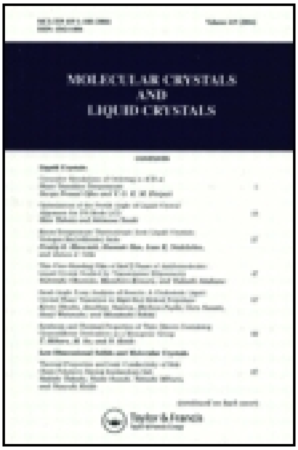

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Phase Transitions and Solid Polymorphis of Cholesteryl Acetate

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Phase Transitions and Solid Polymorphs of Cholesteryl Acetate

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The thermal behavior of cholesteryl acetate has been studied by means of thermal analytic microscopy (microscopy synchronized with thermal analysis) and X-ray powder diffraction. The main results of the work are as follows:

Thermal Analytic Microscopy: 1. Cholesteryl acetate (99.7 mol%) purified with 1-pentanol exhibits a solid–solid transition on first run, similarly to the case of cholesteryl acetate purified with ethanol; 2. The sample displays the cholesteric phase only when special thermal treatment is performed; 3. Once melted, recrystallized samples are classified into four solid states of SI, SII, SIII, and SIV; 4. Thermal data for the transition have been estimated.

X-ray Powder Diffraction: 1. Three patterns have been obtained and denoted as A, B, and C. The crystal deposited from the 1-pentanol solution displays "A", the same pattern as that of the crystal deposited from the ethanol solution. "B" is obtained from solid SIII. "C" is obtained from SI, SIV, and the crystal after the first run transition; 2. It has been found that "B" and "C" revert to "A" with the passage of time. The rate of reversion is less at a higher temperature, a longer time of sample treatment, and a lower cooling rate. Impurities delay the reversion.

SIV forms special, colorful figures similar to annual rings of a tree on the course of transition to "A".

INTRODUCTION

The mechanism of phase transitions of cholesteryl acetate (abbreviated to CHA) is rather complicated. Barrall *et al.*[1] observed two endothermic peaks at 81.4°C and 118.2°C on heating a sample recrystallized from ethanol. After rapidly quenching the melt, they observed two peaks at 44.1°C and 118.5°C upon heating. After subsequent slow cooling of the melt, they observed three peaks at 43.2°C, 87.3°C, and 118.6°C upon reheating. Davis *et al.*,[2] however, reported that CHA highly purified with 1-pentanol showed neither multiple transition nor mesophases. On the other hand, Chistyakov[3] proposed two and Kofler[4] suggested three different forms.

Wendorff and Price studied CHA purified with 1-pentanol by dilatometry[5] and X-ray diffraction.[6] They classified the once-melted samples into three solid phases of SI, SII, and SIII. SI is formed directly upon cooling from the isotropic melt and behaves reversibly up to the melting point. SII is formed from the cholesteric phase and transforms reversibly to SIII around 40°C. They reported that the *d*-spacing were identical for all once-melted solids and only slightly different for the solution-crystallized sample.

We have studied the phase transitions of CHA by means of thermal analytic microscopy (microscopy synchronized with thermal analysis) and X-ray powder diffraction.

EXPERIMENTAL

The type of apparatus for thermal analytic microscopy has been reported previously.[7] The heat calibration by Joule's heat will be published elswhere.[8]

The CHA sample was obtained from Tokyo Kasei Company. The sample was recrystallized twice from 1-pentanol and washed with an ethanol–water (4:1) mixture.[9] It was dried at 50°C *in vacuo* until no further change in weight could be observed. A Perkin–Elmer DSC1B was employed for determining the purity of the solution-crystallized sample.[10] The purity was 99.7 mol % from fusion curves at a scan rate of 4°C/min. The same sample showed 99.6 % purity in a gas chromtograph of the FID type.

RESULTS

Thermal Analytical Microscopy (TAM)

(1) *Thermal analytical microscopy of CHA deposited from the solution* Cholesteryl Acetate recrystallized from 1-pentanol exhibits a large endothermic peak on the first run, similar to CHA recrystallized from ethanol. Figure 1 shows the thermogram of the crystals along with photographs. Photograph 1 shows a rod crystal deposited from the 1-pentanol solution, which reveals parallel interference fringes clearly. These fringes, due to the interference of D-lines of sodium, prove that the crystal is almost perfect. The crystal has a discontinuous area in the center part, which indicates some defects of the lattice order. Photograph 2 shows that some fusion-like change originates from part of the lattice imperfection. Photograph 3 shows that the same kind of change covers the entire crystal. The point corresponding to Photograph 3 on the thermogram is at the onset of the sharp endothermic peak. Photograph 4, taken at a temperature above the peak,

reveals much the same condition as Photograph 3, although some bending appears in the outward form of the crystal. The temperatures and the heats of transition and fusion are shown in Table I.

