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Short Communication

THERMAL TRANSFORMATION OF A CHIRAL, NON-RACEMIC EPOXIDE INTO A CONGLOMERATE
A case study

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Abstract

Formation of conglomerates is of general interest because they offer the possibility of enantiomeric separation by preferential crystallization.

A surprising result was obtained for the chiral epoxide 1a,2,7,7a-tetrahydro-3-methoxynaphth-(2,3b)-oxirene, for which we have shown that the racemate crystals of a non racemic mixture can be easily transformed into a conglomerate by gentle heating and cooling within a defined temperature range. This transformation is not possible with the pure racemic mixture. Thus the enantiomeric excess seems to be the driving force for the conglomerate formation.

Experiments have been carried out on analytical and preparative scale. Non racemic mixtures have been characterized by high pressure liquid chromatography on chiral stationary phase and crystal transformation has been monitored with differential scanning calorimetry (DSC) and infrared spectroscopy (IR).

Keywords: chiral epoxide, conglomerate, non racemic mixture, enantiomeric separation

Introduction

The enantiomers of the chiral epoxide 1a,2,7,7a-tetrahydro-3-methoxynaphth-(2,3b)-oxirene (Fig. 1) are important intermediates in the synthesis of enantiomerically pure compounds. The absence of a derivatizable functional group rules out all enantioseparation techniques except chromatography, prefer-

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ential crystallization or complex formation (e.g. inclusion). The latter however, has shown little preparative application [1].

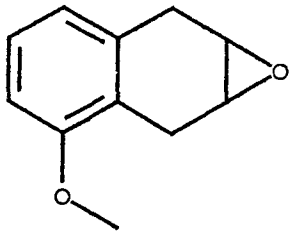

Fig. 1 Structure of 1a,2,7,7a-tetrahydro-3-methoxynaphth-(2,3b)-oxirene

In an earlier study we have demonstrated the successful enantioseparation of our epoxide using cellulose triacetate as the stationary phase in high performance liquid chromatography [2]. Although this method could be scaled up (1 g racemate is separable on 1 kg stationary phase per run) further scale up is limited because of increasing mobile phase consumption.

For a structurally related epoxide, existing as conglomerate, it was demonstrated [3] that preferential crystallization could be successfully used for enantioseparation on industrial scale. It was therefore envisioned to study within our crystallization program the possibility that the compound of interest exists also as a conglomerate. The results obtained from that investigation are herein reported.

Experimental

Differential scanning calorimetry measurements were made on a Perkin Elmer DSC-2. Temperatures were calibrated using zinc and indium phase transition, and enthalpy calibrated using melting of indium. Sample amounts and heating rates are given in the figures individually.

1a,2,7,7a-tetrahydro-3-methoxynaphth-(2,3b)-oxirene is an intermediate of SANDOZ PHARMA LTD and its preparation has been described elsewhere [4]. The enantiomers were obtained after chromatography on chiral stationary phase as indicated [2]. A racemic mixture (crystal A) was obtained after crystallization from methanol; those obtained from optically pure enantiomers (crystallized also from methanol) are referred to as crystal B.

Infrared spectra were measured in KBr. Enantiomeric excess of investigated mixtures was determined on a Daicel Chiralcel-OD column (4 mm I. D.×25 cm length) using hexane/isopropanol = 9/1 as mobile phase and a flow rate of 0.5 ml/min ($k_2' = 2.4$ *and* $\alpha = 1.63$).

