

Crystalline Transitions of Carbohydrates

FRED SHAFIZADEH* AND RONALD A. SUSOTT

Wood Chemistry Laboratory, Department of Chemistry and School of Forestry,
University of Montana, Missoula, Montana 59801

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Several types of transitions which precede the melting of crystalline carbohydrate compounds have been investigated by thermal analysis and the existence and interconversion of different stable and metastable forms have been confirmed by recording their X-ray powder diffraction pattern. The observed phenomena include dehydration, plastic crystal transition, and monotropic and enantiotropic polymorphism. Because of the possibility for these transitions, melting point and X-ray diffraction provide convenient but not necessarily unequivocal methods for characterization of crystalline organic compounds.

The melting point of crystalline materials determined by visual methods has been traditionally considered as a characteristic constant and criterion of purity for organic compounds in general and carbohydrates in particular. However, since the fusion process could be accompanied or preceded by other transitions and transformations, the visual determination of the melting point often provides partial or inadequate description of the changes which are taking place. Wide range and multiple melting points or melting points accompanied by decomposition, sintering, and sublimation are common examples. During the investigation of model compounds for thermal decomposition and combustion of cellulose materials,^{1,2} it was found that thermal analysis provides convenient and comprehensive description of the transitions and transformations which precede or accompany the fusion. Some of these phenomena, such as the plastic crystal transition of 1,6-anhydro- β -D-hexopyranoses,³⁻⁵ simultaneous melting and thermal anomerization of reducing sugars,^{6,7} and the consecutive melting and decomposition of phenyl 2-acetamido-2-deoxy- β -D-glucopyranosides,⁸ have been already reported. This article provides further examples of dehydration, plastic crystal phase transition, and monotropic and enantiotropic polymorphism of carbohydrates, which hitherto have received little or no attention.

Results and Discussion

Dehydration.—The crystal lattice of carbohydrates often contains molecules of water or organic solvents which are removed on drying or heating. Since the crystalline materials are generally analyzed after drying and melting points are determined with anhydrous forms, the original form of the crystalline material and its transformations before melting could easily escape detection. In some cases, when the dehydration process takes place before the melting of the anhydrous form and, depending on the prevailing conditions, it may or may not be accompanied by a separate fusion, there could be considerable confusion about the accuracy of melting point data.

Thermal analysis instruments provide useful tools for investigating the transformation of the carbohydrates and determining the cause of such confusions. The amount and rate of solvent loss under different conditions could be determined by thermogravimetric analysis (tga) and derivative thermogravimetry (dtg), while the changes in crystalline structure, melting, and crystallization and the accompanying changes in enthalpy and entropy could be determined by differential thermal analysis (dta) and differential scanning calorimetry (dsc).

Phenyl β -D-glucopyranoside,⁹ phenyl 2-amino-2-deoxy- β -D-glucopyranoside,⁸ and *p*-aminophenyl β -D-glucopyranoside,¹⁰ which have been investigated in this laboratory, show sharp tga, dtg, and dta signals for dehydration before melting. The first compound was originally reported in 1879 as anhydrous material,¹¹ in a subsequent preparation crystallization from water gave a dihydrate,¹² and a commercial sample recently analyzed in this laboratory was found to be a monohydrate. The reported melting point of this compound has varied within the range of 174–175° for the anhydrous compound¹² to 176° for the monohydrate^{12a} and 144–145° for the dihydrate.^{12b}

Tga analysis of a sample freshly crystallized from aqueous ethanol in a covered pan showed the loss of 11.3% water at 85°, which corresponds nearly to the theoretical value of 12.3% for the dihydrate. Loss of moisture from the dihydrate at room temperature and lower water vapor pressure (humidity) gave a monohydrate. The monohydrate has a different X-ray diffraction from the dihydrate and, as shown in Figure 1, loses 6.6% water, corresponding exactly to 1 mol, at about the same temperature as the dihydrate. The rate of dehydration, as expected, depends on the temperature and the ambient vapor pressure.

