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THE EFFECT OF STRUCTURE ON THE THERMODYNAMIC PROPERTIES OF A LIQUID CRYSTALLINE DIASTEREOMERIC PAIR OF CHIRAL ALKANOATES

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ABSTRACT

The thermodynamic properties of a diastereomeric pair of a cholesteryl chiral alkanoate were investigated. Studies on the thermal behavior, optical activity and the phase diagram confirmed that the diastereomeric pair exhibit similar mesomorphic behavior. It is concluded that the structural effects due to the chiral ester moiety do not contribute significantly to the mesomorphic structure of the diastereomers, but are pronounced in the crystalline structure.

INTRODUCTION

The influence of molecular structure upon liquid crystalline properties has been the subject of many investigations. Studies have been carried out to obtain empirical rules relating molecular structure to the appearance of liquid crystalline states. Among these studies, attempts have been made to understand the relationship between the molecular structure of the derivatives of cholesterol and their mesomorphic behavior. Homologue series of both normal and branched chain (chiral) cholesteryl ester have been thoroughly investigated and some qualitative explanations, relating the molecular features to the physical properties of these series have been deduced [1–7]. The steric interactions resulting from configurational and conformational changes of the alkanoate moiety are, in general, the major contributing factors to both inter- and intramolecular changes and consequently, are responsible for alterations in their thermodynamic characteristics.

The first attempt to study the effect of structure on the mesomorphic behavior of a diastereomeric pair of chiral cholesteryl alkanoates has been reported in the previous work [8]. In the present study, the effect of chirality of the alkanoate residue on the optical, thermal and mesomorphic properties of the diastereomeric pair of cholesteryl-2 methylpentanoate is investigated. The phase diagram of these esters is also independently studied. The application of NMR spectroscopy as a

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quantitative method for determining the optical purity of diastereomers is also presented. The results of this work confirm those of the previous studies and also provide some new information about the configurational and conformational effects of structure on the mesomorphic state of chiral alkanoates.

EXPERIMENTAL

The compounds used for this study are a diastereomeric pair of cholesteryl (R)- and (S)-2-methylpentanoate, as well as their equal weight mixture; cholesteryl (racemic)-2-methyl pentanoate. The esters were synthesized in our laboratories from active and racemic-2-methylpentanoic acids by modification of the method initially employed by Swell and Treadwell [9].

The active and racemic acids were obtained from the Norse Laboratories, Inc., with a reported optical purity of about 90%. The measured optical rotations of the (S)- and (R)-acids at 22°C were: $[\alpha]_D = +13.9°$ and $[\alpha]_D = -17.1°$, respectively. Details of the ester preparation procedure which will be briefly described here have been mentioned elsewhere [10]. The acid chloride was prepared by adding the acid dropwise for about 1 hour to a freshly distilled thionyl chloride and vacuum distilling the acid chloride. It was then heated to 80°C and high-purity cholesterol added in small portions. Anhydrous pyridine was then added and the mixture was heated for about half an hour. Finally, the esters were re-crystallized from ethanol five times with about 70% yield.

Transition temperatures and textural analysis were performed using a Nikon LKE polarizing microscope equipped with a Mettler FP-52 hot stage. The optical rotation measurements were done with a Model 63 Rudolph polarimeter at 22°C. A Perkin-Elmer differential scanning calorimeter (DSC-1B) with a scanning rate of 5 cm min^{-1} was used to determine the transition temperatures, the heats of fusion, and for phase diagram studies. Determination of diastereomeric purity was carried out at ambient temperature with a Varian-XL100 NMR spectrometer. The diastereomeric binary mixtures were prepared by mixing weighed samples in the melt and allowing them to stand for a few days at room temperature. The mixtures were then examined both calorimetrically and microscopically. Transition temperatures were verified by making more than one determination.