Results and discussion

A non racemic sample* of crystal A with 13.4% e.e. (*m.p.* = 48.6°C) is heated (5 deg·min^{-1}) up to 60°C and afterwards cooled down to room temperature. This experiment first operated in our DSC-equipment produced crystal B (with *m.p.* = 44.4°C). The observed thermal transformation proved to be reproducible outside the DSC-apparature on a preparative scale. The DSC-curves of this experiment are given in Fig. 2. The infrared spectrum of crystal B (so

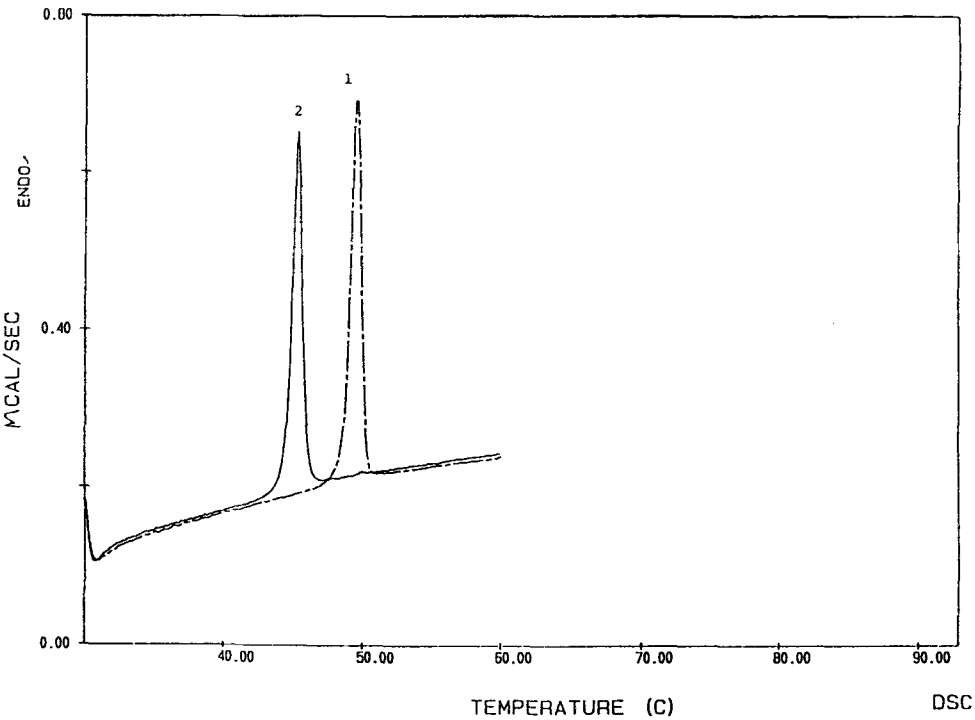

Fig. 2 Thermal transformation of the epoxide (0.27 mg) with 13.4% e.e. Curve 1 is obtained with a heating rate of 5 deg·min^{-1} up to 60°C, showing the melting peak of crystal A at 48.4°C. After cooling to 25°C the sample is again heated up with 5 deg·min^{-1} showing now the melting behaviour of the conglomerate crystal B at 44.4°C (see curve 2)

* A non racemic mixture of our epoxide was synthezised for the first time by epoxidation of the corresponding alkene with hydrogen peroxide (35%) in toluene, and chiral catalyst prepared from phosphortungstanate and (-)-N-dodecyl-N-dimethylephedrinium bromid analogous to literature procedures [7]. Under this conditions epoxidation yielded 66% with an enantiomeric excess of 5.0% e.e. After one crystallization from tert.-butylmethylether/n-hexane material with 13.4% e.e. was obtained.

