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CHROMATOGRAPHIC RESOLUTION OF RACEMATES ON CHIRAL STATIONARY PHASES

I. INFLUENCE OF THE SUPRAMOLECULAR STRUCTURE OF CELLULOSE TRIACETATE

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SUMMARY

The influence of the supramolecular structure of cellulose triacetate (CTA) on the chromatographic resolution of several racemates has been investigated in detail. The best optical resolution power was displayed by the crystallographic form CTA I, obtained by the heterogeneous acetylation of microcrystalline cellulose. Enhancing the crystallinity of CTA I (by annealing) was found to have a negative influence on its separation power. The other crystallographic modification of cellulose triacetate, CTA II, in general yielded poor optical resolutions. Models for different possible interaction mechanisms between the racemates and the optically active polymer are discussed on the basis of experimental results. The inclusion of low-molecular-weight chiral molecules into a specific spatial arrangement of the glucose units of the polysaccharide chains is proposed as a pre-requisite for the chiral discrimination process.

INTRODUCTION

Of relevance to the growing interest in biological, often highly stereoselective, processes, the chromatographic resolution of racemic compounds on optically active stationary phases has developed in parallel to asymmetric synthesis and has become a powerful analytical and preparative tool (for reviews also to the previous literature see refs. 1–4). Different types of sorbents have been used for this purpose, but polymeric stationary phases are preferred because of their insolubility in most commonly used eluent mixtures. The polymeric sorbents can be divided into three main classes: polymers bearing optically active side chains, *i.e.*, substituents with chiral centres, *e.g.*, derivatized silica gels, poly(meth)acrylamides, polystyrenes[5–13]; polymers having chiral centres in the main chain, *e.g.*, polyamides, polypeptides, polysacchar-

ides[14–21]; polymers without chiral centres, but with an asymmetric secondary structure which induces optical activity, *e.g.*, a helical structure as in poly(triphenylmethylmethacrylate)[22].

Polymers of the first group are mostly amorphous, *i.e.*, they have no well defined secondary structure. Their resolution power resides in the strong and highly specific interactions between their chiral side groups and the enantiomers. Very often, an optimum retention (one premise for chromatographic separation) is achieved only by derivatizing the racemates with groups assuring a strong interaction, *e.g.*, the formation of charge-transfer complexes[5–7]. Polymers of the third class must necessarily have a highly ordered secondary structure since this is the only reason for their optical activity and thereby for their capability of chiral recognition. The second category of polymers represents an intermediate state between the two extremes above. Since their secondary structure can range from mostly amorphous to highly crystalline, they are perfectly suited to an investigation of the influence of secondary structure on the optical resolution power. Cellulose and its derivatives are the most frequently used chiral sorbents of this kind.

The outstanding optical resolution power of cellulose triacetate (CTA) has been recognized[17–19]. To our knowledge, Hesse and Hagel[23,24] were the first to point out the importance of a definited secondary structure of CTA for the separation power. However, they differentiated only between amorphous and partially ordered (crystalline) structures. They concluded that the structurally ordered polymer is far more effective than its amorphous form, and that the primary interaction between the polymer matrix and low-molecular-weight enantiomers is the formation of inclusion complexes[17,24], first described for cellulose and cellulose nitrate by Staudinger and Döhle[25].

The results of Hesse and Hagel are basically confirmed by our investigations. However, we will not only discern between amorphous and crystalline CTA, but we will also consider the different structural modifications of the polymer and their influence on the chromatographic resolution power. Recently, Ohara *et al.*[26] reported on the influence of the secondary structure of amylose on the selective adsorption of optical antipodes. Their findings resemble in several respects the phenomena discussed here for cellulose triacetate.

THE DIFFERENT CRYSTALLOGRAPHIC MODIFICATIONS OF CELLULOSE AND CTA

Cellulose

Cellulose is a highly crystalline polymer which occurs with various crystal structures, depending sometimes on the source, but mostly on the treatment during and after its isolation and purification. The two major crystallographic forms are "native" cellulose (form I) and the regenerated or mercerized product (form II)[27]. The two forms show distinctive X-ray diffraction patterns, but up to now their detailed interpretation has been rather speculative. A cellulose chain has a polar axis. A rotation of 180° around an axis perpendicular to the chain direction does not lead to congruence. Thus the chains point in a definite direction. The present view is that in native cellulose (form I) all chains in the crystal point in the same direction, *i.e.*, they are parallel, whereas in the regenerated form II the chains in adjacent layers are antiparallel[27].

