Investigation of the Heating Rate Dependency Associated with the Loss of Crystalline Structure in Sucrose, Glucose, and Fructose Using a Thermal Analysis Approach (Part I)

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Thermodynamic melting occurs at a single, time-independent temperature with a constant enthalpy value. However, substantial variation in the melting parameters ($T_{\text{m onset}}$, $T_{\text{m peak}}$, and ΔH) for sucrose, glucose, and fructose has been reported in the literature. Although a number of explanations have been put forth, they do not completely account for the observed variation. Thus, this research was performed to elucidate the fundamental mechanism underlying the loss of crystalline structure in the sugars using both thermal (Part I) and chemical (Part II) analysis approaches. A strong heating rate dependency observed in the melting parameters for the sugars implies the occurrence of a kinetic process during the loss of crystalline structure. The difference in heat capacity and modulated heat flow amplitude in the stepwise quasi-isothermal modulated differential scanning calorimetry experiments for the sugars compared to indium and mannitol (thermodynamic melting comparison materials) strongly suggests thermal decomposition as the kinetic process responsible for the loss of crystalline structure, which is the critical difference between our conclusion and others. We propose the term "apparent melting" to distinguish the loss of crystalline structure due to a kinetic process, such as thermal decomposition, from thermodynamic melting.

INTRODUCTION

Melting is a first-order phase transition from the crystalline solid phase to the liquid phase (*1, 2*), with no change in chemical composition. The parameters associated with the melting process (onset melting temperature, $T_{\text{m onset}}$; peak melting temperature, $T_{\text{m peak}}$; and enthalpy of melting, ΔH) are usually measured by heating a crystalline material at a specified rate to a temperature where the melting endothermic peak is complete, using a thermal analysis technique, such as differential scanning calorimetry (DSC) or differential thermal analysis (DTA). The melting parameters provide a good deal of information about the characteristics of the crystalline material (e.g., purity, type, size, etc.), thus, melting parameters have been used as unique material properties for identification and characterization of crystalline materials.

However, for some crystalline sugars a wide range of melting parameters has been reported in the literature (**Table 1**). An important observation contrary to the definition of thermodynamic melting based on **Table 1** is that the melting parameters tend to increase strongly with increasing heating rate. Thermodynamic melting occurs at a single, time-independent (i.e., heating rate independent) temperature (often reported as $T_{\text{m onset}}$), where the crystalline solid and corresponding liquid phases are in thermodynamic equilibrium (same Gibbs energy, $\Delta G = 0$) at a constant pressure (**Figure 1**). Thus, widely varying sugar melting parameters are not consistent with the definition of thermodynamic melting and thus necessitate further investigation.

DSC, one of the thermal analysis techniques used in this research, measures the heat flow difference between a sample and inert reference (typically an empty pan) as a function of temperature and time. Integration of the heat flow signal provides enthalpy (H), which is a function of the material's specific heat (C_p) and energy absorbed or released by the material due to phase

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Table 1. Melting Parameters ($T_{m\,onset}$, $T_{m\,peak}$, and ΔH) and Initial Decomposition Temperature (T_i) Reported in the Literatures for Sucrose, Glucose, and Fructose as a Function of Heating Rate[a]

sugar type	heating rate (°C/min)	melting temp (°C)		enthalpy (ΔH, J/g)	anal. technique	init dec temp (T_i, °C)[b]	ref
		$T_{m\,onset}$	$T_{m\,peak}$				
sucrose A/B[c]	0.5	167.9/181.4	169.9/182.7	54.8/119.8	DSC	159.6/167.0	Hurtta et al., 2004 (*21*)
sucrose A/B	1	173.7/184.5	176.6/186.6	72.1/126.6	DSC	161.1/171.3	Hurtta et al., 2004 (*21*)
sucrose	1	160	185	120	HP-DTA[d]		Raemy, 1983 (*3*)
sucrose A/B	2	178.2/187.1	181.4/189.3	111.4/128	DSC	169.6/178.8	Hurtta et al., 2004 (*21*)
sucrose	5	173	190	118	DSC		Roos, 1995 (*1*); Bonelli et al., 1997 (*4*)
sucrose	5		183.5		DSC		Roos and Karel, 1990, 1991 (*5, 6*)
sucrose	5		186		DSC		Weitz and Wunderlich, 1974 (*7*)
sucrose	10	192			DSC		Levine and Slade, 1988, 1989, 1991 (*8−10*)
sucrose	10	176	183	135	DSC		Gloria and Sievert, 2001 (*11*)
sucrose	10		188		DSC		Saleki-Gerhardt and Zografi, 1994 (*12*)
sucrose	10		190		DSC		Vanhal and Blond, 1999 (*13*)
sucrose	10	165	188.7	135.7	DSC		Smidova et al., 2003 (*14*)
sucrose A/B	10	185.9/188.9	190.5/191.5	126.4/134.4	DSC	179.7/189.2	Hurtta et al., 2004 (*21*)
sucrose	15	187	230		DSC	233	Richards and Shafizadeh, 1978 (*23*)
sucrose A/B	20	187.5/189.6	191.9/192.9	130.8/135.4	DSC	192.2/200.7	Hurtta et al., 2004 (*21*)
sucrose A/B	50	188.3/191.1	193.7/196.1	136.9/138.8	DSC	207.5/214.9	Hurtta et al., 2004 (*21*)
sucrose A/B	100	189.0/190.8	196.1/196.5	143.2/145.4	DSC	235.3/228.4	Hurtta et al., 2004 (*21*)
glucose A/B[c]	0.5	147.5/145.1	149.1/147.5	182.7/180.1	DSC	146.4/147.0	Hurtta et al., 2004 (*21*)
α-D-glucose	1	135	150	180	HP-DTA		Raemy, 1983 (*3*)
β-D-glucose	1	130	150	150	HP-DTA		Raemy, 1983 (*3*)
glucose A/B	1	149.8/146.5	151.7/149.3	189.1/185.4	DSC	149.8/152.0	Hurtta et al., 2004 (*21*)
D-glucose	5	143	158	179	DSC		Roos, 1995 (*1*)
glucose A/B	2	152.8/148.9	154.8/151.9	189.0/187.1	DSC	151.4/159.1	Hurtta et al., 2004 (*21*)
glucose	6	165			DTA	157 (peak 215)	Örsi, 1973 (*48*)
glucose	10	158			DSC		Levine and Slade, 1988, 1989, 1991 (*8−10*)
D-(+)-glucose	10	158.24	163.92		DSC		Wungtanagorn and Schmidt, 2001 (*15, 16*)
glucose A/B	10	160.4/155.2	163.1/159.4	195.9/194.3	DSC	166.4/170.3	Hurtta et al., 2004 (*21*)
glucose A/B	20	164.8/158.3	167.4/163.8	200.1/199.1	DSC	176.5/183.5	Hurtta et al., 2004 (*21*)
glucose A/B	50	169.4/164.4	172.6/168.9	208/206.9	DSC	191.6/201.1	Hurtta et al., 2004 (*21*)
glucose A/B	100	171.8/166.7	176.1/173.8	220.7/218.9	DSC	194.4/204.3	Hurtta et al., 2004 (*21*)
fructose A/B[c]	0.5	108.2/110.0	114.3/113.0	147.6/151.6	DSC	110.7/110.4	Hurtta et al., 2004 (*21*)
D-fructose	1	80	115	180	HP-DTA		Raemy, 1983 (*3*)
fructose A/B	1	113.6/112.7	118.4/116.7	156/154.1	DSC	116.3/113.9	Hurtta et al., 2004 (*21*)
fructose A/B	2	112/116.2	123.2/121.0	161.5/163.9	DSC	122.8/119.0	Hurtta et al., 2004 (*21*)
D-fructose	5	108	127	169	DSC		Roos, 1995 (*1*)
fructose	6	120			DTA	130 (peak 175)	Örsi, 1973 (*48*)
fructose	10	124			DSC		Levine and Slade, 1988, 1989, 1991 (*8−10*)
β-D-fructose	10		104.85		DSC		Fan and Angell, 1995 (*17*)
fructose A/B	10	125.8/125.7	134.1/131.7	174.8/176.7	DSC	138.7/136.8	Hurtta et al., 2004 (*21*)
D-(−)-fructose	10	113.58	132.03		DSC		Wungtanagorn and Schmidt, 2001 (*15, 16*)
fructose	10		133		DSC		Truong et al., 2002 (*18, 19*)
fructose A/B	20	131.3/130.0	137.8/136.0	185.9/185.5	DSC	145.0/147.1	Hurtta et al., 2004 (*21*)
fructose A/B	50	135.7/134.9	140.6/139.8	197.8/199.2	DSC	161.6/157.0	Hurtta et al., 2004 (*21*)
fructose A/B	100	137/136.8	142.6/142.0	212.8/203.7	DSC	166.1/165.4	Hurtta et al., 2004 (*21*)

[a] This table is a comprehensive list of literature melting parameters obtained by the authors at the time of publication. However, it may not be exhaustive. [b] Initial decomposition temperature was determined using TGA. [c] A/B indicates two different sugar samples. Sucrose A and fructose A were bulk materials, the others were fine chemicals made for laboratory use. [d] HP-DTA: High pressure DTA apparatus.

transitions. Specific heat or heat capacity is the result of molecular motion, and therefore, changes in heat capacity reflect changes in the molecular mobility of the material.

Two important characteristics associated with thermodynamic melting, which DSC makes visible, are (1) at any given temperature, there is an absolute difference in enthalpy (H, J/g) between the crystalline and amorphous phases (i.e., the enthalpy difference of amorphization, amorphization being the conversion from a crystalline to an amorphous structure; the laws of thermodynamics require a crystalline material to absorb the difference in enthalpy between the two phases in order to become amorphous), and (2) this difference increases with increasing temperature, due to the difference in heat capacity between the two phases, as shown in **Figure 2**. The absolute difference in enthalpy between the two phases determines the size (J/g) of the endothermic peak when the crystalline material melts and is essentially independent

of what causes the phase transition. Based on these characteristics, the difference in enthalpy between the crystalline and amorphous phases at the thermodynamic melting temperature should be a single, constant value, equal to the area of the endothermic peak (ΔH, J/g) obtained using DSC. Thus, the ΔH value for thermodynamic melting is also independent of time (i.e., heating rate independent).

Theoretically, as discussed above, thermodynamic melting occurs at a single temperature with a constant enthalpy value; however, both material properties and measurement methods can affect experimentally obtained melting parameters. In the case of pure and relatively small molecules, thermodynamic melting usually occurs over a narrow temperature range. However, in the case of larger molecules (e.g., polymers), thermodynamic melting occurs over a broad temperature range due to a number of factors, including molecular weight distribution, crystal purity, type, size, and crystal perfection during heating.

Additionally, measurement methods can influence the experimentally obtained melting parameters, both between methods (e.g., DSC versus a melting point apparatus) and within a method (*21*). An example of within a method is thermal lag in DSC measurements. In DSC analysis, the furnace attempts to heat the sample at the user selected heating rate and a thermocouple, or other temperature sensor, is used to measure sample temperature. However, because of the presence of physical barriers (e.g., sample pan) the sample temperature lags behind the thermocouple temperature. Thermal lag varies with experimental conditions and ultimately affects the determination of the melting temperature. However, use of modest conditions (heating rate, 1 to 25 °C/min; sample sizes, 1 to 5 mg; and sample pan mass) can reduce melting parameter variation caused by thermal lag.

