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Research Paper

Comparative Relaxation Dynamics of Glucose and Maltitol

Sergey Vyazovkin[1,2] and Ion Dranca[1]

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Purpose. To demonstrate the utility of differential scanning calorimetry (DSC) for determining activation energy landscape in amorphous pharmaceutical systems throughout the sub-T_g and T_g regions.
Materials and Methods. DSC was employed to determine the effective activation energies (E) of the relaxation in sub-T_g and T_g regions as well as the sizes of cooperatively rearranging regions in glassy maltitol and glucose.
Results. It has been found that in the sub-T_g region E decreases with decreasing T reaching the values ~60 (glucose) and ~70 (maltitol) kJ mol^{-1} that are comparable to the literature values of the activation energies for the β-relaxation. In the T_g region E decreases (from ~250 to ~150 kJ mol^{-1} in maltitol and from ~220 to ~170 kJ mol^{-1} in glucose) with increasing T as typically found for the α-relaxation. From the heat capacity measurements the sizes of cooperatively rearranging regions have been determined as 3.1 (maltitol) and 3.3 (glucose) nm.
Conclusions. DSC can be used for evaluating the energy landscapes. The E values for maltitol are somewhat greater than for glucose due to the added impeding effect of the bulky substitute group in maltitol. The comparable sizes of the cooperatively rearranging regions suggest a similarity of the heterogeneous glassy structures of the two compounds.

KEY WORDS: amorphous systems; DSC; kinetics; molecular mobility; sugars.

INTRODUCTION

Sugars and sugar alcohols find a wide application in various pharmaceutical systems as sweeteners and/or binding matrices for drug components. As such they are frequently used in the glassy state, which is thermodynamically unstable and unavoidably tends to relax toward the liquid state. Understanding the dynamics of this process is of a great practical importance for designing physically stable formulations of amorphous drugs. The relaxation dynamics of the glassy state is quite complex and strongly depends on the temperature region of the process (1). The glass transition is generally understood as a cooperative process that involves concerted motion of multiple molecules. The cooperative process is usually termed as the α-relaxation. It typically occurs in the temperature region of calorimetric glass transition, i.e., in the T_g-region. The dynamics of the α-relaxation generally has a non-Arrhenius character (1). It means, in particular, that the rate of the process decreases with the temperature faster than predicted by the Arrhenius law or that the effective activation energy increases with decreasing the temperature. Larger deviations from the Arrhenius behavior are described by larger values of the dynamic fragility (2) that is usually defined as follows

$$m = \left[\frac{d \log \tau}{d(T_g/T)}\right]_{T=T_g} \quad (1)$$

where τ is the relaxation time at T_g. The parameter m is large for polymeric glasses and small for inorganic oxide glasses. Organic glasses such as sugars seem to fall in between.

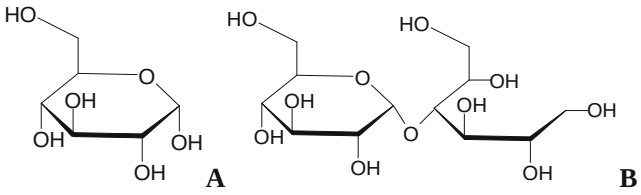
At temperatures significantly below T_g, i.e., in the sub-T_g region, the cooperative motion is impeded, although a localized motion of individual molecules persists. This local motion also contributes to the overall relaxation dynamics giving rise to the so-called β-relaxation. The β-relaxation obeys the Arrhenius law and demonstrates activation energies that are several times smaller than those for the α-relaxation (1). Therefore, the effective activation energy for the relaxation of a glassy system should generally change with the temperature as follows. It should be small in the sub-T_g region but should increase significantly as the temperature approaches the glass transition region where the cooperative motion becomes possible. Further increase in temperature should facilitate the cooperative motion causing a decrease of the effective activation energy. This type of the activation energy landscape can be determined experimentally by using mechanical and dielectrical spectroscopy. We have recently demonstrated (3) for polymeric systems that a similar landscape can be also obtained from differential scanning calorimetry (DSC) measurements by deriving effective ac-

