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Optically Active and Racemic Glycerides. II. Thermodynamic Studies on the Polymorphic Transition of (*R*)- and (*RS*)-1,2-Diglycerides

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The polymorphic relationship between optically active (*R*)- and for racemic (*RS*)-forms of 1,2-distearin and 1,2-dipalmitin were studied by X-ray diffraction, infrared spectrum, and the thermal analysis. These glycerides have two crystalline forms, α and β, wherein α is metastable and β is stable under ordinary conditions. The $\alpha\rightarrow\beta$ transformation for the (*RS*)-1,2-distearin crystal was extremely slow as compared with that for the (*R*)-form crystal, implying that the β-form crystal of (*RS*)-1,2-distearin is an eutectic mixture of small (*R*)- and (*S*)-crystals while the α-form crystal of (*RS*)-1,2-distearin is composed of a replacement type solid solution of (*R*)- and (*S*)-1,2-distearin molecules. Almost the same results were obtained with 1,2-dipalmitin, for which the rate of $\alpha\rightarrow\beta$ transformation is higher than that for the 1,2-distarin, probably because of a higher mobility of this compound.

In the preceding paper[1)] on stability of (*S*)- and (*RS*)-α-monostearin crystals, it was pointed out that the (*RS*)- form crystal is a racemic compound, and that the interaction between (*R*)- and (*S*)-molecules in the (*RS*)-crystal is stronger than that between (*S*)- and (*S*)-molecules even above the melting point of the (*RS*)-crystal. Such polymorphic stabilities have been discussed frequently with monoglycerides and triglycerides[2,3)] but fewly with 1,2-diglycerides. Thus, the present study deals with the polymorphic relationship of optically active (*R*)- and racemic (*RS*)-forms of 1,2-distearin as well as of 1,2-dipalmitin. Attempts have been made to clarify the mechanism of the extremely slow $\alpha\rightarrow\beta$ transition of (*RS*)-1,2-glycerides as compared with that of (*R*)-1,2-diglycerides by means of X-ray diffraction, infrared spectrum and the thermal analysis for these glycerides. A similar mechanism could be applied to 1,3-diglycerides for which rapid $\alpha\rightarrow\beta$ transformation had been reported.[4—6)]

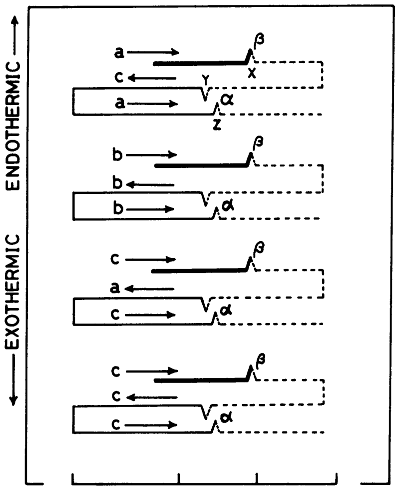

Fig. 1. The DSC performance for (*RS*)-1,2-distearin crystal; a=1 K min^{-1}, b=5 K min^{-1}, and c=10 K min^{-1}. Bold and thin lines express the phases of β- and α-forms, respectively, and dotted lines the liquid state. The enthalpy values for the peaks: X=123.1 kJ mol^{-1}, Y=77.2 kJ mol^{-1}, and Z=76.4 kJ mol^{-1}.

Experimental

Materials. Chemically pure (≥99%) samples of (*R*)- and (*RS*)-1,2-dipalmitins and (*R*)- and (*RS*)-1,2-distearins from Fluka AG (Switzerland) were further purified by repeated recrystallization from hexane to give β-form (stable) crystals of these 1,2-diglycerides. The samples of α-form (metastable) were obtained by rapid cooling of molten samples of the stable glycerides. Melting points of these samples (Table 1) were in good agreement with the reference values.[4,8,9)]

Apparatus and Procedures. The calorimetric experiments were carried out with a differential scanning calorimeter (Shimadzu Model DSC-30 equipped with Model LTC-30 cooling unit) in a temperature range from 173 to 473 K (accuracy $\pm$2.5 mJ s^{-1}) by the use of a standard sample of KNO$_3$[10)] for thermal calibration. Identification of the polymorphic