However, the variation due to the material properties and measurement methods discuss above are relatively small and
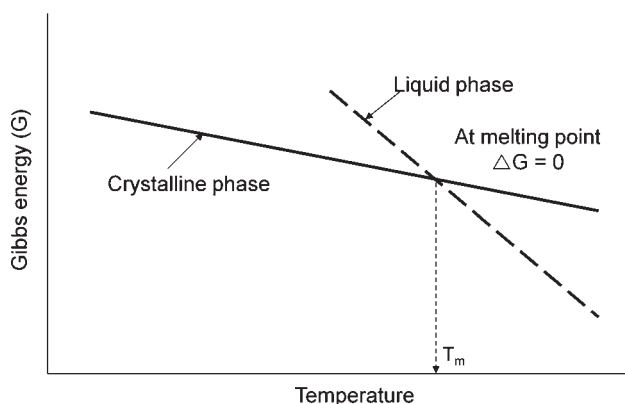

Figure 1. Schematic illustration of Gibbs energy as a function of temperature, at a constant pressure, for a one-component system. Thermodynamic melting (T_m) occurs at the intersection of the crystalline and liquid phases, where the phases are in equilibrium, having the same Gibbs energy, $\Delta G = 0$ (adapted from ref *2*).

cannot explain the heating rate dependency and large differences observed in **Table 1**. Then what is the underlying cause of these observations? Even though a complete explanation was not found in the literature, a number of publications have discussed the large variation and have offered the following possible explanations: origin, impurity, polymorphism, superheating, liquefaction, and thermal decomposition and/or mutarotation in addition to melting.

The origin of the sugar may be responsible for the wide variation of melting points, since there are different sources (e.g., cane and beet sugar) and manufacturing methods. For example, it is well documented in the literature that sucrose prepared by different manufacturing methods (e.g., reagent grade versus commercial grade) yields different shapes and numbers of DSC melting peaks (one, two or three), which can give rise to different $T_{m\,onset}$ values (*21, 23–32*). To date, these findings on the variation in sucrose melting peaks have mainly been related to impurity or polymorphism. However, it is important to note that the $T_{m\,onset}$ still exhibits a heating rate dependency for a single type of sucrose (*21, 29, 31*).

In general, the presence of impurities significantly decreases the melting temperature and broadens the melting peak (*22, 33, 34*). However, it has been reported that the sucrose melting temperature was not always depressed by impurities; but was dependent on the type and amount of impurities, e.g., organic solvents, mineral salts, water, and thermal decomposition components (*31, 35–37*). Okuno and others (*27–29*) reported a similar observation; however, they concluded that the large variation in the sucrose melting temperature was because during crystallization the impurities contained in the sucrose solution cause formation of an additional crystal structure (polymorphism). A number of other publications also attribute the difference in sucrose melting temperatures to the presence of conformational polymorphs (*26, 32, 38, 40*). However, Saska (*39*) specifically disagreed with the presence of sucrose polymorphs as reported by Lee and Lin (*38*).

Superheating occurs when heat is supplied to the crystals faster than they can melt. Typically, melting is sufficiently fast so that
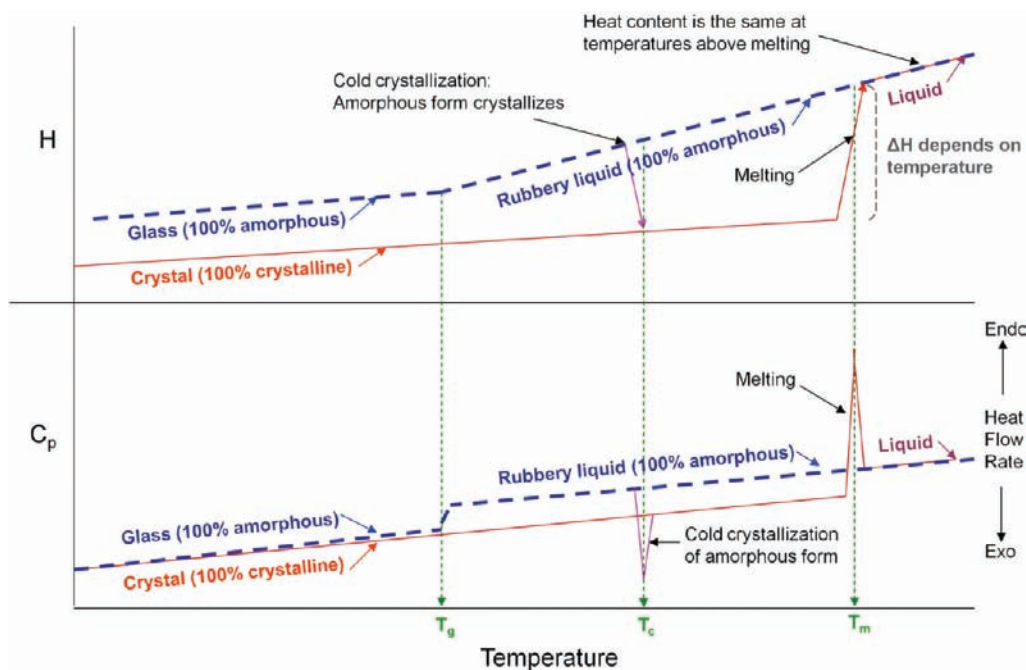
Figure 2. Temperature dependence of the enthalpy (*H* in J/g, also termed latent heat of fusion) and heat capacity (C_p in J/g · °C) of a material in the crystalline and amorphous phases. Typical transitions observed in crystalline (T_m, melting temperature) and amorphous (T_g, glass transition temperature and T_c, cold crystallization temperature) materials are shown in the plot.

its "rate" is determined by the conduction of the heat of fusion into the crystal; thus, the temperature of the crystal does not rise above the melting temperature until the end of the transition (*43*). In superheating, the surface of the crystals still begins to melt at or close to the equilibrium melting temperature, but because melting occurs slowly the temperature of the interior of the crystals rises above the equilibrium melting temperature before the end of the transition (*20*). Tammann (*41*), and later Hellmuth and Wunderlich (*42*), ascribed the heating rate dependency they observed in glucose melting curves to superheating. However, in recent studies performed on glucose, as well as other sugars (*21, 44, 45*), $T_{m\,onset}$ has been shown to actually shift to higher starting temperatures with increasing heating rate, proving that superheating is not the underlying cause of the heating rate dependency of the sugar melting parameters. Magoń and Pyda (*45*) reported that sucrose, glucose, and fructose exhibited superheating, but their data clearly shows that $T_{m\,onset}$ continues to increase gradually with increasing heating rate. It appears that they incorrectly attempted to quantify the amount of superheating by subtracting the $T_{m\,onset}$ at the lowest heating rate from the $T_{m\,onset}$ at the highest heating rate. However, based on the definition of superheating there should be no change in $T_{m\,onset}$, rather just a change in $T_{m\,peak}$.

Tombari et al. (*46*) proposed the theory of spontaneous "liquefaction" to explain why isomerizable crystals, such as fructose, glucose, and galactose, exhibit a large variation in their melting temperatures. Their theory is based on the formation of tautomers via mutarotation during heating. When an isomerizable crystalline material is held isothermally, the energy of the molecules next to a vacancy in the crystal lattice increases, which may be sufficient to isomerize it to a tautomer that no longer fits in the lattice site nor is able to revert to its original state. This gives rise to the formation of a liquidlike local region embedding the vacancy. Similar regions may appear elsewhere in the lattice, and when the number of such regions becomes high enough, they coalesce and the crystal spontaneously liquefies at an isothermal temperature, which is significantly below the melting temperature of the material. The time required for liquefaction was dependent on the difference between the isothermal temperature and the reported crystalline melting temperature. A point important to the current study is that these authors also mentioned that their results could be a consequence of chemical decomposition, however, they did not find evidence for fructose decomposition within their work or within the literature they cited.

By comparing the $T_{m\,onset}$, measured by DSC, to the initial decomposition temperature (T_i), measured by thermogravimetric analysis (TGA), Hurtta et al. (*21*) and Lappalainen et al. (*44*) concluded that the observed heating rate dependency of $T_{m\,onset}$ for sucrose, glucose, fructose (*21*), and xylose (*44*) at low heating rates was due to the occurrence of thermal decomposition and mutarotation (no mutarotation in the case of sucrose), in addition to melting. In the case of sucrose at relatively high heating rates, they reported that melting occurred before thermal decomposition. However, from our observation of their sucrose data, it appears that, at relatively high heating rates, $T_{m\,onset}$ continues to increase slightly, in addition to a relatively large increase in enthalpy (no explanation for the large increase in enthalpy was offered). In the case of glucose, fructose, and xylose at relatively high heating rates, the authors concluded that mutarotation was predominantly responsible for the observed increase in $T_{m\,onset}$ with increased heating rate. Regarding the observed increase in enthalpy for all heating rates employed for fructose and glucose, Hurtta et al. (*21*) mentioned that endothermic/exothermic changes associated with caramelization/decomposition might have also affected the enthalpy values.

Two aspects of the conclusions drawn by Hurtta et al. (*21*) and Lappalainen et al. (*44*) require further discussion. First, both studies included mutarotation, in addition to decomposition and melting, as a possible explanation for the observed heating rate dependency of $T_{m\,onset}$ for glucose, fructose, and xylose; however, no specific mechanism of action was suggested. Since mutarotation in crystalline sugars is induced only after melting begins (*47*), it should only affect the melting parameters associated with the shape of the melting peak, $T_{m\,peak}$ and ΔH, but not the temperature at which melting begins, $T_{m\,onset}$. Thus, we assert that mutarotation is not a possible explanation for the observed heating rate dependency of $T_{m\,onset}$.

Second, both studies may not have fully considered the difference in thermal lag between DSC and TGA measurements. Because the TGA thermocouple is not in direct contact with the sample pan, the TGA thermal lag grows larger than the DSC thermal lag as heating rate increases. Therefore, it is possible that, in these two studies, at relatively high heating rates (up to 100 °C/min), T_i is actually much closer to, or even lower than, $T_{m\,onset}$ for the sugars. Thus, caution is needed when comparing T_i to $T_{m\,onset}$ for determining thermal event order, especially at high heating rates. Besides these two studies (*21, 44*), a number of other researchers have concluded that thermal decomposition (but not mutarotation), in addition to melting, is responsible for the observed variation in sugar melting temperatures (*1, 25, 30, 37, 45, 48, 49*).

As pointed out in the above discussion, these explanantions do not completely account for the large variation observed in the melting parameters for these sugars. Specifically, variation in $T_{m\,onset}$ is still observed as a function of heating rate, despite using the same sugar and the same measurement method and taking thermal lag into account. However, these studies do support the observation that these sugars do not exhibit thermodynamic melting, but rather appear influenced by a kinetic process. We hypothesize that the kinetic process responsible for the "melting" of the sugars studied herein (as well as similar materials) is thermal decomposition; thus, the heating rate dependency "melting" of these materials should be distinguished from thermodynamic melting. Herein, to prevent confusion, the term "loss of crystalline structure" will be used instead of melting. Furthermore, since thermal decomposition is a time−temperature combination process, the loss of crystalline structure occurs not as a single, time independent temperature, but as function of time and temperature.

