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Physicochemical Properties of Crystalline Lactose. II.¹⁾ Effect of Crystallinity on Mechanical and Structural Properties

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It was observed that the crystal lattice was disordered when crystalline lactose (α -monohydrate) was dehydrated to the α -anhydrate by heating in air. The disorder parameter of the α -anhydrate obtained by desiccating α -monohydrate in methanol was smaller than that of the product obtained by heating it in air. This disorder was also induced by grinding the α -monohydrate, and the free energy level of the water of crystallization in the ground sample seemed to be higher than that in the intact sample.

No structural change of amorphous lactose was observed at 30 °C in a P₂O₅ desiccator for 30 d. However, during storage at 30 °C, 60% R.H. for 24 h, crystal growth of α -monohydrate in the solid state occurred and the degree of the crystallinity reached *ca.* 75%. Further crystal growth hardly proceeded. Crystals of β -anhydrate were also formed. The disorder parameter of this transformed lactose was larger than that of the intact sample.

The degree of stress relaxation of lactose was reported to be small, but that of amorphous lactose was nearly equal to that of crystalline cellulose. The tablet hardness of amorphous lactose was *ca.* ten times that of crystalline lactose.

Keywords—lactose; crystallinity; disorder parameter; X-ray diffraction; Ruland's method; thermal analysis; grinding; dehydration; stress relaxation; tablet hardness

Lactose has been widely used for solid pharmaceutical preparations and many grades are commercially available, *e.g.*, official grade, crystalline, anhydrous, spray-dried, or granulated lactose. Anhydrous, spray-dried, and granulated lactose preparations have been used in direct compression applications.³⁾ This classification of lactose is, however, based only on the manufacturing methods.

On the other hand, lactose has four crystallographic forms, namely, α -monohydrate, α -anhydrate, β -anhydrate, and amorphous form.⁴⁾ There are few reports on structural properties of lactose, even though it is frequently used.⁵⁾ Buma^{6a)} reported the constituents of spray-dried lactose on the basis of density measurements. Fell *et al.*^{6b)} examined the form of lactose in spray-dried lactose by the polarimetric technique and thermogravimetric measurements.

In the previous report,¹⁾ the crystallinity and the disorder parameter in crystalline lactose used as the 100% crystalline standard in various methods⁷⁾ were measured by Ruland's method⁸⁾ (an X-ray diffraction method), and the validity of measurements by this method was discussed. In this report, many kinds of solid lactose were prepared and the relationship of the crystallinity and the disorder parameter to mechanical and structural properties was examined.

Experimental

Materials—Crystalline lactose (Wako Pure Chem. Ind. Ltd.) was of reagent grade and crystalline cellulose

(Avicel PH101, Asahi Kasei Ind. Ltd.) was of JP grade. Well-refined crystalline lactose as a reference standard was kindly supplied by Meiji Nyugyo Co., Ltd. Amorphous lactose obtained by freeze-drying was kindly supplied by Chugai Pharmaceutical Co., Ltd.

Preparation of β -Anhydrous Lactose— β -Anhydrous lactose was recrystallized from hot water (above 93 °C).⁹⁾

Preparation of Ground Samples—Crystalline lactose and crystalline cellulose were used. For 1 g-scale preparations, the grinding conditions were the same as reported in the previous paper.¹⁾ For 50 g-scale preparations, a shaker mill (Chuoh Kakouki Co., Ltd., Type B-1) was used. The volume of the mill was *ca.* 3500 cm³, the number of balls was 800, the diameter of the ball was 15 mm, and the grinding time was 72 h.

Preparation of Dehydrated Sample by Heating—A Shimadzu DT-10-TG thermogravimeter (TG) was used. Crystalline lactose (200 mg) was heated at a rate of 5 °C/min till the dehydration was complete.

Preparation of Dehydrated Sample by Desiccation in Methanol—*Ca.* 5 g of crystalline lactose and 500 ml of methanol were placed in a 1000 ml three-necked round-bottomed flask with a mechanical stirrer, and the mixture was boiled under reflux with vigorous agitation at 800 rpm for 8 h. The contents were filtered and the residue was dried under reduced pressure at 60 °C for 3 h.

