance of amorphous, water-soluble materials, and the technological significance to the food processing industry of their glass transitions. They thus

provided an impetus for much of the scientific activity that followed, mainly by a prodigious number of well-referenced reviews in the food science literature (7,8,9). They were thus able to provide a rational physical basis to several imperfectly understood phenomena, commonly observed in food processing, e.g. the storage properties of low and intermediate moisture foods. It required the repeated statement that water is the ubiquitous plasticiser for all organic amorphous materials, before this concept was reluctantly adopted by the food industry (10). In recent years it has become apparent that the applicability of amorphous PHCs is even wider in scope. The thermomechanical properties of vitreous PHCs can be exploited as stabilising matrices for a whole range of chemically labile molecules, such as conventional drug substances and proteins (11). The significance of glass transitions to pharmaceutical processing, such as freeze-drying, has also received attention. (12).

The outstanding scientific puzzles posed by vitreous materials are still many. Supersaturated aqueous solutions and their transitions into glasses upon drying still require thoroughgoing fundamental investigations by physical chemists. Several puzzles that were already highlighted three years ago (13) still require resolution. This review aims to summarise briefly some of the progress made in the study of solid aqueous solutions of sugars, as well as some of the topical problems.

The reluctance of sugars to crystallise from their liquid states or from aqueous solution is probably related to their crystal structures, consisting of hydrogen-bonded networks, similar to that of ice, but much more complex. It is surprising, therefore, that mannitol presents an exception, crystallising rapidly, whereas its stereoisomer glucitol behaves in a more typical manner, i.e. it does not crystallise in real time. This raises the question of the nature of any relationship between the molecular structure of a given sugar and its propensity to vitrification. The hydrogen bond topology of carbohydrate molecule networks remains to be studied in detail. It is likely that, in the vitreous state, near-neighbour intermolecular links between sugar molecules resemble those characteristic of the crystal, even though long-range order has been broken down.

The detailed interpretation of thermal changes accompanying the glass transition is also still open to discussion. It has been shown that in disperse sugar-water mixtures (e.g. ice/supersaturated solution or air/supersaturated solution) two thermal transitions are detected by DSC, where only the transition occurring at the lower temperature is reversible and reproducible (14). This is illustrated in Fig. 3 for freeze-dried amorphous sucrose. The interpretation that has been advanced to explain this observation assigns the lower temperature transition T_1 to the "true" structural glass transition, corresponding to a viscosity of ca. 10^{14} Pa s which is too high for viscous flow to be observable within the period of the measurement. The other discontinuity in the heat flow, shown as T_2 , is believed to correspond to a viscosity of ca. 10^7 Pa s and represents the onset of measurable viscous flow, also termed collapse during

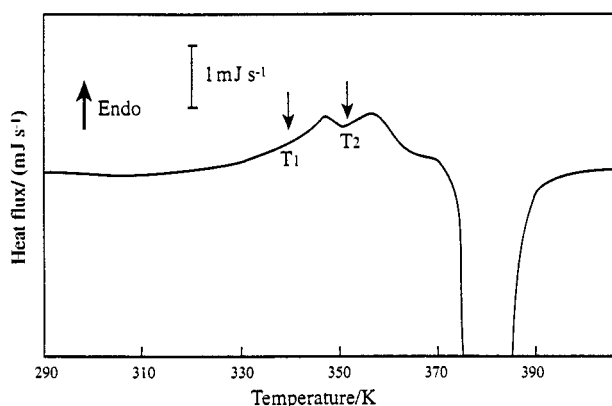


Fig. 3 DSC heating scan for freeze-dried sucrose, showing two discontinuities in the heat flow, followed by an exotherm, indicating crystallisation. Reproduced, with permission, from ref. 14.

freeze-drying, or the "softening point" observed with powders. Unlike the "true" T_g , it does therefore not

reflect a discontinuity in the specific heat, but merely a change in the thermal conductivity, produced by a change of the sample configuration inside the sealed DSC pan.