Thus, loss of crystalline structure in these sugars can occur at temperatures well below their literature reported "melting" temperatures, if held for a long enough time. Therefore, the ultimate objective of this study is to elucidate the fundamental mechanism underlying the loss of crystalline structure in these sugars, addressing a major controversy that currently exists in the literature. The results of this study are presented in two papers: the present one focuses on thermal analysis for all three sugars and the following one on chemical analysis (HPLC) for just sucrose. The specific objectives of this part of the study are (1) to explore the heating rate dependency associated with the loss of crystalline structure in sucrose, glucose, and fructose using standard DSC (SDSC) and (2) to investigate the underlying kinetic process responsible for the loss of crystalline structure in sucrose, glucose, and fructose using modulated DSC (MDSC) and SDSC/TGA.

MATERIALS AND METHODS

Materials. Crystalline sucrose (≥99.5%), D-(−)-fructose (≥99.5%), D-(+)-glucose (99.5%), and mannitol (≥99.9%) were purchased from

Sigma-Aldrich Co. (St. Louis, MO). These analytical reagent grade materials were used without further purification and stored under room conditions in their original containers, wrapped tightly with parafilm after opening. The water contents (wet basis, wb) of the three sugars and mannitol were measured by coulometric Karl Fischer titration with Hydranal Coulomat AG as a solvent and were 0.004% wb for sucrose, 0.048% wb for glucose, 0.033% wb for fructose, and 0.060% wb for mannitol. Material information, including trace anions and cations, for sucrose, glucose, fructose, and mannitol obtained from the Sigma-Aldrich Co. and analyzed by the authors of this study is available as Supporting Information.

Methods. SDSC and stepwise quasi-isothermal MDSC experiments were carried out using a DSC Q2000 (TA Instruments, New Castle, DE), equipped with a refrigerated cooling system (RCS 90). The TGA experiments were carried out using a TGA Q500 (TA Instruments, New Castle, DE).

SDSC Experiments. The DSC Q2000 was calibrated for enthalpy (cell constant) and temperature prior to sample measurements. Temperature calibration was performed to correct the difference between the known melting temperature of a standard (indium, $T_{m\,onset}$ of 156.6 °C, ΔH of 28.71 J/g, TA Instruments, New Castle, DE) and its measured melting temperature. Hermetic aluminum Tzero pans and lids (TA Instruments, New Castle, DE) were used for all calibration and sample measurements, including an empty pan as the reference. Dry nitrogen, at a flow rate of 50 mL/min, was used as the purge gas.

Hermetically sealed sucrose, glucose, and fructose (approximately 2.75 mg) samples were equilibrated at 25 °C and then heated at rates of 2, 5, and 10 °C/min over the temperature range where an entire endothermic peak was obtained. Using a similar method, mannitol (approximately 2 mg) and indium (3.8 mg) were analyzed at heating rates of 1, 5, and 25 °C/min. All samples were measured in triplicate at each heating rate. Universal Analysis (UA) software (Version 4.4A, TA Instruments, New Castle, DE) was used to obtain the melting parameters ($T_{m\,onset}$, $T_{m\,peak}$, and ΔH) and to plot the average heat flow signal of triplicate measurements at each heating rate against temperature.

Stepwise-Isothermal MDSC Experiments. Stepwise-isothermal MDSC experiments were performed using the modulated mode in the DSC Q2000. In advance of sample measurements, DSC heat capacity calibration was done using a 22.93 mg sapphire disk (TA Instruments, New Castle, DE) hermetically sealed in a pan for accurate determination of changes in heat capacity (Rev C_p). With the same sapphire disk, MDSC heat capacity calibration was conducted using the temperature modulation conditions used for the sample measurements; that is, a modulation amplitude of ±1.0 °C and a period of 100 s for sucrose, glucose, and fructose, and a modulation amplitude of ±0.1 °C and a period of 60 s period for indium and mannitol. Dry nitrogen purge gas was set at a flow rate of 50 mL/min.

For sample measurements, sucrose (approximately 2 mg) was heated from 80 to 160 °C using a modulation amplitude of ±1.0 °C, a period of 100 s, a stepwise temperature-increment of 1 °C, and an isothermal time of 25 min with a data off period of 5 min for initial equilibration. With the same modulation conditions as used for sucrose, glucose and fructose were heated from 70 to 160 °C and from 60 to 120 °C, respectively. Indium (4.7 mg) was heated from 155 to 165 °C using a modulation amplitude of ±0.1 °C, a period of 60 s, a stepwise temperature-increment of 0.1 °C, and an isothermal time of 25 min with a data off period of 5 min for initial equilibration. Mannitol (approximately 2 mg) was heated from 149 to 159 °C using the same modulation conditions as in indium. All sample measurements were done in duplicate. Results were displayed as plots of Rev C_p, modulated heat flow, and temperature against isothermal time using the UA software.

TGA Experiments. The TGA Q500 was calibrated for weight and temperature in advance of sample measurements. Unlike in DSC, the TGA thermocouple is not in direct contact with the sample pan, which causes a larger thermal lag than in DSC. Thus, in order to reduce the effect of this large thermal lag three things were done. First, the TGA thermal couple was positioned as close as possible to the sample pan. Second, since thermal lag in TGA becomes larger with increasing heating rate, the maximum heating rate of 10 °C/min (identified via preliminary experiments) was used and the TGA was calibrated at each heating rate (2, 5, and 10 °C/min) using indium (67.05 mg). Indium was used for TGA temperature calibration so as to make the experimental conditions for both TGA

and DSC as identical as possible. Third, helium, at a flow rate of 50 mL/min, was used as the furnace purge gas to improve the contact between the sample and the thermocouple. Dry nitrogen at a flow rate of 10 mL/min was used for the balance purge gas. The DSC Q2000 was also calibrated using the same methods as described in the SDSC experiments.

For TGA experiments, sucrose, glucose, and fructose (approximately 84 mg) were heated at a rate of 2, 5, and 10 °C/min over the same temperature range as in the SDSC experiments. Mannitol (approximately 25 mg) was heated at a heating rate of 10 °C/min from 25 to 230 °C. All TGA measurements were done in triplicate. To facilitate comparison, the average TGA thermal data were compared with the average SDSC thermal data using the UA software. The TGA thermal data were displayed as % weight loss and TGA derivative temperature signals against temperature, while the SDSC thermal data was displayed as heat flow and SDSC derivative temperature signals against temperature.

RESULTS AND DISCUSSION

SDSC Experiments. SDSC experiments were performed in order to explore the heating rate dependency of the melting parameters ($T_{m\,onset}$, $T_{m\,peak}$, and ΔH) for sucrose, glucose, and fructose by comparing to indium, a thermodynamic melting material. Although indium is a well-established thermodynamic melting material, it is not an organic material like the sugars. It would be desirable to employ a material more similar to the sugars than indium, as a comparison thermodynamic melting material. Sugar alcohols, such as mannitol and sorbitol, are frequently used to prevent food products from browning during heat processing, since they are very stable to heat and are thought to melt without thermal decomposition (*51*). Even though no literature was found regarding the use of sugar alcohols as comparison thermodynamic melting materials, a recent report by Lappalainen et al. (*44*) used xylitol instead of indium to measure thermal lag in their experiments on L- and D-xyloses, noting that xylitol's melting behavior is normal, that is, it appears to be a thermodynamic melting material. Therefore, mannitol, the alcohol form of fructose, and sorbitol, the alcohol form of glucose, were selected as possible comparison thermodynamic melting materials, in addition to indium. Through preliminary SDSC experiments (*52*), mannitol was selected as the comparison material, because it more closely resembled the thermal behavior of indium.

Figure 3 shows the melting parameters ($T_{m\,onset}$, $T_{m\,peak}$, and ΔH) for indium and mannitol at heating rates of 1, 5, and 25 °C/min. For both indium and mannitol these parameters did not exhibit significant heating rate dependency. Over the heating rate range of 1 to 25 °C/min, $T_{m\,onset}$ and $T_{m\,peak}$ for indium increased by 0.75 and 1.31 °C, respectively, and ΔH changed by 0.38 J/g. Similar to indium, mannitol showed only a slight increase in $T_{m\,onset}$ and $T_{m\,peak}$, 0.30 and 0.73 °C, respectively, and ΔH changed by 1.54 J/g. Although the differences in $T_{m\,onset}$ and $T_{m\,peak}$ for indium and mannitol were statistically significant ($p = 0.05$) as a function of heating rate (**Table 2**), the difference is not meaningful, rather the result of a very small standard deviation. In addition to similar T_m parameters, the endothermic peak shape of mannitol was very similar to that of indium, however mannitol exhibited a larger ΔH standard deviation. These results suggest that the use of mannitol as a thermodynamic melting comparison material is justified.

Unlike indium and mannitol, the melting parameters of sucrose, glucose, and fructose (**Table 3**) exhibited strong heating rate dependency as shown in **Figure 4**. Over the heating rate range of 2 to 10 °C/min, $T_{m\,onset}$, $T_{m\,peak}$, and ΔH increased by 12.95 °C, 10.71 °C, and 12.03 J/g for sucrose (large endothermic peak), by 7.51 °C, 8.21 °C, and 23.60 J/g for glucose, and by 6.34 °C, 9.40 °C, and 15.66 J/g for fructose, respectively. This strong heating rate dependency suggests that there is a kinetic process associated with the loss of crystalline structure occurring in these sugars.