Figure 2 shows the dsc data for phenyl β -D-glucopyranoside monohydrate.⁹ Heating under conditions which prevent (Figure 2a) or limit (Figure 2b) the loss of water from the system gives two sharp endotherms at 85 and 176° for the dehydration of the monohydrate and melting of the anhydrous crystals, respectively. Since there is no exotherm between the two transitions, the anhydrous crystals must be formed simultaneously with the dehydration of the original

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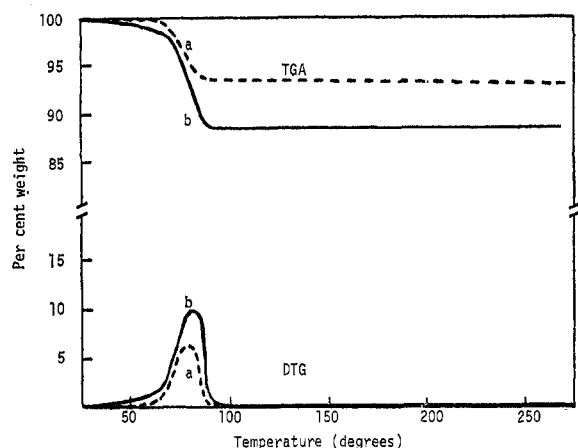


Figure 1.—Tga and dtg of phenyl β -D-glucopyranoside: a, monohydrate; b, dihydrate.

materials. Visual observation indicated that dehydration is not accompanied by fusion. When the water vapor is allowed to escape freely, as in an open pan (Figure 2c) or under vacuum (Figure 2d), the dehydration process takes place gradually with development of a broad endotherm at about 60°. This process gives a solid material which lacks sharp X-ray diffraction but changes to a crystalline, anhydrous form with a sharp X-ray pattern after minor exotherms at 100 and 120°. The anhydrous, crystalline material then melts with a sharp endotherm at 176°. The X-ray powder diffraction patterns obtained for the different phases of these transitions are listed in Table I.

TABLE I

DIFFERENT PHASES OF DEHYDRATION AND MELTING OF PHENYL β -D-GLUCOPYRANOSIDE AND TREHALOSE ON HEATING AND REMOVAL OF WATER

Temp. °C	Phase present	X-Ray diffraction
Phenyl β -D-Glucopyranoside		
20	Dihydrate crystal	14.8 (24), 8.15 (100), 4.91 (31), 4.66 (41), 4.22 (17)
20	Monohydrate crystal	7.89 (74), 4.74 (100), 4.23 (68), 4.01 (59), 3.75 (60)
80	Solid intermediate	18.8 (100) very broad 4.93 (62) very broad
145	Anhydrous crystals	20.2 (45), 18.7 (100), 15.5 (47), 4.62 (35), 3.68 (32)
176	Isotropic liquid	
Trehalose		
25	Dihydrate crystals	5.39 (38), 5.34 (39), 3.78 (100), 3.46 (42), 2.11 (43)
125	Amorphous glass	No diffraction peaks
135	Supercooled liquid	
200	Anhydrous crystals	5.10 (100), 4.32 (64), 3.96 (80), 3.93 (48), 3.54 (67)
215	Isotropic liquid	

The broad endothermic peak at 215° in Figure 2d is due to vaporization. Under vacuum, phenyl β -D-glucopyranoside vaporizes without decomposition, while in a covered pan it could be completely decomposed.^{8,9} The different end results show the care which must be taken in selecting proper conditions for investigating the decomposition and thermal properties of carbohydrates.

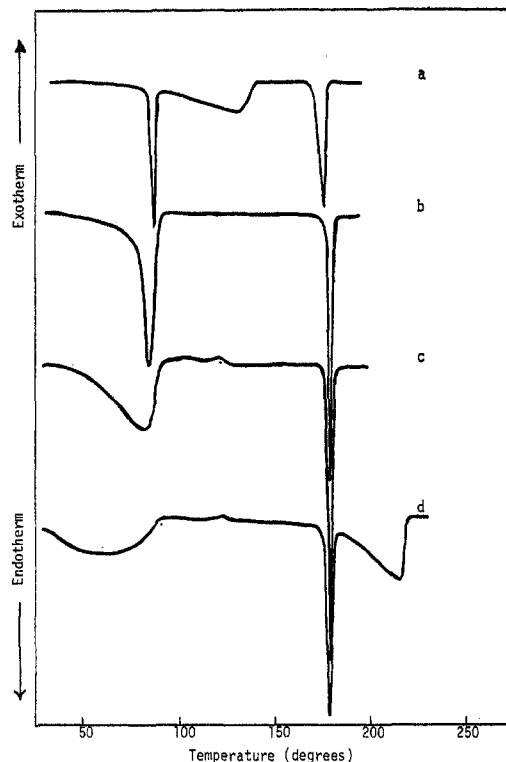


Figure 2.—Dsc of phenyl β -D-glucopyranoside under different conditions: a, hermetically sealed; b, covered pan; c, open pan; d, open and vacuum (1 mm).