(2) *Solid SI formed directly from the isotropic melt* Cholesteryl Acetate usually crystallizes to SI directly from the isotropic melt between 94–107°C.

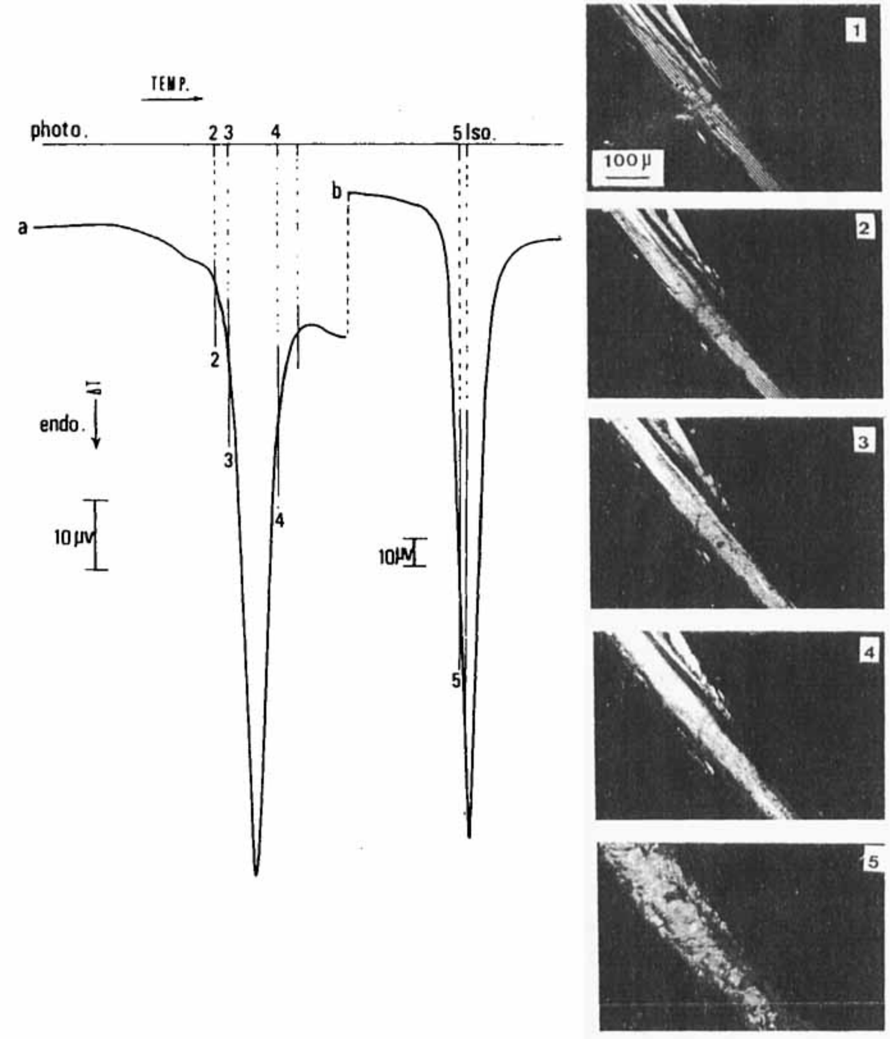

FIGURE 1 TAM of CHA deposited from the 1-pentanol solution; sample weight, 46.06 mg, heating rate, 2.5°C/min ΔT full scale: (a) 100 μV, (b) 250 μV; chart speed: 240 mm/h; peak temperatures: 78.2°C and 114.5°C; photos, Na-lamp, crossed polars; temps. of photos: (1) room temp. (2) 70.4°C, (3) 72.9°C, (4) 83.7°C, (5) 113.2°C, clear point, 113.9°C.

TABLE I

Transition values for cholesteryl acetate on first heating run

Author apparatus	Rate C/min	Solvent for crystzn.	Irrev. transition		Fusion	
			T(°C)	Q(cal/g)	T(°C)	Q(cal/g)
TAM apparatus	0.3 ~ 2.5	*n*-pentanol[a]	75	4.7 ± 0.2	114.0 ± 0.5	11.2 ± 0.2
P. E. DSC1B (this work)	1 ~ 4	*n*-pentanol[a]	68	4.8 ± 0.2	113.5 ± 0.5	11.2 ± 0.2
Barrall II[1] *et al.* (P. E. DSC1B)	5	ethanol	81–87	4.89	118.4	11.2
Davis *et al.*[2,9] (P. E. DSC1B)	2.5	*n*-pentanol	—	—	114.6	11.4

[a] A sample crystallized from ethanol gave the same result as the above.