[1] Department of Chemistry, University of Alabama at Birmingham, 901 S. 14th Street, Birmingham, AL 35294, USA.
[2] To whom correspondence should be addressed. (e-mail: vyazovkin@uab.edu

tivation energies for two types of runs. In the first set of runs the activation energy is derived from the shift of annealing peaks generated in the sub-T_g region. In the second set, the activation energy is evaluated by applying an advanced isoconversional method to the glass transition step (4). In this paper the aforementioned approach is applied to the relaxation of two carbohydrates: glucose and maltitol. These two systems have been chosen because they have been previously studied by using the classical techniques of mechanical and dielectrical spectroscopy whose results can be used as reference data. Also because structurally maltitol is a hydrogen substituted derivative of glucose (Scheme 1), their comparison may elucidate the effect of the bulky substitute group on the relaxation dynamics.

MATERIALS AND METHODS

Anhydrous glucose (Dextrose) and maltitol were, respectively, purchased from Fisher and MP Biomedicals and used without further purification. In order to produce amorphous (glassy) samples, ~15 mg of a sample was placed in 40 μl closed Al pans and heated to ~10°C above their respective melting points, 161°C (glucose) and 149°C (maltitol). Shortly after heating the samples were quenched into liquid nitrogen. The glass transition temperatures of the amorphous samples were estimated as midpoint temperatures of the DSC glass transition steps measured at 10°C min^{-1}. The resulting values were 36 (glucose) and 48°C (maltitol). For sub-T_g measurements, freshly quenched samples were quickly placed into the DSC cell (Mettler-Toledo DSC 822^e) that was maintained at −40°C. From −40°C the samples were heated to an annealing temperature, T_a and held at it for 30 min. The annealing temperatures were −30, −25, −20, −10°C for glucose, and −30, −20, −10, 0°C for maltitol. After completion of the annealing segment, the samples were cooled down to −40°C and immediately heated above T_g. The heating rates were 15, 20, 25 and 30°C min^{-1}. The resulting endothermic peaks observed on heating were used to determine the peak temperature, T_p by using the standard DSC analysis software (Mettler-Toledo, STAR^e 7.01) that subtracts an extrapolated baseline and finds the peak position. For the relaxation in the T_g region, the glassy samples were heated ~40°C above its glass transition temperature and held at this temperature for 10 min to erase thermal history. The samples were then cooled down to ~40°C below the glass transition temperature at the rates 10, 15, 20, 25 and 30°C min^{-1}. Immediately after completion of the cooling segment, the samples were heated at a rate whose absolute value was equal to the rate of preceding cooling. The temperature and heat flow calibration of DSC were performed by using an In standard at the heating rate 20°C min^{-1}, and its validity was checked at other heating rates used. All these tests yielded the correct melting point of In within the manufacturer specified precision, i.e., 156.6 ± 0.3°C. Since the expected heating rate dependent systematic error was within the precision of the measurement and markedly smaller than the shift in T_g with the heating rate (i.e., ~2°C per 5°C min^{-1}), the single heating rate calibration was considered to be sufficient. The temperature dependence of the heat capacity was determined by using a standard procedure (5). Sample sizes were ~30 mg. A sapphire sample was used as a calibration standard.



Scheme 1. Structures of glucose (**A**) and maltitol (**B**).

Results and Discussion

Sub-T_g Region

While reheating polyvinyl chloride samples annealed significantly below the glass transition temperature, T_g, Illers (6) detected small endothermic DSC peaks that appear before the main glass transition step. The effect was later studied more extensively for metallic glasses by Chen (7,8) and for various polymers by Bershtein and Egorov (9,10) An interpretation of the effect was given by Chen as a partial enthalpy relaxation and recovery that occur at the expense of the faster part of a broad relaxation spectrum of the glassy state. It was suggested (7–10) that the effective activation energy, E of the underlying process can be determined from the shift in the annealing peak temperature, T_p with the heating rate, q as

$$E = -R\frac{d\ln q}{dT_p^{-1}} \qquad (2)$$

where R is the gas constant. The E values determined this way were found (7–10) to be several times smaller than the activation energies of the α-relaxations in the respective glassy systems.

