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Report

Amorphous-to-Crystalline Transformation of Sucrose[1]

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The transformation of amorphous sugar in the form of lyophilized spheres into crystalline sucrose was studied. The lyophilisate, when exposed to moist atmospheres, picks up moisture to a constant weight. The amount of moisture addition is a function of relative humidity of the atmosphere and temperature. The loose "lyophilisate structure" collapses to form a denser amorphous phase ("hydrated amorphate"). After a lag time which varies with relative humidity of the atmosphere and temperature, the hydrated amorphate loses moisture (weight) and, in the process, forms crystalline sucrose. The phase nature of the hydrated amorphate is equivalent to an aqueous solution that is supersaturated with respect to crystalline sucrose. A model was developed for the lag time which accounts for the experimental results.

KEY WORDS: sucrose; rubbery state; amorphous sucrose; crystalline sucrose; amorphous–crystalline transformation.

INTRODUCTION

Amorphous sugar transformation have been previously studied (1,2). Sucrose is difficult to produce completely amorphously and converts to crystalline sucrose at rates that depend on the relative humidity and the temperature. In previous publications (3,4) the general pattern of transformation was described. Lyophilisate spheres that were placed so they did not touch one another in a moist atmosphere, absorbed moisture up to a certain level (1,2). Subsequently the sample loses weight again (Fig. 1), and the phase 0–A is the stage where moist lyophilisate is formed, phase A–B is the phase where hydrated amorphate is formed, phase B–C is the lag time, and phase C–D is the phase where hydrated amorphous sucrose converts into anhydrous crystalline sucrose.

Van Scoik (3) and Van Scoik and Carstensen (4) treated the latter part of the curve as a normal cumulative undersize distribution (with mean t^* and standard deviation s) of fraction not nucleated versus time. The mean nucleation time, t^*, was obtained as the point where $N/N_o = 0.5$, and the point in time given by $t^* - 3s$ was denoted the lag time. N here is the number of nonnucleated spheres, and N_o the total number of spheres.

Both the percentage water uptake (mg water per mg dry amorphate) at the plateau level and the lag times are plottable by Van't Hoff and Arrhenius plots (Figs. 2 and 3). Use is made of these facts in the following article to develop a theory of the kinetic phenomena in the transformation.

MATERIALS AND METHODS

Amorphous sucrose was produced by preparing 10% sucrose solutions, placing these in a burette, and running drops of the solution into liquid nitrogen. The frozen spheres were placed on petri dishes so that no sphere was in contact with its neighbor; this was then placed in a lyophilizer, and the moist solid was lyophilized.

This method used for producing amorphous sugar worked the best in our hands, whereas other methods (spray drying, bulk lyophilization) never rid the substance completely of crystalline material. Melting followed by cooling does produce good-grade amorphous solid, but poorly reproducible amounts of decomposition products are formed. This method produced material that is free of crystallites as judged by optical microscopy with crossed Nichols and by X-ray diffraction. The produced sucrose spheres are essentially anhydrous [0.2% after outgassing on a high-vacuum rack (<0.5 μm) for 2 days].

Atmospheres of given relative humidities were created by means of supersaturated salt solutions in desiccators. Petri dishes were equilibrated in desiccators and tared, and netted amounts of amorphous sugar beadlets were placed on them. The petri dishes were places open (i.e., both body and lid) in the desiccator. At various times the desiccators were opened, the lid placed on the petri dish, and its weight determined. It was then placed back in the desiccator, the lid removed (but left in the desiccator), and the experiment continued. Experiments were carried out at several other temperatures and humidities.

The dry sucrose lyophilisate spheres will typically have a diameter of $d_o = 4.6 \pm 0.2$ mm. When exposed to the moist atmosphere they will gain weight up to a given plateau level (q g water/100 g sucrose) as shown as point A in Fig. 1. After a while they will visually shrink (point B in Fig. 1).