This phase is stable up to the melting point. The solid state agrees with SI designated by Wendorff and Price. Smectic I is fiber-like as shown in Figure 2-a. Without a polarizing microscope the sample is transparent. The fibers expand greatly in volume in the vicinity of the melting point. The expanding fibers resemble oily streaks in the cholesteric phase; for example, those for cholesteryl nonanoate.[7] Figure 2-b shows the CHA crystals at 105.8°C, forming fibers in the rods. It appears that crystals above the transition temperature change into SI.

(3) *Isotropic–cholesteric transition and SII–SIII transition* Cholesteryl acetate displays a cholesteric phase only in those cases involving special treatments: sufficient holding above the melting point or rapid quenching. The higher the temperature for holding, the less time it requires to form the cholesteric phase. Half an hour was sufficient to hold a sample at around 140°C. Multiple fusion of a sample also helps to form the mesophase.

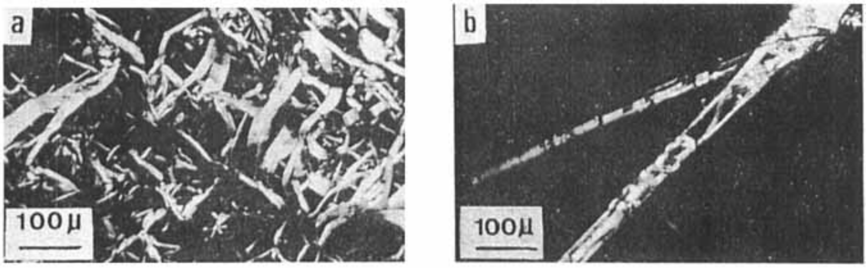

FIGURE 2 Solid SI.

The solid formed from the cholesteric phase transforms into another solid phase around 35°C with a small exothermic peak (cf. Table II). Upon reheating, the thermogram shows an endothermic peak of the same extent as the peak on cooling around 40°C. The two solid states agree with SII and SIII given by Wendorff and Price. The SII–SIII transition reveals no perceptible changes in the microscopic view.

Figure 3 shows the thermogram upon cooling, passing through the mesophase from the isotropic melt. Curve-a shows the peak of the isotropic–

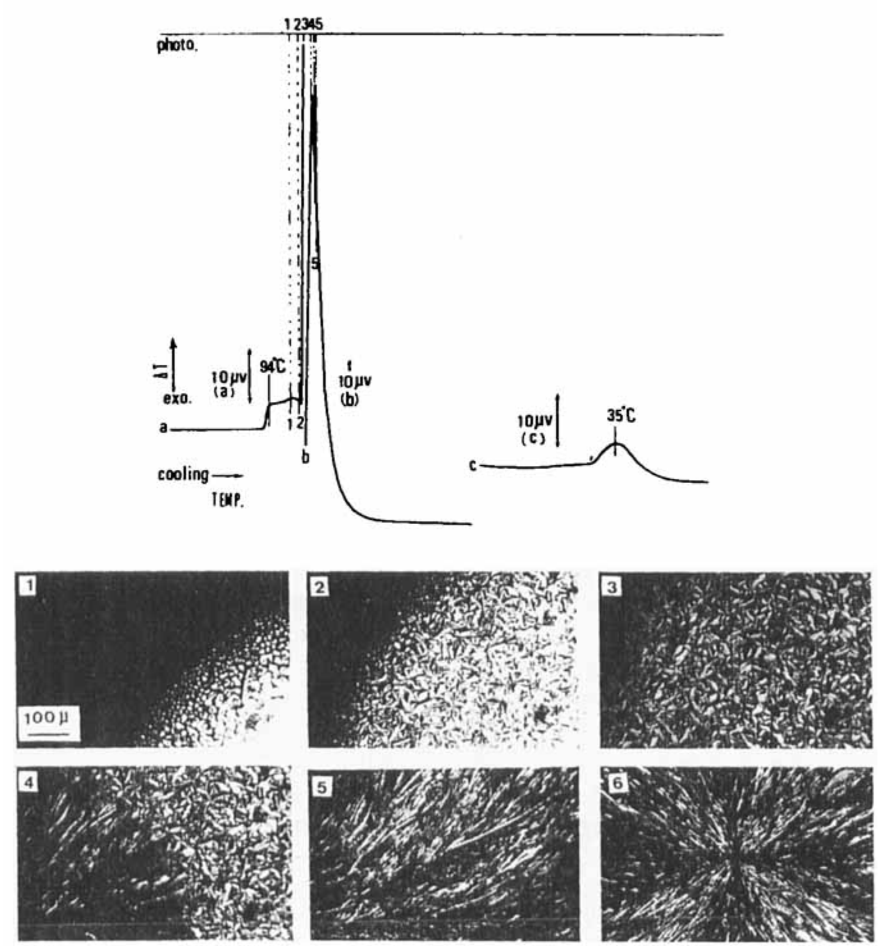

FIGURE 3 TAM on cooling with the cholesteric phase; sample weight, 75.86 mg, rate, 2.5°C/min; ΔT full scale: (a) 100 μV, (b) 500 μV, (c) 100 μV, chart speed: 240 mm/h temps; of photos: (1) 90°C, (2) 88.5°C, (3) 87.5°C, (4) 86°C, (5) 85°C, (6) room temp. (different position from others).