Article

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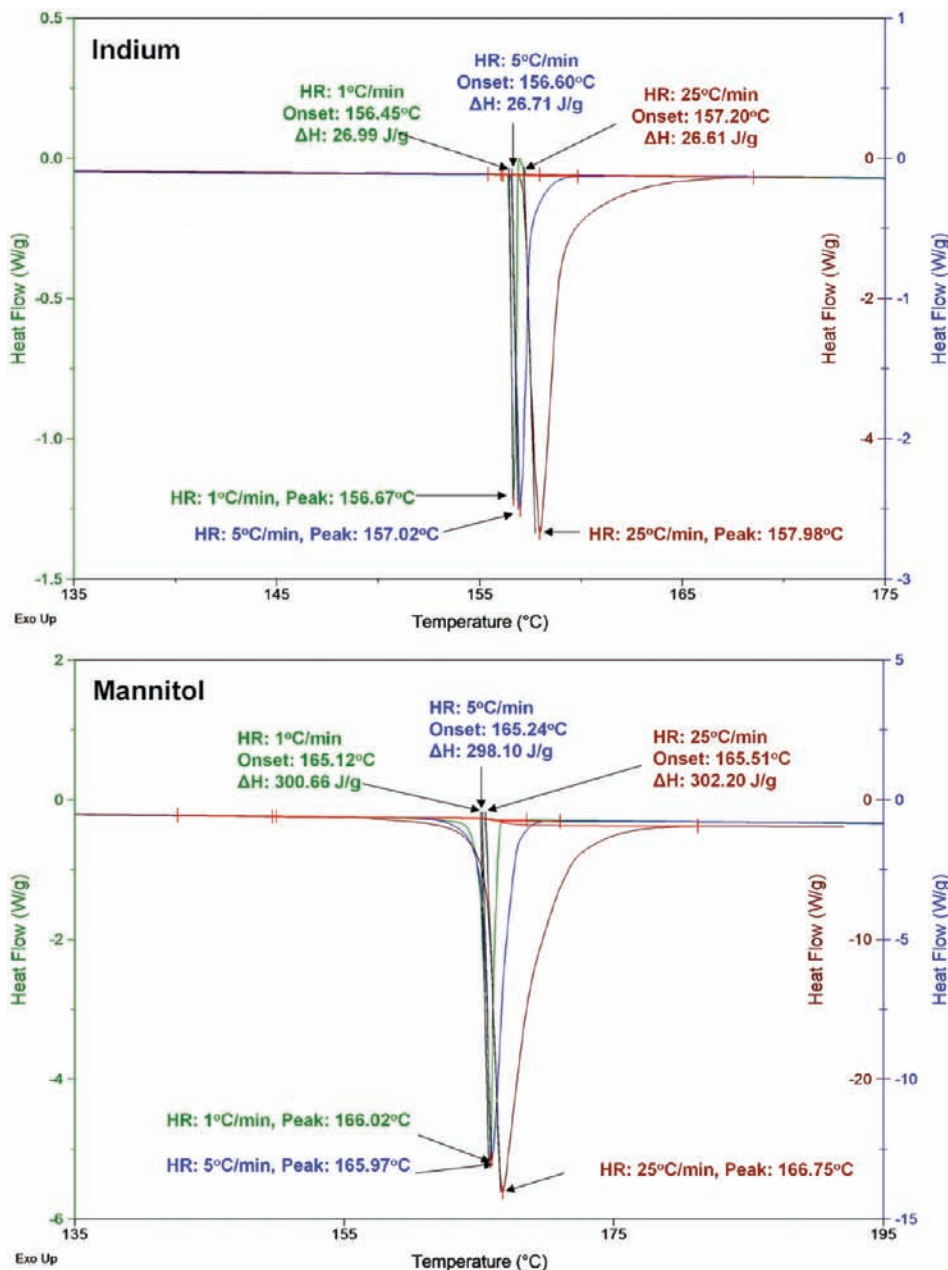
Figure 3. SDSC scans and melting parameters ($T_{m\,onset}$, $T_{m\,peak}$, and ΔH) associated with the loss of crystalline structure in indium and mannitol over the heating rate (HR) range of 1 to 25 °C/min.

Table 2. Melting Parameters ($T_{m\,onset}$, $T_{m\,peak}$, ΔH) for Indium and Mannitol as a Function of Heating Rate ($N = 3$, $n = 3$; Where N = Replication Number and n = Data Analysis Number)[a]

	thermodynamic melting materials					
	indium			mannitol		
heating rate (°C/min)	$T_{m\,onset}$[b] (°C)	$T_{m\,peak}$ (°C)	enthalpy (ΔH, J/g)	$T_{m\,onset}$ (°C)	$T_{m\,peak}$ (°C)	enthalpy (ΔH, J/g)
1	156.45 ± 0.01 a	156.67 ± 0.01 a	26.99 ± 0.04 a	165.21 ± 0.05 a	166.02 ± 0.18 a	300.66 ± 4.54 a
5	156.60 ± 0.00 b	157.02 ± 0.01 b	26.71 ± 0.03 b	165.24 ± 0.01 b	165.97 ± 0.05 b	298.10 ± 4.75 a
25	157.20 ± 0.00 c	157.98 ± 0.00 c	26.61 ± 0.08 c	165.51 ± 0.06 c	166.75 ± 0.07 c	302.20 ± 4.92 a

[a] A linear baseline for indium and a sigmoidal tangent baseline for mannitol were used for determining their melting parameters using the UA software. A linear baseline was used in the case of indium because the difference in the C_p between the crystalline and liquid phases was very small, whereas a sigmoidal tangent baseline was used for mannitol because the difference in the C_p between the crystalline and liquid phases was large (see **Figure 5**). [b] Means with the same letter within a column (difference among different heating rates) are not significantly different ($p = 0.05$).

Similar increases in heating rate dependency were reported by Hurtta et al. (*21*), also studying sucrose, glucose, and fructose, though the magnitude of the increases varied somewhat between the present study and Hurtta et al. (*21*). This variation can be attributed to differences in the sugar samples, as well the nonreproducible (nonuniform) nature of the kinetic process of

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Table 3. Melting Parameters ($T_{m\,onset}$, $T_{m\,peak}$, ΔH) for Crystalline Sucrose, Glucose, and Fructose as a Function of Heating Rate ($N = 3$, $n = 3$; Where N = Replication Number and n = Data Analysis Number)[a]

	apparent melting materials						
	sucrose (small endothermic peak)			sucrose (large endothermic peak)			total
heating rate (°C/min)	$T_{m\,onset}$[b] (°C)	$T_{m\,peak}$ (°C)	enthalpy (ΔH, J/g)	$T_{m\,onset}$ (°C)	$T_{m\,peak}$ (°C)	enthalpy (ΔH, J/g)	enthalpy (ΔH, J/g)
2	138.01 ± 0.12 a	146.00 ± 0.68 a	9.77 ± 0.80 b	173.24 ± 2.26 a	179.84 ± 0.10 a	115.07 ± 7.81 a	124.83 ± 7.26 a
5	145.15 ± 0.49 b	154.48 ± 0.51 b	6.59 ± 0.60 a	179.64 ± 0.67 b	188.28 ± 0.54 b	117.80 ± 1.50 a	124.40 ± 1.69 a
10	150.97 ± 0.51 c	156.64 ± 0.92 c	10.03 ± 0.66 b	186.19 ± 0.27 c	190.55 ± 0.14 c	127.10 ± 4.60 b	137.13 ± 4.60 b

	apparent melting materials					
	glucose			fructose		
heating rate (°C/min)	$T_{m\,onset}$ (°C)	$T_{m\,peak}$ (°C)	enthalpy (ΔH, J/g)	$T_{m\,onset}$ (°C)	$T_{m\,peak}$ (°C)	enthalpy (ΔH, J/g)
2	150.89 ± 0.08 a	154.06 ± 0.08 a	185.11 ± 5.91 a	107.25 ± 1.05 a	116.91 ± 0.20 a	172.93 ± 8.91 a
5	155.11 ± 0.10 b	158.58 ± 0.13 b	199.21 ± 5.52 b	110.45 ± 0.30 a	120.64 ± 0.08 b	177.92 ± 3.61 b
10	158.40 ± 0.14 c	162.27 ± 0.10 c	208.71 ± 5.58 c	113.59 ± 1.51 c	126.31 ± 2.49 c	188.59 ± 3.57 c

[a] A sigmoidal tangent baseline and perpendicular drop function in the UA software was used for determining the melting parameters for sucrose, since sucrose showed two overlapping endothermic peaks. A sigmoidal tangent baseline was used for determining the melting parameters for glucose and fructose using the UA software. A sigmoidal tangent baseline was used for the sugars because the difference in the C_p between their crystalline and liquid phases was large (see **Figure 6**). [b] Means with the same letter within a column for each sugar (difference among different heating rates) are not significantly different ($p = 0.05$).

decomposition. In Hurtta et al. (*21*) the two sucrose samples used (bulk [A] and fine chemical [B]) showed different numbers of endothermic melting peaks, with sucrose A exhibiting two peaks and sucrose B one peak. In the present study, the analytical reagent grade sucrose exhibited two endothermic melting peaks, which has been reported by other researchers for analytical grade sucrose (*23, 25, 31, 38*). The difference in the number of peaks, as well as the temperature at which decomposition begins, observed for different sucrose samples (e.g., analytical grade versus commercial grade) in the literature may be related to the difference in the presence of trace amounts of water, salts, reducing sugars (i.e., glucose and fructose), and organic acids in the sucrose. These components cannot be completely removed during the sucrose manufacturing process; thus, different sucrose samples contain varying types and amounts of these trace components. According to Eggleston and others (*25, 55*), trace amounts of salts vary among analytical sucrose products and even between lots of the same analytical sucrose product. It is important to note that these components have been reported in the literature to accelerate sucrose decomposition (*25, 53–56*). This suggests that there is a link between the number of endothermic peaks and the presence and amount of these trace components, with the endothermic peak(s) being due to decomposition, not thermodynamic melting. The difference in the number of peaks between different sucrose sources is currently under study in our laboratory; however, an important point in regard to this study is that the T_m parameters for both sucrose samples used by Hurtta et al. (*21*) and the sucrose sample used in this study, as well as other studies (*21, 29, 31*), all exhibited heating rate dependency (**Figure 4**).

Stepwise Quasi-isothermal MDSC Experiments. Stepwise quasi-isothermal MDSC experiments were conducted to further investigate the presence of a kinetic process occurring during the loss of crystalline structure in sucrose, glucose, and fructose, as suggested by the heating rate dependency experiments presented above. Stepwise quasi-isothermal MDSC is used to measure the heat capacity (C_p) and heat capacity changes (ΔC_p) caused by structural transformations, such as phase transitions, in a material during heating. In the case of thermodynamic melting, the phase transition (structural change) of a material from the crystalline solid phase to the corresponding liquid phase results in an increase in molecular mobility, such as vibrational, rotational,

and translational motions, and is reflected in a corresponding increase in C_p. Once the phase transition is completed, C_p is larger for the liquid phase than it was for the crystalline solid phase. However, for a material where the loss of crystalline structure involves a kinetic process, the change in C_p associated with the phase transition may be different than for a thermodynamic melting material, because the kinetic process may chemically alter the material. For example, in the case of thermal decomposition as the kinetic process, the material's molecules are, at least initially, broken down into smaller components, which results in an increase in molecular mobility and thus a continuous increase in C_p with temperature.

It is important here to mention that the C_p of a thermodynamic melting material is also dependent on temperature (and, to a lesser degree, other factors, such as atmospheric pressure) before and after a phase transition, but increases predictably (able to be modeled) with temperature and at a much slower rate than the changes in C_p with temperature associated with a material that loses its crystallinity via a kinetic process. All changes in C_p involving a structural change in a material are displayed in the Rev C_p signal in stepwise-isothermal MDSC. The Rev C_p signal is calculated from the amplitude of the modulated heat flow (*57*), which reflects the response of the material to the modulated heating rate used in stepwise quasi-isothermal MDSC. Therefore, if a kinetic process is occurring during the loss of crystalline structure in the three sugars, it should be able to be observed by comparing the changes in the Rev C_p and modulated heat flow of the three sugars to those of indium and mannitol.

Figure 5 shows the stepwise quasi-isothermal MDSC thermograms for indium and mannitol. For indium, a thermodynamic melting material, the solid to liquid phase transition in the Rev C_p signal occurred over a very narrow temperature range ($\sim$0.3 °C) and then the Rev C_p leveled off and regained its predictable and small temperature dependency (as mentioned above) after the phase transition, as it had before the phase transition. The amplitude of the modulated heat flow dramatically changed during the phase transition and also leveled off after the phase transition. Similar observations were found for mannitol, used herein as a thermodynamic melting comparison material, where the change in the Rev C_p took place over $\sim$4.09 °C.

