

## Thermoanalytical Studies on Phases of D-Mannitol

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### Abstract

D-mannitol exists in several polymorphic crystalline forms. The conditions of crystallization are not well-defined, and in some cases mixtures of the different forms are obtained. In the DSC study the different forms melted nearly at the same temperature ( $166 \pm 2$  °C). The heat of fusion of the  $\kappa$  form was lower than those of the other forms. With slow heating rate (2 °C/min) the  $\delta$  form changed to  $\kappa$  between 140 and 165 °C. The crystallization of D-mannitol from the melt gave from one to seven peaks in the DSC between 95 and 126 °C depending on cooling rates and the amounts of sample.

### INTRODUCTION

On the basis of x-ray diffraction seven possible phases of D-mannitol have been reported [1-6]. The crystal data of the polymorphic forms of mannitol are given in Table 1. Berman et al. suspected that some of these forms are identical with each other. Jones and Lee [4] have found three phases of D-mannitol produced by spontaneous crystallization of the melt.

Table 1  
Crystal data of the polymorphic forms of mannitol.

	Space group	Z	a (Å)	b (Å)	c (Å)	$\beta$ (°)	D <sub>x</sub> (g cm <sup>-3</sup> )	ref.
$\alpha$	Pmna	4	8.94	18.41	4.92		1.494	5
$\alpha(=\kappa)^1$	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	4	8.959	18.778	4.896		1.470	3
$\alpha'$	C222 <sub>1</sub>	4	8.94	4.92	18.24		1.494	1
$\beta$	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	4	8.672	16.875	5.560		1.487	1
$\gamma$	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	4	9.33	17.36	4.99		1.496	5
$\delta$	P2 <sub>1</sub> / P2 <sub>1</sub> /m	2	5.095	18.254	4.919	118.36	1.501	3
$\kappa^1$	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	4	8.942	18.798	4.893		1.471	2
	orthorhombic	2	10.36	8.10	4.55		1.555	6

<sup>1</sup>These will later be called  $\kappa$

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They analyzed crystals by microscope and x-ray powder method, and came to the conclusion that  $\alpha$  [3] and  $\kappa$  represent the same form. Only  $\beta$  and  $\kappa$  have been determined by single crystal methods and their molecular and crystal structures are reliable [1,2].

In the present study TG, DSC and powder diffraction were used to study the phase transitions of the D-mannitols. D-mannitol skeleton is shown in Figure 1. The  $\beta$ - and  $\kappa$ -mannitols have the same conformation and they differ from each other in the orientations of hydrogens in hydroxyl groups and in hydrogen bonding.

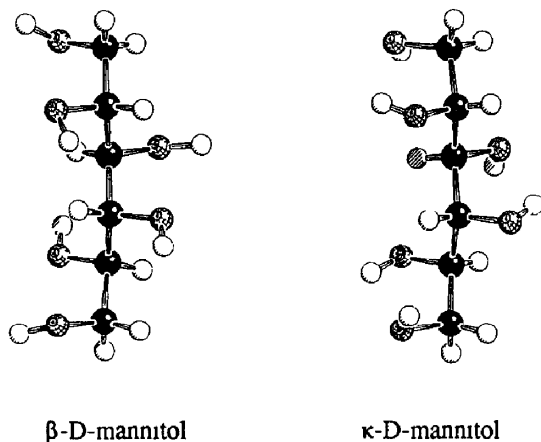


Figure 1. A Schakal plot of the molecular structures of  $\beta$ - and  $\kappa$ - D-mannitol [1,2,7].

## EXPERIMENTAL

The crystals were obtained by following the methods reported in the papers [1-6]. Open vessels were used for evaporating the solvent. Sometimes the vessels were, however, covered to delay the evaporation and in some cases evaporator was used. Crystals were formed in the liquid and often also on the wall of the vessel.