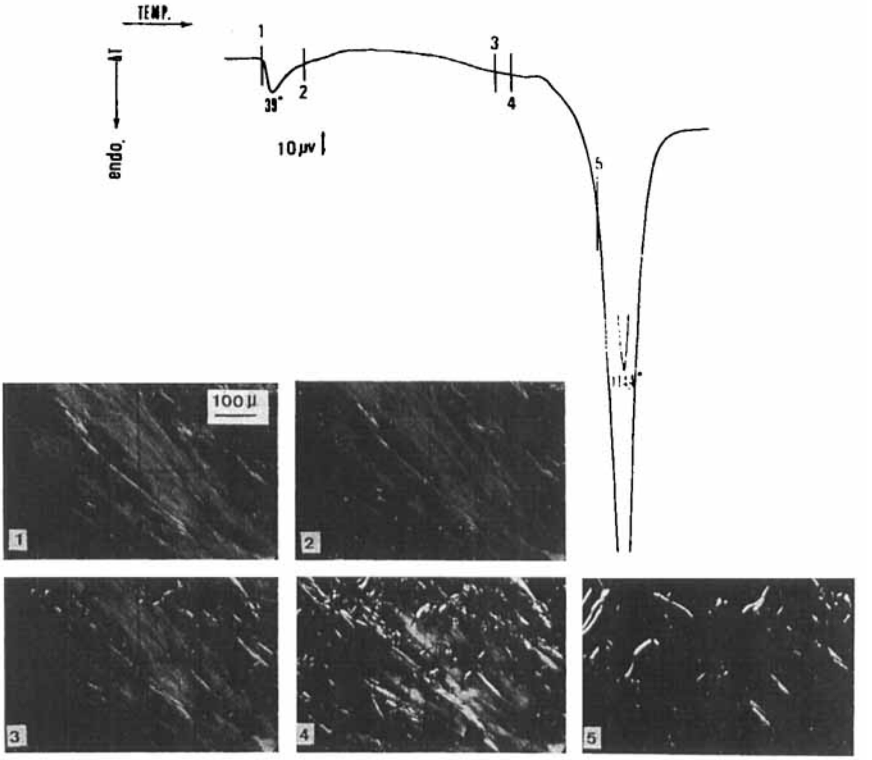

FIGURE 4 TAM starting from SIII; ΔT full scale: 250 μV, other conditions; the same as Figure 3, temps. of photos: (1) 37°C, (2) 47°C, (3) 88°C, (4) 92°C, (5) 108.5°C.

cholesteric transition at 94°C. Photographs 1–3 show the developing cholesteric focal conic texture. Curve-b shows the peak of crystallization, and Curve-c shows the peak of SII–SIII transition. Photographs 4–5 illustrate the developing state of SII. Photograph 6 taken at room temperature shows that the small needle-like SII developed radially on the course of the growth, although the photograph shows SIII transformed from SII.

Figure 4 shows the thermogram on heating SIII to the isotropic melt. Photographs 1–2 reveal no differences in appearance below and above the transition peak. Photographs 3–5 indicate that SII transforms into SI gradually on heating.

(4) *Solid SIV obtained by rapid quenching* The spherulitic solid obtained by rapidly quenching the isotropic melt has been designated as SIV in this paper. SIV has never been produced in the TAM apparatus.† Iridescent

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† Sufficiently rapid cooling cannot be obtained in the apparatus.

colors by light scattering appear while quenching. The flow of the cholesteric phase can be observed through a polarizing microscope during the quenching.

