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# Chiral crown ether-anchored polysiloxanes as capillary gas chromatography stationary phases[1]

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**Abstract**

Two chiral stationary phases, named Chirasil-man-18C6-25 and Chirasil-aza-15C5-25, were prepared by hydrosilylating two allyl-crown ethers onto polyhydromethylsiloxane containing 25% Si–H units, respectively. The chiral allyl-crown ethers were synthesized using D-mannitol and (+)-2-amino-1-butanol as chiral sources. Fused-silica capillary gas chromatography showed that the two novel phases had similar characteristics as previously reported crown ether bounded polysiloxanes. It was found that the Chirasil-man-18C6-25 phase had enantioselectivity to racemates bearing both an aromatic moiety and a primary amino or hydroxyl group in their structure. This phase also exhibited good thermal stability.

*Keywords:* ; Chiral stationary phases, GC; Polysiloxanes; Crown ether-anchored polysiloxanes; Enantiomer separation; Crown ethers; Phenolic compounds; Amino acids; Anilines

## 1. Introduction

Gas chromatography (GC) has become an essential tool for the separation of enantiomers during the past decades. Basically, three types of chiral phases have been introduced by now. The first type were the amide compounds, whose enantiomeric separation was based on hydrogen bonding force [1–5]. The second type, introduced by Schurig's group, were the metal complexes which were based on the enantiospecific coordination of enantiomers with chiral transition metal complexes [6,7]. These phases extended enantioselective GC to compounds lacking a functional group for hydrogen bonding. The successful exploitation of modified cyclodextrin derivatives for chromatographic enantioselectivity, which is based on chiral recognition via inclusion, presented the third type of chiral phase [8–10]. Some other materials, such as amylose and cellulose carbamates, were also used as stationary phases by authors [11]. Furthermore, polysiloxane-bound chiral selectors have already emerged as Chirasil–Val [12], Chirasil–Metal [13] and Chirasil–Dex [14]. These strategies in GC enantiomeric separation enabled the enantioselectivities of chiral selectors to be combined with high thermal stability and excellent coating properties of organic polysiloxanes.

Chiral macrocyclic molecular receptors have attracted considerable interest in the past few years as a potential means for the resolution of enantiomeric species [15,16]. The interaction between a chiral host molecule and an enantiomeric guest species leads to

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[1] Dedicated to Prof. Cai-Ying Wu and Prof. Yuan-Yin Chen on the occasions of their 60th birthday.

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inclusion complexes whose thermodynamic properties are different. Enantiomeric separation employing chiral crown ethers (CCEs) in liquid chromatography was pioneered by Cram's group [17–19]. Recently, many chiral crown ethers have been used as stationary phases in LC systems, which are immobilized onto solid support by covalent binding [20,21], physical adsorption [22–25] or substitution in a polymer matrix [18]. These phases exhibited excellent enantioselectivity for amines [18,19], amino acids [22,25] and dipeptides [23]. Recently, Joly et al. developed a new chiral crown ether for the separation of aromatic amino acids [26], Zukowski synthesized a crown ether for the separation of α-phenylglycine [27]. The great success of using chiral crown ethers for enantioselectivity in LC raised the question whether the chiral crown ether materials could be used in gas chromatography as well.

In gas chromatography, macrocyclic receptors have also been utilized as stationary phases. Bayona et al. first reported the preparation of crown ether bonded polysiloxane phase by the hydrosilylation technique [28]. In our previous work, we prepared a series of crown ether-anchored polysiloxane phases, and demonstrated that these phases could provide unique selectivity for polar compounds, such as alcohols, amines and position isomers [29–31]. In this contribution, we report on the preparation of two chiral crown ether-anchored polysiloxanes and their capillary GC performances.

## 2. Experimental

### 2.1. Apparatus and reagents

$^1$H NMR spectra were obtained on a EM-360L spectrometer and chemical shifts were expressed in parts per millions relative to tetramethylsilane as the internal standard. FTIR spectra were obtained on a Nicolet-IR spectrometer. Optical rotations were measured on a WZZ-2 automatic polarimeter.