Trehalose provides another interesting example.⁷ It forms a dihydrate which has been widely reported to melt at $100 \pm 3^\circ$.^{13,14} Further investigation has shown that in a tightly packed capillary tube it melts at the above temperature, but, when the capillary contains single crystals and is gently heated, it melts at 135° .¹⁴ Furthermore, heating on a microscope melting block shows sintering and loss of birefringence at 100° and melting at 135° . It has also been shown that, when the dihydrate is heated at 130° , it forms anhydrous crystals which melt according to the earlier reports at about 205° ^{13,15} and according to a later report at 216 – 218° .¹⁴

The thermal analysis data for trehalose shown in Figure 3 indicate that when the dihydrate is heated in a closed system which prevents the free evaporation of water (Figure 3a), two sharp endotherms appear at 100 and 215° . At the first endotherm, the dihydrate melts and simultaneously forms anhydrous crystals which remelt at 215° . The situation is quite different when water is allowed to escape freely (Figure 3d). Under this condition, dehydration starts at lower temperatures and proceeds gradually. Consequently, it gives a broad endotherm at about 60° , and leaves an amorphous glass which liquefies with a minor endotherm at 133° . The liquid material then crystallizes with a broad exotherm at 185° and the resulting anhydrous, crystalline form melts with a sharp endotherm at 215° . The sequence of events (in Figure 3d) involving conversion of the crystalline dihydrate to an amorphous glass, an intermediate or supercooled liquid,

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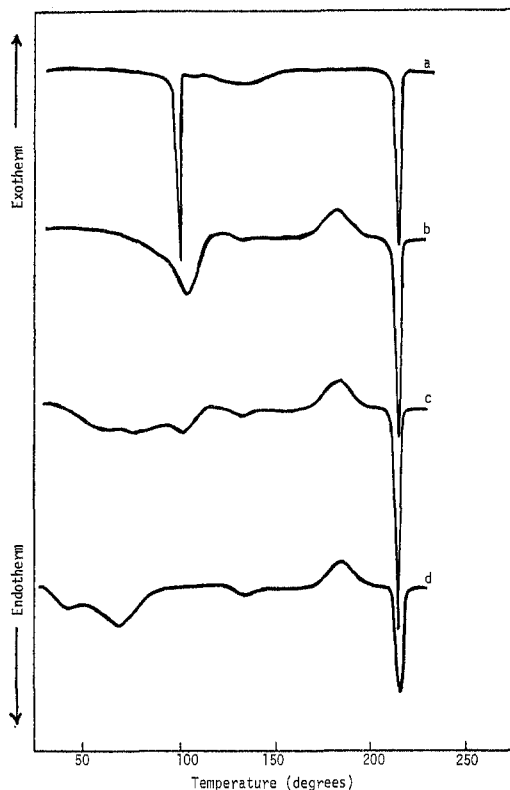


Figure 3.—Dsc of α,α -trehalose under different conditions: a, hermetically sealed; b, covered pan; c, open pan; d, open pan and vacuum (1 mm).

an anhydrous crystalline form, and a final liquid phase has been confirmed by X-ray powder diffraction data of the solids and the visual observation of the liquids. The X-ray data presented in Table I show the highly crystalline patterns of the dihydrate and the anhydrous crystalline forms and amorphous nature of the glass phase.

According to these data, the commonly reported sharp melting of the dihydrate at $100 \pm 3^\circ$ is observed under high ambient vapor pressure, when the moisture is kept within the system, and the reported alternate melting at 135° is due to the softening or liquefaction of the amorphous glass which is formed on gradual dehydration under lower ambient vapor pressure.