Solid IV transforms gradually into SI as shown in Figure 5. The thermogram shows a wide pre-melting and a very low peak of fusion. This sample was carried out twice by fusions and with a slow cooling before quenching for the preparation of SIV. A sample which had several scans using the TAM shows a wide pre-melting. It has been found that the spherulitic figure changes into other figures at room temperature with the passage of time. (cf. appendix)

(5) *Thermal behavior of CHA* The thermal behavior of CHA can be summarized in Figure 6. Run 1 corresponds to Figure 1, while runs 2–3 show that SI is stable from room temperature to the melting point on both courses

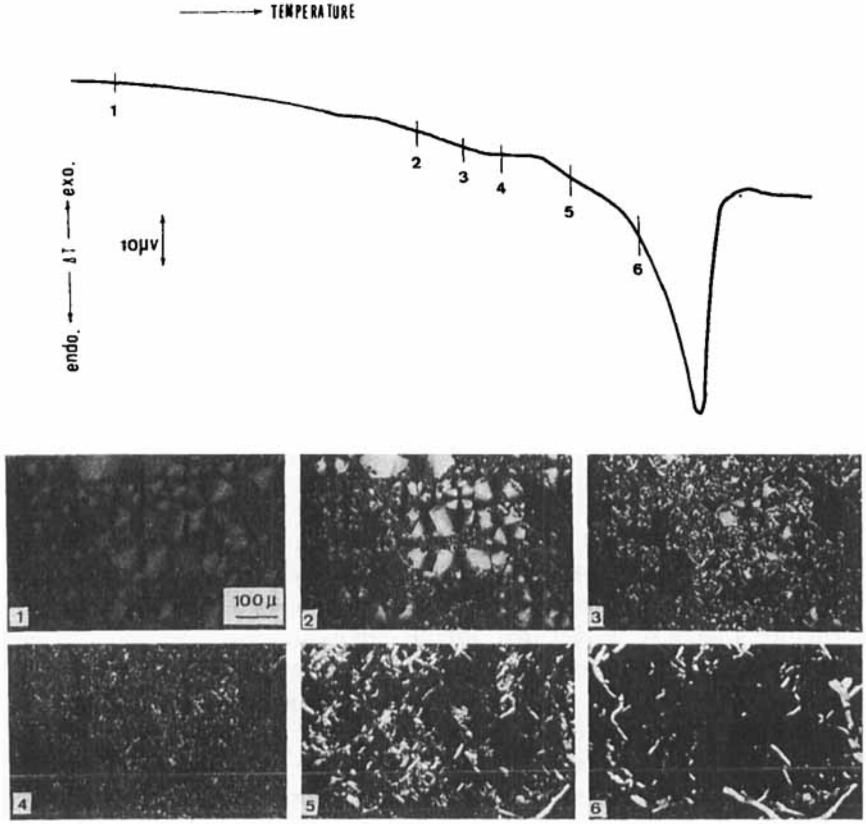

FIGURE 5 TAM starting from SIV; sample weight, 31.74 mg, heating rate, 1.25°C/min, ΔT full scale: 100 μV, chart speed: 240 mm/h; peak of fusion: 110°C; temps. of photos: (1) room temp. (2) 80°C, (3) 85°C, (4) 89°C, (5) 96°C, (6) 103°C.

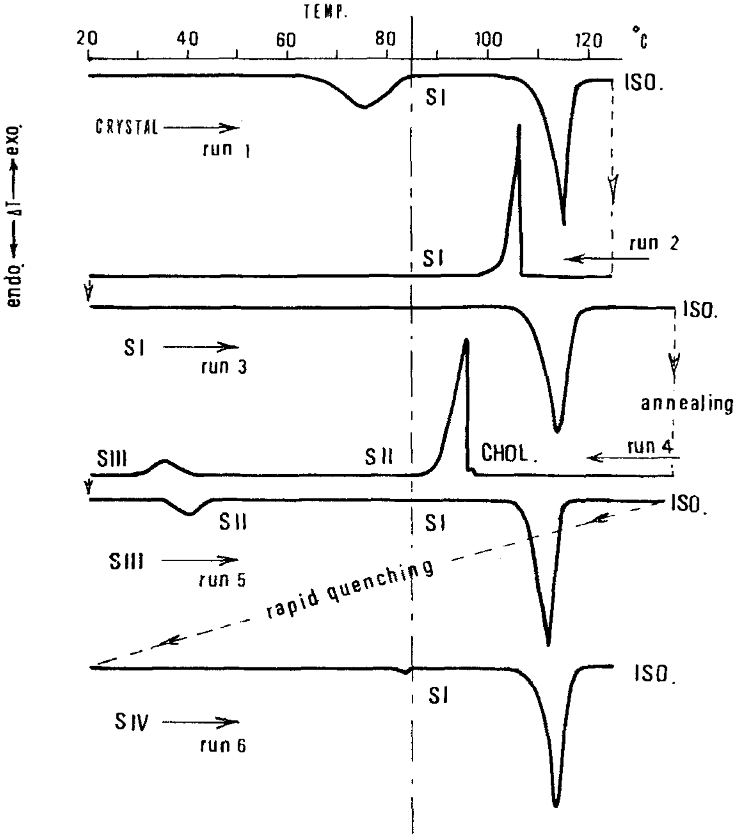

FIGURE 6 Thermal behavior of CHA.

of cooling and heating in TAM. Runs 4–5 correspond to Figures 3–4 respectively. Run 6 shows the thermogram for SIV, which reveals a faint heat anomaly sometimes observed, indicating decomposition of the spherulitic structure. Figure 6 clarifies that only SI can exist above 85°C when heated.