Gas chromatographic analysis was performed with a SC-7 gas chromatograph (Sichuan Analytical Equipment Factory, China) equipped with a split injector and a flame ionization detector. The carrier gas was nitrogen and the split ratio was 1:100. Isothermal GC was preferred for the determination of the $\alpha$ value (separation factor) of enantiomeric separation.

Polyhydromethylsiloxane (25% Si–H units) was obtained from Jiangxi Xinghuo Chemical Plant (China). D-Mannitol and (+)-2-amino-1-butanol were purchased from Fluka (Switzerland). α-Phenylpropanol, α-phenylpropylamine, α-phenylbutanol, 2-bromo-1-octanol, 3-methyl-1-heptylamine, 2-methyl-1-octanol and amino acid racemates were commercial samples. Amino acid isopropyl esters were prepared from amino acids and isopropanol according to reference [32]. Trifluoroacetyl derivatives were carried out as described in reference [33].

### 2.2. Preparation of chiral crown ether-anchored polysiloxanes (Fig. 1)

#### 2.2.1. Synthesis of 1,2:5,6-di-O-isopropylidene-3,4-O-[1,2-(4-allylbenzenediyl)bis(oxyethoxyethyl)]-D-mannitol

In an atmosphere of nitrogen, 0.90 g (6 mmol) of 4-allylcatechol (2) (prepared according to literature [34]) was placed into a 500-ml, three-necked round-bottomed flask equipped with a nitrogen inlet, dropping funnel and reflux condenser and was dissolved in 100 ml of anhydrous *n*-butanol. To this solution was added 2.240 g (0.04 mol) of powdered potassium hydroxide and stirring was continued for 1 h at room temperature. To the vigorously stirred solution, was added 2.850 g (6 mmol) of 1,2:5,6-di-O-isopropylidene-3,4-bis-O-[(2-chloroethoxy)ethyl]-D-mannitol (1) (prepared according to literature reference [26] from D-mannitol) in 100 ml of THF dropwise. Stirring was continued for 16 h at room temperature. The reaction mixture was separated from potassium chloride and unreacted potassium hydroxide by filtration, and subsequently concentrated. The residue was diluted with 100 ml of dichloromethane, washed with water, dried by anhydrous magnesium sulfate, filtered and concentrated to a light yellowish oil, which was further purified by silica gel column on elution with diethyl ether to give the pure chiral crown ether (1.00 g, yield 30.2%). $[\alpha]_D^{25} = +17.5°$ ($c$=0.5, $CH_3COOCH_2CH_3$). IR ($\nu_{max}$): 2990, 2940, 2890, 1640, 1550, 1370, 1065 and 850 $cm^{-1}$. $^1$H NMR (ppm) $\delta$: 1.33 and 1.38 (s, 12H), 3.8–4.4 (m, 26H), 5.2–6.1 (m, 3H), 6.9–7.2 (m, 3H). $m/e$: 552 ($M^+$).

