

## Notes

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### Thermal Behavior of the Delta Form of Chloramphenicol Palmitate

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The thermal behavior of the  $\delta$  form of chloramphenicol palmitate was examined by differential scanning calorimetry. The previous prediction<sup>2)</sup> that by very rapid quenching the melted chloramphenicol palmitate would crystallize to the  $\delta$  form was realized on cooling at 80°/min using helium as a purge gas in the Perkin-Elmer DSC 1B. The heat of crystallization from the melt to the  $\delta$  form ( $-2.8 \pm 0.2$  kcal/mole) and the heat of transition from the  $\delta$  form to the sub- $\alpha$  form ( $-2.7 \pm 0.2$  kcal/mole) coincided with the predicted values ( $-2.9 \pm 0.5$  and  $-2.2 \pm 0.7$  kcal/mole), respectively. The area under the broad exothermal peak ( $P_2$ ) corresponding to the change from the sub- $\alpha$  form to the  $\alpha$  form could not be determined directly in this experiment and was calculated from the equation (1).

The thermal behavior of the  $\delta$  form of chloramphenicol palmitate was predicted from the data of the mixture of the  $\delta$  form and the sub- $\alpha$  form in the previous paper<sup>2)</sup> (Pattern IV). At that time the maximum cooling velocity of the differential scanning calorimeter was 40°/min.

On cooling the melt of chloramphenicol palmitate at 40°/min, two exothermic peaks,  $Q_1$  and  $Q_2$ , were found.  $Q_1$  was ascribed to the heat of crystallization from the melt to the sub- $\alpha$  form and  $Q_2$  to that from the melt to the  $\delta$  form. On heating two exothermic peaks,  $P_1$  and  $P_2$ , and one endothermic peak,  $P_3$ , were found and each peak was ascribed to the heat of transition  $\delta \rightarrow$  sub- $\alpha$ , sub- $\alpha \rightarrow \alpha$  and  $\alpha \rightarrow$  melt, respectively. The sub- $\alpha$  form was thought to be a transitional state and to be composed of the crystallites of the  $\alpha$  form.<sup>2)</sup>

On ideally rapid quenching it was predicted that all the melt crystallizes to the  $\delta$  form, i.e.,  $Q_1$  would not appear on the cooling curve. Postulating  $Q_1$  value be zero, the heat of crystallization from the melt to the  $\delta$  form and the heat of transition from the  $\delta$  form to the sub- $\alpha$  form were calculated.

In the present work for the purpose of simulating an ideally rapid quenching the differential scanning calorimetry was run at the cooling velocity of 80°/min. The obtained heats of transition were compared with the predicted values and the prediction was proved to be correct.

#### Experimental

The preparation of the thin-layer chromatographically pure chloramphenicol palmitate was described elsewhere.<sup>2)</sup>

Helium was used as a purge gas of a Perkin-Elmer DSC 1B. For rapid quenching the low-temperature cover was filled with liquid nitrogen. The cooling was run at 80°/min and the heating rate was 5°/min. The range used was 8 mcal/sec for cooling and 4 mcal/sec for heating.