Plastic Crystal Transition.—Normally the melting process involves loss of crystal coherence owing to diffusional motion accompanied by isotropy or randomized orientation of the molecule. In the previous studies in this program, it was found that 1,6-anhydrohexopyranoses show a transition in which the orientation of the molecule is randomized but the crystal coherence is maintained until melting at a higher temperature. Wide-line nmr investigation of crystalline 1,6-anhydro- β -D-glucopyranose, which melts at 180° , showed that before transition at 112° it possessed a rigid lattice and after the transition the molecules begin to reorient about their center of gravity and show increased self-diffusion as the temperature is raised further. The transition affects the heat capacity, hardness, X-ray diffraction, hydrogen bonding, vapor pressure, and ir spectra of the crystalline material.²⁻⁵ This phenomenon, known as plastic crystal phase transition, is readily detected by thermal analysis because the major changes of enthalpy and

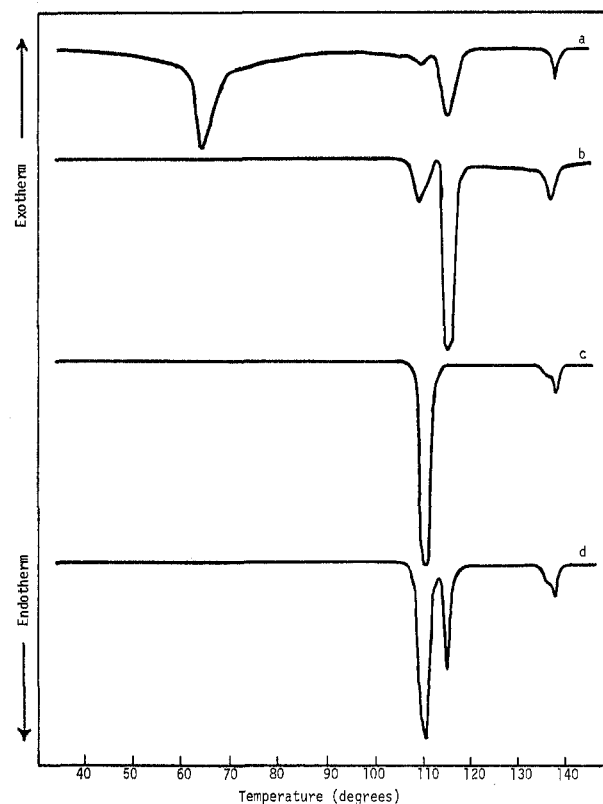


Figure 4.—Dsc of different samples of 1,6-anhydro- β -D-altropyranose: a, monohydrate; b, finely powdered anhydrous crystals; c and d, anhydrous single crystals from tetrahydrofuran at 50° .

entropy take place at the transition rather than melting.¹⁶

The thermogram of 1,6-anhydro- β -D-altropyranose,^{2,4} in addition to a major endotherm for the transition at 115° ($\Delta S_t = 11.1$ eu) and a minor endotherm at 137° ($\Delta S_t = 1.3$ eu) for melting, showed another minor endotherm before the transition ($\Delta S_t = 1.5$ eu) which remained unaccounted for. The situation was further complicated by the fact that 1,6-anhydro- β -D-altropyranose has been also reported to melt at 58 – 59° ¹⁷ and later has been found to form a monohydrate.¹⁸ Investigation of these transformations initially increased the confusion and complexity of the problem because the thermal analysis data (Figure 4) did not seem to be reproducible. However, the key to the problem was found when it was recognized that there are at least four different crystalline forms of the anhydro sugar: the monohydrate form, which dehydrates with an endotherm at about 62° (see Figure 4a), two types of pretransition anhydrous forms IIa and IIb, and finally the plastic crystal form I. The X-ray powder diffraction of these forms and their transformation temperatures are given in Table II. The forms IIa and IIb that could exist as a mixture have different plastic crystal transition temperatures. The transition for IIa is at 115° and for IIb at 110° . Heating of the monohydrate (Figure 4a) and finely powdered anhydrous crystals (Figure 4b) produce a minor transition endotherm at 110° and a major transition endotherm at

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TABLE II
DIFFERENT PHASES AND TRANSFORMATIONS OF
1,6-ANHYDRO- β -D-ALTROPYRANOSE

Phase	Transformation Temp, °C	Form	Characteristics
Monohydrate	→	IIb	8.50 (84), 6.10 (66), 5.55 (45), 4.23 (57), 2.81 (100) ^a
IIb	110	IIa	5.54 (100), 4.66 (93), 4.39 (80), 3.66 (26), 2.77 (32)
IIa	110	I	12.6 (25), 5.23 (100), 4.92 (40), 4.83 (27), 4.67 (32), 3.37 (27)
IIa	80		
I	115	Liquid	Plastic crystal
I	138		
I	134		

^a X-Ray powder diffraction pattern.