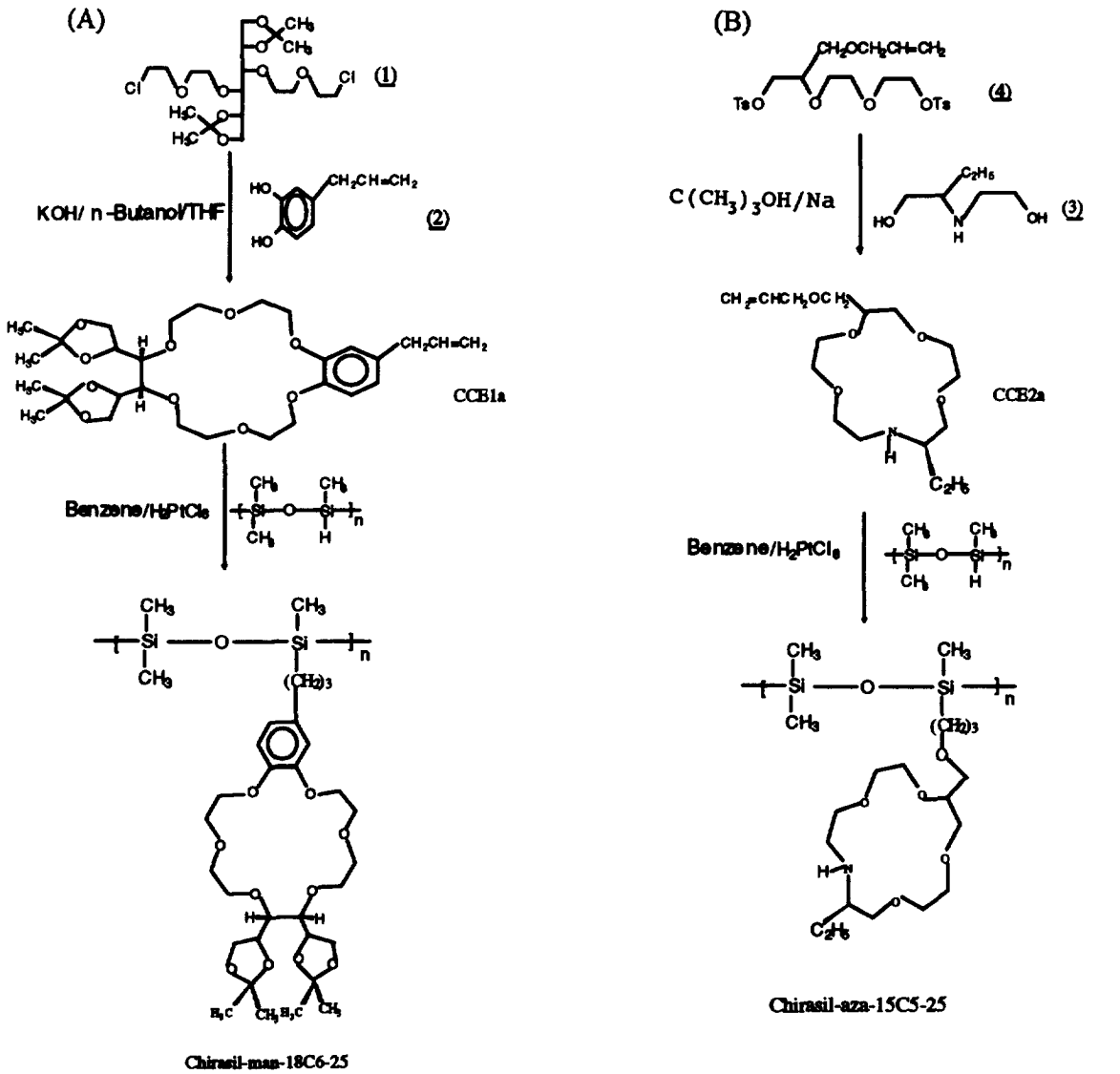



Fig. 1. Synthesis of chiral crown ether-anchored polysiloxane phases, (A) Chirasil-man-18C6-25, (B) Chirasil-aza-15C5-25.

Microanalysis for $C_{20}H_{44}O_{10}$: calculated, C 63.08, H 7.97; found, C 62.91, H 8.04%.

*2.2.2. Synthesis of (+)-2-allyloxymethyl-8-ethyl-1,4,10,13-tetraoxa-7-azacyclopentadecane (CCE2a)*

2.620 g (0.02 mol) of (+)-N-(β-hydroxyethyl)-2-amino-1-butanol (3) (prepared according to literature [35] from (+)-2-amino-1-butanol) and 1.10 g (0.048 mol) sodium metal were dissolved in 240 ml of *tert*-butyl alcohol, 9.16 g (0.02 mol) of 2-allyloxymethyltriethylene glycol ditosylate (4) (prepared according to literature reference [36]) was added dropwise into the solution over a period of 2 h under stirring at 60°C. The reaction was continued for ten more hours. After cooling, the reaction mixture was filtered and the solvent was evaporated. The residue mixture was dissolved in 30 ml of dichloromethane, washed with 4×20 ml of water and dried over anhydrous magnesium sulfate. After evaporating the solvent, the residue was distilled at 100–105°C/10