CTA

CTA is obtained by acetylation of cellulose. The relationships between cellulose and its triacetate were investigated in detail by Sprague *et al.*[28]. They confirmed that the crystal structure depends on the crystallographic form of the original cellulose and on the experimental conditions used for the acetylation process. They found that cellulose I, acetylated heterogeneously (*i.e.*, without dissolution), yields a crystallographic form of CTA, called CTA I in accordance with the source. If dissolution of the forming triacetate occurred during the acetylation, the final product, after reprecipitation, was found to have a different crystal structure, defined as CTA II. Furthermore, they claimed that the acetylation of regenerated cellulose (form II) always leads to CTA II, independently of the acetylation conditions, either homogeneous or heterogeneous.

EXPERIMENTAL

Sorbents

CTA I was obtained by the heterogeneous acetylation of microcrystalline cellulose Avicel (Merck No. 2331) or native cellulose, according to the Schering process[29], as described also by Hesse and Hagel[23]: cellulose was stirred in a mixture of acetic acid, acetic anhydride and toluene in presence of a catalytic amount of perchloric acid at 35°C. CTA II was purchased from Fluka (No. 22200). The X-ray diagram of this material showed well resolved diffractions corresponding to the crystalline form II, in accordance with literature data. Samples of CTA II from EGA (No. 18, 100-5) and Eastman (No. 2314) had a far lower degree of crystallinity. For all samples of CTA I and CTA II, the crystallinity could be enhanced by annealing the powders for 30 min at 240°C under vacuum. Table I summarizes the sorbents tested in this investigation.

Racemates

Troeger's base (1) (m.p. 133–134°C), 2-phenylcyclohexanone (2) (98%, m.p. 53–56°C), γ-phenyl-γ-butyrolactone (3) (m.p. 36–37°C), 4-phenyl-1,3-dioxane (4) (99%), *trans*-stilbene oxide (5) (m.p. 65–67°C) and 2,3-epoxypropyl phenyl ether (10) were commercial products from Aldrich.

1-(4-Aminophenyl)-1,2-cyclopropanedicarboximide (6) (m.p. 198–201°C) and the corresponding N-propyl derivative (7), 5-benzoyl-2,3-dihydro-6-hydroxy-1H-in-

TABLE I

CELLULOSE TRIACETATE SAMPLES USED AS CHIRAL SORBENTS

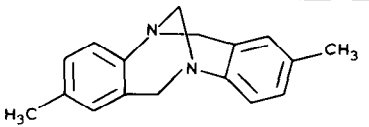
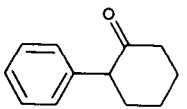
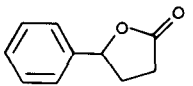
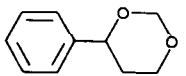
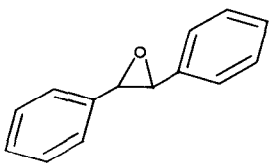
CTA I*	CTA I-1	Cellulose triacetate obtained by heterogeneous acetylation of microcrystalline cellulose for 1 h
	CTA I-10	10 h
	CTA I-72	72 h
CTA I-AN		CTA I-72 annealed for 30 min at 240°C
CTA II		Commercial cellulose triacetate (Fluka No. 22200)

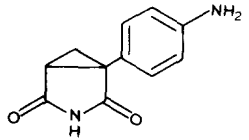
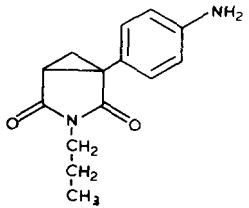
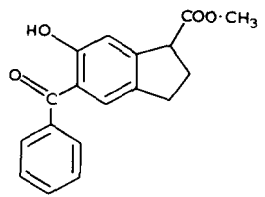
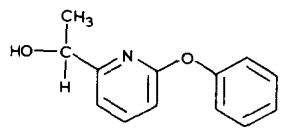
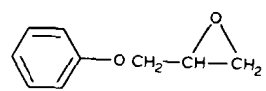
* In the text, a distinction between the three different CTA I samples is made only when necessary.