115°. Large anhydrous single crystals prepared by recrystallization from tetrahydrofuran solution at 50° produce the major endotherm at 110° (Figure 4c) and sometimes also a minor endotherm at 115° (Figure 4d). The immediate dehydration product and the crystalline material formed on reversing the transition at 75° both show the IIb X-ray diffraction pattern of the large, anhydrous, single crystals obtained by direct recrystallization from tetrahydrofuran. The X-ray pattern for the IIa form could only be obtained from samples which are heated beyond 110° without major transition. These data suggest that IIa is formed as a thermodynamically stable form from minor rearrangements of IIb (see Table II).

Polymorphism.—The phenyl glycosides^{6,8,9} investigated in this laboratory as model compounds for pyrolysis and combustion of cellulosic materials provide interesting and highly complex examples of polymorphism in carbohydrates which, with the notable exception of recent X-ray studies on three forms of mannitol,^{19,20} has received very little attention.

The dsc data on transition of *p*-methoxyphenyl β -D-glucopyranoside⁹ and phenyl and *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucopyranoside⁸ are shown in Figure 5. These transitions are generally characterized by an endothermic peak which is closely followed by an exotherm. They could not be easily reversed and show some variation for different preparations, sample sizes, and the heating rates. Table III shows the X-ray pattern for each phase and the temperature of its transition to the next phase. These transitions can be classified as monotropic²¹ resulting from the conversion of a metastable crystalline phase to a stable crystalline phase. The succession of endothermic and exothermic peaks shows that the transformation involves melting of the metastable form and subsequent crystallization of the stable form.

The transitions of *p*-methoxyphenyl β -D-glucopyranoside (Figure 5a) and phenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucopyranoside (Figure 5b) are quite similar and rather simple. In both cases, the liquid formed on melting of the stable phase can be super-

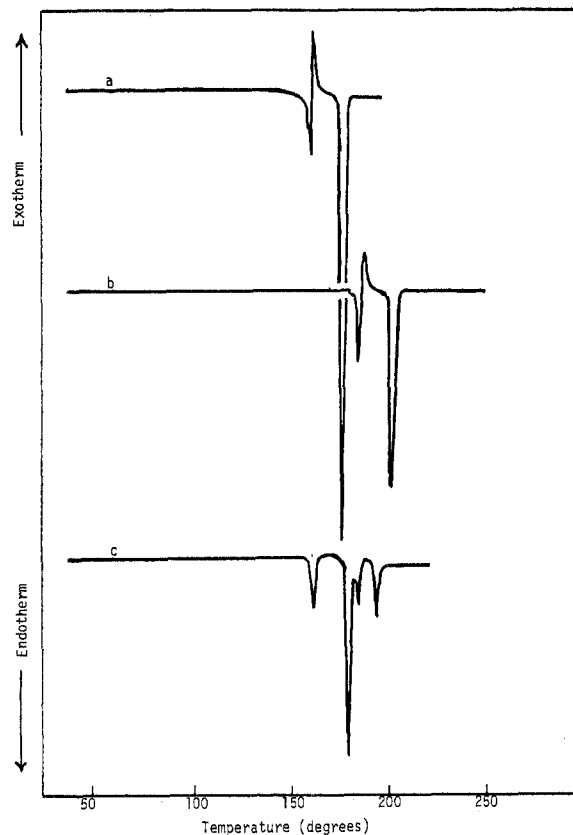


Figure 5.—Dsc of polymorphic glycosides: a, *p*-methoxyphenyl β -D-glucopyranoside; b, phenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucopyranoside; c, *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucopyranoside.

TABLE III
MONOTROPIC POLYMORPHISM OF PHENYL GLUCOSIDES

Phase	Transformation Temp, °C	Form	Characteristics
<i>p</i> -Methoxyphenyl β -D-Glucopyranoside			
II	161	I	14.0 (60), 5.97 (100), 4.82 (37), 4.59 (67), 4.21 (76) ^a
I	176	Liquid	19.6 (71), 4.94 (67), 4.54 (75), 4.09 (70), 3.66 (100)
I	30		
Phenyl 2-Acetamidotri- <i>O</i> -acetyl- β -D-glucopyranoside			
II	185	I	12.0 (100), 10.5 (29), 8.39 (36), 4.15 (36), 3.84 (28)
I	201	Liquid	12.2 (100), 5.74 (39), 4.81 (51), 4.41 (90), 4.21 (38)
I	160		
<i>p</i> -Methoxyphenyl 2-Acetamidotri- <i>O</i> -acetyl- β -D-glucopyranoside			
IV	158	III	11.0 (100), 8.69 (62), 7.20 (59), 3.89 (78), 3.58 (78)
III	177	II	11.4 (100), 9.31 (81), 4.73 (50), 3.99 (41), 3.62 (64)
II	183	I	11.0 (100), 4.98 (40), 4.35 (48), 4.04 (46), 3.95 (42)
I	183		
I	192	Liquid	10.8 (100), 4.98 (77), 4.37 (62), 4.26 (49), 4.13 (44)