Pa to give a pale yellowish oil. The distillation product was further purified by silica gel column in acetone–hexane elution to give the pure product of CCE2a (2.1 g, yield 33.1%). $[\alpha]_D^{20} = +29.06°$ ($c$= 0.46, $CH_3OH$). IR ($\nu_{max}$): 3310, 2873, 1640, 1120, 1067 and 1454 $cm^{-1}$. $^1H$ NMR (ppm) $\delta$: 0.8–1.0 (t, 3H), 1.3–1.6 (m, 2H), 2.1 (s, 1H), 2.6–2.9 (m, 3H), 3.2–3.8 (m, 17H), 4.0–4.2 (m, 2H), 5.0–5.6 (m, 3H). $m/z$: 316 ($M^+-1$). Microanalysis for $C_{16}H_{31}NO_5$: calculated, C 60.57; H 9.78, N 4.42%; found, C 60.31, H 9.82, N 4.37%.

*2.2.3. Synthesis of chiral polysiloxanes containing 25% chiral crown ether substituents*

In an atmosphere of argon, 3.7 mmol of chiral crown ether CCE1a or CCE2a, 0.50 g of polyhydromethylsiloxane and 5 ml of anhydrous benzene were placed into a 25-ml three-necked round-bottomed flask equipped with a argon inlet, dropping funnel and reflux condenser. The mixture was stirring at reflux for 1 h. To the refluxing mixture was added 5 μl of chloroplatinic acid hexahydrate solution (1% $H_2PtCl_6 \cdot 6H_2O$, 1% ethanol in 98% THF solution) as catalyst. The reaction was monitored by IR spectrum. After 12 h, the IR spectrum showed there were still traces of Si–H groups. 0.05 ml of *n*-octene was then dropped into the resulting mixture to react with the residual Si–H units at the same conditions for 1 h. The solvent was removed and the residue was dissolved in 10 ml of dichloromethane and washed four times with 30 ml of methanol–water (1:1, v/v) to remove the catalyst. After filtration, the solution was concentrated and the gummy product was dried over night in a vacuum oven at 60°C. $^1H$ NMR (ppm, $C^2HCl_3$): for Chirasil-man-18C6-25, 0.2 (s, Si–$CH_3$), 0.53–0.60 (t, Si–$CH_2$), 1.40–1.48 (s, $C(CH_3)_2$), 3.6–4.5 (m, OCH, $OCH_2$), 7.0–7.6 (m, Ph–H); for Chirasil-aza-15C5-25: 0.29 (s, Si–$CH_3$), 0.50–0.56 (t, Si–$CH_2$), 0.8–1.0 (t, $CH_2$), 1.2–1.5 (m, $CH_3$), 2.8 (s, NH), 3.2–4.0 (m, $OCH_2$).

*2.3. Preparation of open-tubular columns*

Fused-silica capillary tubing (25 m×0.30 mm I.D., obtained from Yong Nian Optical Plant, China) was purged with a low nitrogen gas at 270°C for 2 h. The column was coated, without further deactivation, with chiral phases dissolved in methylene chloride (0.5%, w/v) by static method. The film thickness of the phase was 0.25 μm as determined by microscopy. Columns were then subsequently conditioned with nitrogen gas at a temperature range from 40 to 260°C at 1°C/min.