TABLE II

CHROMATOGRAPHIC RESOLUTION OF RACEMATES ON DIFFERENT CELLULOSE TRIACETATES

Eluent: ethanol–water (95:5).

Compound	*Structure*	*CTA**	*Capacity factors*		*Separation factor,* α	*Resolution factor,* R_s
			k'_1	k'_2		
1		I	1.97 (−)**	4.58	2.32	2.00
		I-AN	0.47 (+)	0.47		
		II	0.58 (+)	0.58		
2		I	1.91 (+)	3.30	1.73	2.12
		I-AN	0.94 (+)	0.94		
		II	0.67 (+)	0.67		
3		I	2.24 (+)	8.42	3.76	3.30
		I-AN	1.56 (+)	2.26	1.45	0.65
		II	1.07 (+)	1.07		
4		I	3.06 (+)	12.64	4.13	2.70
		I-AN	0.97 (+)	1.88	1.94	1.40
		II	0.62 (+)	0.62		
5		I	3.45 (−)	3.45		
		I-AN	0.91 (−)	1.21	1.32	0.60
		II	0.67 (−)	0.67		

6		I I-AN II	5.97 (−) 4.24 (−) 2.48 (−)	14.27 5.41 2.81	2.39 1.28 1.13	2.70
7		I I-AN II	5.91 (+) 3.59 (−) 2.05 (−)	7.48 3.59 2.36	1.26 1.15	0.70 0.40
8		I I-AN II	2.18 (−) 1.44 (−) 0.93 (−)	3.24 1.44 0.93	1.49	1.20
9		I I-AN II	1.30 (−) 0.41 (+) 0.29 (+)	1.70 0.41 0.29	1.30	1.10
10		I I-AN II	3.57 (+) 1.64 (+) 1.02	6.03 1.64 1.02	1.69	1.80

* In this set of experiments, CTA I was always CTA I-72.

** Sign of optical rotation at 365 nm of the first eluted enantiomer.

dene-1-carboxylic acid methyl ester (8) and 1-(6-phenoxy-2-pyridyl)ethanol (9) were prepared by Ciba-Geigy (Basle, Switzerland).

Chromatographic conditions

Glass columns (60 or 30 × 1.25 cm I.D.) were used in all the experiments described below. The sorbent samples had a particle size of 32–56 μm, adjusted by brief ball milling (if necessary) and sifting. Their specific surface area was 2–8 m^2/g. The pressure at the top of the columns was 0.4–4 bar for a flow-rate of *ca.* 0.5 ml/min. The racemates were injected as solutions, typically 6 g/l, in the eluent (ethanol–water, 95:5). The concentration and the optical rotation of the eluate were measured by a UV spectrophotometer (Shimadzu UV-120-02) in series with a polarimeter (Perkin-Elmer 241MC). The data were recorded and processed by a Hewlett-Packard HP-85B calculator on-line with the UV detector and the polarimeter through a Hewlett-Packard 3421A data acquisition/control unit.

X-Ray diffraction

Philips powder diffraction equipment was used with a vertical goniometer PW 1050, nickel-filtered Cu-K_α radiation, 1° divergence and scatter slits, a 0.2-mm receiving slit, and a scan speed of 1° (θ)/min. The goniometer was adjusted to fit best the alpha-quartz lines.

Differential scanning calorimetry (DSC)

DSC measurements were performed with a Mettler TA-3000 system, using samples, typically 4–5 mg, of cellulose triacetate in the standard 40-μl aluminium crucible. Prior to the actual measurements, the samples were briefly heated to 100°C in order to expel remnants of volatile products and water. The measurements were made in the temperature range 30–330°C at a heating rate of 10°C/min.