The annealing peaks are easily produced by annealing a glassy material in the temperature region around 0.8 T_g. For maltitol, we were able to obtain good annealing peaks at T_a = −20, −10, and 0°C, and for glucose at T_a = −25, −20, and −10°C. At the annealing temperatures lower than the respective low limits (i.e., −30°C) the annealing peaks practically disappear. A representative example of the annealing peaks obtained for maltitol is shown in Fig. 1. The resulting peaks are very broad and shallow but readily noticeable especially when comparing DSC curves for annealed samples against those for not annealed samples. When using larger annealing temperatures, the peaks shift closer to the main glass transition step. In order to avoid any significant overlap of the peaks with the glass transition step, we did not use the annealing temperatures above the respective upper limits (0°C for maltitol and 10°C for glucose).

At a constant annealing temperature, the peak temperature increases with increasing the heating rate (Fig. 1) that allowed us to estimate the effective activation energies by Eq. 2. The respective ln$q$ *vs* T^{-1} plots are shown in Figs. 2 and 3. It is seen that for both maltitol and glucose the slopes of the plots increase with increasing the annealing temperature. This means that the effective value of E rises with T_a. For maltitol, the obtained values of E are 71, 77, and

95 kJ mol^{-1} (Fig. 4) For glucose, E rises from 59 to 61 and to 72 kJ mol^{-1} (Fig. 5). The values are obviously smaller than the activation energies of the α-relaxation whose typical values for sugars lie in the region 200–400 kJ mol^{-1}. The smaller values of E suggest that the underlying relaxation process is either noncooperative or weakly cooperative. Apparently, the observed increasing dependence of E with T_a reflects an increasing contribution of the cooperative molecular motion that starts to unfreeze as the annealing temperature approaches the T_g-region. Therefore, the effective E value obtained at the lower temperature limit should yield a better estimate for the activation energy of the local molecular motion. Note that in extended (tens of hours) isothermal aging experiments performed by Kawai *et al.* (11) in the region from T_g −10 down to T_g −30°C, glucose and other sugars demonstrated a significant increase in cooperativity and in the effective activation energy on going from the unrelaxed glassy to supercooled liquid state. Although this effect may in principle affect our E values, it is unlikely to be significant because our samples are aged at considerably lower temperatures (from ~T_g −45 down to ~T_g −70°C) and for much shorter times so that the degree of relaxation of the glassy state in our aging runs is drastically smaller compared to that reached in experiments by Kawai *et al.*

By analyzing the E values derived from the annealing peaks for several polymers, Bershtein and Egorov (9,10) found that these values correlate well with the activation energies of the β-relaxation as measured by dynamic mechanical and dielectric techniques. We also noticed this correlation for such polymers as polystyrene (3) and poly (vinylpyrrolidone) (12). Does this correlation hold for maltitol and glucose? In the case of maltitol, our best estimate for the local process is 71 kJ mol^{-1}. For the β-relaxation in maltitol the reported values of the activation energy are as follows: 57 (13) and 61 (14) kJ mol^{-1} by using dielectric spectroscopy and 62 (14) kJ mol^{-1} by using mechanical spectroscopy. The use of the method of thermally stimulated depolarization current demonstrated (15, 2) that the activation energy of the β-relaxation increases from 45 to 65 kJ mol^{-1} with increasing the temperature from −120 to −30°C. Therefore our estimate correlates quite well (within ~15%) with the activation energies of the β-relaxation in for maltitol.

For glucose, our best estimate is 59 kJ mol^{-1}. The literature reports the following values for the activation energy of the β-relaxation: 42 (16), 52 (17), and 62 (18) kJ mol^{-1}, all of which were determined by using dielectric spectroscopy. Clearly, our estimate falls within the region of the reported values that constitutes its good correlation with activation energies of the β-relaxation. Lastly, both estimates