Measurements of X-Ray Diffraction—The measurement conditions were the same as reported in the previous paper.¹⁾

Calculation of the Degree of Crystallinity and Disorder Parameter—The calculation methods were the same as described in the previous paper.¹⁾

Thermal Analysis—A Shimadzu TGC-20 thermogravimeter, and a differential scanning calorimeter (DSC), Perkin-Elmer DSC-1B, were used to study the dehydration process of lactose.

1. TG Measurement: A sample (between 9.0 and 11.0 mg) was accurately weighed in a platinum cup. The weight loss due to dehydration was measured at a heating rate of 7.5 °C/min from ambient temperature to 180 °C.

2. DSC Measurement: *Ca.* 2 mg of the sample was analyzed in an aluminum pan on the apparatus. Thermograms of the samples were run at a heating rate from 2 to 8 °C/min from ambient temperature to 180 °C. Temperature was calibrated with an indium standard.

Measurement of Nitrogen Gas Adsorption—The measurement conditions were the same as described in the previous paper.¹⁰⁾

Measurement of the Degree of Stress Relaxation—A sample of 300 mg was compressed using circular, flat-faced 10 mm motorized punches at a constant speed till the compressive force reached 500 kg/cm², and this state was held for 2 min. The pressure changes during this process were detected by using a load-cell on the upper punch.

Measurement of Tablet Hardness—Tablets were prepared on the apparatus described above. A sample of 300 mg was compressed at a constant speed till the compressive force reached 1 t/cm² and this state was held for 30 s. Then, the reduced pressure resulting from stress relaxation was increased to 1 t/cm² and after 30 s, the tablet was ejected. Tablet hardness was determined from the force required to fracture it by diametrical compression between motorized flat-faced punches at a constant speed. This force was detected by using a load-cell on the upper punch. The reported values of tablet hardness are based on 20 determinations.

Results and Discussion

Structural Properties of Various Preparations of Lactose

Well-Refined Crystalline Lactose—The X-ray diffraction pattern is shown in Fig. 1. This is α -monohydrous lactose, and the degree of crystallinity, X_{cr} , and the disorder

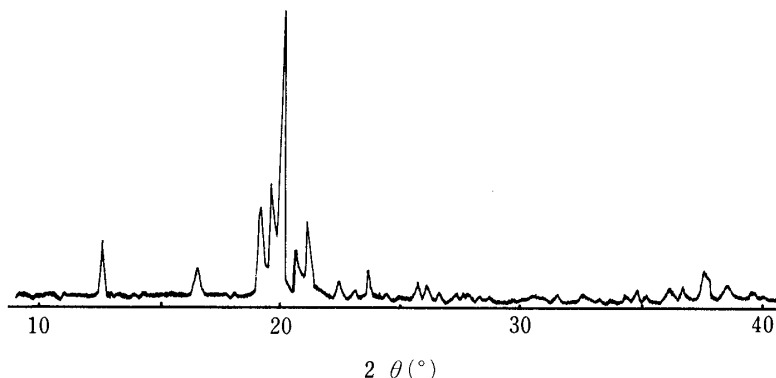


Fig. 1. X-Ray Diffraction Pattern of Crystalline Lactose Used as a Reference Standard

parameter, k , were 75% and 3.5 \AA^2 , respectively. The TG thermogram indicated that adsorbed water did not exist on the surface, and the water of crystallization was lost in the range from 110 to 140°C . In the DSC thermogram, the corresponding endothermic peak was observed. The measurement of nitrogen gas adsorption and the microscopic observation gave mean particle diameters of *ca.* $13 \mu\text{m}$ and *ca.* $6\text{--}15 \mu\text{m}$, respectively. These data suggested that the micropores were not present in the structure.