RESULTS

Influence of the duration of acetylation on the resolution power of CTA I

All previously reported chromatographic resolutions of racemates on CTA have been carried out with cellulose acetylated heterogeneously for *ca.* 72 h. In an attempt to reduce this rather long time of acetylation, we tested three samples of CTA, acetylated heterogeneously for 1, 10 and 72 h. For the chromatographic separation of the enantiomers of Troeger's base (1 in Table II), the resolution factors, R_s, were 0.9, 1.4 and 2.0 respectively. The longest acetylation time clearly resulted in the adsorbent with the best chromatographic properties. The separation factors, α, were practically identical ($\sim$2.0) in all three cases.

It has been noted before that partially acetylated cellulose is only a moderately useful chiral sorbent[23]. In order to determine whether an incomplete acetylation was responsible for the different resolution power of the three samples above, the course of the heterogeneous acetylation was followed. From elemental analysis, determination of the acetyl groups, proton NMR spectroscopy and solubility in chloroform (a good solvent for completely acetylated cellulose), it can be concluded that the acetylation is complete within 1 h (CTA I-1). The X-ray diffractogram of this cellulose triacetate is identical to that of CTA material prepared by acetylation for 72 h (CTA

I-72, shown in Fig. 2a). CTA I-1 and CTA I-72 were found to differ only in molecular weight, in the extent of swelling (in ethanol) and in the shape of the particles, *cf.*, Fig. 1.

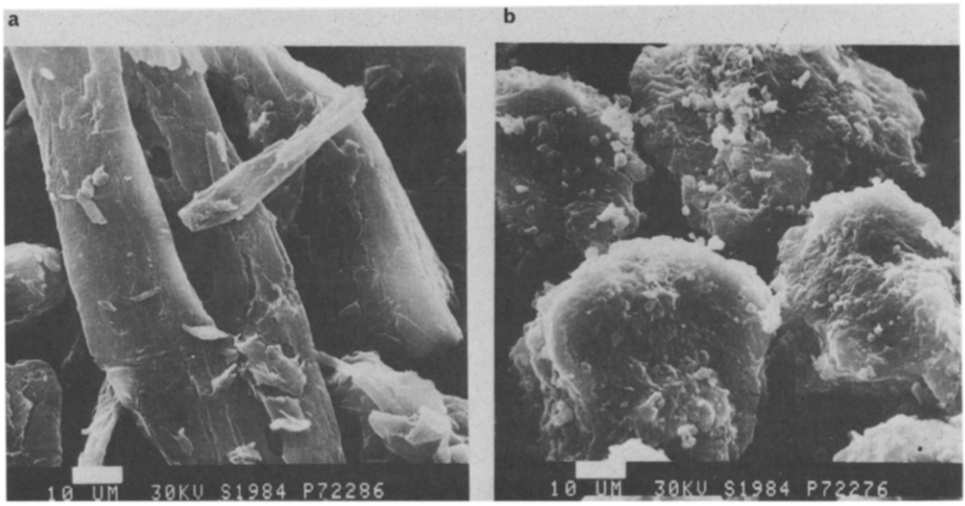


Fig. 1. Scanning electron micrographs of CTA prepared by heterogeneous acetylation for 1 h (CTA I-1) (a) and for 72 h (CTA I-72) (b).

It is seen that the morphology of the CTA particles changes drastically during prolonged acetylation. The initially fibrous particles are slowly converted into more or less spherical beads, *cf.*, Fig. 1. A spherical particle shape leads to a better column packing. Furthermore, the particle surface which was smooth at the beginning becomes flaky with prolonged acetylation. The specific surface area of the material was thus found to increase by about 100% from 1 h to 72 h of acetylation. The better packing and the larger specific surface area are most probably the main reasons for the higher resolution power of celluloses acetylated for a longer time. This is supported by the almost identical separation factors, α, for CTA samples which had been acetylated for different long periods*.

Influence of the crystal structure of CTA on the resolution power

Up to now, most successful racemate separations by liquid chromatography on CTA were obtained with heterogeneously acetylated cellulose. In 1973, Hesse and Hagel[23] observed that this material, once dissolved and reprecipitated, largely lost its separation ability and that the elution order of the enantiomers of compound 1 (Table II) was inverted. They concluded that the crystallinity of the polymer is a pre-requisite for the chromatographic properties and that the resolution power of the presumably amorphous CTA is strongly diminished.