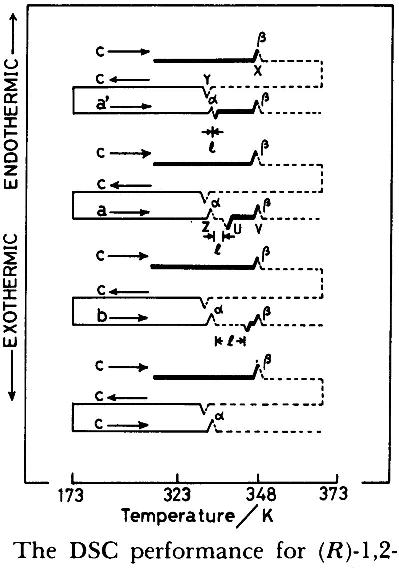

Fig. 2. The DSC performance for (*R*)-1,2-distearin crystal; a'=0.5 K min^{-1}, a=1 K min^{-1}, b=5 K min^{-1}, and c=10 K min^{-1}. Bold and thin lines express the phases of β- and α-forms, respectively, and dotted lines the liquid state. The enthalpy values for the peaks: X=124.0 kJ mol^{-1}, Y=79.4 kJ mol^{-1}, Z=73.3 kJ mol^{-1}, U=121.0 kJ mol^{-1}, and V=120.2 kJ mol^{-1}.

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crystals was achieved with an X-ray diffraction unit (Rigaku Denki Model 2001), and an IR spectrometer (Hitachi Perkin-Elmer Model 215). For more details, an X-ray small-angle diffraction unit (Rigaku Denki Model 2202El) was used.

Results and Discussion

In Figs. 1 and 2 which show the DSC performance for (*RS*)- and (*R*)-1,2-distearins, respectively, the first (X) and the second (Z) endothermic peaks are attributable to the fusion of crystals of β- and α-forms, respectively. This was confirmed by the data based on the measurements of X-ray diffraction (Fig. 3), IR spectrum (Fig. 4), melting point and enthalpy of fusion (Table I). The first exothermic peaks (Y), therefore, are attributable to the formation of α-form crystals: The enthalpy amounts calculated from the peaks (Y) were 77.2 and 79.4 kJ mol^{-1} for (*RS*)- and (*R*)-distearins, respectively, in approximate agreement with our observed values (75.8 and 73.3 kJ mol^{-1} for (*RS*)- and (*R*)-forms) for the α-form crystals. This was indeed the case of (*RS*)-distearin for which the DSC performance (Fig. 1) remained unchanged when heating and/or cooling rates were varied.

On the other hand, (*R*)-stearin showed rather peculiar behavior in its performance (Fig. 2); After formation of α-crystal, it was molten (mp of β-form) by re-heating to give an endothermic peak followed by an exothermic one indicative of formation of β-form: The enthalpy value (121.1 kJ mol^{-1}) for the exothermic peak *U*, in good agreement with that (120.0 kJ mol^{-1}) for the endothermic one *V*, agrees well with the enthalpy of fusion (124.0 kJ mol^{-1} from Table 1) for the β-form crystal. It seems that the interval (in temperature scale), *l* in Fig. 2, between the $\alpha \rightarrow$ liquid and liquid $\rightarrow \beta$ transformations is longer for higher

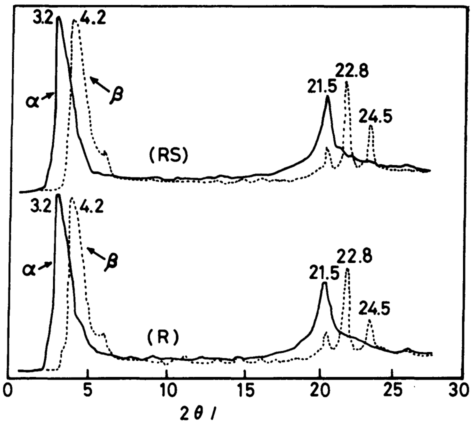

Fig. 3. X-Ray diffraction patterns for (*RS*)-(upper curves) and (*R*)-(bottom) 1,2-distearin crystals in α-(full curves) and β-(dotted) states.

