Crystal Properties of Stearate Esters of Racemic and L(+) Propylene Glycol

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Abstract

The l-monostearate and the distearate of propylene glycol were prepared with racemic propylene glycol and L(+) propylene glycol, and their crystal properties were compared. Racemic propylene glycol-l-monostearate shows four different polymorphic modifications whereas optically active propylene glycol-l-monostearate is monomorphic, with a melting point of 54.0C and a long spacing of 50.6A. Racemic propylene glycol distearate has an unstable Form II, which transforms irreversibly to Form I near 44C. Form I melts at 58.8C. The two forms have long spacings of 53.4A (Form II) and 43.4A (Form I). Optically active propylene glycol distearate exhibits three crystalline modifications: an unstable Form II which transforms irreversibly to Form I near 37C, with Form I melting at 53.9C, and a third, stable form, termed Form III, melting at 58.8C. The long spacings of the three forms are 51.9A, 43.6A, and 46.9A respectively. Heats of transition for the various phase changes are given.

Introduction

THE POLYMORPHISM of crystalline fatty acid compounds has been a topic of study for many years and has been reviewed recently (1,2). Most of this work has been done with optically inactive material, either symmetrical compounds or racemic mixtures. Optically active fatty acid derivatives have been prepared but, in only one instance known to the author, has the polymorphism of these materials been examined (2). Schlenk (3) has studied the effect of stereo-isomerism on several different properties of the most stable crystal form of various glycerides. The properties of various crystalline phases of propylene glycol (propane-1,2-diol) esters have been reported (4) as the racemic mixtures. Since the middle carbon of propylene glycol is asymmetric, there are two enantiomorphs; the primary and secondary monoester and the diester are also enantiomorphic. This paper reports on the crystal properties of the l-monostearate and the distearate of L(+) propylene glycol and compares it with the corresponding racemic compounds.

Experimental

Racemic propylene glycol-l-monostearate was prepared by the specific method of Martin and Lutton (4). Infrared spectroscopy (5) showed that there was less than 2% of the secondary isomer. Racemic propylene glycol distearate was prepared by J. B. Martin of this laboratory.

Synthesis of the optically active esters was carried out by the method discussed by Mattson and Volpenhein (6). Stearoyl chloride was prepared from stearic acid which was >99% pure, as judged by gas chromatography. L(+) propylene glycol was obtained from the Aldrich Chemical Company ($[\alpha]_{542}^{25}$ + 19.03°, undiluted, lit. value (7) $[\alpha]_{D}^{23}$ + 15.4°). After reaction of the materials in pyridine:chloroform (1:2 V/V) the distearate was separated from the monostearate by chromatography on a column of silica gel. The distearate was recrystallized at 20C from 10 volumes of acetone. By repeated crystallization from hexane at 25C, L-propylene glycol-l-monostearate was obtained free from the 2-monostearate (3). Isomeric purity was better than 98% as measured by infrared spectroscopy (5). No impurities were found in the mono- and diester by thin-layer chromatography.

Two melting-point procedures were used: a "complete melting-point" (CMP) and a "rapid melting-point" (RMP) (8). The former is the melting point obtained by slowly warming the material in a capillary tube. For the latter, the sample was melted, chilled rapidly in an ice bath, and thrust into a bath at various temperatures. The temperature at which the melted and chilled sample immediately remelted was the RMP. Measurements of heats of transition and fusion were obtained by using the Perkin-Elmer Differential Scanning Calorimeter, according to the published method (9). Sample sizes were between 1 and 1.5 mg.

Flat film x-ray diffraction data were obtained with the powdered sample in thin-walled Pyrex glass capillaries with a General Electric XRD-1 unit, employing CuKα radiation (nickel-filtered) and a 0.025 pinhole system. Sample-to-film distances were 10 cm. Intensities were estimated by visual inspection.

Results

The esters of optically active propylene glycol had specific rotations which were somewhat larger than comparable glycerides: thus for L-l-PGMS (10) $[\alpha]_{542}^{25}$ + 6.09° (C = 4.97 in n-heptane) and for L-PGDS (10) $[\alpha]_{542}^{25}$ + 2.20° (C = 4.97 in n-heptane). For comparison, Baer and Fischer found values of +4.95° for the optically active monostearin (11).