* In fact, since α is a purely thermodynamic factor, reflecting only the interaction energies with the polymer, it should be identical for sorbents with the same molecular and supramolecular structure. In contrast to R_s, α is independent of intrinsic chromatographic properties like particle size and shape.

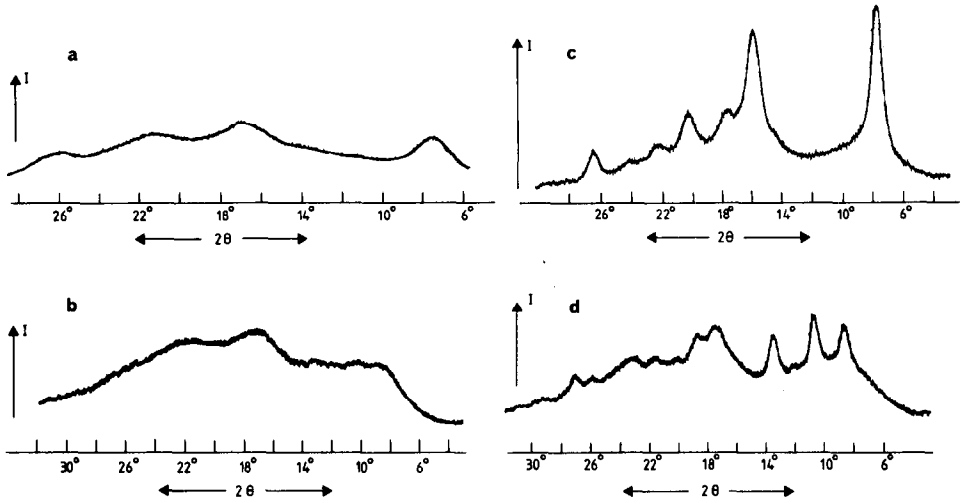


Fig. 2. X-Ray diffractograms of heterogeneously acetylated CTA (CTA I) (a), dissolved and reprecipitated CTA (b), annealed CTA I (CTA I-AN) (c) and commercial CTA II (d).

In order to elucidate the relationship between the supramolecular structure and the chromatographic properties, four different CTA sorbents were studied in this work. Fig. 2 shows the X-ray diffractograms of a heterogeneously acetylated cellulose (CTA I) (a), a CTA reprecipitated from solution, under conditions identical to those described earlier[23] (b), an annealed sample of CTA I (CTA I-AN) (c) and a commercial CTA II (d). The diffraction patterns c and d are in perfect agreement with literature data[30,31] and are clearly identified as due to the two crystalline forms of CTA, called forms I and II. The diffractogram a is also similar to the poorly resolved patterns generally obtained for heterogeneously acetylated cellulose before annealing[28]. The X-ray diagram b indicates that the reprecipitated CTA[23] was indeed mainly amorphous. After being heated above 180°C (annealing), this material exhibits the clearly resolved X-ray diffraction pattern of the crystalline form II, in accordance with the literature. (It must be noted that all crystallographic data presented in the literature for both forms I and II of CTA were obtained with annealed material.)

Fig. 3 shows DSC thermograms for the four different sorbents. The labels a–d correspond to those in Fig. 2. The heterogeneously acetylated celluloses CTA I (a) and CTA I-AN (c) display very similar DSC behaviours. The large melting peak at 291°C is preceded by a smaller endothermic peak at *ca.* 270°C. From X-ray diffractograms recorded between 270 and 290°C, it was seen that the crystalline form I was rapidly converted into form II in this temperature range. Although a reliable assignment of the peak at 270°C to a definite transition is difficult, its presence identifies form I, since no trace of a peak or shoulder around 270°C could be detected in the DSC of reprecipitated CTA (b) and commercial CTA II (d). The exothermic peak between 190 and 200°C in the DSC of reprecipitated CTA will be reconsidered in the Discussion below.