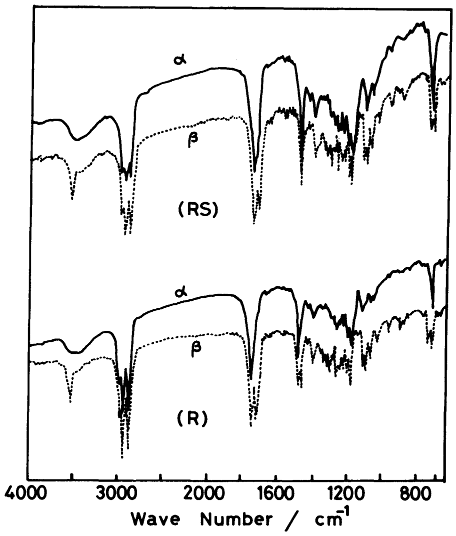

Fig. 4. Infrared spectra for (*RS*)-(upper curvers) and (*R*)-(bottom) 1,2-distearin crystals in α-(full curves) and β-form (dotted).

Table 1.

	1,2-Dipalmitin				1, 2-Distearin			
	(*R*)		(*RS*)		(*R*)		(*RS*)	
	α	β	α	β	α	β	α	β
Mp θ_m/K	322.5	341.1	322.1	336.3	333.1	349.1	332.8	344.9
		341.1 ∼ 342.1[8]	323.1[4]	336.6[4]		349.1 ∼ 350.1[8]	332.6[4]	344.1[4]
		340.1 ∼ 340.6[9]				347.6 ∼ 348.1[9]		344.6 ∼ 345.6[8]
Enthalpy of fusion / kJ mol^{-1}	52.7[a]	97.2	52.0	98.7	73.3	124.0	75.8	123.1
Entropy of fusion / J K mol^{-1}	163.4	284.9	161.2	293.4	220.0	355.1	227.7	356.9

a) Enthalpy of crystallization: Enthalpy of fusion for α-(*R*)-crystal of 1, 2-dipalmitin could not be obtained for overlaping of the endo-thermic peak due to the fusion of α-crystal with the subsequent peak (exothermic) due to rapid formation of β-crystal.

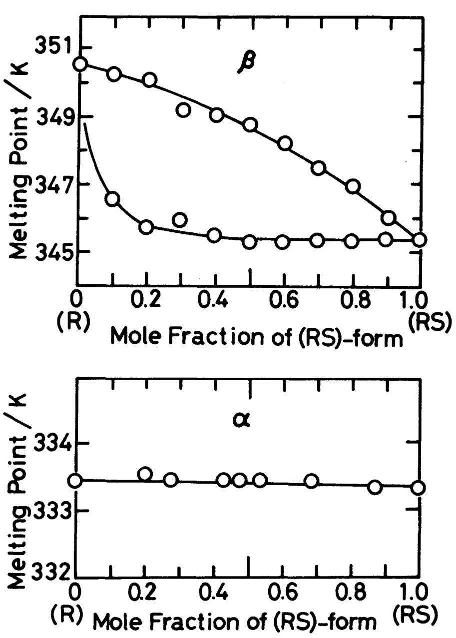

Fig. 5. Melting point-composition diagrams for mixtures of (*R*)- and (*RS*)-1,2-distearins in α-(bottom figure) and β-(upper) forms. Mixture of (*R*)- and (*RS*)-1,2-distearins were prepared by mixing (*R*)- and (*RS*)- forms with hexane and standing overnight *in vacuo* to evaporate the solvent.[1]

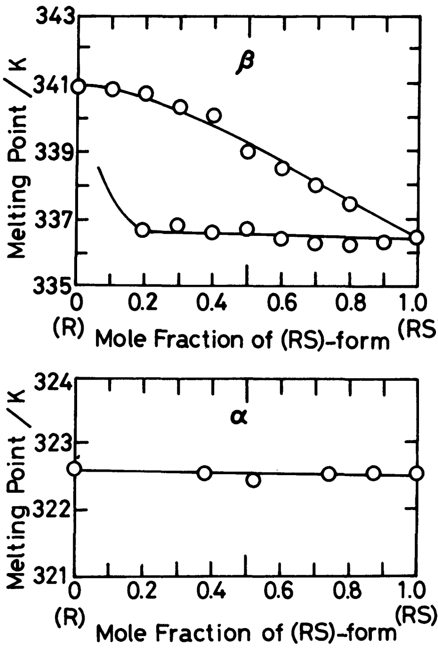

Fig. 6. Melting point-composition diagrams for mixtures of (*R*)- and (*RS*)-1,2-dipalmitins in α-(bottom figure) and β-(upper) forms. Mixture of (*R*)- and (*RS*)-1,2-dipalmitins were prepared by mixing (*R*)- and (*RS*)-forms with hexane and standing overnight *in vacuo* to evaporate the solvent.[1]