## 3. Results and discussion

The technique of $H_2PtCl_6$-catalyzed hydrosilylation affords availability to prepare polysiloxane phases by anchoring chiral moieties with polyhydromethylsiloxane containing appropriate Si–H groups. The chiral polysiloxanes thus obtained were characterized by $^1H$ NMR, FTIR spectroscopy and polarimetry, confirming the chemical link of chiral crown ethers to the polysiloxane backbone. The specific rotations of the polymeric products clearly differ from the chiral allyl-crown ether used as starting materials. In the IR spectra, the characteristic Si–H bands at 2150 $cm^{-1}$ were absent, while bands typical for the crown ethers were present. The signals due to the olefinic protons in the $^1H$ NMR disappeared completely, while peaks at 0.5–0.6 ppm (t, Si–$CH_2$) appeared after hydrosilylation.

The physical properties of the chiral polysiloxanes are listed in Table 1. The polysiloxanes being gummy materials afford good wetability to obtain high column efficiency, which is evident from the chromatograms of the Grob test mixtures as shown in Fig. 2a,b. The McReynolds' constants in Table 2 indicate that the two phases have moderate polarity, similar to that of the previously reported POSB-3-

Table 1
Physical properties of chiral crown ether-anchored polysiloxanes

| Polymer | $M_r$ | Appearance | Phase transition temperature (°C) | $[\alpha\sim]_D^{25}$ (°) | Yield (%) |
|---|---|---|---|---|---|
| Chirasil-man-18C6-25 | 2000 | Yellowish gum | 148 | +40.03 | 83 |
| Chirasil-aza-15C5-25 | 2000 | Yellowish gum | 126 | +8.02 | 87 |

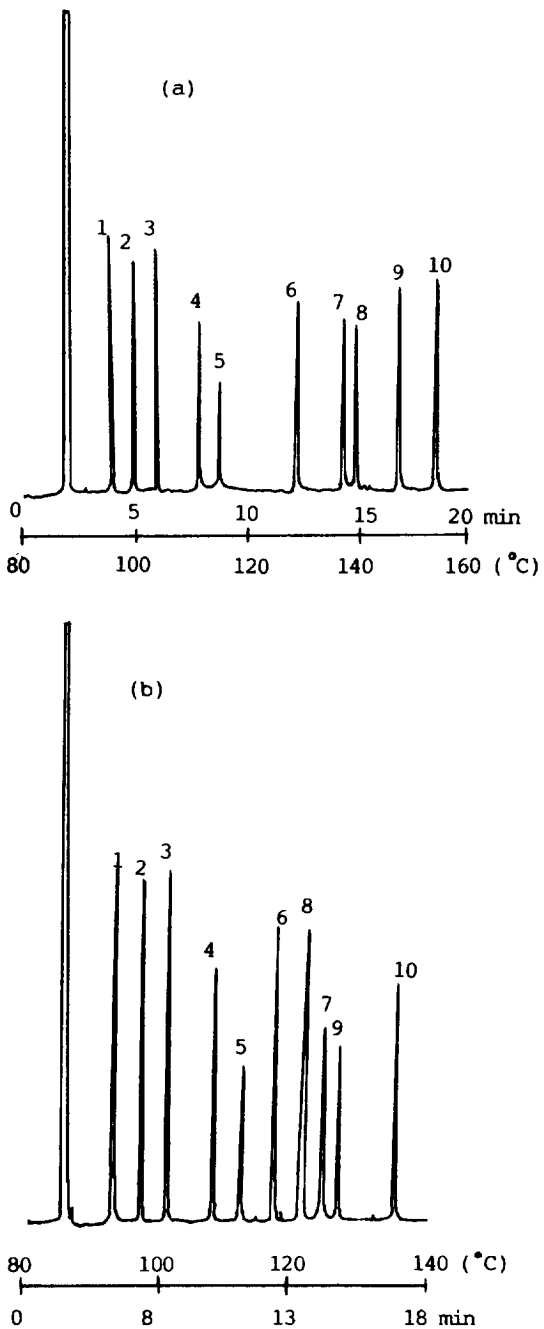



Fig. 2. Chromatograms of Grob test mixtures on (a) Chirasil-man-18C6-25 column. Temperature was programmed from 80 to 160°C at 4°C/min. (b) Chirasil-aza-15C5-25 column. Temperature was programmed from 80°C (3 min) to 140°C at 4°C/min. Peaks: 1=*n*-decane; 2=*n*-undecane; 3=*n*-dodecane; 4=1,3-butanediol; 5=1-octanol; 6=naphthalene; 7=2,4-dimethylaniline; 8=2,6-dimethylphenol; 9=methylundecanoate; 10=methyldodecanoate.