RESULTS AND DISCUSSION

Mesomorphic and thermal behaviors

Mesomorphic and melting behaviors of the esters were obtained by microscopic analysis. Textural studies showed that all three esters exhibit liquid crystalline structure with monotropic smectic mesophase. Upon cooling the esters from the isotropic phase, a typical fan-shaped texture of smectic A phase developed and on further cooling, crystallization occurred. The rate of crystallization in (R)-2-methylpentanoate was much faster than in the (S)-form and directly related to the smaller smectic temperature range of the former. When the smectic mesophase was directly produced from the isotropic melt of either diastereomer, elongated smectic particles, namely the "batonnets", were observed. The melting behavior of the three esters is summarized in Table 1. With reference to Table 1, it can be observed that the transition temperatures of the (racemic)-2-methylpentanoate are intermediate between those of the two diastereomeric forms. This is expected because the racemic form produced from the initial racemic acid is in fact a mechanical mixture of the two diastereomers. Furthermore, from the mesomorphic and melting behavior of the diastereomeric esters, it can be realized that the configurational mobility of the chiral alkanoate moiety is more effective in the crystalline structure differences of the two diastereomers than in their mesomorphic structures (Table 1).

The transition temperatures of the (racemic)- and (R)-2-methylpentanoate are in satisfactory agreement with those reported by Gibson [7] which are also outlined in Table 1. Aside from the experimental error, the slight differences between the results of the present study and those of Gibson [7] could be attributed to the different optical purities of the initial active and racemic acids.

Thermal studies and the evaluation of the ΔH_f and ΔS_f parameters of cholesteryl (R)-, (S)- and (racemic)-2-methylpentanoates were obtained by differential scanning calorimetry (DSC). These values, for all three esters, are also summarized in Table 1. The results of this study on the individual esters again confirm the existence of a single monotropic mesomorphic state with ΔH_f and ΔS_f values of a smectic character. Evaluations of the enthalpies of transition at solid–isotropic and smectic–isotropic temperatures were made from the relative transition peak area measurements. During this study, it was observed that the (S)-2-methylpentanoate, upon repeated heating from solid, exhibited two successive solid–isotropic transition enthalpies which were due to polymorphism in its crystalline state. In fact, the intensity ratio of the two successive peaks depended on the thermal history of this ester in its crystalline state. Such a phenomenon was not observed at all with the (R)-2-methylpentanoate. However, it was not clear how much this crystalline polymorphism was due to initial impurities and to different nucleation rates of the polymorphs. Thermodynamic data in Table 1 also show that although the ΔH_f and ΔS_f values of the two diastereomers are significantly different from each other at the solid–isotropic transition temperature, they provide similar values at the smectic–isotropic temperature. These results also confirm that the two diastereomers have quite different crystalline structures and energies, but exhibit similar smectic mesomorphism. Also in Table 1, are outlined the ΔH_f values of the (racemic)- and (R)-2-methylpentanoate reported by Gibson [7]. The differences between these values and those of the present study are partly due to the experimental errors, but mostly arising from the different optical purities of the initial acids and resultant racemic and chiral esters utilized in these studies. Referring to Table 1 and the phase diagram (Fig. 3), indicates that the optical purity of the initial (R)-2-methylpentanoic acid and the consequent diastereomeric purity of the (R)-ester (90.5%) are larger

TABLE 1

Thermodynamic properties of cholesteryl 2-methylpentanoates

Cholesteryl ()- -2-methylpentanoate	Transition temp. ±0.1 (°C)		Mol. rotation $[\alpha_m \times 10^{-4}]$[d] (deg)	ΔH_t[f] (kcal mole^{-1})		ΔS_t[f] (cal mole^{-1} K^{-1})	
	S→I[a]	I↔Sm[a]		S→I[a]	I↔Sm[a]	S→I[a]	I↔Sm[a]
-(S)-	74.3	65.5	−1.3	5.9	0.62	17.0	1.8
-(racemic)-	80.1[b]	68.2[b]	−1.7[e]	7.5[g]	0.65	21.0	1.9
-(R)-	90.4[c]	69.1[c]	−2.0	8.1[g]	0.63	22.0	1.9

[a] Notations: S=solid, I=isotropic, Sm=smectic.

[b] Transition temperatures from ref. 7 are 82°C and estimated 68°C, respectively.