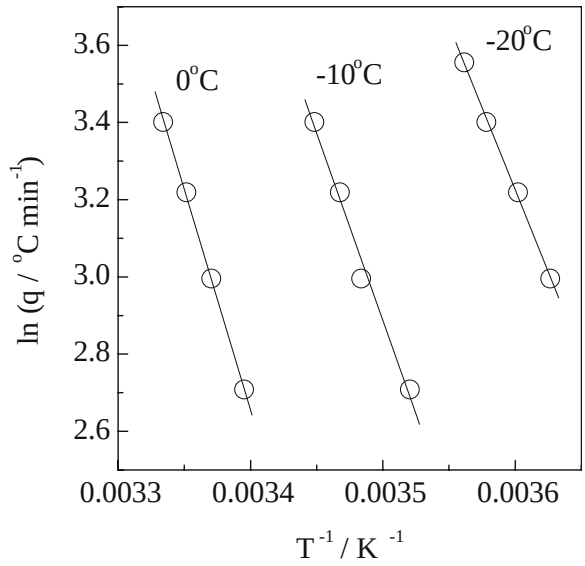


Fig. 2. Evaluating activation energies (Eq. 2) for sub-T_g relaxation of maltitol annealed at different temperatures. The magnitudes of the annealing temperatures shown by the *straight lines*.

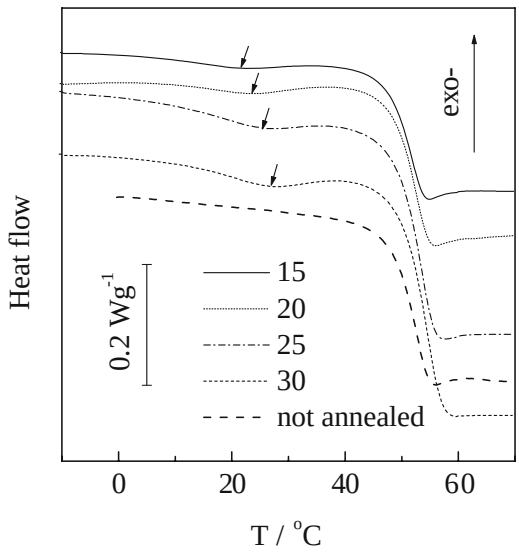


Fig. 1. DSC curves obtained on heating of maltitol at the heating rates 15 – 30°C min^{-1} (*numbers by the lines* represent the heating rates) after annealing at 0°C for 30 min. "Not annealed" curve obtained by heating a sample immediately after quenching. *Arrows* show the location of the annealing effect.

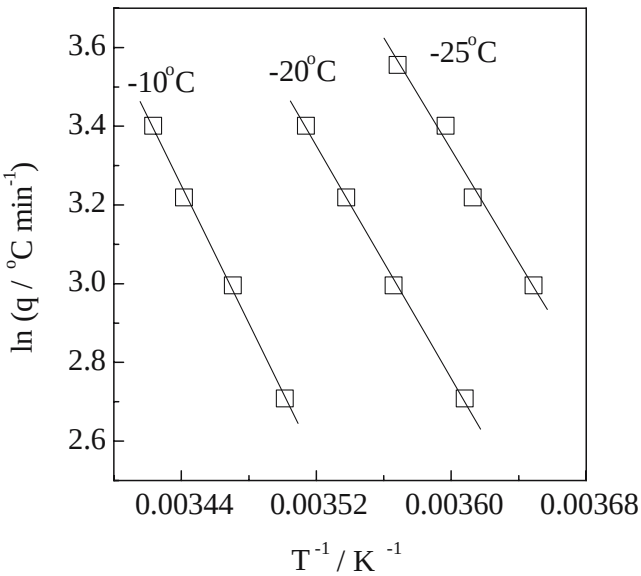


Fig. 3. Evaluating activation energies (Eq. 2) for sub-T_g relaxation of glucose annealed at different temperatures. The magnitudes of the annealing temperatures shown by the *straight lines*.

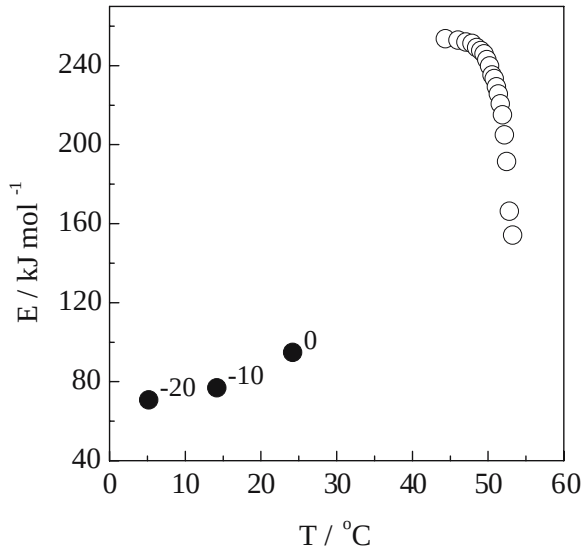


Fig. 4. Variation of the activation energies for the sub-T_g (*solid symbols*) and T_g (*open symbols*) relaxation of maltitol with average temperature of the process. Numbers by the points represent annealing temperatures.