The two discrete relaxation processes are particularly well revealed in the dielectric spectrum of supersaturated sugar solutions (15), although the interpretation of the dielectric loss of a mixture cannot be unambiguous. The complex relaxation behaviour of the two species in such mixtures has been studied by means of nuclear magnetic relaxation spectroscopy, using ^1H , ^2H , ^{17}O and ^{13}C (16). Figure 4 shows the mobility of water relative to that of pure D_2O as function of sucrose concentration (c) and temperature. The rotational correlation time τ first increases markedly at $c = 40\text{--}50\%$, then shows little concentration dependence until $c > 70\%$, where another marked decrease in the water mobility occurs. The comparison of the relative mobilities of sucrose and water in Fig. 5 is even more remarkable: at $c > 40\%$ the mobility of water is reduced, possibly resulting from the integration of water molecules into the sucrose network. At $c > 50\%$, the motions of the two species become decoupled, with sucrose solidifying at $c > 70\%$, while water molecules remain mobile, even down to 125 K!. A detailed analysis of the data remains to be performed.

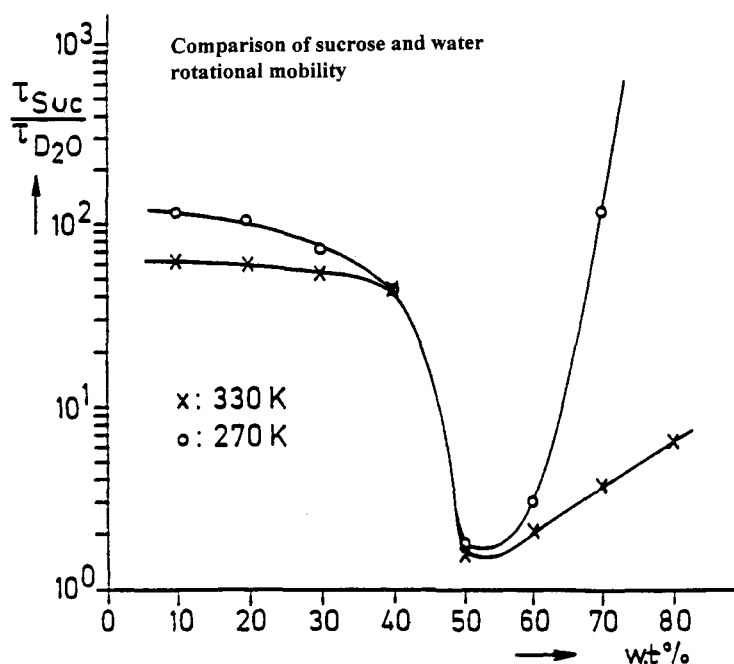


Fig. 4 Rotational correlation time of water (relative to pure D_2O) in aqueous sucrose solutions at 270 and 330 K; after ref. 16.

Recently the real-time crystallisation of sugar hydrates from amorphous aqueous solids and its implications have been investigated by DSC. Figure 6 shows sample results for trehalose dihydrate (17). A dried trehalose solution, containing 8.5% residual water, was cooled to 240 K and heated; the DSC response is shown as Scan 1 and reveals a typical glass transition response at 305 K. The preparation was then heated to 350 K and maintained at that temperature overnight. It was subsequently cooled back to 240 K and reheated. Scan 2 exhibits a glass transition at ca. 355 K and a pronounced endotherm at 358 K, the known melting point of the dihydrate. Crystallisation of the dihydrate had thus taken place during overnight storage. After heating the preparation to 400 K to ensure the completion of melting, the temperature was once again reduced to 240 K. The final heating run (scan 3) shows the original feature of the glass transition, indicating that crystallisation had not occurred during cooling of the melted dihydrate, at least at a rate of 5 K/min. This process of sugar hydrate crystallisation from an initially amorphous solid enables residual water to be removed *in situ*, a device that might be significant for labile preparations that are subject to hydrolysis.