In the measurement TG and DSC were used in the following hardware configurations (PE=Perkin-Elmer, HP=Hewlett-Packard):

- TG PE TGA7, TAC7/DX, IBM PS/2 Model 55 SX
- HP PLOTTER 7475A, PE TADS.TGS(software)
- DSC PE DSC-7, TAC7/PC, EPSON PC AX 2,
- HP PLOTTER 7475A, PE DSC7(software)

The TG curves were run with sample weights of 4-14 mg in Pt-pans and in dynamic air with a flow rate of 40-60 cm<sup>3</sup>/min. The heating rate was 2 °C/min and the temperature range 20-200 °C. The DSC run with heating rates of 0.5 - 12.5 °C/min to 200 °C using aluminum pans with holes, in dynamic nitrogen atmosphere. For studying the phases on cooling we

weighed 1–12 mg of D-mannitol into aluminium pan for the DSC and melted them at 170 °C. Then the samples were cooled with the cooling rates of 0.5–12,5 °C/min to 80 °C. The cycle was repeated twice. Power diffraction method was used to confirm the polymorphic forms of D-mannitol. The x-ray powder diffraction patterns are known to  $\beta$ ,  $\delta$  and  $\kappa$  forms [3,4].

## RESULTS AND DISCUSSION

All the studied samples were anhydrous according to TG. We took efforts to crystallize hydrous forms, but did not succeed.

The samples on the walls of the crystallization vessels were often mixtures of different phases. The extreme case was, when we tried to crystallize  $\kappa$ -form at 100 °C. The DSC-curve gave five peaks (Figure 2). The total heat of fusion was 45.9 kJ/mol. Often the heats of fusion of the mixtures were slightly smaller than those of the pure forms. Close examination usually revealed the  $\kappa$  phase to be most abundant when crystals were formed on the walls of vessels. In liquid one or sometimes two phases were formed

The  $\beta$ ,  $\delta$  and  $\kappa$  forms crystallized from water. They have been confirmed by powder diffraction methods. The onsets, peaks and heats of fusion are given in Table 2. The  $\delta$  phase was also formed when the fluid mannitol (2–5 g) was cooled with very slow rate in the temperature test chamber. This curve (Figure 3) differs from the curves of the other phases

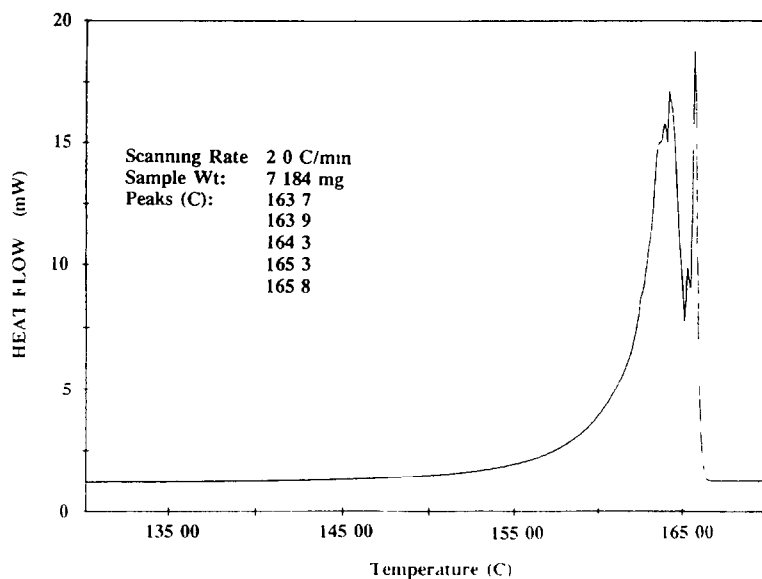
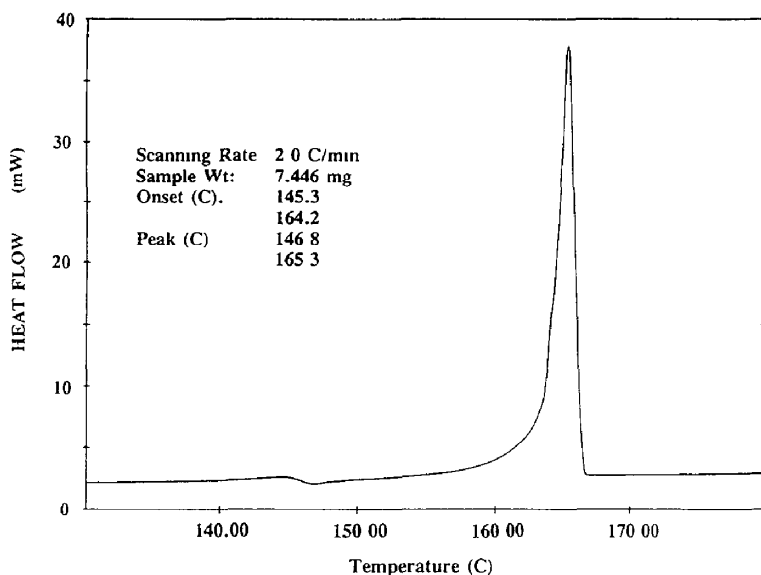