fit well into the empirical correlation, $E_\beta = (24 \pm 3)RT_g$ reported by Kudlik *et al.* (19) According to this, the activation energies of the β-relaxation in maltitol and glucose should, respectively, lie within ~8 kJ mol^{-1} limits of 64 and 62 kJ mol^{-1}.

T_g-Region

Heating glassy maltitol and glucose throughout the temperature region of the glass transition results in obtaining typical step-like DSC traces (Fig. 6). The steps shift to higher temperature with increasing the heating rate. The effect is the basis of the popular method by Moynihan *et al.* (20) that allows the effective activation energy to be determined from the slope of the ln$q$ vs T_g^{-1} plots. In the original paper, Moynihan *et al.* (20) proposed to use three different definitions of T_g (the extrapolated onset, the inflection point, and the peak temperature), however, did not observe any significant difference in E for different T_g definitions. It later became a commonplace practice to determine E by using only one of the T_g definitions such as the midpoint temperature or the limiting fictive temperature. Such approach produces a single value of E that is assumed to hold throughout the whole glass transition step. This assumption is equivalent to assuming the Arrhenius temperature dependence for the relaxation time that contradicts (21,22), to the typically observed Vogel–Tammann–Fulcher (VTF) and/or Williams–Landel–Ferry (WLF) type of dependencies. Low variability of the effective activation can be expected only for the strong glass-forming systems such as B_2O_3 and As_2Se_3 that were used in the original work by Moynihan *et al.* (20) Their respective dynamic fragilities, m, are 32 (23) and 37 (24). On the other hand, for sorbitol (m = 93 (23)) Angell *et al.* (25) obtained a significantly smaller E when T_g is taken as the temperature of the heat capacity peak than when it is estimated as the onset temperature. A decrease in the E values determined, respectively, from the onset, midpoint, and offset temperature was also observed by Hancock *et al.* (26) on heating and on cooling of several glassy sugars, including sucrose, raffinose, trehalose, and lactose. Needless to say, a decrease in the effective activation energy with increasing temperature is consistent with the VTF/WLF type of the temperature dependence (27).

In order to better elucidate a variation of the activation energy throughout the glass transition step, we proposed (4) to use an advanced isoconversional method (28,29). For a set of n experiments conducted under different temperature programs, $T_i(t)$, the method allows one to evaluate the activation energy at any given extent of conversion, α by finding E_α, which minimizes the function

$$\Phi(E_\alpha) = \sum_{i=1}^{n} \sum_{j \neq i}^{n} \frac{J[E_\alpha, T_i(t_\alpha)]}{J[E_\alpha, T_j(t_\alpha)]} \tag{3}$$

where:

$$J[E_\alpha, T_i(t_\alpha)] \equiv \int_{t_{\alpha-\Delta\alpha}}^{t_\alpha} \exp\left[\frac{-E_\alpha}{RT_i(t)}\right] dt \tag{4}$$

In Eq. 4, α varies from $\Delta\alpha$ to $1-\Delta\alpha$ with a step $\Delta\alpha = N^{-1}$, where N is the number of intervals selected for analysis. The integral, J in (4) is computed numerically. The minimization is carried out iteratively for each α to determine the dependence of E_α on α. The conversion, α, is determined from DSC traces (Fig. 6) as the normalized heat capacity (30)

$$C_p^N = \frac{(C_p - C_{pg})|_T}{(C_{pe} - C_{pg})|_T} \equiv \alpha \tag{5}$$

where C_p is the current heat capacity, and C_{pg} and C_{pe} are the glassy and equilibrium heat capacity, respectively.