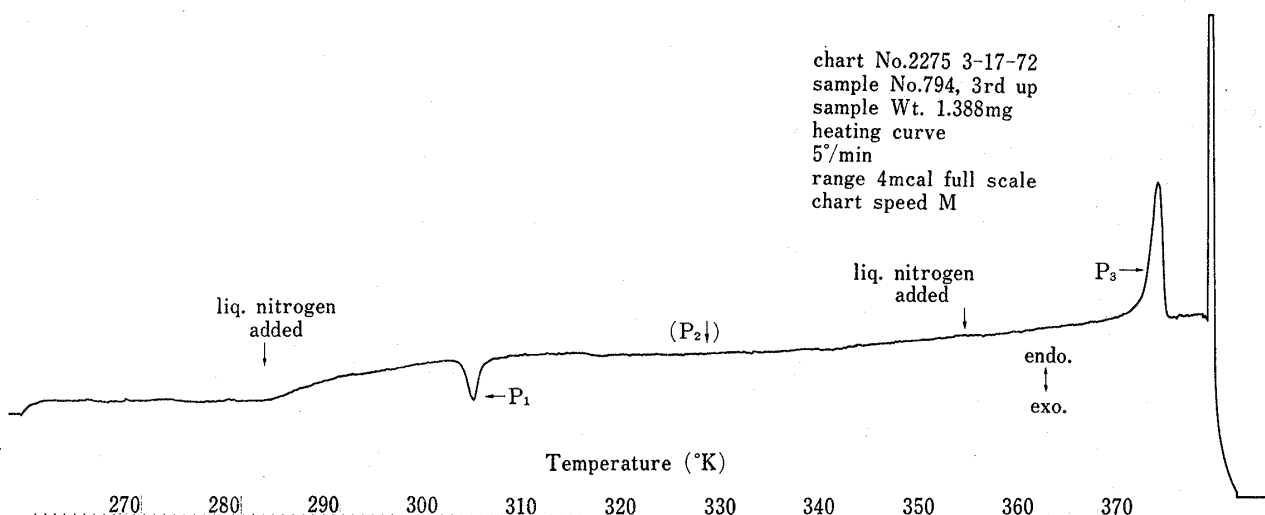
A solid sample pan containing about 1 mg of the specimen, whose weight was measured with a Shimadzu Electric Balance PMC-50 accurately, was crimped. The scanning was repeated three times on three specimens. The area under a peak was measured planimetrically three times. The peak area and the temperature indication were calibrated with 99.999% pure indium and azobenzene for melting point determination, respectively.

1) Location: 151 Oada-Kuragauchi, Ibaraki, Osaka, 567, Japan.

2) M.A. Miyamoto, T. Kiyotaki, N.A. Kisoh, T. Mitsunaga and T. Maeda, *Chem. Pharm. Bull.* (Tokyo), **21**, 1857 (1973).

## Results

The specimen of chloramphenicol palmitate was melted in the differential scanning calorimeter and quenched from 127° to -50°. The heating curve of the quenched specimen from -50° to 127° was also recorded.



Some parts of a typical cooling-heating curve is shown in Fig. 1, in which only one exothermic peak, Q<sub>2</sub>, was found on cooling and two exothermic peaks, P<sub>1</sub> and P<sub>2</sub>, and an endothermic peak, P<sub>3</sub>, on heating.

Using helium as a purge gas, the rapid cooling at 80°/min could be proceeded until -90°.

## Discussion

Some troubles which were not experienced in the previous work were encountered in the present study. They might be attributed to helium as a purge gas, to the coolant liquid nitrogen and to the rapid cooling of 80°/min.

The first trouble was that on rapid cooling a straight horizontal base line was not obtained until around 20°. As the low-temperature cover can not be used above around 130°, the cooling could not be started from much higher temperature than 127° to get a straight horizontal base line at a higher temperature than 20°. Although the base line was not straight above 20°, it was smooth and the peak Q<sub>1</sub> was not found on it.

Secondly on heating from -50° to 127° at 5°/min it took around 37 min and liquid nitrogen was to be added once or twice while running the calorimeter. The addition of liquid nitrogen sometimes caused the drift of a base line and/or an erroneous peak. The third trouble was the noises of a base line which were more exaggerated by using helium as a purge gas than in the case of nitrogen. These two troubles made it difficult to evaluate the very broad P<sub>2</sub> peak area planimetrically. The existence of this P<sub>2</sub> peak was discussed in view of differential scanning calorimetry, thermomicroscopic observation and X-ray diffraction study and P<sub>2</sub>