The transition values on cooling have been estimated as shown in Table II. The heat of the isotropic–cholesteric transition is about one-third that found by Price and Wendorff.[5] The entropy of the mesophase transition is 0.20 ± 0.05 cal/mol.K, which agrees, within the limits of error, with 0.25 cal/mol.K, the value extrapolated from the entropies for saturated aliphatic esters of cholesterol given by Barrall *et al.*[11] The Price–Wendorff value was obtained by extremely rapid quenching (such as 40–80°C/min) and the entropy calculated from it seems too high. The SII–SIII transition heat is

TABLE II
Transition values for cholesteryl acetate on cooling

Author	Iso.–SI crystzn.		Iso.–Chol. transition		SII–SIII transition	
	T(°C)	Q(cal/g)	T(°C)	Q(cal/g)	T(°C)	Q(cal/g)
this work	94–107	9 ± 1	92–94	0.17 ± 0.05	35 (40)[a]	0.35 ± 0.05
Barrall II[1] *et. al.*	92–98	10.7	—	—	44	<0.1
Price and[5] Wendorff	94–107	—	94	0.59 ± 0.01	41	—

[a] The value in the parentheses refers to heating.

considerably larger than the value of Reference 1. Our value is reproducible within the limits of error.

X-Ray Powder Diffraction Analysis at Room Temperature

The differences between the various solid states have been studied qualitatively by X-ray powder diffraction. Geigerflex, Ni-filtered Cu–Kα radiation was used. Solid II was not studied inasmuch as SII transforms into SIII at room temperature.

(1) *Identification of the diffraction patterns* Three patterns have been identified between the various solids, denoted as A, B, and C as shown in Figure 7. Pattern "A" is that for the solution–crystallized sample. Pattern "B" has been obtained from solid SIII. Pattern "C" has been obtained from SI, SIV, and the crystal just having finished first-run transition.

"A" is considerably different from "B" and "C". The *d*-spacings in "A" coincide with those computed from the unit cell for CHA from ethanol or acetone.[4] A sample recrystallized from ethanol displayed the same pattern "A" as that of the sample from 1-pentanol solutions. The *d*-spacings of "B" or "C" are similar to those for SI obtained by Wendorff and Price, rather than those for CHA recrystallized from petroleum ether above 58°C.[4] The Miller indices in "B" and "C" of Figure 7 are based on the unit cell of SI determined by Wendorff and Price.[6] The difference between "B" and "C" is that 112 and 113, as well as 201 and 202 are distinctive in "B", while both of the corresponding couples of the lines, 112–113 and 201–202, are not distinguishable in "C".

Our result and Wendorff–Price's are greatly different in the specification of the solution–crystallized sample. In the former, regardless of whether the solvent is ethanol or 1-pentanol, CHA crystallized from the solution displays