^a X-Ray powder diffraction pattern.

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(20) H. S. Kim, G. A. Jeffrey, and R. D. Rosenstein, *Acta Crystallogr., Sect. B*, **42**, 1449 (1968).

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cooled considerably below the transition temperature. The supercooled liquid always crystallizes in the stable form even when seeded with the metastable form. On

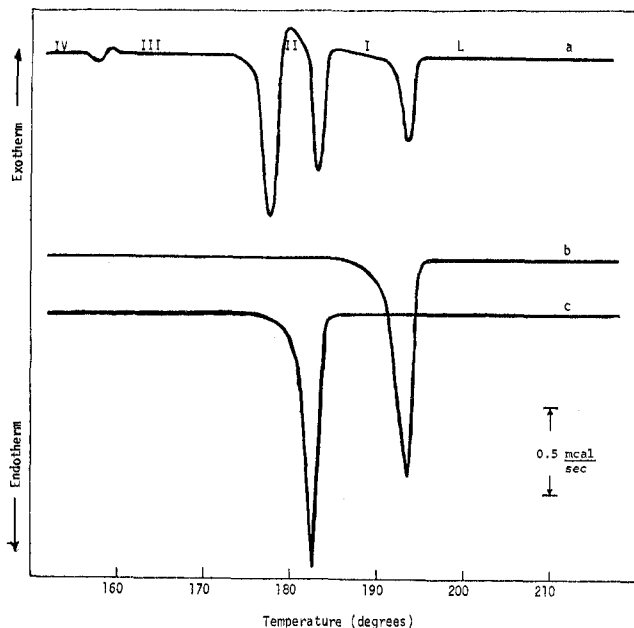


Figure 6.—Dsc of *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucopyranoside: a, complete transition from phase IV to the final liquid L; b, fusion of phase I formed after melting of phase II at 183°; c, fusion of phase II formed after melting of phase I at 192°.

the other hand, crystallization from ethanolic solutions always gives the metastable form even when the solution is seeded with the stable form.

The transitions of *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucopyranoside (Figure 5c) are more complex and involve crystalline phases of IV to I and the final liquid phase L. Figure 6 shows a more detailed dsc analysis of these transitions, when the heating rate is 5°/min instead of 15°/min employed in the previous experiments. Under this condition, the successive transitions (phases IV to L) of a sample that has not been heated before show more pronounced exotherms (compare Figure 6a with Figure 5c). This phenomenon indicates that crystallization of the new forms, which is an exothermic process, is more complete when the sample is heated slowly. Figure 6b shows the melting endotherm at 192° for a sample that has been previously melted at 183° and recrystallized in phase I.

It is interesting to note that cooling and recrystallization of the final liquid phase L, formed on melting at 192°, gives phase II rather than phase I. Figure 6c shows the melting endotherm at 183° for a sample of phase II which is formed after the fusion of phase I at 192°. However, recrystallization from aqueous methanol at 0° gives IV and at room temperature gives a mixture of III and IV crystalline forms.

Another type of polymorphism is observed for phenyl β -D-xylopyranoside⁶ and *p*-bromophenyl and *p*-iodophenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucopyranosides.⁸ The transitions of these compounds are signaled by the minor endotherms shown in Figure 7. Unlike the previous cases of monotropic polymorphism, these transitions are readily reversible on cooling. The enthalpy and entropy of the transition and fusion of these compounds measured by dsc are given in Table IV. According to these data, the entropy of transition, ΔS_t (0.37–1.5 eu), is considerably smaller than the