[c] Transition temperatures from ref. 7 are 90°C and 68°C, respectively.

[d] $[\alpha_m]=M[\alpha]_D$, where M is the molecular weight and $[\alpha]_D$ is the specific rotation of the neat ester at sodium D-line at 25°C.

[e] From R.E. Rondeau et al., J. Am. Chem. Soc., 94 (1972) 1096 for cholesteryl-*n*-pentanoate, $[\alpha_m]=1.65\times10^4$ (deg).

[f] Experimental error is within 10%.

[g] ΔH_t values for (racemic)- and (R)-esters reported in ref. 7 are 9.26 and 7.17 kcal mole^{-1}, respectively.

than those reported in refs. 7 and 11. This resulted in a slightly higher ΔH_f value for (R)-ester in this work.

With reference to the thermodynamic and phase diagram studies of the present work and also the pitch measurements of the previous work [10], the most probable configurational assignment of the two diastereomers is presented in Fig. 1. On the basis of the present results and in agreement with the study in ref. 7, a qualitative explanation of the conformational arrangements of the chiral ester chain suggests that there are two interrelated effects responsible for the mesomorphic behavior of the cholesteryl chiral alkanoates; namely the configurational or steric bulk effect, and the conformational effect or the stereochemical changes based on the rotations about carbon–carbon single bonds. The conformational effect of chirality would serve to make the alkanoate chain less flexible than its normal alkanoate homologues. Following this argument, it can be seen (Fig. 1) that branching in cholesteryl normal pentanoate has stabilized the ester chain through the preferred conformations about the carbon–carbon single bond adjacent to branching, to such an extent that due to the rigidity of 2-methylpentanoate moiety, the cholesteric mesophase is completely quenched. Instead, a thermodynamically higher structural order, i.e., smectic mesophase, is established. However, neither the configurational nor the conformational arrangements of the (R)- and (S)-2-methylpentanoate molecules contribute significant effects on the mesomorphic phase of the diastereomers. Conformationally, the preferred arrangement of the groups attached to the asymmetric carbon about the single bond (CO–alkyl bond), is such that, in the solid state the (R)-2-methylpentanoate moiety shows slightly more rigidity than the (S)-form. The increased rigidity of the chiral moiety restricts the thermal motion of the (R)-form with a relative increase in its crystalline order. A comparison of the smectic temperature range of the two diastereomers (Table 1) shows that the smectic phase stability of the (R)-2-methylpentanoate has been increased at the expense of the organization in its crystalline state. Therefore, the present results suggest that the structural effects arising from the chirality are more pronounced in the crystalline phase of chiral alkanoates than in the mesomorphic phase.

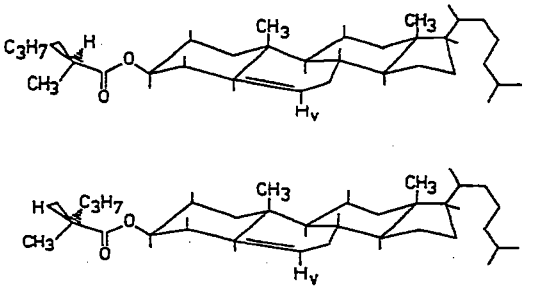

Fig. 1. Configuration of cholesteryl (S)-2-methylpentanoate (top) and cholesteryl (R)-2-methylpentanoate (bottom) showing changes in spatial relationships between the cholesteryl moiety and the methyl and propyl groups. H_v is the C-6 vinyl proton, from which the diastereomeric ratios were determined by NMR method.

Optical activity and diastereomeric purity

Determination of the values of molecular optical rotations of cholesteryl (R)-, (S)- and (racemic)-2-methylpentanoate esters was carried out by the conventional polarimetric method. Values of the molecular rotations of the esters are summarized in Table 1.