α -Anhydrous Lactose—This lactose gradually transforms to the α -monohydrate by absorbing moisture in air.⁹⁾ It was reported that the α -anhydrate obtained by desiccating the α -monohydrate in dry methanol did not absorb moisture at 50% R.H.^{6c)} Thus, α -anhydrate obtained by heating in air and by desiccation in methanol were compared as regards the crystallinity and the disorder parameter. No endothermic peak due to dehydration or desolvation of methanol was observed in the DSC thermograms. No solvent of crystallization was found in the sample obtained by desiccation in methanol. The X-ray diffraction patterns are shown in Fig. 2. These patterns show that the integral breadths become wider than that of intact crystalline lactose, and that the intensities of the peaks are remarkably attenuated in the region of large values of 2θ , namely, dehydration of the α -monohydrate decreased the crystallite size and also affected the degree of order of the crystal lattice. The obtained values of X_{cr} and k are shown in Table I. These data show that the k -values of α -anhydrate obtained by both methods become larger than that of the intact crystalline lactose. When the mixture of α -monohydrate and β -anhydrate was heated to 140°C , the integral breadths of the original peaks of β -anhydrate did not increase. Therefore, the increase of the k -value of the α -anhydrate seems not to be directly caused by the heating but to be caused by the destruction of the crystal lattice during dehydration. The difference between the k -values of α -anhydrate obtained by heating α -monohydrate in air and that obtained by desiccating it

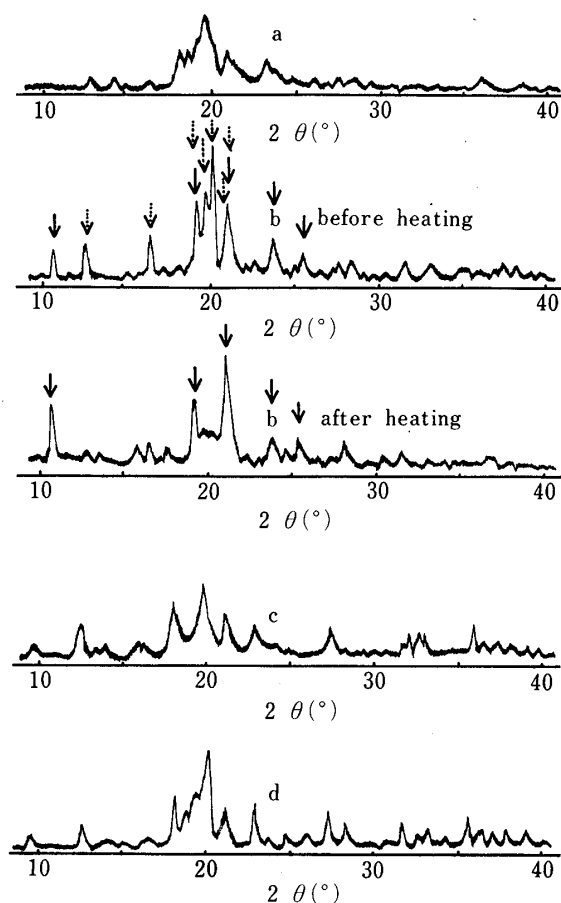


Fig. 2. X-Ray Diffraction Patterns of α -Anhydrous Lactose Obtained by Heating α -Monohydrous Lactose in Air and by Desiccating It in Methanol

a, by heating alone; b, by heating with β -anhydrous lactose, ($\downarrow = \alpha$ -monohydrate, $\downarrow = \beta$ -anhydrate); c, by desiccating in 100% methanol; d, by desiccating in 99.4% methanol.

TABLE I. Comparison of Degrees of Crystallinity and Disorder Parameters in Various α -Anhydrous Lactose Samples Obtained by Various Treatments of α -Monohydrous Lactose

$S_0^a - S_p^b$	Treatment		
	Heating $k = 7.7$	100% methanol $k = 4.6$	99.4% methanol $k = 4.6$
0.10—0.32	0.766	0.630	0.811
0.10—0.86	0.760	0.631	0.803
0.10—1.20	0.769	0.634	0.805
\bar{X}_{cr}	0.77	0.63	0.81