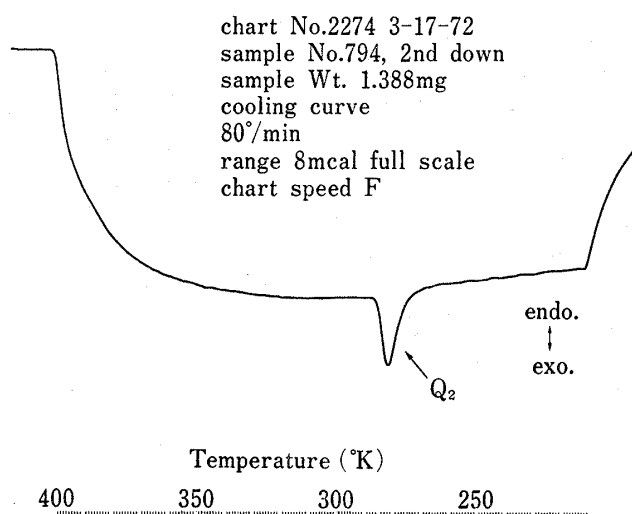


Fig. 1. Typical Cooling and Heating Curves of Quenched Chloramphenicol Palmitate

lower: cooling curve; upper: heating curve

was ascribed to the heat of crystal growth from the sub- $\alpha$  form, which is the crystallite of the  $\alpha$  form, to the  $\alpha$  form in the previous paper.<sup>2)</sup> Then  $\Delta H_{\text{sub-}\alpha \rightarrow \alpha}$  was calculated from the equation,

$$\Delta H_{\text{sub-}\alpha \rightarrow \alpha} = -\Delta H_{\alpha \rightarrow \text{melt}} - \Delta H_{\text{melt} \rightarrow \delta} - \Delta H_{\delta \rightarrow \text{sub-}\alpha}, \quad (1)$$

because the heat balance should be zero.

The fourth trouble was that the temperature indication was unstable.

These troubles must have left some uncertainties in determining the heats of transition.

As the peak  $Q_1$  representing the heat of crystallization of the sub- $\alpha$  form was not found on the cooling curve, the present quenched chloramphenicol palmitate is thought to be the  $\delta$  form. The ideal rapid quenching was performed at the cooling rate of 80°/min.

The quantitative comparison between the observed and the predicted heats of transition

TABLE I. Comparison between the Observed and the Predicted Values of the Heat of Transition

Peak Phase transition	$Q_2$ melt $\rightarrow$ $\delta$ exothermic	$P_1$ $\delta \rightarrow$ sub- $\alpha$ exothermic	$P_2$ sub- $\alpha \rightarrow$ $\alpha$ exothermic	$P_3$ $\alpha \rightarrow$ melt endothermic
$\Delta H$ (kcal/mole) <sup>a)</sup>				
Predicted	$-2.9 \pm 0.5$	$-2.2 \pm 0.7$	$-6.1 \pm 0.9$	$11.1 \pm 0.3$
Observed	$-2.8 \pm 0.2$	$-2.7 \pm 0.2$	$-5.4 \pm 0.4^b)$	$11.0 \pm 0.5$

a) The 95% confidence limits are also shown.

b) Calculated from the equation (1).

is summarized in Table I. The data could not be compared statistically for their variances could not be redeemed to be equidistributed by  $F$ -test. The observed  $\Delta H_{\text{melt} \rightarrow \delta}$  and  $\Delta H_{\alpha \rightarrow \text{melt}}$  were in good accord with the predicted values.<sup>3)</sup> The remaining two  $\Delta H$ 's were close to the predicted values but the observed  $\Delta H_{\delta \rightarrow \text{sub-}\alpha}$  was a little larger and the observed  $\Delta H_{\text{sub-}\alpha \rightarrow \alpha}$  was a little smaller than the predicted values. Both observed and predicted  $\Delta H_{\text{sub-}\alpha \rightarrow \alpha}$ 's were calculated from the equation (1), so the difference in  $\Delta H_{\text{sub-}\alpha \rightarrow \alpha}$ 's might come from the difference in  $\Delta H_{\delta \rightarrow \text{sub-}\alpha}$ 's.

At least qualitatively and to some extent quantitatively the prediction based on the data of the cooling velocity of 40°/min was proved to be correct. On rapid quenching the melted chloramphenicol palmitate crystallizes to the  $\delta$  form and on heating it is transformed into the sub- $\alpha$  form.

3) The coincidence of the predicted and the observed values of  $\Delta H_{\alpha \rightarrow \text{melt}}$  indicated that the chloramphenicol palmitate did not decompose while repeated melting and solidifying and therefore suggested the validity of the equation (1) for it is valid only when the chloramphenicol palmitate does not decompose.