From the results in Table 1, the contribution of the chiral pentanoate moiety configurations to the molecular rotations of the diastereomers is noticeable. The effects of the induced laevorotation of the (R)-2-methylpentanoate and dextrorotation of the (S)-2-methylpentanoate are to increase and decrease, respectively, the molecular rotational values in the diastereomeric pair. The optical activity of the (racemic)-2-methylpentanoate, an equal weight mixture of the two diastereomers, exhibits an expected intermediate value.

The difference between $[\alpha_m] = -2.0°$ of the (R)-ester (see Table 1) with that reported in ref. 11, $[\alpha_m] = -1.71 \times 10^{4}°$, is attributed to the optical purity differences of the initial active acids. The specific rotation of (R)-2-methylpentanoic acid observed in this work was $[\alpha]_D = -17.7°$, while Gibson [11] reported $[\alpha]_D = -16.2°$ for this acid with 88% optical purity. Finding that our (R)-ester is 90.5% pure, it explains that the optical purity of the starting active acid should have been larger than 90.5%.

Determination of diastereomeric purity of the esters was carried out using NMR spectroscopy [12–14] by recording the PMR spectra of the compounds while

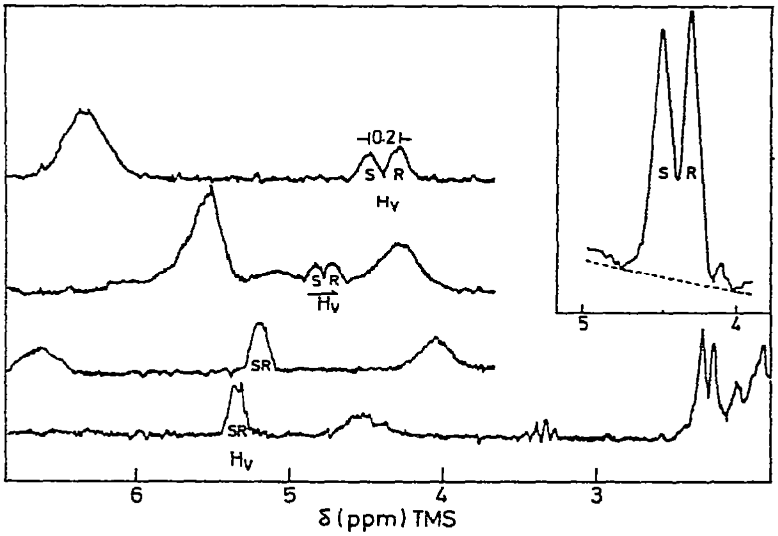

Fig. 2. Portion of the PMR spectrum of cholesteryl-(racemic)-2-methylpentanoate showing the chemical shifts and splitting of the C-6 vinyl proton due to successive addition of Eu(III)(DPM)$_3$. This proton signal, in contrast to other signals, is shifted upfield and is split due to the diastereomeric contributions (which are marked with S and R letters on the spectrum). Reading from the bottom to the top, the molar ratios of Eu(III)/ester are: 0.0, 0.15, 0.55, 1.0. The amplified form of the split signal is also inserted at the top right of the figure for the diastereomeric ratio of the (racemic)-ester.

increments of lanthanide shift reagent 2,2,6,6-tetramethylheptane-3,5-dionato Eu(III), [Eu(DPM)$_3$], were successively added to the solutions of the esters in CCl_4. The experiment showed the induced downfield shifts of all proton signals with the exception of C-6 vinyl proton resonance (see Fig. 1). The unexpected shift of C-6 vinyl proton resonance has not yet been reported elsewhere and is a matter for further study. The optimal splitting on this signal ($\Delta\Delta\delta = 0.2$ ppm) shown in Fig. 2, was obtained at a 1 : 1 molar ratio of Eu(DPM)$_3$/ester. Unambiguous identification of the resolved signal arising from (R)- and (S)-forms was directly accomplished by examination of a series of samples enriched with either diastereomer.