a) Integral lower limit.⁸⁾

b) Integral upper limit.⁸⁾

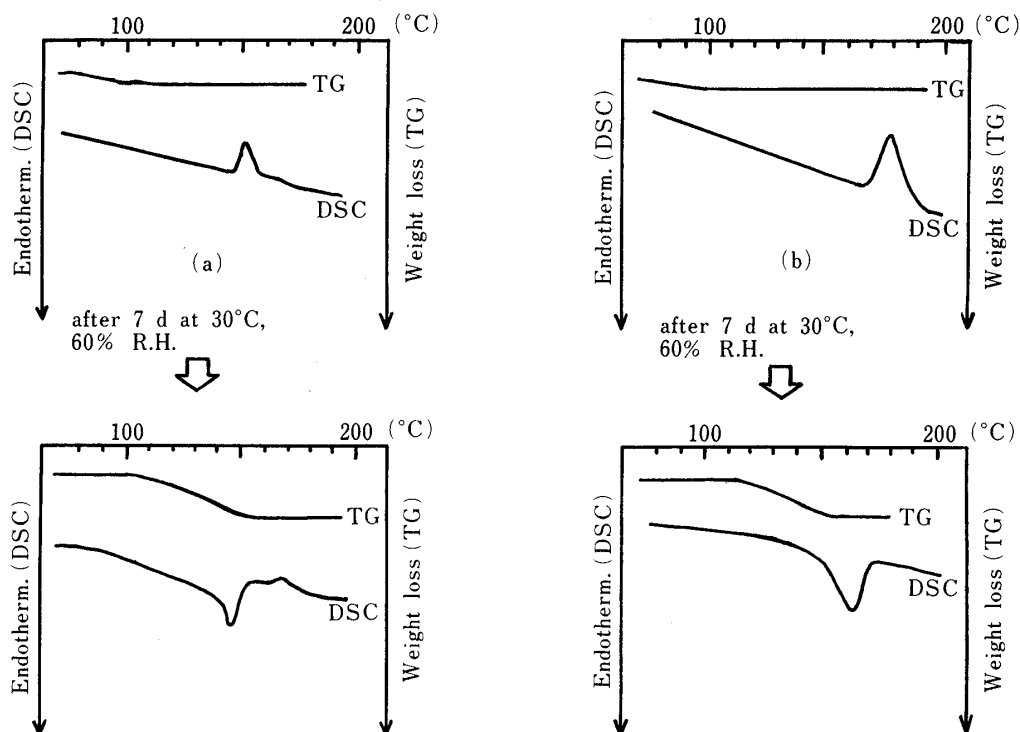


Fig. 3. Effects of Accelerated Storage at 30 °C, 60% R.H. for 7 d on Thermal Properties of Amorphous Lactose

a, amorphous lactose obtained by grinding; b, amorphous lactose obtained by freeze-drying.

in methanol seems to be due to the difference of dehydration mechanisms. Table I indicates that the existence of a little water in methanol made the dehydrating conditions mild, so that the X_{cr} -value of α -anhydrate obtained by desiccation in 99.4% methanol became larger than that of the anhydrate obtained by desiccation in 100% methanol. This disorder of the crystal lattice seems to affect the ability to absorb moisture.

Amorphous Lactose—This lactose was obtained by grinding and also by freeze-drying. The thermal properties were examined by TG and DSC. The thermograms are shown in Fig. 3. An exothermic peak was observed in the DSC thermogram. The amorphous state was stable at 30 °C in a P_2O_5 desiccator for 30 d. However, after storage at 30 °C, 60% R.H. for 7 d, the exothermic peak of the freeze-dried sample had almost disappeared, whereas that of

TABLE II. Degrees of Crystallinity and Disorder Parameters in Lactose Transformed from Amorphous Lactose Stored at 30 °C, 60% R.H.

Amorphous Lactose Obtained by Grinding					
$S_0^{a)}-S_p^{b)}$	1 d $k=7.0$	3 d $k=5.7$	7 d $k=4.9$	14 d $k=4.7$	30 d $k=4.1$
0.10—0.32	0.781	0.739	0.740	0.718	0.657
0.10—0.86	0.790	0.728	0.732	0.711	0.667
0.10—1.20	0.754	0.752	0.763	0.735	0.658
\bar{X}_{cr}	0.78	0.74	0.75	0.72	0.66

Amorphous Lactose Obtained by Freeze-Drying					
$S_0^{a)}-S_p^{b)}$	1 d $k=6.6$	3 d $k=5.0$	7 d $k=4.5$	14 d $k=5.6$	30 d $k=5.4$
0.10—0.32	0.782	0.704	0.674	0.703	0.646
0.10—0.86	0.767	0.697	0.708	0.709	0.659
0.10—1.20	0.792	0.711	0.670	0.705	0.644
\bar{X}_{cr}	0.78	0.70	0.68	0.71	0.65