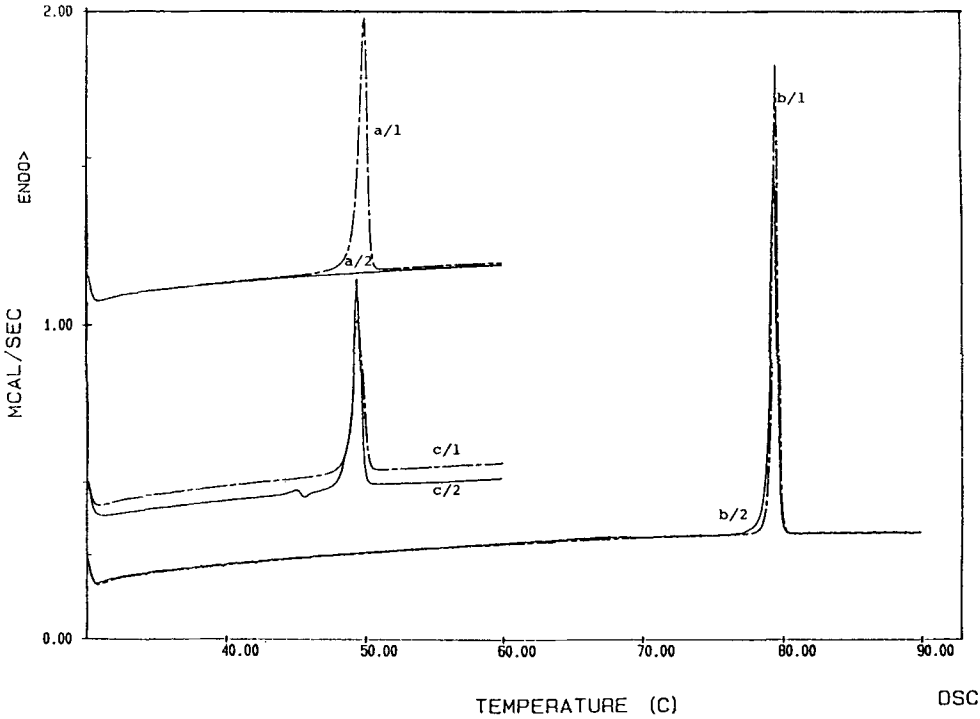

Fig. 3 a) Thermal behaviour of the racemic epoxide (0.32 mg) (thermal treatment as in Fig. 2). Crystal A in curve a/1 is replaced by amorphous material represented by curve a/2

b) Thermal behaviour of the (−) enantiomer (0.39 mg). The sample has been heated up (5 deg·min^{-1}) to 90°C (curve b/1). After cooling to 25°C the sample is heated up again with 5 deg·min^{-1} (curve b/2). In both curves crystal B are realized

c) Thermal behaviour of the epoxide (0.31 mg) with 13.4% e.e. The sample (curve c/1) is heated up as in Fig. 2. Afterwards the sample is cooled down in a refrigerator down to −25°C. Heating up for a second time with 5 deg·min^{-1} (curve 2/c) shows that only a small amount of crystal B is obtained

obtained) is identical to those of the pure enantiomers (Fig. 4) and differs significantly from that of crystal A. This thermal transformation into a conglomerate is similar to the literature known thermal behaviour of α-bromocamphor [5, 6].

Interestingly, the racemate could not be transformed by the described procedure. After heating and cooling the sample, amorphous material was isolated (Fig. 3). The same result was obtained when a non racemic sample was heated above the melting temperature of the individual enantiomers (e.g. 90°C). This is however not observed for the pure enantiomers (as demonstrated in curve 2 of Fig. 3). The upper temperature limit of 60°C as well as gentle cooling down