Another finding for both indium and mannitol in **Figure 5** is the collections of exothermic and endothermic peaks that appear in
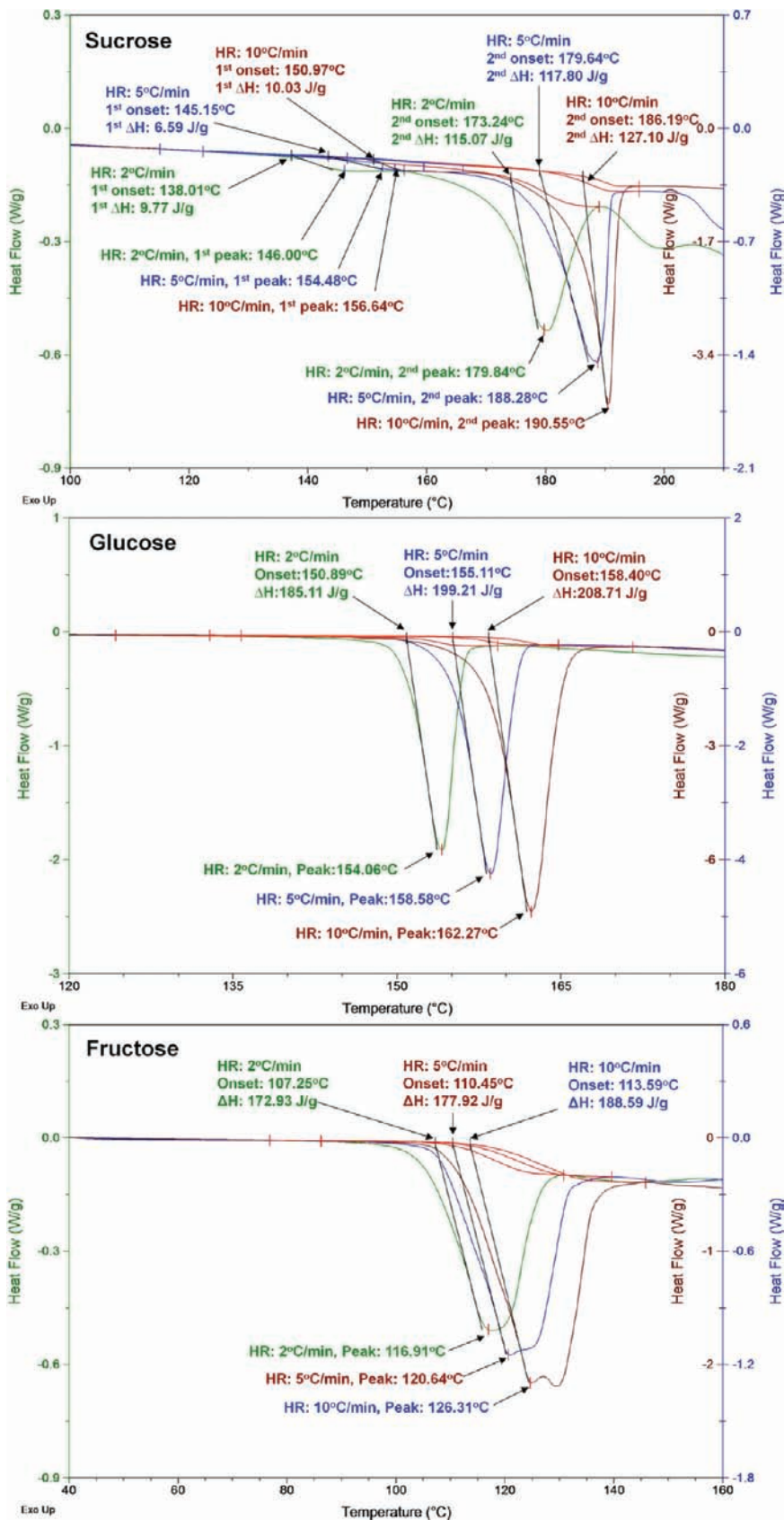
Figure 4. SDSC scans and melting parameters ($T_{m\,onset}$, $T_{m\,peak}$, and ΔH) associated with the loss of crystalline structure in sucrose, glucose, and fructose at heating rates (HR) of 2, 5, and 10 °C/min.

the modulated heat flow during the phase transition. These collections of peaks are the result of the sinusoidal heat/cool temperature profile used in the stepwise quasi-isothermal MDSC experiment.

During the phase transition, when the modulation temperature increases above the average temperature, some of the material melts, and when the modulation temperature drops below the
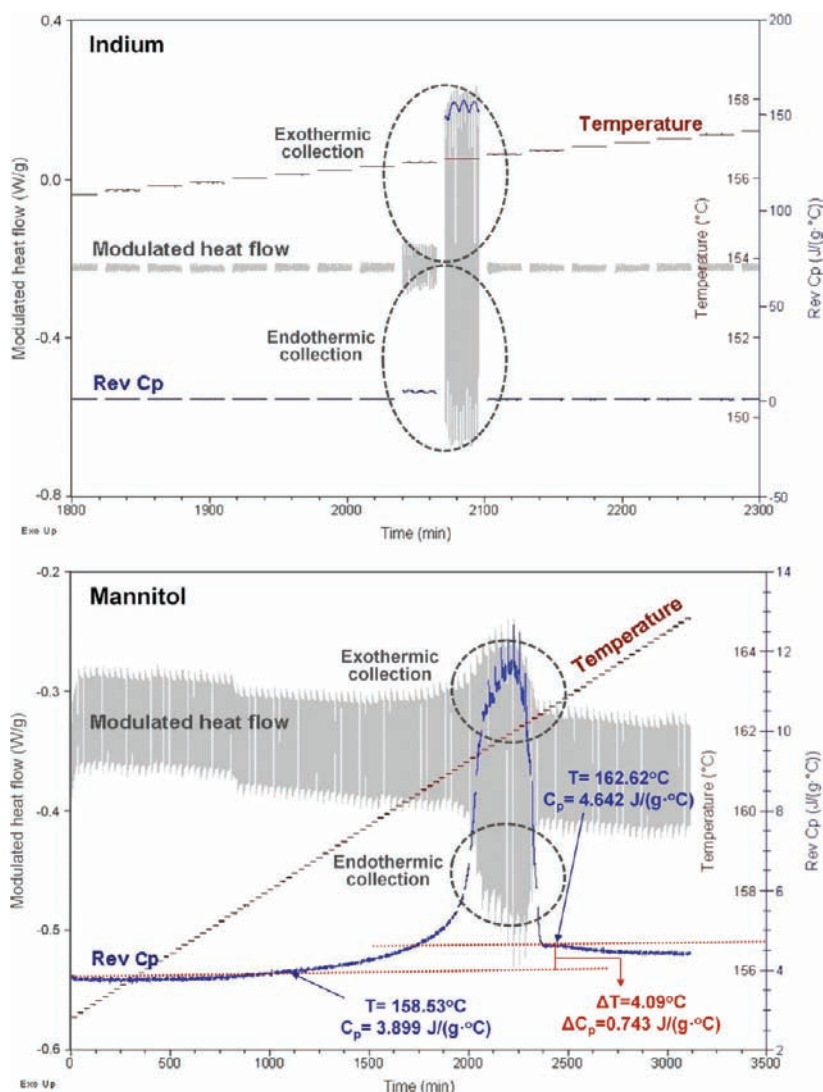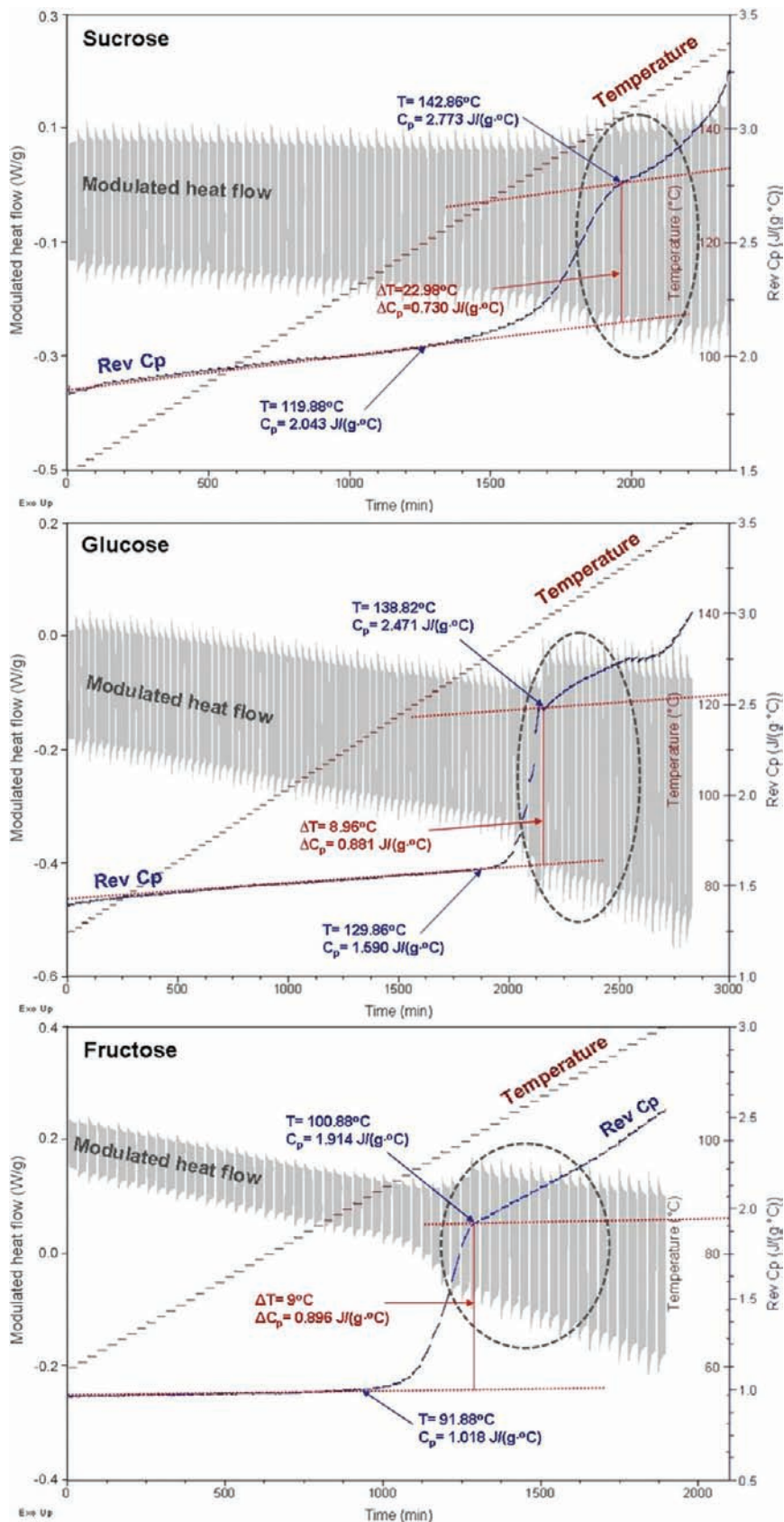
Figure 5. Changes in heat capacity (Rev C_p) and modulated heat flow amplitude during the loss of crystalline structure in indium and mannitol, measured using stepwise quasi-isothermal MDSC.

average temperature, some of the material crystallizes. Thus, while the modulation temperature is applied to the material at an isothermal temperature, the modulated heat flow amplitude remains almost constant because a similar amount of the material melts and recrystallizes continuously. However, when the isothermal temperature is increased or decreased even a small amount, the modulated heat flow changes a great deal, since a different amount of material melts and recrystallizes at each different isothermal temperature. For indium and mannitol, therefore, the presence of the collections of exothermic and endothermic peaks in **Figure 5** shows that both materials were able to melt and recrystallize successively, which suggests that from a structural perspective the molecules can easily respond to the applied modulated temperature and, in turn, from a chemical perspective that the molecules were not altered during the phase transition, that is, the chemical composition of the solid phase was the same as that of the liquid phase.