Pure L-l-PGMS is monomorphic in its crystalline behavior, as opposed to racemic l-PGMS, which has four different crystal forms (4) (Table I). The powder pattern from L-l-PGMS was quite sharp; several orders of long spacings were noted. The crystal appears to have a double-chain, slightly tilted structure, with an interplanar distance of 50.6A. It has two strong short-spacings of 4.31A and 4.16A and does not correspond with any of the crystal forms of racemic l-PGMS.

The L-PGDS shows three crystalline modifications as compared with two forms found in racemic PGDS (Table I). In the racemate there is a form which is stable at temperatures up to its melting point. By rapidly chilling a melt, an unstable Form II is obtained which transforms to the stable form either upon heating to 44C or upon standing at room temperature for some time. Two similar forms were seen in L-PGDS; the one difference was the slightly shorter long spacing in Form II of L-PGDS (51.9A *vs.* 53.4A). However Form I L-PGDS was not stable and, upon aging at room temperature, it transformed into a stable configuration termed Form III. Form III

TABLE I
Diffraction Data for Propylene Glycol Esters

Ester	Crystalline form	A	Long spacings Intensity of orders	Short spacings A and intensities
L-l-PGMS	I	50.6	1VS,2M,3S,4S,6S	4.47M,4.31VS,4.16S
l-PGMS[a]	II	29.4	2W,6W	9.75M,4.07VS,3.66S
	α	52.5	1VS,4M,6M—	4.13S,4.5W,3.95W,3.85W
	III	53.4	1VS,2W,4M,5W,6M—	4.14VS,3.79S
	I	48.5	1VS,4M+,6M,7VW,8VW	4.20W,4.04S,3.79W 3.64M,3.48W
L-PGDS	II	51.9	1VS,4M,6VW	4.16VS,3.80S
	I	43.6	1VS,2VW,3S,5VW,6W	4.16VS,3.97S,3.78W,3.60S
	III	46.9	1VS,3S,4M,6M,8M	4.83W,4.41M,4.22VW, 4.02S,3.76M
PGDS[b]	II	53.4	4M, 6VW	4.15S,3.81M
	I	43.4	1VS,3W,5VW,6VW+,8VW	4.10VS,3.93W,3.78W,3.56M

[a] Data from reference 4.
[b] Private communication from E. S. Lutton.

of L-PGDS is distinguished by the single strong spacing of 4.02A as opposed to three strong short spacings of 4.16, 3.97, and 3.60A of Form I. The Form II obtained by chilling a melt transforms into Form I at 37C upon heating or at room temperature over a period of time.

Thermal data also aid in comparing properties of the various crystal phases (Table II). The single crystal form of L-l-PGMS melts at 54.0C, about two degrees lower than the melting point of the stable form (Form II) of racemic l-PGMS. The lower RMP shown by l-PGMS is indicative of the presence of the metastable α phase, which is not seen in the case of L-l-PGMS.

Both PGDS and L-PGDS have a CMP at 58.8C, but L-PGDS also has a lower RMP not observed in PGDS, owing to the metastable Form I L-PGDS (Table II). This RMP is obtained by rapidly melting, chilling, and re-melting the sample. When Form I is obtained by crystallization from the solvent, it has a capillary melting point of 53.9C, somewhat higher than the RMP. The unstable Form II of both racemic and L-PGDS is too fleeting near its melting point to give an observable capillary melting-point.

The enthalpies of transition (crystalline transformation or fusion) also discriminate among the crystalline forms (Table III). The single form of L-l-PGMS melts with a heat of fusion of 47.1 cal/g. This is close to ΔH_f for the stable form (Form II) of l-PGMS of 50.0 cal/g but much higher than the ΔH_f of 31.5 cal/g for the metastable α form. Likewise values of ΔH_f for the stable forms of L-PGDS and PGDS are close (47.6 and 49.1 cal/g respectively) whereas the metastable Form I of L-PGDS has a somewhat lower ΔH_f of 39.8 cal/g.

The methods of obtaining the various polymorphic forms of these materials may be summarized as follows. For L-l-PGMS, slow or fast crystallization from solvent or cooling of a melt all give Form I. For l-PGMS (4), slow crystallization from solvent gives Form II whereas rapid crystallization gives Form I. Cooling of a melt gives α at temperatures between 38.5–47C, which, upon cooling below 38.5, transforms to Form I or Form III. (The factors governing which form is obtained have not been precisely defined as yet.)

The stable form of PGDS, Form I, is obtained by crystallization from solvent whereas rapid chilling of a melt gives Form II. Crystallization of L-PGDS from solvent gives Form I but, upon standing at room temperature for a few weeks, this changes into Form III. Presumably crystallization from solvent under the proper conditions also would yield Form III, but this has not been achieved experimentally. Rapid chilling of a melt again gives Form II.