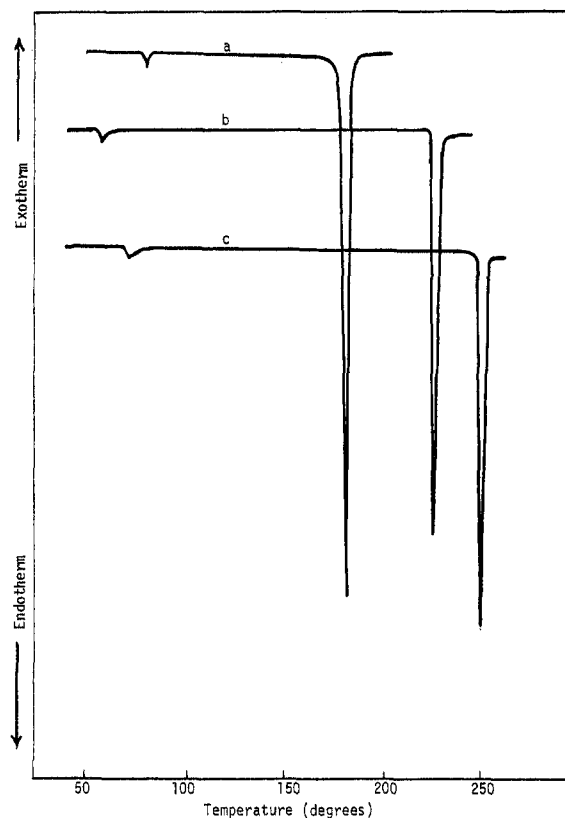


Figure 7.—Dsc of polymorphic glycosides: a, phenyl β -D-xylopyranoside; b, *p*-bromophenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucoside; c, 3, *p*-iodophenyl 2-acetamidotri-*O*-acetyl-2-deoxy- β -D-glucoside.

TABLE IV
THERMODYNAMIC FEATURES OF THE ENANTIOTROPIC
TRANSITION AND FUSION OF PHENYL GLYCOSIDES

Compd	T_t , °C	ΔH_t , kcal/mol	ΔS_t , cal/mol deg	T_f , °C	ΔH_f , kcal/mol	ΔS_f , cal/mol deg
Phenyl β -D-xyloside	81	0.13	0.37	181	7.47	16.5
<i>p</i> -Bromophenyl 2-acetamido-2-deoxy- β -D-glucoside triacetate	61	0.51	1.5	229	10.7	21.4
<i>p</i> -Iodophenyl 2-acetamido-2-deoxy- β -D-glucoside triacetate	72	0.47	1.4	253	12.9	24.5

entropy of fusion, ΔS_f (16.5–24.5 eu), indicating minor changes in the solid state. As noted before, the situation is reversed for the plastic crystal phase transition, which involves major changes of entropy on transition.¹⁶ These considerations point out to an enantiotropic inversion,²¹ involving the reversible transition of two stable crystalline forms.

Experimental Section

Dynamic Thermal Analysis.—The dta and dsc scans were obtained with a Du Pont 990 thermal analyzer and calorimeter cell programmed at 5 or 15°/min. These experiments were carried out with a 2-mg sample in a nitrogen atmosphere. The ΔH determinations were made on a Perkin-Elmer DSC-1B instrument

calibrated against the heat of fusion of indium at 156.6° , $\Delta H_f = 6.75$ cal/g.

X-Ray Diffraction.—The X-ray powder diffraction spectra were obtained with a North American Philips Co. diffractometer and a recording geiger counter using $\text{Cu K}\alpha$ radiation. Different crystalline forms were obtained by crystallization from solvent or controlled heating in the thermal analysis equipment. Lightly ground samples of each form (~ 10 mg) were scanned at $1^\circ 2\theta \text{ min}^{-1}$. More severe grinding was avoided to prevent possible distortion of the soft crystals and decreased resolution of the pattern. The d spacing in \AA (with relative intensity in parentheses) is given in Tables I–III for the most intense lines.

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Registry No.—Phenyl β -D-glucopyranoside, 1464-44-4; trehalose, 99-20-7; 1,6-anhydro- β -D-altropyranose, 10339-41-0; *p*-methoxyphenyl β -D-glucopyranoside, 6032-32-2; phenyl 2-acetamidotri-*O*-acetyl- β -D-glucopyranoside, 13089-21-9; *p*-methoxyphenyl 2-acetamidotri-*O*-acetyl- β -D-glucopyranoside, 38229-72-0; phenyl β -D-xyloside, 4756-31-4; *p*-bromophenyl 2-acetamido-2-deoxy- β -D-glucoside triacetate, 38229-74-2; *p*-iodophenyl 2-acetamido-2-deoxy- β -D-glucoside triacetate, 38229-75-3.