The application of the method to several systems demonstrated (4) that the variability in E correlates with the dy-

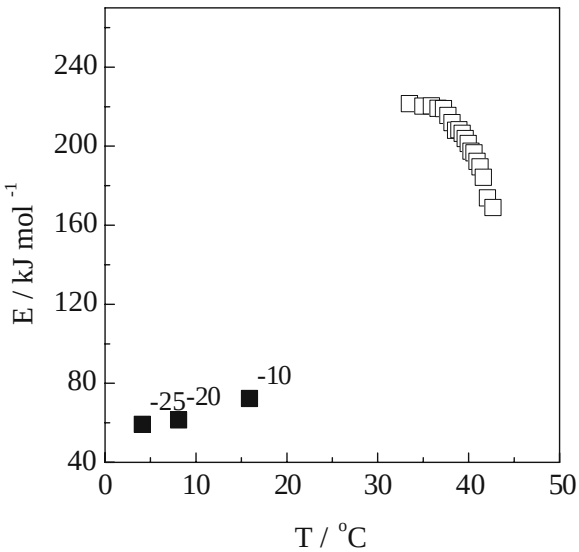


Fig. 5. Variation of the activation energies for the sub-T_g (*solid symbols*) and T_g (*open symbols*) relaxation of glucose with average temperature of the process. Numbers by the points represent annealing temperatures.

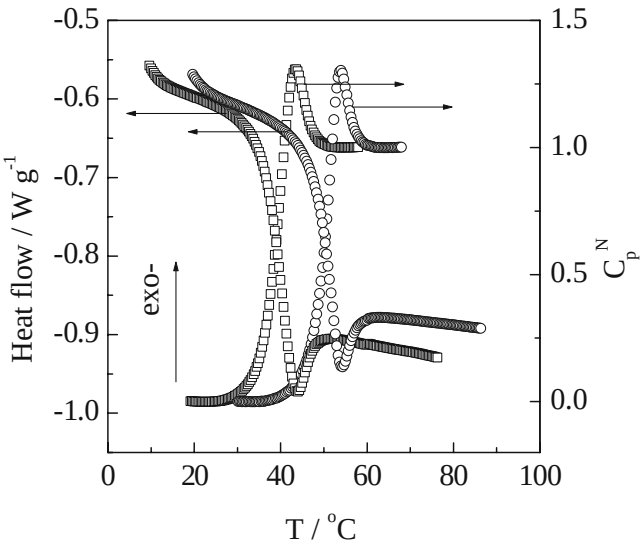


Fig. 6. DSC curves and normalized heat capacities for the glass transition of maltitol (*circles*) and glucose (*squares*) at 20°C min^{-1}. Prior to heating the samples were heated ~40°C above their T_g, held at this temperature for 10 min, and cooled down to ~40°C below T_g without aging.

namic fragility. For maltitol and glucose the reported values of the dynamic fragility, respectively, are 75 (31) and 70 (32). As these values are not very large, we may expect a moderate variability in E throughout the glass transition. The actual dependencies of the effective activation energy on conversion are shown in Fig. 7. As expected, we observe a moderate decrease for both systems. For maltitol the activation energy decreases from ~250 to ~150 kJ mol^{-1} whereas for glucose from ~220 to ~170 kJ mol^{-1}.

The E_α *vs* α plots (Fig. 7) were converted into E_α *vs* T plots by replacing α with the temperature which is estimated as an average of the temperatures corresponding to this α at different heating rates. The resulting dependencies are shown in Figs. 4 and 5. As mentioned earlier, a decrease in the effective activation energy with temperature is typical for the glass transition (α-relaxation). We observed similar effects for polystyrene and polystyrene composite (3) as well as for poly(ethylene terephthalate) and boron oxide (4). For the most fragile system studied (4), poly(ethylene terephthalate) (m = 166), the value of E decreased more than 2 times per 7°C, whereas for boron oxide (m = 32) it decreased less than 1.5 times per 57°C. Maltitol and glucose have intermediate fragilities of about the same value so that they demonstrate similar variability in E that amounts to 1.7 times per 10°C for maltitol and 1.3 times per 8°C for glucose. Therefore, the correlation of the variability in E with the fragility appear to hold for these two systems as well.