Figure 2 The DSC-curve of a mixture of D-mannitols crystallized on the wall of the vessel at 100 °C.

Table 2

The Onsets, peaks and heats of fusion of the phases of D-mannitol.

	heating rate °C/min	onset °C	peak °C	heat of fusion kJ/mol
$\alpha$ (or $\alpha'$ )	10	165.6	167.9	$55.0 \pm 0.5$
$\beta$	2	165.4	166.4	$54.1 \pm 0.5$
$\gamma$	2	164.6	166.4	$51.0 \pm 0.5$
$\delta$	10	165.4	167.1	$50.8 \pm 0.5$
$\kappa$	2	164.1	165.6	$48.1 \pm 0.5$

Figure 3 The DSC-curve of  $\delta$ -D-mannitol in nitrogen

in containing a minor exothermic peak before the melting peak. The transformation was not found with fast heating rate (10 °C/min). The  $\delta$  phase crystallized from water did not show such an exothermic peak. It is possible that these samples which were prepared by different methods do not represent the same phase. The x-ray powder diffraction patterns of the  $\delta$  phase in the references [3] and [4] differ slightly from each other.

Some samples were transformed on heating and by mechanical treatment [4]. The  $\delta$  phase (crystallization of the melt) transformed partly to  $\kappa$  and  $\alpha$  to  $\gamma$ . The  $\beta$ ,  $\gamma$  and  $\kappa$  forms were nearly stable on grinding of the samples. Strong pressing of the  $\beta$  form decreased its heat of fusion to 51.4 kJ/mol, which is near the heat of fusion of  $\gamma$ - or  $\delta$ -phase. According to our experiments all forms tended to transform to the  $\kappa$  form when they were heated for a long

period near the melting point. This is well understood for the  $\beta$  phase because both phases are crystallized in the same space group and the volume of the unit cell of the  $\beta$  phase is smaller than that of the  $\kappa$  phase. Thus, low temperature favours the  $\beta$  phase and high temperature the  $\kappa$  phase.

The phases were confirmed with x-ray powder diffraction method. To analyze the diffraction patterns the pirum analyses [7] were used and the x-ray diffraction patterns were compared with the spectra found in literature [3,4]. As literature values for  $\alpha$  and  $\gamma$  were not given, they were computed with Bragg-equation starting from the unit cell. The effect of mechanical treatment on samples made phase identification difficult. Peaks in powder diffraction patterns became broader and extra peaks appeared

The melting points of different phases are nearly the same,  $166 \pm 2$  °C (peak). On the other hand, there are differences in the enthalpies of the melting. If the conformations of the carbon skeleton in the different phases are the same, the differences in the enthalpies depend on the densities of the phase. When the  $\Delta H$  values in Table 2 are compared to the density values in Table 1  $\alpha$ ,  $\beta$  and  $\kappa$  belong to the same group and  $\gamma$  and  $\delta$  to another. Two groups can be explained by low accuracy of determinations e.g. the unit cell parameters have not been determined by single crystal method. Also the  $\delta$  and  $\alpha$  phase are transformed more easily to other forms than the other phases. On the other hand the  $\delta$  form crystallizes in monoclinic unit cell while the others are orthorombic.