a) Integral lower limit.⁸⁾

b) Integral upper limit.⁸⁾

the ground sample was still observed. New endothermic peaks due to the dehydration of both samples were observed. This peak of the freeze-dried sample had a larger area and, moreover, existed in a higher temperature region than that of the ground sample. These results suggest that since the freeze-dried sample is structurally in a more complete amorphous state and has a larger surface area than the ground sample, the adsorbed water on the surface of the former may more easily occupy stable positions so that transformation to the crystalline state of α -monohydrate can occur easily. X_{cr} - and k -values of the transformed lactose are shown in Table II. The X-ray diffraction patterns of these lactose preparations exhibited crystal growth of α -monohydrate and β -anhydrate. Therefore, X_{cr} in Table II is given as the sum of X_{cr} in these two forms. It is considered that the ratio of α -monohydrate and β -anhydrate from the freeze-dried sample would have been determined when the solution was frozen and that β -lactose molecules crystallized with displacement due to the crystallization of α -lactose molecules including water molecules. The amorphous region transformed to a disordered crystalline region within 1 d. While the disorder of the crystal lattice gradually decreased, the degree of crystallinity obtained by the X-ray method was calculated to be decreasing. This can be explained by considering that the crystal lattice was ordered but that the crystallites were fragmented as transformation proceeded. The k -values of these transformed lactose samples are rather large.

The contents of the transformed α -monohydrate were measured by TG and DSC. The calculation was based on the assumption that the weight loss in the range from 110 to 150 °C and the corresponding endothermic energy were proportional to the quantity of α -monohydrate. The results are shown in Fig. 4. The contents of α -monohydrate calculated from the results of TG were larger than those from the results of DSC. This discrepancy suggested that the water of crystallization of the transformed α -monohydrate might be lost at smaller energies than that of well-refined crystalline lactose. The results of TG may be more reliable than those of DSC. However, the data seem to provide some insight into the energy-state of the water of crystallization.

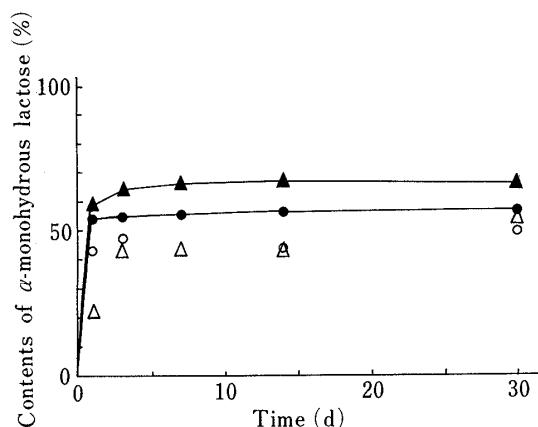


Fig. 4. Contents of α -Monohydrus Lactose Transformed from Amorphous Lactose Stored at 30 °C, 60% R.H.

Open symbols, calculated from DSC data; closed symbols, calculated from TG data; \circ and \bullet , amorphous lactose obtained by grinding \triangle and \blacktriangle , amorphous lactose obtained by freeze-drying.

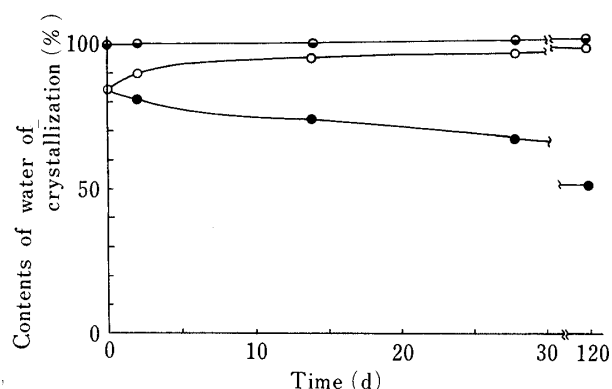


Fig. 5. Effects of Accelerated Storage at 30 °C on the Loss of Water of Crystallization of Intact Crystalline Lactose and 8-h-Ground Sample

\circ , ground sample stored at 60% R.H.; \bullet , ground sample stored in a P_2O_5 desiccator; \ominus , intact sample stored in a P_2O_5 desiccator.