The Arrhenius activation energies reported for the α-relaxation in maltitol and in glucose span a rather wide range which is not surprising as their values depend on the temperature and, therefore, on the temperature region used for their determination. For this reason, single values of E (440 (13) and 460 (31) kJ mol^{-1}) reported for maltitol are difficult to compare with our variable values. On the other hand, our dependence fits well within the reported (14) decrease in E from 560 to 50 kJ mol^{-1} with increasing temperature. Single values of E for the α-relaxation in glucose are: 180 (11), 320, (16) and 420 (32) kJ mol^{-1}.

It should be stressed that the effective activation energy landscapes presented in Figs. 4 and 5 are remarkably similar to the temperature dependence of the effective activation energy for stress relaxation as well as for viscous flow in polymers. These latter also show a significant increase in E on approaching the glass transition region from the glassy state, followed by a significant decrease in E while further relaxing toward the liquid state. This effect was originally predicted by Fox and Flory (33) and observed experimentally by McLoughlin and Tobolsky (34). Passing of the E value

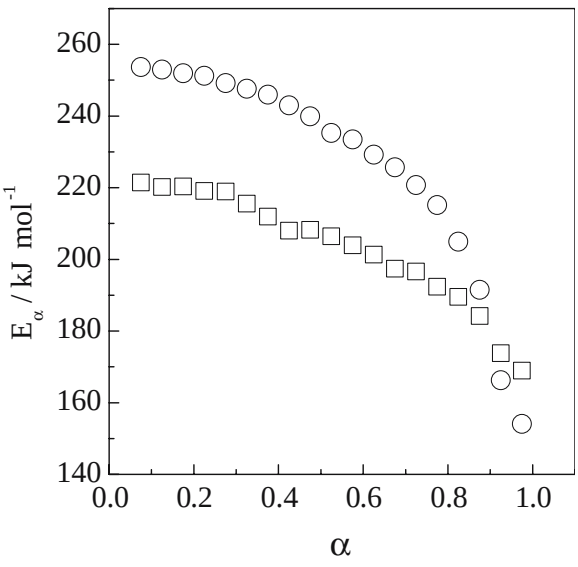


Fig. 7. Variation of the activation energy with the extent of relaxation for the glass transition in maltitol (*circles*) and glucose (*squares*).

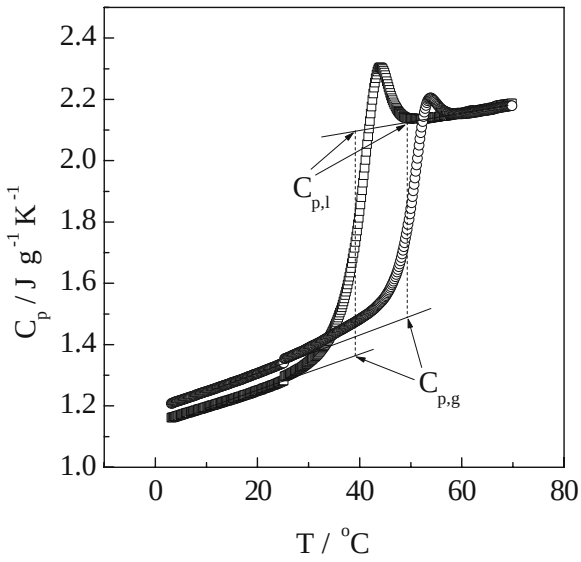


Fig. 8. Temperature dependence of the heat capacity for maltitol (*circles*) and glucose (*squares*). $C_{p,l}$ and $C_{p,g}$ show the values extrapolated to the T_g values (*dashed lines*) that are used in evaluating ξ by Eq. 6.

through a maximum can be understood in terms of molecular cooperativity that is very low significantly below T_g where relaxation occurs via a noncooperative local process that has a small activation energy. As the temperature rises, the molecular motion intensifies increasing cooperativity and the activation energy that reach their maximum in the region of T_g. Above T_g, the free volume starts to quickly increase with temperature so that cooperativity decreases, and the effective activation drops down to the values characteristic of the viscous flow.