The weight will stay constant at q until a certain time t^*,

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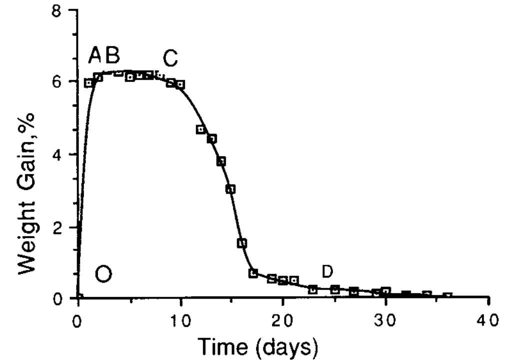

Fig. 1. Moisture uptake curve for amorphate at 23°C over saturated $MgCl_2$ solutions.

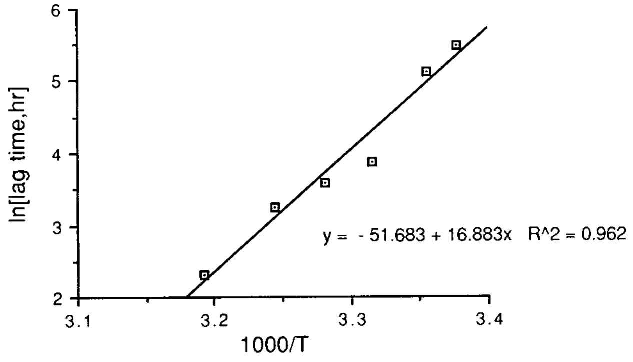

Fig. 3. Arrhenius plot of lag times of hydrated amorphate.

the lag time, at which time weight loss will be experienced (point C in Fig. 1). Once crystallization occurs, the sucrose cannot retain the relatively large amount of moisture of the hydrated amorphate, and the loss of moisture is indicative, both qualitatively and quantitatively, of the conversion. This view has been substantiated by electron micrographs in previous communications (3,4).

X-ray diffraction patterns were conducted on samples at various storage times and have been reported elsewhere (3,4). Surface areas of dry lyophilisate spheres were carried out by nitrogen adsorption and found to be 3.8 m^2/g. Differential scanning calorimetry was carried out on anhydrous amorphate (0.2% moisture) from −20 to 210°C.

RESULTS AND DISCUSSION

Figure 1 shows a typical moisture uptake curve at 23°C and 33% RH. The final weight approximates the weight of the anhydrous sucrose at the onset of the experiment. Hence the anhydrous sucrose becomes hydrated and then dehydrates into crystalline sucrose. X-ray diffraction of anhydrous amorphate shows only one broad, noisy band. If spiked with 5% crystalline sucrose, the expected peaks appear.

Modeling analysis of such curves has not been carried out previously, other than the curve-fitting acquisition of parameters reported (4). One logical explanation for the shape of the curve is that once the plateau is reached it consists of a lag period. At a given point in time, a sphere will nucleate; the crystal growth will be rapid, so that a particular sphere, once nucleation starts, will become 100% crystalline in a very short period of time.

The method used here of having isolated spheres of amorphous material thus allows separation of nucleation and crystallization phenomena, which is a great advantage, since otherwise it would be difficult to separate out which of the two phenomena were responsible for the various parts of the curve.

Since the amorphous spheres are independent of one another, the fraction of mass, ϕ, converted to crystalline material is given by

$$\phi = (N_o - N)/N_o = 1 - (N/N_o) \quad (1)$$

If M denotes recorded gross weight of petri dish plus sucrose at time t, M_o denotes gross weight right before nucleation, and M_∞ denotes final gross weight, then it follows that $(N/N_o) = (M - M_\infty)/M_o - M_\infty)$.

The first phase (OA in Fig. 1), as mentioned, is presumably the simple collapse of the porous lyophilisate into the more compact, hydrous amorphate form. The diameter of the spheres, during this phase, decreases as a function of time as shown in Fig. 4. No further analysis of this is attempted here, but the fact is recorded that there is an initial contraction event.