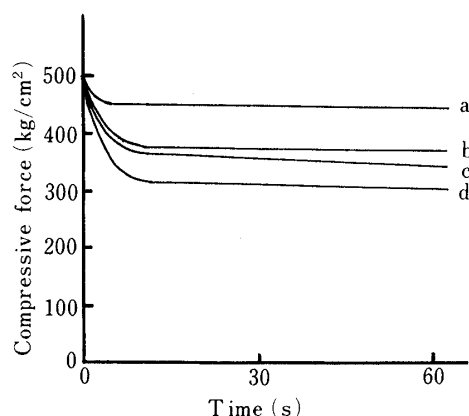


Fig. 6. Effects of Crystallinity on Stress Relaxation of Lactose and Crystalline Cellulose

a, crystalline lactose; b, amorphous lactose; c, crystalline cellulose; d, amorphous cellulose.

Effect of Grinding on Water of Crystallization of the α -Monohydrate

The grinding of the α -monohydrate seems to affect the free energy of the water of crystallization in the crystal lattice. Therefore, the change of its content in 8-h-ground sample was examined by TG measurements. The results are shown in Fig. 5. Ca. 15% of the water of crystallization was lost after 8 h of grinding and further dehydration occurred at 30 °C in a P_2O_5 desiccator, whereas the intact sample did not dehydrate under the same conditions. On storage at 30 °C, 60% R.H., however, the adsorbed water on the surface of the ground sample was transformed into water of crystallization. The ground sample was agglomerated by moisture in air, so that its flowability became poor. It is considered that the amorphous layer on the surface dissolves in the adsorbed water, leading to agglomeration. The macroscopic properties of lactose as regards agglomeration and flowability seem to be influenced by the disorder of the crystal lattice, which is related to the free energy level of the water of crystallization.

Effect of Crystallinity on Mechanical Properties

Anhydrous, spray-dried, and granulated lactose samples have been subjected to direct compression.³⁾ The stress relaxation of lactose is, however, small and crystalline lactose is not suitable for direct compression.^{6d)} The effect of the crystallinity on the stress relaxation was examined. The degree of stress relaxation of crystalline lactose and that of crystalline cellulose

TABLE III. Effects of Crystallinity and Storage Condition on Hardness of α -Monohydrous Lactose Tablets

Crystallinity	Initial	30 °C, 0% R.H. for 60 d	30 °C, 60% R.H. for 60 d
75%	1.87 kg/cm ² (0.41 kg/cm ²) ^{a)}	1.62 kg/cm ² (0.40 kg/cm ²)	2.24 kg/cm ² (0.63 kg/cm ²)
0%	18.00 kg/cm ² (3.81 kg/cm ²)	2.96 kg/cm ² (1.32 kg/cm ²)	15.00 kg/cm ² (4.27 kg/cm ²)

a) Standard deviation.

were compared with those of their amorphous forms, obtained by freeze-drying and by grinding, respectively. The results are shown in Fig. 6. The degrees of stress relaxation of the amorphous forms became large, since the viscous region seemed to increase as the amorphous region increased. A negative correlation was observed between crystallinity and stress relaxation.

The compressibility of lactose seems to be affected in a complex manner by the particle shape, the deformation characteristics, the surface conditions, moisture content, stress relaxation, and so on. The effect of crystallinity on tablet hardness was also examined, and the results are shown in Table III. The tablet hardness of amorphous lactose obtained by freeze-drying was *ca.* 10 times that in the case of crystalline lactose. These results seem to be related to the increase of stress relaxation, and the existence of adsorbed water and water of crystallization with a rather high energy level.

The tablet hardness of amorphous lactose clearly decreased at 30 °C in a P₂O₅ desiccator for 60 d, and *ca.* 3% weight loss due to the loss of adsorbed water in the tablet was observed. The decrease of the tablet hardness seems to result from the disappearance of this water. The adsorbed water on the surface of amorphous lactose was transformed to water of crystallization at 30 °C, 60% R.H. for 60 d. The obtained X_{cr} - and k -values were 72% and 5.8 Å², respectively. The rather large disorder of the crystal lattice should be related to the tablet hardness. Some decrease of tablet hardness presumably results from the decrease of the binding power between the particles due to the volume change with crystallization, as was reported by Otsuka *et al.*^{6e)} It is considered that the tablet hardness of these lactose preparations is related to the crystallinity, especially, the adsorbed water and the disorder of the crystal lattice.

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