18C-6 [30] and PUAC-3-15C5 phases [31]. Fig. 3 and Fig. 4 are the separation chromatograms of phenolic isomers and aniline isomers on these two new phases. These results confirm that the new phases show the same excellent separation ability for positional isomers as the previously reported crown ether phases [30,31].

Resolution of amines, amino acids and dipeptide enantiomers has been achieved in liquid chromatography with chiral crown ethers as stationary phases. The separation mechanism is attributed to the formation of diastereomeric inclusion complexes, where the interactions are different for each enantiomer. The host crown ether was thought to complex more tightly with one antipode than the other, and both attractive (hydrogen binding) interactions and repulsive (steric) interactions contribute to the overall stability of the complex [22]. Reasonably, various classes of compounds, such as amines, amino acids, alcohols, have been selected as typical racemics to study the enantioselectivity of the new phases. Results show that the Chirasil-man-18C6-25 phase exhibits enantiomeric separation power to some racemates, but the Chirasil-aza-15C5-25 phase, unfortunately, does not display any enantioselectivity under the experimental conditions used. A representative chromatogram obtained from the Chirasil-man-18C6-25 phase is shown in Fig. 5. Inspection of the chromatogram reveals the excellent coating and separation efficiency. The absence of peak tailing for underivatized amino acid isopropyl ester is noteworthy, although the fused-silica column was not deactivated prior to coating.

Table 3 gives the analytical data for the racemates belonging to different classes of compounds obtained on the Chirasil-man-18C6-25 phase. Inspection of the data in Table 3 reveals that not only the primary amino or hydroxyl group but also the aromatic group are the functional group requirements for the analytes to obtain enantiomeric separation in this phase. For instance, analytes with aromatic groups, such as α-phenylpropanol, α-phenylpropylamine and phenylalanine isopropyl ester, appeared to have greater separation factors. Compounds that do not possess an aromatic group lost the enantiomeric separation. Compounds, not listed in Table 3, that were attempted but not separated include proline isopropyl ester, valine isopropyl ester, 2-bromo-1-octanol and 3-

Table 2
McReynolds' constants of chiral crown ether-anchored polysiloxanes (determined at 120°C)

| Stationary phase | Benzene | Butanol | 2-Pentanone | Nitropropane | Pyridine | Mean |
|---|---|---|---|---|---|---|
| Chirasil-man-18C6-25 | 271 | 287 | 258 | 469 | 397 | 336 |
| Chirasil-aza-15C5-25 | 130 | 247 | 253 | 342 | 267 | 248 |
| PSOB-3-18C6 | 210 | 381 | 452 | 461 | 465 | 394 |
| PUAC-11-15C5 | 147 | 258 | 261 | 224 | 231 | 231 |

methyl-1-heptylamine as well as 2-methyl-1-octanol. This fact substantiates that the π-stacking interaction between the solute and the crown ether plays an important role in the chiral recognition.

Racemates in Table 3 have been transformed to amide (for amines and amino acid) or ester (for alcohols) derivatives by trifluoroacetic anhydride reagent, in which the hydrogen groups were replaced with $COCF_3$ groups. Attempts to separate these TFA derivatized compounds in the two phases were not successful. After the derivatization of –OH or $-NH_2$ groups of these racemics by trifluoroacetic anhydride, the –OH or $-NH_2$ groups have been transformed to $-OCOCF_3$ or $-NHCOCF_3$ groups, respectively. Thus, the hydrogen-bonding between the oxygen atoms of the chiral crown ether and the derivatized molecules will be lost. This fact confirms that the formation of an inclusion complex between the chiral crown ether and the analyte molecules via hydrogen bond is crucial in the enantioselectivity.