The extent to which moisture is taken up (q) as a function of relative humidity (at a constant temperature) is tabulated in Table 1. If this is plotted as a BET plot, then the profile in Fig. 5 results. There is a fairly good correlation, but the intercept would correspond to a monolayer coverage of 38 mg of water per g of sucrose. This is two orders of mag-

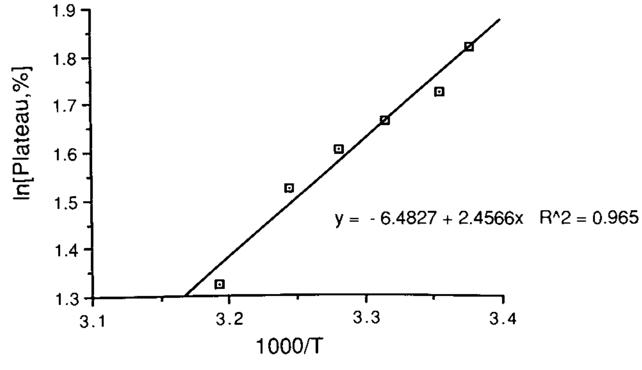

Fig. 2. Van't Hoff plot of plateau weight values for hydrated amorphate.

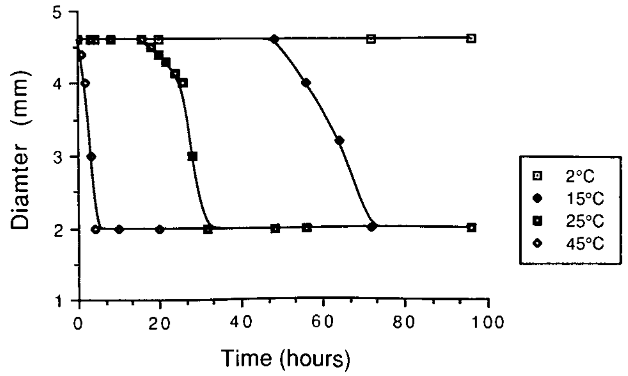

Fig. 4. Shrinkage of moist lyophilisate spheres as a function of time.

Table I. Values of q as a Function of Relative Humidity at 25°C

Relative water vapor pressure, $\pi = P/P_0$	Plateau level, q g/g sucrose	Mole fraction water
0.698	0.125	0.703
0.544	0.08	0.603
0.40	0.07	0.571
0.32	0.055	0.488

nitude higher than the specific surface area obtained from nitrogen adsorption (3.8 m^2/g) and hence the water (as expected) is not simply surface adsorbed water. Although cases of this type have been reported and can be explained for macromolecules (6,7), such explanations would hardly apply to smaller molecules such as sucrose.

The fact that the concentration level is a function of the relative humidity is not deterrent to this view, but simply implies the equilibrium vapor pressure over the sucrose solution. If the hydrated amorphate is simply considered to be a solution (of high viscosity), then one may plot the vapor pressures above it (actually the relative humidities at which the moisture pickup took place) as a function of the sucrose mole fraction. These data are shown in Table 1 and plotted in Fig. 6. The vapor pressure of the solution, assuming it to be ideal, is shown as well. Also shown is the vapor pressure over sucrose solutions (8), and the data in this work can be seen to be simply an extension of the vapor pressure data of crystalline sucrose into a supersaturated region.

Visually and by electron micrographs (3) it is apparent that the hydrated amorphate is a solid, and hence the state is assumed to be one which may simply be described as a highly viscous solution supersaturated with respect to crystalline sucrose. Such states of matter have been referred to as "rubbery" for one component systems (9,10), but for chemical considerations it is probably best to think of them simply as solutions. A case in point is the stability of drug substance, where decomposition is often assumed to take place in a saturated solution adsorbed onto the solid (11), and for an amorphous substance above the glass transition point, the state of the hydrated amorphate would be comparable to the traditional view of bulk solution kinetics. There is no evidence of other types of water (12), e.g., nonfreezable water (13).