The results of the chromatographic resolution of several racemates on the three sorbents CTA I, CTA I-AN and CTA II are summarized in Table II. Fig. 4 shows

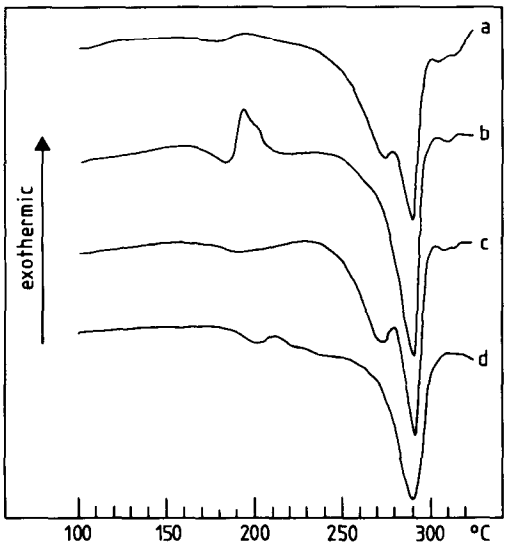


Fig. 3. DSC recordings. Details as in Fig. 2.

the chromatograms obtained on CTA I for the racemates 3, 4 and 6 of Table II. The capacity factors of all substances in Table II are larger on CTA I than on CTA II. This indicates that the interactions of the racemates with CTA I are much stronger than with CTA II. Furthermore, except for compound 5 (which is resolved on CTA I-AN), CTA I completely resolves all other racemates and shows a much higher chiral discrimination than CTA II.

The evidence that the actual crystal structure strongly influences the chromatographic properties of the sorbent had led us to enhance the crystallinity of the heterogeneously acetylated cellulose by annealing the powder at 240°C for 30 min. However, this sorbent (CTA I-AN in Tables I and II) displays chromatographic properties similar to those of CTA II, *i.e.*, the retention times (capacity factors) decrease, the separation power becomes weaker in most cases and the elution order is inverted for the enantiomers of compounds 1, 7 and 9.

The results of separations on reprecipitated CTA are not shown explicitly, but several previously reported experiments[23] have been repeated and yielded similar poor results. Recently, a new sorbent was introduced for the resolution of enantiomers[20,32]. It is prepared by coating silica gel with CTA from a solution in dichloromethane–ethanol (9:1). This sorbent yields moderate α values and behaves like reprecipitated CTA or CTA II, as regards the elution order of certain racemates.

DISCUSSION

The observations described call for a detailed analysis of possible mechanisms of interaction between the low-molecular-weight racemates and the chiral polymeric support. The premise for the chromatographic separation of enantiomers is retention and chiral discrimination. Retention times for numerous aromatic compounds on

