Thermochimica Acta, 5 (1973) 355–356

Note

Polymorphism in cholesterol

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(Received 18 August 1972)

In a recent communication Labowitz[1] reported that cholesterol undergoes a polymorphic phase transition at 37 °C, with heat of transition, 0.66 kcal/mole. Labowitz speculated on the possible significance this phase transition may have in the etiology of atherosclerosis.

Two polymorphic phase transitions have previously been reported for cholesterol[2,3]. In 1965 Spier and van Senden[2], using differential thermal analysis (DTA), observed an endothermal lattice change in the thermogram of cholesterol at 40 °C. This report was confirmed by Van Putte and co-workers through the use of NMR, dilatometry, and differential scanning calorimetry[3]. They obtained a value of 0.7 kcal/mole for the enthalpy of the 40 °C transition, and also reported a second phase transition, detectable only by dilatometry, occurring between 70 and 100 °C.

Recent studies in these laboratories on cholesterol and on binary mixtures of cholesterol and seven cholesteryl esters have confirmed the fact that cholesterol does undergo a phase transition near 37 °C. However, the transition could only be observed at this lower temperature in highly purified samples of chiolesterol if the samples were first reduced in particle size by grinding, or heated to fusion, allowed to resolidify at room temperature, and to remain at this temperature for a period of three days. Thermograms of rigorously purified cholesterol not subjected to these treatments displayed endotherms at 40 °C.

Quantitative estimates of the heat of transition of cholesterol obtained by the technique of DTA calorimetry were somewhat lower (550 ± 13 cal/mole at 40 ± 0.5 °C) than those previously reported, but these results were confirmed by an independent method. From heat of solution measurements, an estimate of 575 ± 58 cal/mole at 37 ± 3 °C, was obtained for the heat of transition. The similarity of the values obtained for the heat of transition of cholesterol in these studies, as well as those of Van Putte, to the reported value of 0.66 kcal/mole in the Labowitz study, clearly suggest that the phase transition detected by the latter worker is the same as that reported previously.

Labowitz has stated that the close proximity of the temperature of the polymorphic phase transition of cholesterol to normal human body temperature may have

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interesting biological implications. He speculated that the etiology of atherosclerosis could be attributed to a departure of a person's body temperature from 37°C, resulting in the presence of the "undesirable one of the two phases"[1]. The "undesirable phase" might be expected to have a different solubility in the blood serum, perhaps influencing the precipitation of cholesterol in plaques. While this is an interesting possibility, it should be pointed out most of the cholesterol found in the blood stream is not present as unesterified cholesterol, but in cholesteryl esters and in lipoproteins[5]. Few of these derivatives of cholesterol undergo phase transitions near body temperature[6].

Furthermore, although some unesterified cholesterol is found in atherosclerotic plaques, it is almost always found in close association with cholesteryl esters[7]. Results of the present study have shown that the 40°C phase transition of cholesterol did not occur when cholesterol and the cholesteryl esters studied were intimately mixed by the process of fusion, followed by cooling to room temperature. If the results of these studies can be extrapolated to the *in vivo* situation, it seems likely that the phase transition near body temperature will be inhibited from occurring in atherosclerotic plaques.

This is not to suggest that the polymorphic phase transition occurring in cholesterol at temperatures near body temperature is without physiological significance. Indeed, we are particularly intrigued with the fact[8] that a phase transition has been detected in the membranes of cell walls at 40°C. Unesterified cholesterol is known to be an important component of virtually all cell membranes[9]. Träuble[10] has speculated that phase transitions may be implicated in membrane transport, furnishing the energy required to form apertures in the membrane. He calculates that the amount of energy required to form such dislocations should be roughly 0.6 kcal/mole. It is interesting that the energy associated with the phase transition of cholesterol is of the same order of magnitude.

A more detailed account of the studies described here is to be published shortly.

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