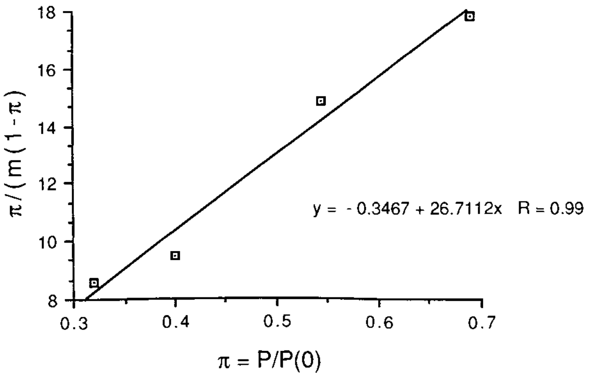

Fig. 5. BET plot of maximum uptake levels of hydrated amorphate.

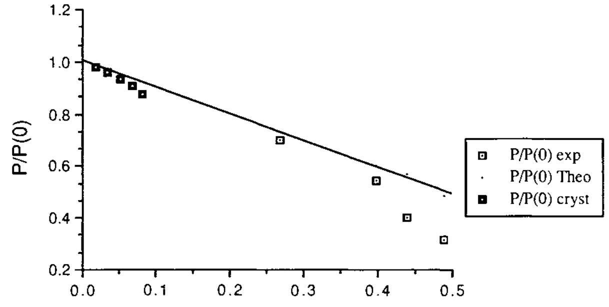

Fig. 6. Ideal pressure versus mole fraction of sucrose curve (top line). Vapor pressures of solutions made with crystalline sucrose (Ref. 8) (filled squares) and vapor pressures of hydrated amorphate (open squares).

Differential thermograms of anhydrous amorphate samples show a small peak at 0°C (presumably as a result of the small amount found on loss in vacuo). A peak (1.2 cal/mg) at 22.4–25.6°C is observed. This is the glass transition temperature for *anhydrous* amorphate. Water is known to decrease T_g (14). A study of T_g versus moisture content was not undertaken but there is evidence that amorphate, containing 7.5% water, at 2°C, is below its glass transition point.

The data from the experiment at 2°C are not included in Fig. 2. It should be pointed out that for this experiment the lag time was in excess of 500 hr. (The point *is* included in Fig. 5.) No shrinkage occurs and the amount taken up at the plateau level for this sample is 7.5%. If 2°C ($1000/T = 3.634$) is inserted in the Van't Hoff equation in Fig. 2, then the expected level, (q{2°C}), of moisture would be In[q{2°C}] = 2.446 or q{2°C} = 11.5%. This value is significantly ($P = 0.05$) higher than the actual value, and it points to the amorphate at 2°C being different from the remainder, which are all assumed to exist above any possible glass transition temperature.

The DSC of anhydrous amorphate gives evidence of a glass transition at 22.4–25.6°C, but the hydrated amorphate would have lower glass transition temperatures. Hence all the other temperatures (starting with 23°C) would be above this point. It is interesting to note that differential scanning thermograms of anhydrous amorphate with various additives (e.g., raffinose) that prolong the lag time show either a marked increase in or an elimination of T_g (3).

The lag times versus temperature are plotted in Fig. 3. It is noted that the Arrhenius type plot is quite linear. An explanation to this may be found in the schematic shown in Fig. 7. It is assumed that at the onset (at the point where the equilibrium moisture level has been reached) the sucrose molecules are randomly arranged in the solid phase. In order for them to form a nucleus (and then crystallize) a certain number of them must orient properly (orientation Q, shown here as vertical and aligned) and also achieve the proper intermolecular distance (L, shown here as, examplewise, five molecules).

If it is assumed that aligned molecules have a lower Gibbs energy, then they will, once formed, not be prone to dissociate again. The probability (denoted $P\{\ \}$ in the following) of two molecules lining up (Q) must increase with time, and in its simplest form