It is obvious that the recognition mechanisms of the chiral crown ether and the cyclodextrin (CDs) phase are different. The CD phases can include guest racemates completely or partially in their conical cavity. In addition, cyclodextrins can also adsorb molecules on the exterior surface or on the top of the torus or on its narrow bottom via hydrogen bonding and/or dipole–dipole interaction [37]. So the CDs can provide enantioselectivities to a wide types of racemates. In the case of chiral crown ether, the analytes only form complexes on the top of the heterotopic cavity of the chiral host, and the π-stacking interaction and the steric properties of other groups are able to stabilize one of the two diastereomeric adsorbates. As an example, the NFA–proline isopropyl ester, which is difficult to separate

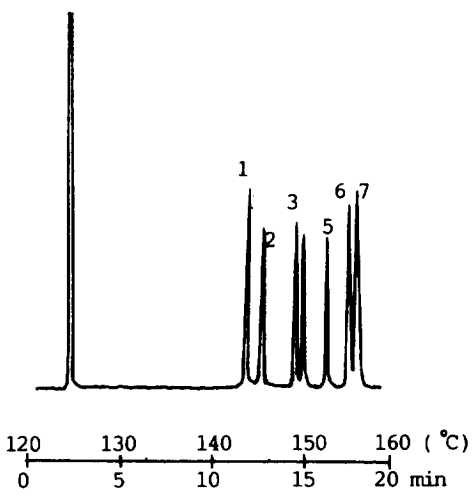



Fig. 3. Separation of phenolic isomers on Chirasil-man-18C6-25 phase. Temperature was programmed from 120 to 160°C at 2°C/min. Peaks: 1=phenol, 2=*o*-cresol, 3=2,6-dimethylphenol, 4=*m*-cresol, 5=*p*-cresol, 6=2,3-dimethylphenol, 7=2,4-dimethylphenol.

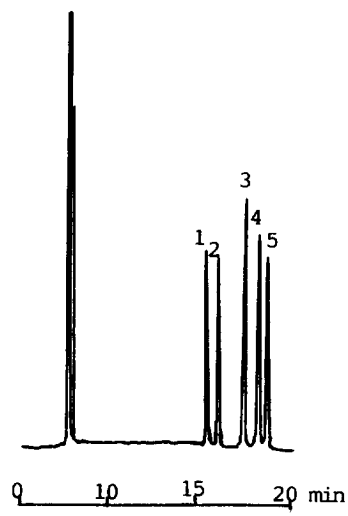



Fig. 4. Separation of aniline isomers on Chirasil-aza-15C5-25 phase. Temperature was 130°C (isothermal). Peaks: 1=*o*-methylaniline, 2=*m*-methylaniline, 3=*p*-methylaniline, 4=N,N-diethyl-*m*-methylaniline, 5=N-ethylmethylaniline.

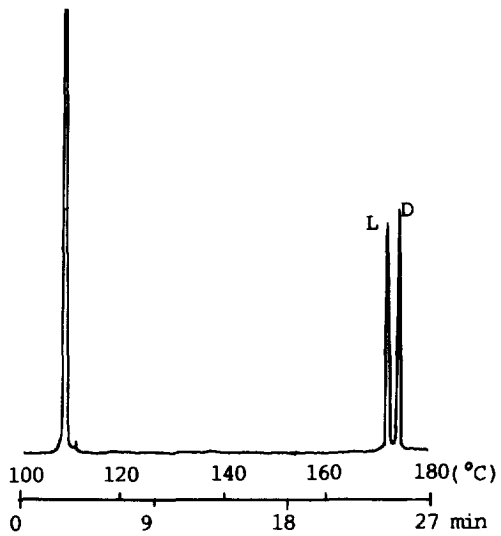



Fig. 5. Optical resolution of phenylalanine isopropyl ester on Chirasil-man-18C6-25 phase. Temperature was programmed from 100 to 180°C at 3°C/min. Carrier gas was nitrogen at 12 cm/s linear velocity.