TABLE II
Melting Points of Propylene Glycol Esters

Ester	Melting point, C	
	CMP	RMP
L-l-PGMS	54.0	53.5
l-PGMS	55.9[a]	47.1[a]
L-PGDS	58.8	53.0
PGDS	58.8[b]	58.8[b]

[a] Data from reference 4.
[b] Private communication from E. S. Lutton.

Discussion

The nomenclature used in this paper has followed that of Martin and Lutton (4). They discuss the reasons for not using the terms β and β′ as applied by Kuhrt et al. (12). Essentially the use of these terms would imply some relationship between the crystalline structures seen in the present instance and the structures of glycerides. Except in the case of α, such a relationship cannot be unequivocally stated at the present time. In order to prevent undue confusion, the simple designation of the various forms as Form I, II, etc., has been preferred.

The only published work, known to the author, of the influence of stereo-isomerism on the polymorphic relationships of fatty acid derivatives is that of Larsson (2), who examined some L-l-monoglycerides. He reported finding two crystal forms for L-l-monolaurin and four forms for L-l-monostearin. He found that crystals of β′ racemic l-monostearin gave x-ray diffraction data identical with that for the form of L-l-monostearin which he termed β_1'. He assumed that a racemic crystal and an optically active crystal form of a compound cannot have crystal structures so similar that no differences in intensity distribution are noted. From this he concluded that racemic β′ l-monostearin is actually a mixture of antipode crystals.

In the case of PGDS and L-PGDS a similar situation is found, but the opposite conclusion is reached.

TABLE III
Enthalpies of Thermal Transitions of Propylene Glycol Esters

Ester	Transition	Temperature, C	ΔH, cal/g
L-l-PGMS	Form I → liquid	54.0	47.1
l-PGMS	Form I → α	38.5[a]	9.7
	Form III → α	38.5[a]	9.3
	α → liquid	47.1[a]	31.5
	Form II → liquid	55.9[a]	50.0
L-PGDS	Form II → Form I	37	~ 3
	Form I → liquid	53.9	39.8
	Form III → liquid	58.8	47.6
PGDS	Form II → Form I	44	~ 6
	Form I → liquid	58.8	49.1

[a] From reference 4.

The spacings and intensity distributions of Form I of these two compounds are similar, yet the melting point of Form I PGDS is higher than that of Form I L-PGDS by some 5C. If Form I PGDS were indeed a physical mixture of crystals of L- and D-PGDS, its melting point would be expected to be the same as or lower than that of Form I L-PGDS (3). Furthermore ΔH_f of a mixture of antipode crystals should be the same as that for crystals of one enantiomer. This also is not the case in the present instance: ΔH_f for Form I PGDS is 49.1 cal/g, ΔH_f for Form I L-PGDS is 39.8 cal/g.

The relationship between chain packing and ΔH_f of the various forms is not clear but can be rationalized. The simple fact that side chains in two crystals are packed similarly (based on x-ray diffraction data) does not necessarily imply that ΔH_f for the crystals will be identical. For example, the Form I crystals of PGDS and L-PGDS have similar short spacings, yet there is a 9.3 cal/g difference in ΔH_f for these two forms. On the other hand, ΔH_f is about 50 cal/g for the most stable form of PGDS and of L-PGDS although the chain packing is different in the two cases. These facts are consonant with the following hypothesis. The optimum packing of head groups in crystals of the racemic and of the optically pure propylene glycol esters will be different. Because of these different orientations the packing of the chains will be different in the two types of crystals, and the energy of interaction between the side chains (London—van der Waals forces) will be different. In Form I L-PGDS the chain packing is altered from that in the most stable crystal (Form III) and, in order to effect this change, the packing of the head groups must be altered. In this different orientation the interactions between the head groups will be less than maximum, and this decrease in crystal energy is reflected in the decreased ΔH_f. Estimation of the relative contributions of side-chain interactions (London—van der Waals dispersion forces) and head group interactions (hydrogen bonding) to total crystal stability must await further analysis of the crystals involved.

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10. Abbreviations are as follows: l-PGMS, racemic propylene glycol-l-monostearate; PGDS, racemic propylene glycol distearate; L-l-PGMS, the dextro-rotatory l-PGMS; L-PGDS, dextro-rotatory PGDS.
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