Stereochemistry of the Exhaustive Methylation of Alcohols with Trimethylaluminum

ROBERT G. SALOMON AND JAY K. KOCHI*

Department of Chemistry, Indiana University, Bloomington, Indiana 47401

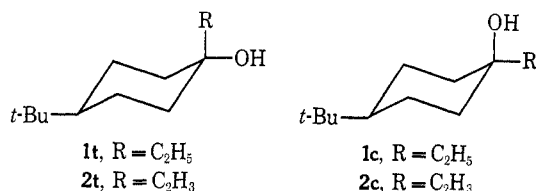
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Exhaustive methylation of the pair of epimeric 4-*tert*-butyl-1-cyclohexanols with 1-ethyl and 1-vinyl substituents using trimethylaluminum proceeds with the loss of stereochemistry at the new quaternary carbon center. Axial and equatorial cyclohexanols give the same mixture of axially and equatorially methylated products with a preference for axial methylation. Methylation occurs *via* a common intermediate, which is not the olefin (the major side product of exhaustive methylation), since separate experiments show that methylalumination of olefin is not important under reaction conditions. A carbonium ion pair intermediate containing an oligomeric aluminum oxide counterion is proposed. Under forcing conditions, methylalumination of the olefins occurs with a strong preference for equatorial methylation. Exhaustive methylation of the allylic cyclohexanols proceeds with predominant rearrangement. Unrearranged products are formed nonstereospecifically as with the saturated analog. However, a common allylic carbonium ion intermediate cannot alone account for all the products.

Exhaustive methylation of tertiary alcohols given in eq 1 can be achieved with trimethylaluminum.¹ Since



the quaternization of carbon centers is a useful synthetic objective, we examined the stereochemistry of the replacement of the hydroxyl function by a methyl group in the stereoisomeric alcohols, *cis*- and *trans*-4-*tert*-butyl-1-ethylcyclohexanol (**1c** and **1t**)² and *cis*- and *trans*-4-*tert*-butyl-1-vinylcyclohexanol (**2c** and **2t**).³

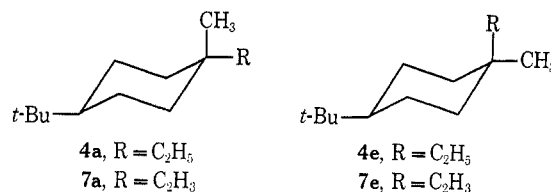


Results

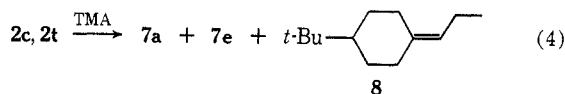
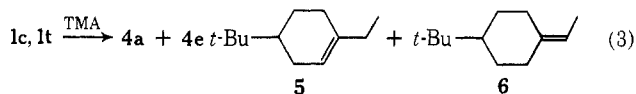
Each of the *tert*-butyl-substituted cyclohexanols (ROH) reacted vigorously with trimethylaluminum (TMA) on mixing at room temperature to afford a mixture of alkoxydimethylalanes and methane (eq 2).



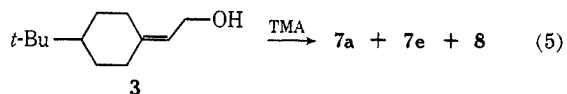
Heating the benzene solution of the alkoxydimethylalanes with a threefold excess of trimethylaluminum and a small amount of water in sealed tubes afforded the expected methylated products as a mixture of *cis* and *trans* isomers. Significant amounts of elimination



products **5** and **6** shown in eq 3 were also formed. The



allylic isomer of **2c** and **2t**, the cyclohexylidene alcohol **3**, also afforded in eq 5 the same products as those



derived from **2c** and **2t**, although in different isomeric ratios, as shown in Table I.

The structures of the axial and equatorial methylation products (**4a** and **4e**) were assigned by an analysis of the nmr spectra of isolated samples. The C-1 methyl resonance (δ 0.77) in **4e** appears at higher field than the corresponding methyl resonance (δ 0.80) in **4a** owing to steric deshielding of the axial methyl by the axial 3 and 5 hydrogens.⁴ These assignments were confirmed by

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