on Chirasil–Val phase because of the lack of hydrogen bonding, can easily be separated in a CD phase [38]. However, neither the proline isopropyl ester nor the NFA–proline isopropyl ester can be separated in chiral crown ether phases, owing to the lack of hydrogen bond and π-stacking interaction. The chiral crown ether in Chirasil-man-18C6-25 phase possesses a diisopropylidene-D-mannitol unit as chiral auxiliary and a phenyl moiety which might be helpful to form inclusion complexes with some enantiomeric guest molecules for enantiomeric recognition. The fact that there is no enantioselectivity of the Chirasil-aza-15C5-25 phase may be attributed to the lack of π-stacking interaction and the small size of the chiral auxiliary in the skeleton of CCE2a. However, more information is required concerning the effect of chiral crown ether structure on enantioselective recognition. A systematical study of the chromatographic behavior of chiral crown ether phases is now being performed.

Whenever possible, the elution order was determined by comparison with the pure enantiomer. The elution order of the separated amino acids was the L-enantiomer eluting before the D-antipode on Chirasil-man-18C6-25. The same elution order was also observed by Joly et al. for the separation of aromatic amino acids in LC with a chiral crown ether that had a similar structure to CCE1a. [26].

The changes in the capacity factors of naphthalene and separation factors of some racemates on

Table 3
Analytical data for some enantiomer separations on Chirasil-man-18C6-25 phase

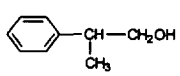
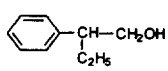
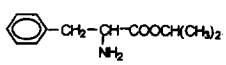
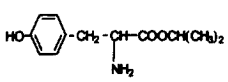
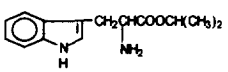
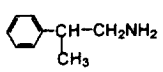
| Structure | Compound | $T$ (°C) | $\alpha$~ (Separation factor) |
|---|---|---|---|
|  | α-Phenylpropanol | 140 | 1.046 |
|  | α-Phenylbutanol | 140 | 1.023 |
|  | α-Phenylalanine isopropyl ester | 150 | 1.068 |
|  | Tyrosine isopropyl ester | 160 | 1.018 |
|  | Trytophane isopropyl ester | 150 | 1.010 |
|  | α-Phenylpropylamine | 140 | 1.027 |

Table 4
Changes of chromatographic performances of Chirasil-man-18C6-25 phase after 20 h conditioning at 260°C

| Time ageing | Column efficiency[a] (plates/m) | Capacity factor[a] ($k'$) | Separation factor for α-phenylpropanol[b] | Separation factor for phenylalanine isopropyl ester[b] |
|---|---|---|---|---|
| Before conditioning | 4072 | 3.28 | 1.037 | 1.064 |
| After 20 h conditioning | 4063 | 3.26 | 1.031 | 1.057 |

[a] determined at 120°C.
[b] determined at 160°C.

Chirasil-man-18C6-25 after 20 h conditioning at 260°C are shown in Table 4. It shows almost no loss in chromatographic performance during long time ageing under high temperature. This dramatic extension of the upper temperature limit, compared to earlier reported chiral phases, is a result of the incorporation of chiral substituents which are more stable towards racemization onto the polysiloxane backbone.

## 4. Conclusion

The Chiral-man-18C6-25 phase, which represents one of the first examples of a chiral crown ether-anchored polysiloxane stationary phase, provides enantioselectivity to racemates bearing both an aromatic group and an amino or hydroxyl group. The chiral recognition takes place mainly by hydrogen bonding force, π-stacking interaction and steric hindrance interaction between the chiral crown ether and the racemic molecule. The Chirasil-man-18C6-25 phase also exhibits good thermostability.

## Acknowledgments

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