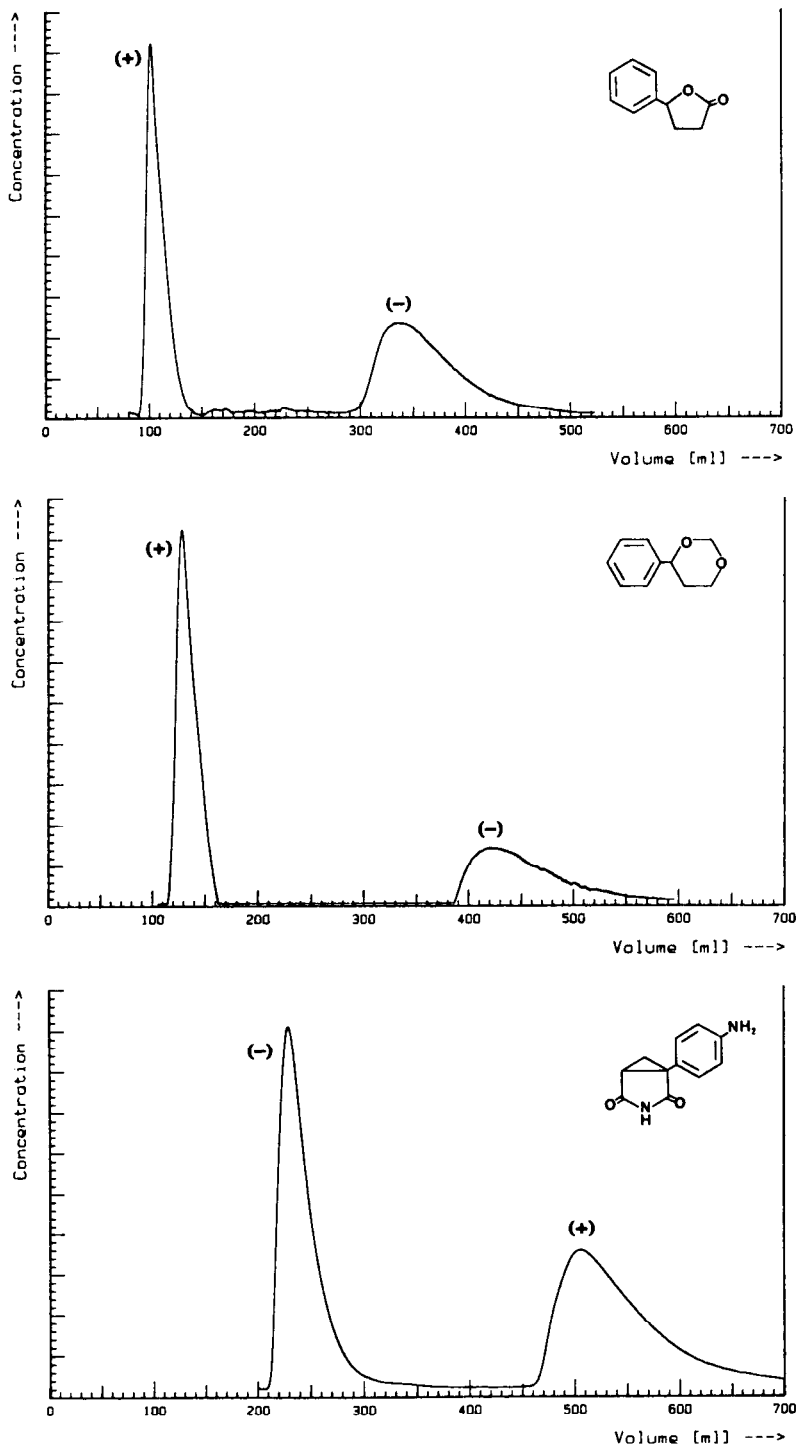


Fig. 4. Chromatographic resolution of the enantiomers of compounds 3, 4 and 6.

heterogeneously acetylated cellulose and on reprecipitated CTA have been reported[18,24]. The much higher retention times observed on CTA obtained by heterogeneous acetylation have been ascribed to the inclusion of the aromatic molecules in the polymer matrix.

The high capacity factors on CTA I in Table II support the idea that the retention of all those compounds is based on inclusion-complex formation with CTA I. Furthermore, since CTA I also yields the best optical resolution, it can be assumed that inclusion plays a dominant rôle in the chiral discrimination mechanism. Most probably, the more or less rigid molecules can enter (totally or partially) the space between the polysaccharide chains in crystalline cellulose and some of its derivatives[17,24,25]. The concerted interactions of polymer chains of adjacent layers in the crystal with a small molecule could thus lead to very high binding energies. Obviously, the space between polyglucoside chains constitutes a highly ordered, chiral environment, each glucose unit having five chiral carbon atoms. Since the interaction energies are very sensitive to the spatial configuration of all atoms in the chiral cavities, even moderate alterations of the crystal structure of the sorbent may strongly influence the chiral recognition.

CTA I and CTA II have different crystal structures, *i.e.*, different three-dimensional arrangements of the glucose units, and therefore they may act as entirely different sorbents. Hence, from the results in Table II as well as from literature data[17,23,24], it can be concluded that CTA I has the more favourable crystal structure for the chromatographic resolution of racemates. The behaviour of CTA I-AN however cannot be explained on this basis. This derivative is formed from CTA I upon annealing. The concept of annealing is that the crystallinity is enhanced while the actual crystal structure is conserved. However, CTA I-AN yields the same elution order and a similar resolution power to CTA II.

Presumably, the interaction of small molecules with CTA I-AN and CTA II is not based on inclusion but on mere adsorption with weaker interaction energies, and hence with lower retention times, as is observed on dissolved and reprecipitated CTA[24]. The adsorption alone lacks the concerted interaction with many surrounding, spacially well ordered glucose units and therefore should lead to a less pronounced chiral discrimination than the inclusion-complex formation. If no inclusion occurs, the supramolecular arrangement of the polymer chains looses its relevance since the chiral recognition only takes place at random on the unordered polymer chains. In this respect, CTA I-AN, CTA II and reprecipitated CTA may behave similarly, *i.e.*, their sometimes satisfactory resolution power resides in fortuitously good chiral discrimination, *e.g.*, for compounds 3–6 in Table II. The remaining question is why can inclusion take place on CTA I but not on the other CTA sorbents.