The stepwise quasi-isothermal MDSC thermograms for sucrose, glucose, and fructose showed completely different thermal behavior compared to indium and mannitol in terms of the temperature range over which the phase transition (i.e., the loss of crystalline structure) occurred, the Rev C_p value after the phase transition, and the absence of the collections of exothermic and endothermic peaks (**Figure 6**). However, the thermal behavior of the three sugars was similar to each other. During the phase

transition, the change in the Rev C_p occurred over a relatively broad temperature range (~23 °C for sucrose, ~9 °C for glucose, and 9 °C for fructose). Once the Rev C_p began to increase (~120 °C for sucrose, ~130 °C for glucose, and ~92 °C for fructose), unlike indium and mannitol, it never decreased, but rather kept increasing, though more gradually, after the complete loss of crystalline structure (~143 °C for sucrose, ~139 °C for glucose, and ~101 °C for fructose). As discussed above, this result can be interpreted in the light of the relation between the Rev C_p and molecular mobility. The sugars are broken down into smaller components by a kinetic process, specifically thermal decomposition. The formation of smaller components leads to an increase in molecular mobility and thus Rev C_p. This continuous increase in the Rev C_p indicates that thermal decomposition continues after all crystalline structure was removed in the sugars.

Unlike indium and mannitol, the three sugars exhibited no collections of exothermic and endothermic peaks in the modulated heat flow. In particular, the absence of the collection of exothermic peaks (i.e., absence of recrystallization) further supports that thermal decomposition is the kinetic process causing the loss of crystalline structure in the sugars. We propose that the absence of recrystallization is due to chemical alteration of the sugar molecules via thermal decomposition, that is, the chemical composition of the solid phase was not the same as the liquid

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Figure 6. Changes in heat capacity (Rev C_p) and modulated heat flow amplitude during the loss of crystalline structure in sucrose, glucose, and fructose, measured using stepwise quasi-isothermal MDSC.

phase. The chemically altered molecules in the material can no longer support the original crystalline structure, leading to the loss of crystalline structure. The presence of thermal decomposition products would make recrystallization difficult, especially over the short modulation period used in the stepwise quasi-isothermal MDSC experiment.

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Table 4. Similarities and Differences between Thermodynamic Melting and Apparent Melting

	thermodynamic melting	apparent melting (caused by thermal decomposition)
similarities	loss of crystalline structure produces an endothermic peak	
differences	a single temperature	temperature depending on heating rate
	time-independent	time-dependent (kinetics)
	constant ΔH (amorphization enthalpy at constant T)	variable ΔH (amorphization enthalpy dependent on heating rate plus decomposition)
	no chemical alteration in material's molecules (pure crystalline material = pure liquid material)	chemical alteration in material's molecules (pure crystalline material $\neq$ chemically altered liquid)
	cause: phases have equal Gibbs energy ($\Delta G = 0$)	cause: kinetic process, e.g., thermal decomposition

Another possible explanation for the absence of the collection of exothermic peaks is mutarotation. Once the loss of crystalline structure is initiated, mutarotation can occur and the tautomer(s) formed could interfere with the recrystallization process (especially over the short MDSC experimental time frame as mentioned above). Two observations make it very unlikely that mutarotation is solely responsible for the absence of the collection of exothermic peaks observed in **Figure 6**. First, mutarotation is not possible in the case of sucrose, so the absence of the collection of exothermic peaks for sucrose cannot be explained by mutarotation only, leaving thermal decomposition as the likely cause. Second, even if mutarotation were responsible for the absence of the collection of exothermic peaks, it would not be the cause of the heating rate dependency of $T_{m\,onset}$, since mutarotation affects the peak shape parameters ($T_{m\,peak}$ and ΔH), but not the beginning of the loss of crystalline structure ($T_{m\,onset}$), as previously discussed in the Introduction. Thus, mutarotation may occur in addition to thermal decomposition in the case of glucose and fructose, but for the reasons given above, it is not solely responsible for the absence of the collection of exothermic peaks observed in **Figure 6**.

It is important here to clarify the role of mutarotation in sugar melting hypothesized by Tombari et al. (*46*). As discussed in the Introduction, Tombari et al. (*46*) proposed that mutarotation was the cause of the loss of crystalline structure in isomerizable sugars, e.g., glucose, fructose, and galactose. However, we found that sucrose, a nonisomerizable sugar, exhibited the same behavior as the isomerizable sugars (glucose, fructose, and galactose studied by Tombari et al. (*46*) and glucose and fructose studied herein), which leads us back to our hypothesis that thermal decomposition is responsible for the loss of crystalline structure in the three sugars.

A number of publications have implicated that thermal decomposition accompanies (along with or right after) sugar melting in sucrose, glucose, and fructose (*1, 21, 25, 30, 37, 45, 48−50, 58*). The critical difference between our conclusion regarding the role of thermal decomposition in sugar melting and others is that we propose that thermal decomposition is the kinetic process that is responsible for the loss of crystalline structure in sucrose, glucose, and fructose; not that thermal decomposition occurs in addition to thermodynamic melting. Thermal decomposition, through the input of heat energy (enthalpy), gives rise to alterations in the chemistry of the molecules (i.e., intramolecular bond breaking, for example, the glycosidic bond between glucose and fructose in the sucrose molecule) that compose the crystalline matrix. Once these intramolecular bonds begin to break, the molecules can no longer maintain their original crystalline structure, resulting in the loss of crystalline structure (matrix is now amorphous) and a commensurate increase in enthalpy equal to the absolute difference in enthalpy (ΔH, J/g) between the crystalline and amorphous phases (as previously discussed in association with **Figure 2**). However, in the case of thermal decomposition as the kinetic process this enthalpy value is not a constant, as it is in

thermodynamic melting (i.e., heating rate independent), but rather increases as the temperature at which thermal decomposition occurs increases (i.e., heating rate dependent). Therefore, the enthalpy of the endothermic "melting" peaks for sucrose, glucose, and fructose in **Figure 4** includes both the enthalpy required for bond breaking due to thermal decomposition and the enthalpy (ΔH, J/g) required for amorphization (loss of crystalline structure) at the temperature at which thermal decomposition begins. A possible apparent paradox that may concern some readers (mentioned by one of the reviewers) is "if sucrose crystals can be grown in the midst of impurities contained in the mother liquor (at levels far greater than shown in Part II) why then should chemical conversion on a relatively minor scale result in destruction of the crystalline structure?" An important point to consider in answering this question is the difference between the ability of sucrose molecules in a supersaturated liquid environment (e.g., mother liquor) to *develop order* in the presence of impurities and the ability of sucrose molecules in a solid crystalline array to *retain order* once the sucrose molecules holding the crystal lattice together begin to break down, forming impurities. In the first case, the impurities are present in the mother liquor naturally or due to the refining process (e.g., residual glucose and fructose, salt, and insoluble substances) and serve to slow down crystal growth, but do not prevent it. However, in the second case, the impurities (e.g., glucose, fructose, 5-HMF, oligosaccharides, and organic acids) are formed as a consequence of the decomposition of the sucrose molecules holding the crystal lattice together, resulting in the falling apart of the crystalline structure. Once a sufficient quantity of the crystalline structure is eliminated through decomposition, it may be possible for the amorphous molecules, including sucrose and the decomposition components, to recrystallize. However, due to the heterogeneity of the resultant amorphous mix, it would require significant molecular mobility for recrystallization to occur, which is one of the important factors in determining the time frame (minutes to years) of the recrystallization process. We do know that the time frame is much slower than that allowed during the stepwise quasi-isothermal MDSC experiment, due to the absence of the collections of exothermic and endothermic peaks.

Finally, because of the fundamental differences between the loss of crystalline structure caused by a kinetic process, such as thermal decomposition proposed herein, and the loss of crystalline structure caused by thermodynamic melting, we propose implementation of a new term, "apparent melting", to describe the loss of crystalline structure caused by a kinetic process. Apparent melting is the amorphization of a material at temperatures below the thermodynamic melting temperature caused by a kinetic process. Kinetic processes that can cause apparent melting include decomposition (studied herein), dehydration (*59−63*), and chemical interactions/reactions (*64−69*). **Table 4** summarizes

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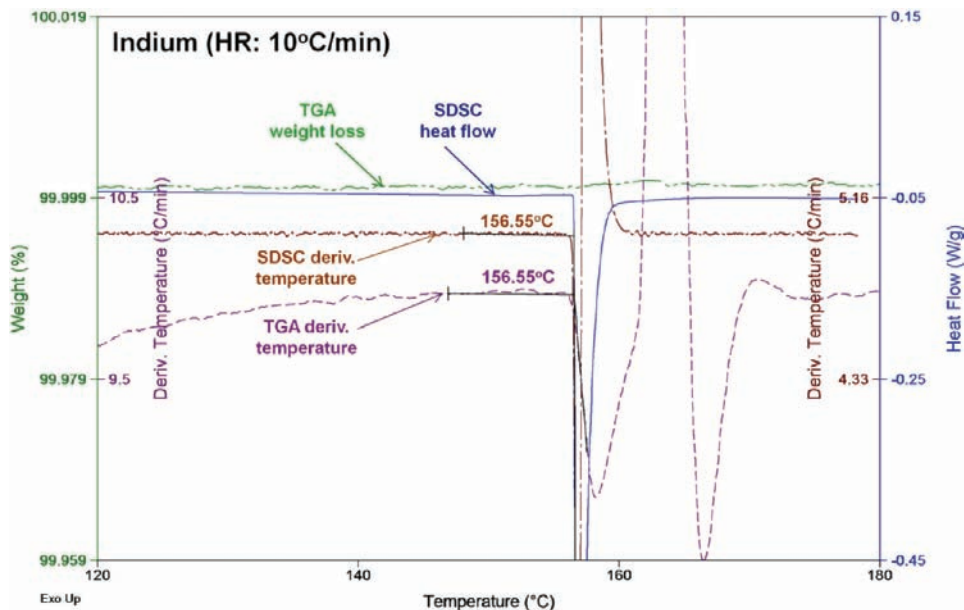
Figure 7. Weight loss, TGA derivative temperature, heat flow, and SDSC derivative temperature for indium heated at a heating rate of 10 °C/min.

the similarities and differences between thermodynamic melting and apparent melting specifically caused via thermal decomposition. In general, the enthalpy associated with apparent melting may be larger or smaller than that associated with thermodynamic melting, since although amorphization is always an endothermic process (increase in entropy), the kinetic process may contain both endothermic (making ΔH larger) and exothermic (making ΔH smaller) events.

TGA Experiments. TGA experiments were performed and compared to the SDSC experiments (previously discussed) in an attempt to further investigate our hypothesis that thermal decomposition is the kinetic process causing the loss of crystalline structure in the three sugars, regardless of the heating rate employed. Although TGA is generally utilized for investigating kinetic processes, it cannot uniquely identify the specific type of kinetic process.