The diastereomeric ratios were directly evaluated from the resolved C-6 vinyl proton peak heights by proper peak intensity amplifications at slow spectral sweep time. With this procedure, the evaluated diastereomeric ratios were accurate within the experimental error of ±0.5%. Notice that, due to small separation of the diastereomeric C-6 vinyl proton signals, direct integration of the spectra did not provide the desired analytical results. Accordingly, it was found that the optical purities of the cholesteryl (S)-, and (R)-2-methylpentanoates studied were 83.5% and 90.5% respectively, and cholesteryl-(racemic)-2-methylpentanoate was enriched 47.5% with the (S)-form.

Phase diagram

The structural effects due to chirality of the ester moiety have been studied in the phase diagram of the two diastereomers. The binary phase diagram of cholesteryl (R)- and (S)-2-methylpentanoate, shown in Fig. 3, indicated that the system forms a

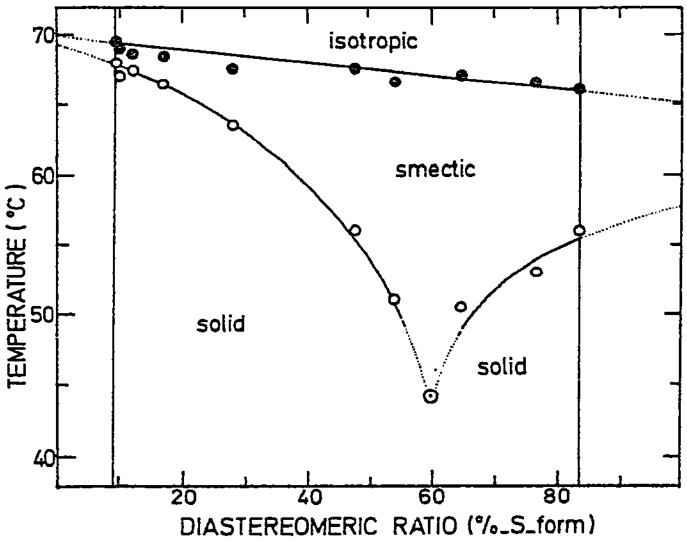

Fig. 3. Binary phase diagram of cholesteryl 2-methylpentanoate diastereomers on cooling. ● = the isotropic–smectic transitions; ○ = the smectic–solid transitions; ⊙ = the calculated value of the eutectic point from the Shroder–VanLaar equations. The diastereomeric ratios are the actual values determined by NMR method.

single eutectic compound. The diastereomeric mixtures do not form solid solution in the crystalline state, but are completely miscible in the smectic and isotropic phases. The smectic–solid transition consists of two branches both decreasing towards the eutectic point, which crystallizes out as a mechanical mixture of the diastereomeric components. The temperature, T_e, and composition, X_e, of the eutectic point of the system were evaluated by means of the Shröder–VanLaar equations in the manner reported by Hsu and Johnson [15]. The calculated values: $T_e = 44°C$ and $X_e = 60\%$ of (S)-2-methylpentanoate, for the predicted eutectic point, are also shown in Fig. 3. The formation of the eutectic mixture and the existence of the limited diastereomeric solid solubility indicate that the crystalline structure and lattice constants of (R)- and (S)-2-methylpentanoate are indeed different from each other. In fact, from Fig. 3, the transition temperatures related to the 47.5% diastereomeric ratio are that of the (racemic)-2-methylpentanoate. Also the extrapolation of the isotropic–smectic transition line and smectic–solid transition curves to the pure diastereomers indicate an insignificant variation in the mesomorphic behavior, while suggesting larger values of smectic–solid transition temperatures for the pure diastereomers.

CONCLUSION

Investigations on the thermodynamic properties of the diastereomeric pair of cholesteryl 2-methylpentanoate showed that chiral moiety restricts the mobility of the ester branch to an extent which suppresses the cholesteric phase in favor of the smectic mesophase. Although the steric effect of chirality is a factor responsible for the different physical properties of the two diastereomers in their crystalline state, this effect does not contribute significantly to their mesomorphic behavior. Conformational and configurational contributions of the chirality are evident in the molecular rotations, melting behavior, enthalpy and entropy of transition and the phase diagram of the diastereomeric pair. These contributions also lead to the determination of the diastereomeric purity of the chiral alkanoates with NMR method.

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