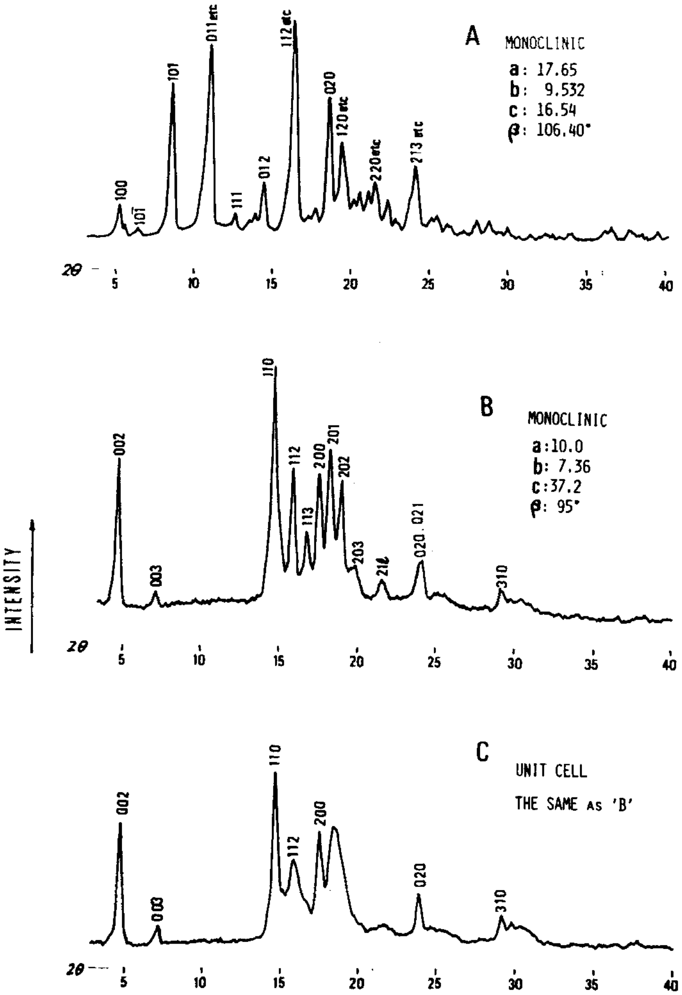

FIGURE 7 X-ray diffraction patterns for the solid polymorphs. (A) Pattern for the crystal from the solutions, solvent; 1-pentanol or ethanol either, (B) Pattern for solid SIII, (C) Pattern for solid SI, SIV, and the crystal after the first run transition.

pattern "A". In the latter, however, CHA recrystallized from 1-pentanol does not show "A" but one similar to "B" or "C".

(2) *Transformation of patterns* It has been found that both pattern "B" and "C" revert to pattern "A" with the passage of the time. The "C"-form reverts to "A" easily, when a solution-crystallized sample receives only a

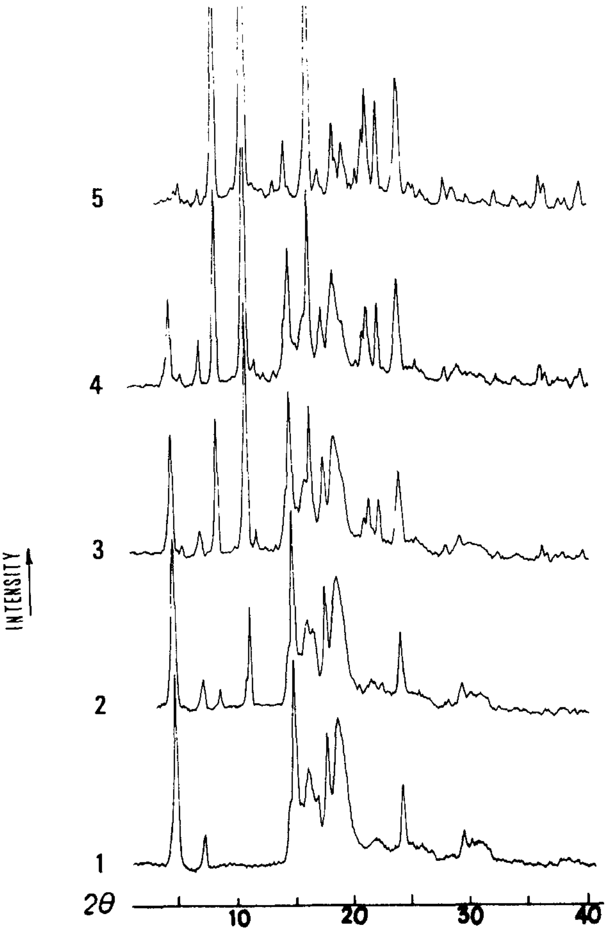

FIGURE 8 Transient states of the reversion of SI from "C" to "A". (1) A whole day after the formation of SI, (2) Two days after the formation, (3) Three days after the formation, (4) Four days after the formation, (5) Three weeks after the formation.

simple scan of TAM without any other treatments. Figure 8 shows the transient patterns on the transition of "C" to "A". In run 1, although one day passed after melting, it is the same as "C". In run 2, two days later, the lines of "A" start to grow about $2\theta = 8.6°$ and $11.0°$. Run 5, three weeks later, perfectly agrees with pattern "A".

Sample treatments delay the reversion. Solution-crystallized samples, X1, X2 and X3 were held at 85°C for 15 min., 30 min., and 2 hrs. respectively and cooled in the atmosphere. X1 and X2 started to revert 4 days later and 3 weeks later respectively. X3 did not revert two months later. A half year later, X3 reverted to "A" for the most part.

The same samples as the above, X4 and X5 were held at 130°C for 30 min. and then X4 was cooled rapidly with ice, while X5 was cooled slowly ($\fallingdotseq$ 1°C/min.). X4 started to revert 3 weeks later and X5 just started a half year later. As the result, the rate of reversion is less with higher temperature, longer holding time and lower cooling rate. The rate is not dependent on the kind of pattern, "B" or "C", but the sample treatment.

Impurities also delay the reversion. Two samples of different purities, 99.6 and 98.8 %, were held at 85°C for 2 hrs. The former (= X3) reverted for the most part a half year later but the latter did not change in the same period.