Sizes of Cooperatively Rearranging Regions

The respective glass transitions can also be characterized in terms of the sizes of cooperatively rearranging regions as follows (1)

$$\xi^3 \equiv V_\alpha = \frac{k_B T_g^2 \Delta\left(C_V^{-1}\right)}{\rho(\delta T)^2} \tag{6}$$

where ξ and V_α are, respectively, the characteristic length and volume of a cooperatively rearranging region, ρ is the density, δT is the mean temperature fluctuation, and C_v is the isochoric heat capacity. Because the densities of the amorphous maltitol and glucose do not seem available in the literature, we used the densities of the crystalline materials (1.62 g cm^{-3} for maltitol (35) and 1.56 g cm^{-3} for glucose (36)) that can be taken as a reasonable approximation. The value of $\Delta\left(C_V^{-1}\right)$ is defined as

$$\Delta\left(C_V^{-1}\right) = C_{Vg}^{-1} - C_{Vl}^{-1} \tag{7}$$

where C_{vg} and C_{vl} are, respectively, the values of the glassy and liquid C_v extrapolated to T_g. The difference between the isobaric and isochoric heat capacities is either neglected (1), or accounted via the following correction (37)

$$\Delta\left(C_V^{-1}\right) = (0.74 \pm 0.22)\Delta\left(C_p^{-1}\right) \tag{8}$$

In either case, C_v is replaced with C_p that is derived from calorimetric measurements. When the glass transition is measured on heating, δT is estimated as

$$\delta T = \frac{\Delta T}{2.5} \tag{9}$$

where ΔT is the temperature interval in which C_p changes from 16 to 84% of the total ΔC_p step at T_g (37) (Fig. 8).

Figure 8 displays C_p *vs* T data for maltitol and glucose. The data agree well with the earlier measurements (31, 38), By applying Eqs. 6, 7, 8, 9 to the C_p data (Fig. 8) we determined the values of V_α to be 30.6 (maltitol) and 36.4 (glucose) nm^3. The values of the characteristic length were determined as $\xi = (V_\alpha)^{1/3}$ yielding, respectively, 3.1 and 3.3 nm. The values are very close to each other and comparable to the value reported (37) for sorbitol, 3.6 nm. By its meaning the value of ξ provides an estimate of the average distance between the mobility islands in the heterogeneous glassy system (1). The closeness of the ξ values suggests similarity of the heterogeneous structures of the maltitol and glucose glasses. The C_p data can also be used to estimate the number of molecules involved in the cooperatively rearranging region as (1)

$$N_\alpha = \frac{R T_g^2 \Delta\left(C_V^{-1}\right)}{M(\delta T)^2} \tag{10}$$

where R is the gas constant and M is the molecular mass. The resulting values are ~90 for maltitol and 190 for glucose. The value for glucose is almost the same as for sorbitol ($N_\alpha = 195$ molecules (1)), whose molecular mass is similar to that of glucose.

CONCLUSIONS

The relaxation dynamics in maltitol and glucose have been characterized in terms of the effective activation energies and sizes of cooperatively rearranging regions. The sub-T_g relaxation data suggest that with decreasing the annealing temperatures the effective activation energies decrease and tend to converge to the activation energies of the β-relaxation. As the temperature rises throughout the T_g region, the effective activation energies for maltitol and glucose demonstrate a moderate decrease of a similar magnitude that correlates with the moderate values of the dynamic fragility in these systems. Both aforementioned effects are consistent with the trends previously found in polymers. In sub-T_g and T_g regions the effective activation energies for maltitol are somewhat greater than for glucose that appears to be associated with the added impeding effect of the bulky substitute group in maltitol. The comparable sizes of the cooperatively rearranging regions suggest a similarity of the heterogeneous glassy structures of the two compounds.

Therefore, DSC can be effectively used to determine the activation energy landscape for relaxation of non-polymer glasses in a wide temperature range covering both the α- and β-relaxation. The resulting information on the effective activation energies and respective temperatures is of a great practical importance for evaluating the physical stability of amorphous pharmaceuticals. Firstly, it allows one to detect the mobility and identify its type (cooperative *vs* noncooperative) in a given temperature region. Secondly, it can help in preparing more stable drug formulations by choosing those in which noncooperative sub-T_g mobility occurs at higher temperatures and with greater activation energies. For instance, the data obtained in this study suggest that using maltitol instead of glucose as binding matrix should give a more stable amorphous drug formulation.

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