A comparison was made between the SDSC measured temperature ($T_{m\,onset}$), at which the phase transition (the loss of crystalline structure) occurs, and the TGA measured temperature (T_i), at which weight loss occurs, hypothesized to be due to thermal decomposition, for the three sugars at the three different heating rates (2, 5, and 10 °C/min). The SDSC and TGA thermal data for the sugars were also compared to that for mannitol, as a comparison thermodynamic melting material. In addition to comparing $T_{m\,onset}$ and T_i, SDSC and TGA derivative temperature signals (in units of °C/min) were used to monitor changes in the heating rate of the sugars during the phase transition to more accurately compare the SDSC and TGA thermal data.

It is difficult to ensure the accurate comparison of SDSC and TGA thermal data. Thus, it would be helpful to have an internal indicator (i.e., within the TGA experiment) of the temperature at which the sample undergoes its crystalline to amorphous phase transition (provided also by the external SDSC experiment). The derivative temperature signal provides this internal indicator, since when a sample undergoes a crystalline to amorphous phase transition the heating rate of the sample exhibits an abrupt decrease. This abrupt decrease in the derivative temperature signal results from the fact that during the phase transition the sample cannot keep up with the predetermined heating rate, due to the large amount of energy required for the phase transition. Thus, the abrupt decrease in the derivative temperature signal

indicates the temperature at which the loss of crystalline structure in the sugars begins within the TGA experiment. This same phase transition temperature is also obtained via the SDSC experiment (both as the heat flow signal and the SDSC derivative temperature signal), but is an external indicator (is from a separate instrument) used for comparison with the TGA experimental data.

Figure 7 shows the SDSC and TGA thermograms for indium at a heating rate of 10 °C/min. An abrupt decrease in the TGA derivative temperature signal was observed at the same temperature (as measured using the extrapolated onset point) as the thermodynamic melting temperature of indium (156.6 °C), and, as expected, no weight loss in the TGA weight loss signal was observed, since, based on literature findings, indium does not experience any weight loss events until its boiling point at 2080 °C (*70*).

Figure 8 shows the SDSC and TGA thermograms for mannitol at a heating rate of 10 °C/min. Originally, no weight loss was expected for mannitol, because it exhibited similar thermal behavior to indium in the SDCS and stepwise quasi-isothermal MDSC experiments discussed above. However, as can be seen in **Figure 8**, a large weight loss is observed for mannitol beginning at its melting temperature ($T_{m\,onset}$ = 165 °C). This large weight loss is attributed to evaporation of liquid mannitol. Additional information on the vapor pressure and evaporation of sugar alcohols is given by Barone et al. (*71*) and Yan and Suppes (*72*). Unlike in SDSC, the TGA sample pan is open, allowing evaporation of volatile materials. All the mannitol in the sample pan completely evaporated, without a trace of decomposition (sample pan was empty and clean), during the TGA experiments (TGA experimental end temperature was 290 °C). A number of other researchers also observed weight loss after melting for mannitol using a TGA; however, the temperature at which appreciable weight loss began varied among these studies, ranging from approximately 190 to 250 °C (240 °C (*73*); 230 °C (*74*); 250 °C (*75*); 190 °C (*76*)). Two additional studies (*77,78*) reported no appreciable weight loss for mannitol after melting using TGA; however, the end temperatures used in these studies were much lower (200 and 180 °C, respectively) than in the studies that reported appreciable weight loss.

The small, but gradual, weight loss observed for mannitol beginning around 120 °C is attributed to the slow sublimation of
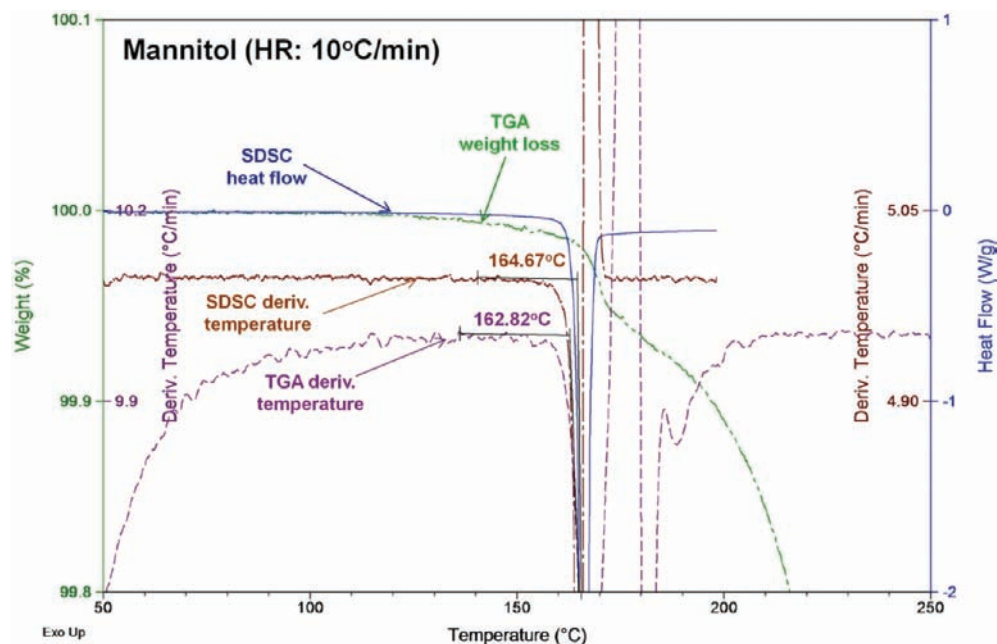
Figure 8. Weight loss, TGA derivative temperature, heat flow, and SDSC derivative temperature for crystalline mannitol heated at a heating rate of 10 °C/min.

mannitol (*71, 79*). Walter-Levy (*80*) reported sublimation of D-mannitol at 130 °C; however, the sublimation of mannitol was not observed by Schwarz et al. (*73*). The difference between these results (observation of sublimation or not) may be because the very small amount of weight loss due to sublimation was overlooked compared to the large weight loss due to evaporation. In addition, a similar TGA weight loss observation (sublimation and evaporation) was found in the case of acetaminophen and phenacetin, which did not exhibit strong heating rate dependency on their T_m parameters over the heating rate range of 2 to 10 °C/min using SDSC (*52*).

Figure 9 shows the SDSC and TGA thermograms for sucrose analyzed at heating rates of 2, 5, and 10 °C/min, respectively. For all three heating rates, the SDSC heat flow signal simultaneously decreased with the TGA weight loss signal, indicating that the T_i was fairly close to the $T_{m\,onset}$. When sucrose began to lose its crystalline structure, an abrupt decrease was observed in both SDSC and TGA derivative temperature signals because of the energy required for the loss of crystalline structure. After complete loss of crystalline structure, the derivative temperature signal of the sucrose jumped to a higher value as the temperature of the sucrose caught up to that of the reference. A similar observation was found for glucose (**Figure 10**) and fructose (**Figure 11**). However, unlike sucrose and fructose, glucose over the heating rate range of 2 to 10 °C/min showed an additional, albeit very small, weight loss (less than 0.0458%) in the temperature range from 53 to 60 °C. We hypothesize that this weight loss was due to water loss associated with the presence of a small amount of α-D-glucose monohydrate in the anhydrous glucose sample (*52*). Hence, the weight (%) in **Figure 10** was lower than 100% even before the loss of crystalline structure in glucose occurred.

In summary, mannitol was being used in this research as a thermodynamic melting comparison material, since it is chemically more similar to the sugars than indium. However, since mannitol exhibited appreciable weight loss immediately after melting due to evaporation in the TGA experiments, the TGA thermogram for mannitol is not distinguishable from that for the simple sugars (weight loss hypothesized to be due to thermal decomposition) in terms of the cause of weight loss. Therefore,

SDSC and TGA experiments alone are not sufficient to identify the specific kinetic process responsible for weight loss. Thus, to determine the cause of weight loss in the case of the sugars, chemical analysis (specifically high performance liquid chromatography, HPLC) was proposed and the results are reported in Part II (*81*) (10.1021/jf104235d). HPLC was selected since it is known to be a successful technique for separating, identifying, and quantifying sugars and their thermal decomposition components (*82−87*). Since the presence of tautomers in the case of glucose and fructose would complicate the HPLC analysis, sucrose was chosen for the further study because it does not form tautomers and it is also the most commonly used sugar in the food and pharmaceutical industries.

Conclusions. This study, using a thermal analysis approach, was conducted to elucidate the fundamental mechanism underlying the loss of crystalline structure in sucrose, glucose, and fructose. Based on the SDSC experiments, all three melting parameters ($T_{m\,onset}$, $T_{m\,peak}$, and ΔH) exhibited a strong heating rate dependency, compared to indium and mannitol, the thermodynamic melting comparison materials. These SDSC results suggested that a kinetic process was responsible for the loss of crystalline structure in the sugars. The stepwise quasi-isothermal MDSC thermograms for sucrose, glucose, and fructose showed completely different thermal behaviors compared to indium and mannitol. The temperature range over which the loss of crystalline structure occurred was much broader for the sugars, the C_p value after the phase transition was much larger and unique for each sugar, and there were no collections of exothermic and endothermic peaks for the sugars, suggesting that thermal decomposition was the kinetic process responsible for the loss of crystalline structure in the sugars. Because of the fundamental differences between the loss of crystalline structure caused by a kinetic process, such as thermal decomposition, and the loss of crystalline structure caused by thermodynamic melting, we propose the implementation of a new term, "apparent melting", to describe the loss of crystalline structure caused by kinetic processes. In the SDSC and TGA comparison experiments, the temperature (T_i) at which weight loss for these sugars began due to thermal decomposition corresponded to the temperature ($T_{m\,onset}$) at which the phase transition began regardless of
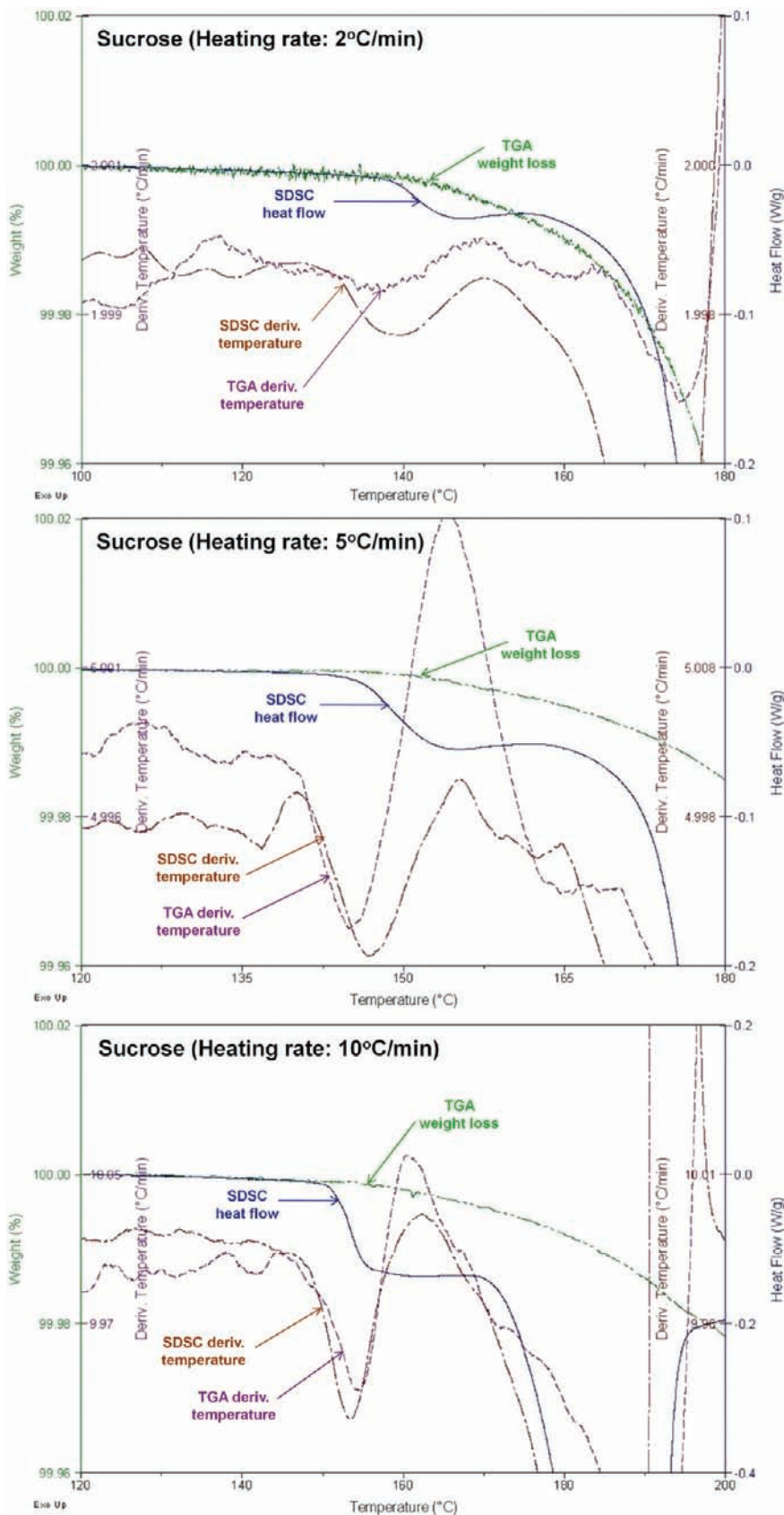
Figure 9. Weight loss, TGA derivative temperature, heat flow, and SDSC derivative temperature for crystalline sucrose heated at heating rates of 2, 5, and 10 °C/min.