Discussion

(1) *Correlations between the polymorphs and the mesophase* The experimental results are summarized in Figure 9. Dashed lines express transitions to "A" from the respective forms.

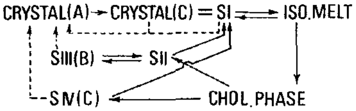

FIGURE 9 Correlations between the polymorphs and the mesophase, dashed lines; reversions to "A" from the respective forms.

It is clear that there are two kinds of lattice crystallographically—one stable at lower temperature and one stable at higher temperature.[†] Once-melted samples are of the latter type. The results from TAM show four kinds of solids. These solids, however, do not differ crystallographically from the "C"-lattice. The small enthalpy change between SII and SIII or the little change between "B" and "C"[‡] suggests the possibilities of various packing orders in the bulk space of the lattice imperfections. These intermediate states may be of almost equivalent stability.

[†] Reference 4 reports another unit cell for CHA crystallized from petroleum ether above 58°C.

[‡] This "C" does not necessarily mean the pattern for SII.

The speedy reversion of SI (Figure 8) suggests that the residue of the nuclei of the original lattice "A" may exist in a considerable amount even after fusion. Maintaining a sample in a high temperature over a long period gives the effect of eliminating the nuclei of "A" and increases lattice imperfections in solidification.

(2) *Sample impurities and "A"-structure* The purity of our sample is of the same order as that obtained by Davis *et al.* They attributed the transition of "A" to "C" to residual impurities in the sample purified with ethanol.[2] However, an unpurified sample of CHA from Eastman Kodak Co. did not display the transition peak, and its X-ray pattern was that of "C". Both samples purified once and then twice with 1-pentanol displayed the same transition peak, and their X-ray patterns were both "A". Purities of the samples, purified once and then twice, were 81 % and 98.8 % respectively when measured with a gas chromatograph. If the "A"-structure is due to impurities, the transition peak and pattern "A" should appear in the unpurified sample. An examination, however, showed the opposite tendencies. Therefore, structure "A" is due neither to impurities nor to ethanol. Furthermore, the higher the sample purity, the shorter time it takes to revert to "A". Impurities may have an effect similar to lattice imperfections.

(3) *Small impurities and metastable states* The purity of our sample is not more than 99.7 mol %. Apart from cholesteryl esters, Hsu and Johnson[12] did not detect the metastable phase for their high-purity PAA sample (99.98 mol %), whereas the metastable phase was readily attained by Chow and Martire[13] (99.7 %) and by Smith (99.0 mol %).[14] Therefore, we may not detect the cholesteric phase and the related solid polymorphs for the high purity CHA sample equal to the pure PAA (Hsu and Johnson). If a meterial becomes increasingly impure during an experiment, the possibility of formation of a metastable phase increases as the experiment proceeds.

Price and Wendorff[15] reported that extra recrystallizations did not significantly decrease the impurity content of their cholesteryl myristate sample (99.4 mol %). Therefore, zone refinement will be necessary to attain further purification.

A zone-refined CHA sample is likely to reveal the C-lattice, stable form at high temperature. This inference can be deduced from the result that maintaining a sample in a high temperature over a long period delays the reversion to "A". The ultimate evidence that "A" is the stable form for CHA may be obtained by X-ray diffraction analysis of a zone-refined CHA sample left below room temperature over more than a few years.

Conclusion

1) Cholesteryl acetate crystallized from 1-pentanol has two forms, "A" and "C"; "A" is stable at room temperature and "C" is stable above 85°C.

2) Various solid polymorphs formed by fusion belong to the "C" form.

3) Absence of impurities helps to form "A".

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Appendix

Solid IV forms special figures similar to annual rings of a tree on the course of transition to "A". Figure 10 hows one of the figures of SIV two months after their formation. The figures are very colorful; some are monochromatic, blue, red, green, and some are mixtures of these colors. The figure shows the extinction position clearly. It suggests that the crystal axes of all crystallites are arranged with a definite regularity in the figure. It seems interesting from the stand point of crystal growth, while the crystallographic meaning is unclear.

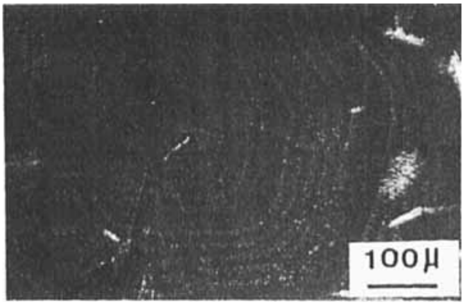

FIGURE 10 The annual ring-like figure on a decay of SIV.