From the poorly resolved X-ray diffractogram of CTA I (Fig. 2a) it can be deduced that this material does not have a supramolecular structure with a pronounced long range order. However, DSC (Fig. 3a) reveals no clear recrystallization peak (in contrast to that for reprecipitated CTA. Fig. 3c), which may be taken as an indication that the material does not comprise large amorphous, *i.e.*, totally disordered, domains. On the other hand, reprecipitated CTA simultaneously displays a very poor X-ray diffraction pattern and shows a distinct recrystallization peak between 180 and 200°C in DSC (Fig. 3c). The analysis of the X-ray diffraction and DSC results indicates that this polymer has really lost a large portion of its short

range order, *i.e.*, it has indeed been rendered partially amorphous by dissolution and reprecipitation.

The obvious inferior optical resolution power of reprecipitated CTA, as compared to CTA I, may be due to its (partial) deficiency of short range order. However, it must be pointed out that, once dissolved and reprecipitated, CTA assumes the crystallographic form CTA II upon recrystallization[28], *i.e.*, even if some short range order is regained in the reprecipitated material the resulting crystal structure does not have the same ability for inclusion as does CTA I. In fact, enhancing the crystallinity of reprecipitated CTA (by annealing) somewhat improves the chromatographic properties[32], but the retention times and the chiral discrimination power remain in general much lower than on CTA I.

The annealing of CTA I (yielding CTA I-AN) introduces long range order as seen by the well resolved X-ray diffraction pattern (Fig. 2b). By assuming that the actual crystal structure (the local order) is identical in CTA I and CTA I-AN, it follows that a strong enhancement of long range order (perfection of crystallinity) is unfavourable for inclusion. Probably the inclusion into ordered regions is possible only if the environment is flexible enough to accommodate small molecules. This flexibility may be guaranteed at the transition areas between locally well ordered domains and less ordered regions in the polymer matrix. Augmenting the long range order would then decrease the overall area at which inclusion could take place. Note that this explanation of the different chromatographic behaviours of CTA I and CTA I-AN is based on the assumption that the actual crystal structure, *i.e.*, the short range order, is identical in both materials. If the crystal is (even slightly) modified upon annealing, CTA I and CTA I-AN are to be differentiated in the same way as CTA I and CTA II, *i.e.*, they can be considered as entirely different sorbents.

CONCLUSION

Heterogeneously acetylated cellulose (CTA I) is the only form of cellulose triacetate which is able to resolve a broad variety of racemic compounds. Its excellent chromatographic properties as a chiral sorbent are based on a supramolecular structure which allows the formation of inclusion complexes with various small molecules, thereby ensuring a strong retention and a high chiral discrimination. The enhancement of the crystallinity of this material by annealing is unfavourable for the inclusion, as concluded from the much lower capacity factors and the rather weak chiral discrimination observed on CTA I-AN. The reduced ability for inclusion might be ascribed to the decreased mobility of the glucose units in the polymeric chains, which are no longer able to adapt to the intruding small molecules. In this respect, it is worthwhile mentioning the similarity with the inclusion-complex formation of cyclodextrins. Cyclodextrins are known to form very strong inclusion complexes with compounds similar to those resolved chromatographically on CTA I[3,9,33–36]. The cyclodextrin rings in such complexes are often distorted in order to form a perfect mould for the included compound[32–34]. It is tempting to conclude that: (a) CTA I has a crystal structure in which the glucose units are locally arranged in such a way that cavities are formed which closely resemble the interior of cyclodextrins; (b) the absence of long range order guarantees the flexibility necessary to accommodate included molecules; (c) the absence of short range order, as in amorphous CTA, or

a different crystal structure, as in CTA II are disadvantageous for the inclusion and thereby for the chromatographic resolution of racemates.

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