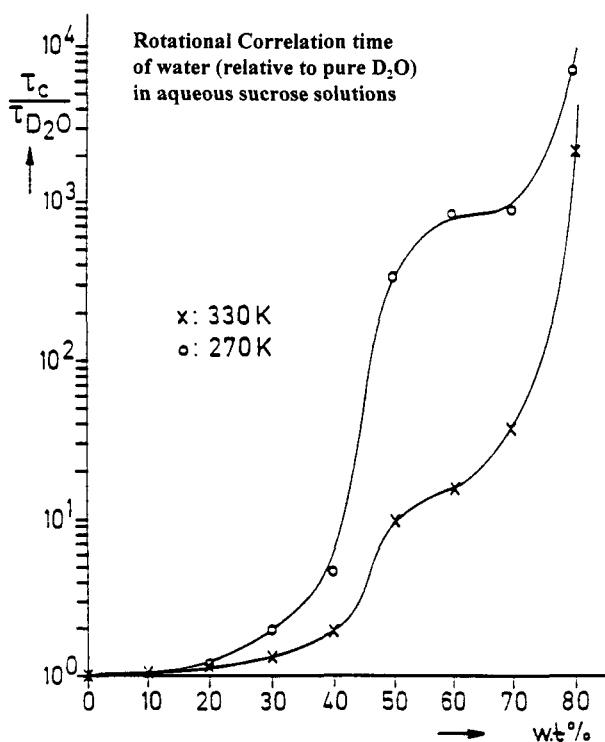


Fig. 5 Comparison of sucrose and water rotational mobilities in aqueous solutions as a function of sucrose concentration; after ref. 16.

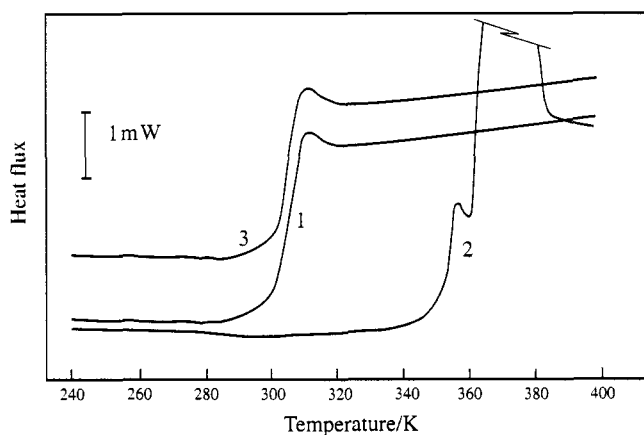


Fig. 6 Power-time curves recorded during the heating of a previously cooled amorphous trehalose, containing 8% residual moisture: 1) first heating scan; 2) heating scan after exposure at 355 K for 15 h; 3) heating scan immediately after scan 2 and cooling to 230 K. Reproduced, with permission, from ref. 17.

The importance of rubber/glass transitions and the attributes of vitreous states to food processing and storage has now been recognised for some years (10) and is being taken into account in product and process development. The involvement of vitreous states in physiological and ecological processes, however, is only gradually receiving attention. Thus, the seasonal tolerance of many organisms (microorganisms, plants, insects) to extremes of desiccation, either by drought or by freezing, is related to their ability to acclimate to these conditions by a conversion of their starch reserves into low molecular weight carbohydrates (18) and/or their ability to synthesise large amounts of free amino acids, proline and glycine betaine figure prominently (19). As water is lost, either by evaporation or freezing, conditions are reached where the body fluids undergo a glass transition, rendering the organism resistant to further dehydration and other environmental stresses. The most extreme examples of such resistance are probably plant seeds and bacterial spores which can exist in substantially desiccated states for millennia.

Although many important scientific questions remain to be answered, solid aqueous solutions should now be set firmly on the map of solution chemistry and in future years be afforded the attention which they deserve, if only because of the widespread applications of such materials.

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