heating rate. These results support our hypothesis that thermal decomposition is the kinetic process responsible for the loss of crystalline structure in the three sugars. However, based on the results for mannitol as a thermodynamic melting comparison material, SDSC and TGA experiments alone are not sufficient to identify the specific kinetic process responsible for weight loss.
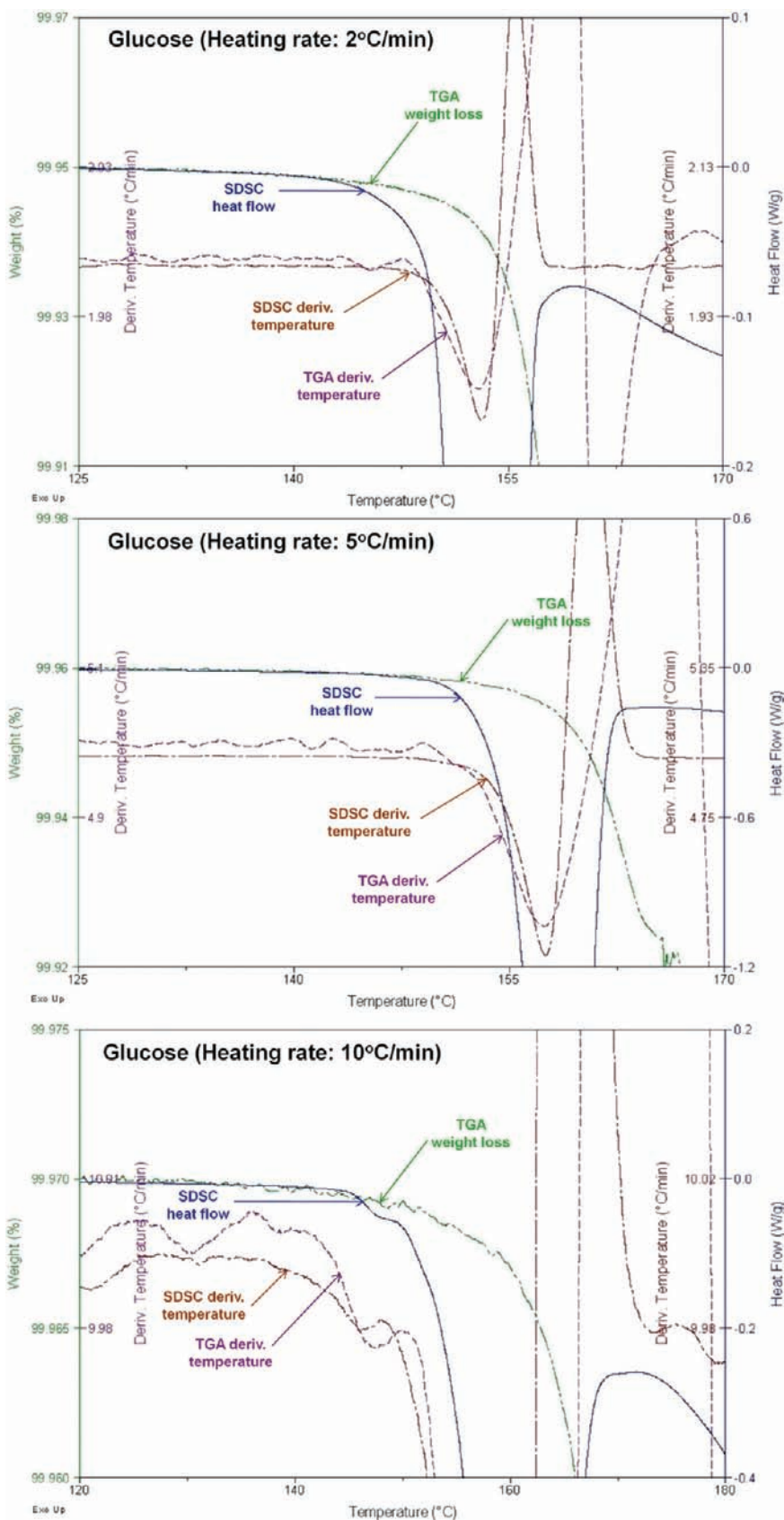
Figure 10. Weight loss, TGA derivative temperature, heat flow, and SDSC derivative temperature for crystalline glucose heated at heating rates of 2, 5, and 10 °C/min.

Thus, to identify the specific cause of weight loss in the case of the sugars, chemical analysis, i.e., HPLC, was proposed and carried out on sucrose in Part II (*81*) (10.1021/jf104235d).

This research is significant because melting is not only a common property used in sugar characterization but also a general method used to prepare amorphous sugars, which are
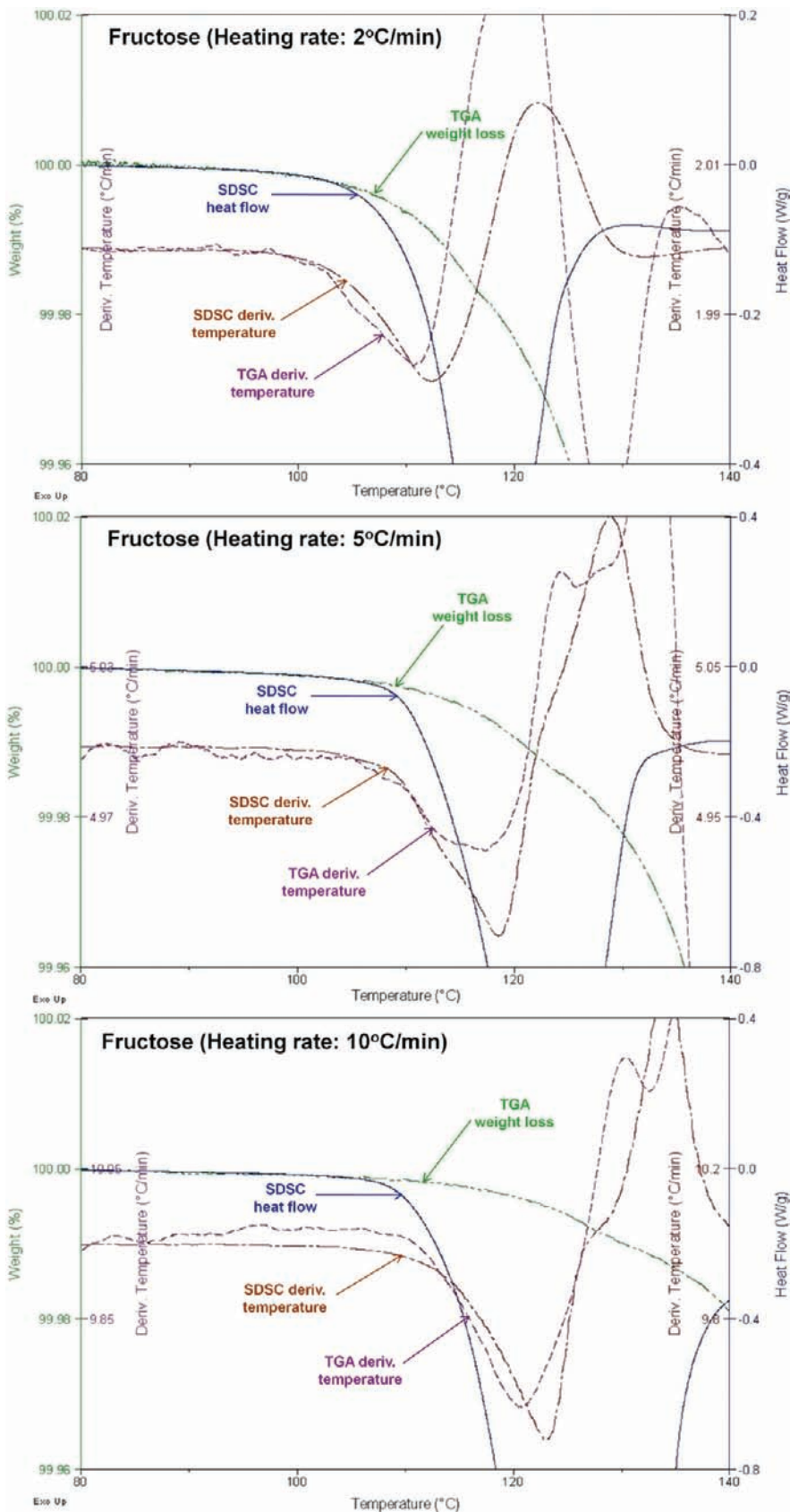
Figure 11. Weight loss, TGA derivative temperature, heat flow, and SDSC derivative temperature for crystalline fructose heated at heating rates of 2, 5, and 10 °C/min.

widely used as ingredients in the food industry and as excipients in the pharmaceutical industry. Since, as proposed herein, thermal decomposition chemically alters the sugar molecules during heating, the subsequent amorphous matrix (sugar molecules plus decomposition components) produced by the melt-quenching method may affect the physicochemical properties of the final product,

such as glass transition temperature, textural attributes, flavor profile and ability to protect active pharmaceutical components, as well as the product's shelf life.

Supporting Information Available: Material information for sucrose and mannitol obtained from the Sigma-Aldrich Co. and analyzed by the authors of this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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