When water is used as a solvent, the phase of the crystallized product depends on the temperature, concentration and rate of crystallization. About at 100 °C the  $\kappa$  form is the main product and at temperatures under 5 °C the  $\delta$  form dominates.  $\beta$  form was obtained,

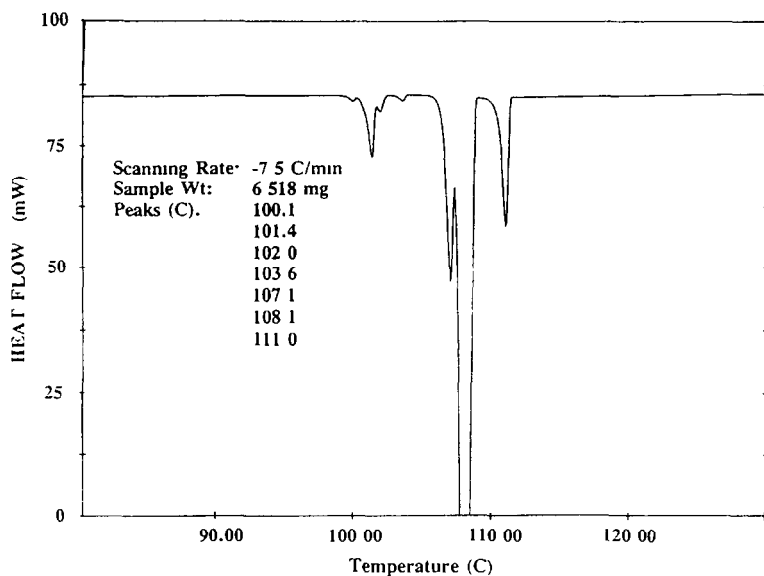


Figure 4 The cooling of the melt D-mannitol.

when high concentrations (1-2 mol/l) was used, nearly over the temperature range. The crystallization rate is fastest for the  $\kappa$  form and slowest for the  $\beta$  form. The other forms were obtained from ethanol water mixtures.

The crystallization from the pure melt was also studied. The outmost example, when seven peaks were formed, is represented in Figure 4. Although the phases of all peaks couldn't be identified, the greatest peak was often the  $\beta$  phase. The heat of fusion after the cooling was nearly same as the heat of fusion of the  $\beta$  phase. Sometimes when the cooling rate was 0.5 °C/min the  $\delta$  form was formed and the temperature of the crystallization (123-126 °C) was higher than in other cases.

Table 3

The effect of the cooling rate on the crystallization of D-mannitol. The sample weight was 10.624 mg. The values are averages from two measurements with the same sample.

Cooling rate °C/min	onset °C	peak °C	$\Delta H$ kJ/mol
12.5	111.1	110.0	33.3
10.0	111.0	110.3	32.2
7.5	112.1	111.6	33.2
5.0	112.0	111.6	32.8
2.0	113.5	113.2	33.2
0.5	115.3	115.2	33.9

In general, cooling in DSC gave with small amount of sample (1-7 mg) and moderate cooling rates (7-10 °C/min) five to seven peaks. When the weights of sample were higher and the cooling rate slower or faster peaks were reduced in number. With 10 mg sample weight DSC gave only one peak with cooling rates at 0.5-12.5 °C/min (Table 3). No transformations were found on heating from -30 to 135 °C or cooling from 90 to -30 °C.

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