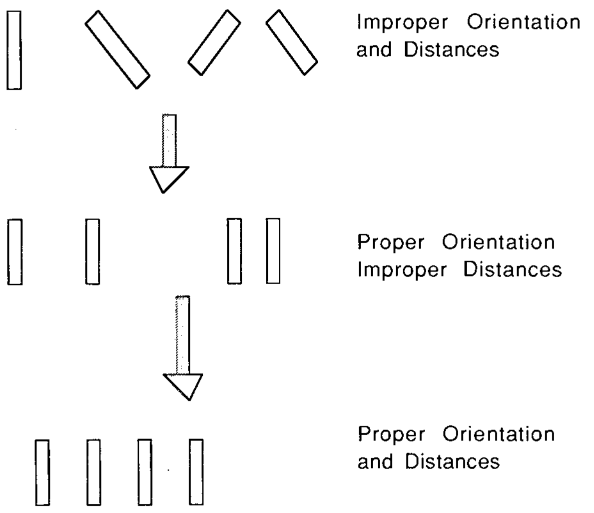

Fig. 7. Schematic of sucrose molecules as a function of time in hydrated amorphate.

$$P\{Q\} = f \cdot t \qquad (2)$$

Because of the original randomness, it is assumed that $P\{Q\} = 0$ at time zero, but this restriction does not limit the arguments to follow.

Similarly the probability of the proper distances being achieved might be expressed as

$$P\{L\} = \beta \cdot t \qquad (3)$$

The compound probability that both occur would be

$$P\{L,Q\} = P\{L\} \cdot P\{Q\} = \mu t^2 \qquad (4)$$

where

$$m = f\beta \qquad (5)$$

Every arrangement is associated with a certain energy state, and the energy associated with the arrangement $\{L,Q\}$ is denoted E^*; this is the critical energy an agglomerate of molecules (nucleus) must achieve before crystallization can start.

If n denotes number of molecules in an energy state E, and n_o the total number of molecules, then the fraction of molecules (n/n_o) in energy state E is given by Boltzmann's distribution law:

$$(n/n_o) = \exp\{-E/RT\}/\Sigma\exp\{-E_i/RT\} \qquad (6)$$

If this is an isolated system ($\Delta E = 0$), then Eq. (6) may be written

$$(n/n_o) = A \cdot \exp\{-E/RT\} \qquad (7)$$

where

$$A = \Sigma\exp\{-E_i/RT\} \qquad (8)$$

It is noted that the term (n/n_o) is also the probability that a molecule is in the given energy state E. At the critical energy, E^*, therefore

$$(n^*/n_o) = P\{L,Q\} = \mu(t^*)^2 = A \cdot \exp\{-E^*/RT] \qquad (9)$$

where use of Eq. (4) has been made for the second to third step and use of Eq. (6) has been made for the last step. t^* here is the lag time, the point in time where the critical energy has been reached.

Taking logarithms of the last equation segment of Eq. (9) then gives

$$\text{In}[\mu] + 2\text{In}[t^*] = -\{E^*/R\}[1/T] + \{\text{In}[A]\} \qquad (10)$$

or

$$\text{In}[t^*] = [-\{E^*/R\}[1/T] + \{\text{In}[A]\} - \text{In}[\mu]]/2 \qquad (11)$$

i.e., the logarithm of the lag time should plot linearly in $1/T$, which indeed it does (Fig. 3).

SUMMARY

1. A method is described which produces good amorphate of sucrose. Amorphicity was ascertained microscopically, by X-ray diffraction, and by DSC.
2. Differential scanning calorimetry of the anhydrous amorphate shows a glass transition point of 22.4–25.6 with a transition enthalpy of 1.2 cal/g.
3. The amorphate takes up moisture in humid atmospheres. Although the equilibrium moisture contents plot linearly by BET, the calculated monolayer amount is orders of magnitudes above that obtained from nitrogen adsorption.
4. The vapor pressures at equilibrium is of the order expected from ideal solution considerations. They, furthermore, fall in line with vapor pressures of unsaturated sucrose solutions, and the hydrated amorphate is therefore simply considered a highly viscous (solid) saturated solution.
5. The moisture content is a function of temperature by a Van't Hoff plot with heat of solution of 5 kcal/mol.
6. The hydrated amorphate eventually crystallizes (yielding a moisture loss equivalent to the originally moisture uptake). The lag time is treatable by Arrhenius plotting with an activation energy of 33.7 kcal/mol.
7. It is postulated, and the appropriate derivations are presented, that the lag time is the time necessary for random molecules to rotate and translate into the proper position to form a nucleus of sufficient size to allow crystallization.

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