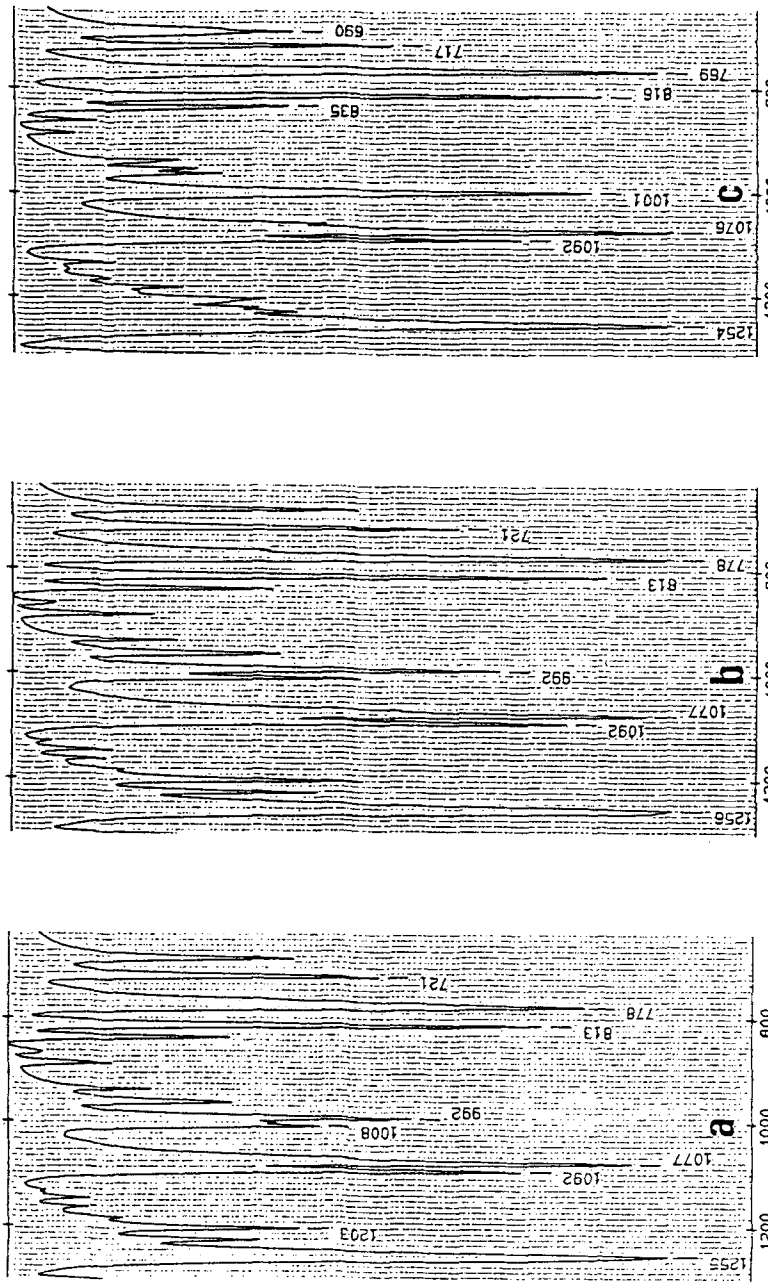

Fig. 4 Infrared spectra (measured in KBr) or a) 1 mg epoxide with 13.4% e.e. (crystal B), b) 1 mg (–) enantiomer and c) 1 mg racemate (crystal A)

to room temperature is required for the thermal transformation of A to B. Curve 3 of Fig. 3 shows a non-racemic sample with 13.4% e.e. (crystal A) which has been heated up to 60°C followed by rapid cooling in a refrigerator down to −20°C. As can be seen from Fig. 3 only a small amount of crystal B is obtained.

It should be mentioned that crystal B has not been observed on the racemic mixture, using our routine crystallization program where the influence of solvent during crystallization is investigated. Crystallization from methanol, ethanol, ethanol/water =50/50, toluene, methylenechloride, acetonitrile and different ethers always resulted in the formation of crystal A.

Having a method in hand which allows the transformation of crystal A into B, it was our wish to demonstrate the possibility of enantioseparation by preferential crystallization. As a result from our investigations it turned out that only the amount of artificially added seed enantiomer could be recovered. Thus the enantiomeric excess seems to be the driving force for the conglomerate formation. So far all attempts to separate the conglomerate by preferential crystallization failed.

Conclusion

We have shown that slight excess of one enantiomer to a racemate occurring in crystal A can easily be transformed into conglomerate crystal B. This can be effected just by gentle heating and cooling of the mixture. Although we failed so far in our endeavour to separate the enantiomers by preferential crystallization, the approach is in principle feasible. Coming from the opposite direction, it is of interest whether slight racemization could lead to a complete change of the crystal modification. If this assumption proves to be valid, the importance of crystallization programs (e.g. in drug development) is emphasized again.

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