the heating rate. Howe and Malkin,[4] and Chapman[11] reported that the formation of the β-form crystal resulted from holding of the α-form crystal of (*RS*)-1,2-distearin for several hours at a temperature slightly below its mp and that both (*R*)- and (*RS*)-1,2-distearins have only two polymorphic forms, α and β, and do not possess a transition temperature between them. Taking account of all these results, we must conclude that the α-form crystal is less stable than the β-form crystal throughout all temperature region; The α- and β-crystals are in monotropic relationship,[12] giving higher stability to the latter. A similar relationship has been observed for the α- and β-crystals of chloramphenicol palmitate.[13]

In order to compare the rate of α→β transformation between (*R*)- and (*RS*)-1,2-distearins, the DSC scanning for the α-crystals of (*R*)- and (*RS*)-form were carried out, after they had been allowed to stand for three months at room temperature. It was found that the α-(*R*)-crystal was transformed into its β-form, whereas the α-(*RS*)-crystal remained unchanged. Such phenomena could probably suggest that, like the case of (*RS*)-α-monostearin,[1] the (*RS*)-1,2-distearin is composed of a racemic compound. However, both X-ray diffraction patterns (including X-ray small-angle diffraction) and the infrared absorption spectra were almost the same between (*R*)- and (*RS*)-forms irrespective of their crystalline forms (see Figs. 3 and 4). In addition, practically no difference is found in entropy of fusion between (*R*)- and (*RS*)-distearins whatever they are in α- or β-form (see Table 1). Nevertheless, the melting point-composition diagrams (Fig. 5) indicates that the β-(*RS*)-1,2-distearin crystal(upper figure) possesses a minimum melting point at which the crystal seems to be an eutectic mixture of (*R*)- and (*S*)-crystallites in 1:1 molar ratio, whereas the α-crystal (bottom) shows a performance typical to solid solution. There are two types of solid solution, replacement and penetration types.[14] In the former, different kind of molecules freely occupy the lattice points in a crystal, whereas in the latter one kind of molecules can penetrate, with certain limit in its composition, among other kind of molecules occupying their lattice points. The Hume-Rothery rules[14] for the replacement type solid solution can be applicable to the (*R*)- and (*S*)-1,2-distearin molecules which are all the same in their size and attractive force. The α→β transformation of (*RS*)-1,2-distearins, therefore, must be accompanied by an entropic decrease corresponding to a molecular rearrangement from a solid solution type to an eutectic type, *i.e.*, replacement-type distribution (random) to microcrystallite mixture (microordered).[15] In the case of (*R*)-1,2-distearin, such an entropic decrease is not involved in such transformation. The same is true for 1,3-distearin which has no asymmetric carbon atoms and which is characterized by higher rate of α→β transformation.[4]

All of the above experimental techniques, DSC scanning, X-ray diffraction, IR spectropy, and the melting point-composition diagrams were applied to α- and β-crystals of (*R*)- and (*RS*)-1,2-dipalmitin, for which essentially the same results were obtained as is summarized in Table 1. A typical example is shown in Fig. 6 which suggests an entropic decrease accompanying the α→β transformation (random→microordered) of (*RS*)-1,2-dipalmitin. Similarly, the DSC performance was almost the same as that in Fig. 1 from which the enthalpies of fusion for α- and β-forms are tabulated in the 4th and 5th column of Table 1. Only one exception is that the α→β transformation of (*R*)-

1,2-dipalmitin was so fast that the *l*-value in Fig. 2 was always zero irrespective of the heating rate, *i.e.*, the peaks *Z* and *U* overlap each other. This is evidently attributable to a higher mobility of the C_{16}-compound than that of the C_{18}-glyceride. One, therefore, could not estimate the enthalpy of fusion for α-form but of crystalization (peak *Y*), which is listed in the second column.

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