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Preparation and evaluation of novel chiral stationary phases covalently bound with chiral pseudo-18-crown-6 ethers

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This paper is dedicated to Emeritus Professor Soichi Misumi on the occasion of his 77th birthday

Note: CSP2=Sumichiral OA-8000

Abstract—Novel chiral stationary phases consisting of silica gel covalently bound with chiral pseudo-18-crown-6 type hosts, which possess either an OH or OMe group as a binding functionality, were prepared for enantiomer-separation of lipophilic amines.

Although Cram and co-workers reported enantiomer-separation of amino acids and amino esters by HPLC using chiral stationary phases (CSPs) consisting of chiral crown ethers attached on polystyrene[1] or silica gel in the 1970s,[2] such were not commercially available. In 1987, Shinbo and co-workers reported the separation of amino acids by using a CSP in which a hydrophobic chiral crown ether was dynamically coated on an ODS column.[3] This type of CSP was commercialised as CROWNPAK CR and it has been proven useful for the resolution of chiral primary amines. However, because of the dynamically coated nature of this CSP, solvents that can be used as a mobile phase are limited. The use of a solvent containing more than 15% methanol would result in leaching of the chiral crown selector and deterioration of the CSP.[4] Since 1998, chemical-bonded type CSPs containing chiral crown ether have been developed actively.[5] However, there is no CSP in which a normal mobile phase is used as an eluent. Due to a recent analytical demand, there is an increasing requirement for separation of chiral lipophilic amino compounds. Therefore, it is desired to develop CSPs which can be used with a normal mobile phase as an eluent. In addition to this requirement, the usage of lipophilic neutral amines rather than their ammonium salts as substrate is required because of their better solubility in a normal mobile phase.

To meet these requirements and achieve good chiral separation, we designed OH type CSP, (*S*, *S*)-**1**, where a selector is immobilised on silica gel covalently and where a chiral phenolic crown ether is adopted as a selector expecting stable salt-complex formation with a neutral amine. As a selector, chiral pseudo-18-crown-6 *meta*-cyclophane frameworks are adopted, because high enantiomer-selective complexations toward primary amines and ammonium salts are reported.[6] In addition to (*S*, *S*)-**1**, OMe type CSP (*S*, *S*)-**2** with the same *meta*-cyclophane framework was prepared. An amide linkage is known to be sufficiently stable for the chromatography. Therefore, CSPs **1** and **2** should be stable, and both the reversed and the normal phases can be used as eluent. For comparison, amides selectors (*S*, *S*)-**3** and (*S*, *S*)-**4** were prepared (Fig. 1).

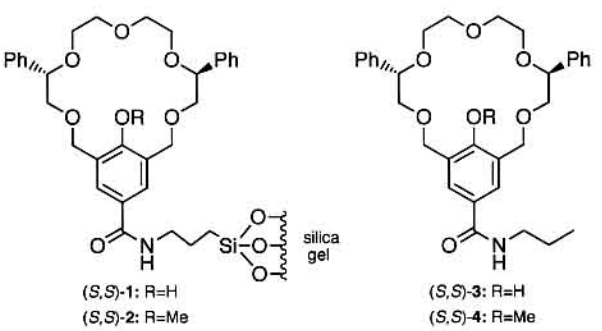

Figure 1. The structures of CSPs **1**, **2** and selectors **3**, **4**.

Keywords: chiral stationary phase; crown ether; chiral recognition.
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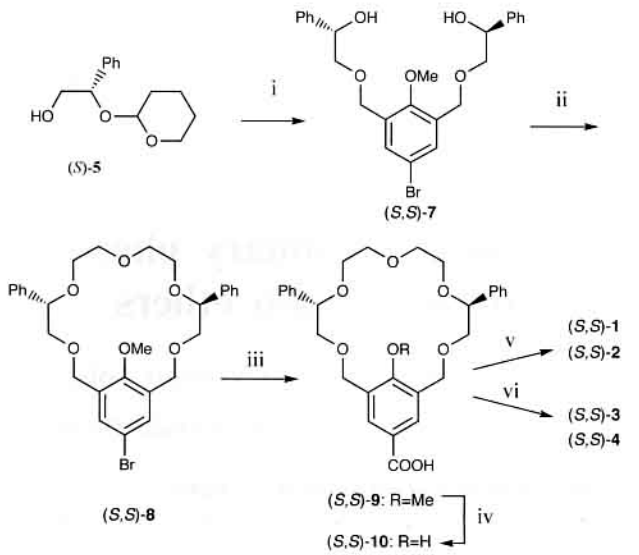

Scheme 1. *Reagents and conditions:* i, (1) 4-bromo-2,6-bis(bromomethyl)anisole, NaH, (2) EtOH, pyridinium *p*-toluenesulfonate, 80%; ii, diethylene glycol ditosylate, NaH, 53%; iii, (1) *n*-BuLi, (2) CO_2 gas, (3) HCl, 87%; iv, EtSNa, 69%; v, for **2**, (1) 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, (2) Ac_2O, 30%*, for **1**, (1) 1-ethyl-3-(3-dimethylamino-propyl)-carbodiimide hydrochloride, (2) Ac_2O, 28%*; vi, 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, **4** 80%, **3** 72%. * The content of selector bound aminopropyl group over total amount of grafted aminopropyl group on silica gel.

The preparation of CSPs **1**, **2** and selectors **3**, **4** are shown in Scheme 1. The chiral monoprotected diol (*S*)-**5** was synthesised from commercially available mandelic acid according to the literature.[7] The alcohol (*S*)-**5** was converted to crown ether (*S*, *S*)-**8** via podand (*S*, *S*)-**7**. The crown ether (*S*, *S*)-**9**, which was obtained by carboxylation of (*S*, *S*)-**8** is the intermediate for both selectors and both CSPs. For the syntheses of CSPs **1** and selectors **3**, (*S*, *S*)-**10** was obtained by the demethylation of (*S*, *S*)-**9** with sodium ethanthiolate. The CSPs **1** and **2** were obtained by the amidation of (*S*, *S*)-**10** or (*S*, *S*)-**9** with 3-aminopropylsilica gel, followed by treatment of the resulting silica gel with acetic anhydride. The amounts of selectors bound to the silica gel were calculated based on the elemental analyses of CSPs **1** and **2**. CSP **1** and **2** were packed into 250×4.6 mm I.D. stainless steel columns using a conventional slurry packing method. The selectors (*S*, *S*)-**3** and (*S*, *S*)-**4** were obtained by the amidation of (*S*, *S*)-**9** and (*S*, *S*)-**10**, respectively, with *n*-propylamine.

First, the separation of racemic organic amines on CSPs **1** and **2** using the normal mobile phase was examined. The amino compounds examined here were selected from commonly used amines, 1-phenylethylamine (**11**), 1-(1-naphthyl)ethylamine (**12**), and phenylglycinol (**13**). As the mobile phase, an ordinarily used normal phase, hexane–ethanol, was employed. In the case of chromatography on CSP **2**, trifluoroacetic acid (TFA) was used as an indispensable acid additive for the protonation of the amino group. In the case of chromatography on CSP **1**, the acid additive was not necessary. The phenolic OH group placed in the binding site might play the same role as an acid derivative in which the amine could be complexed with phenolic crown ether to form ammonium phenolate coined 'saltex'.[8] On the contrary, a base, e.g. triethylamine (TEA), could be used for this CSP and was effective[9] to improve the separation. The chromatograms on CSP **1** are shown in Figure 2 (a)–(c). The separation factors (α) are 2.02, 2.12 and 5.26 using **11**, **12**, **13**, respectively. The corresponding α values on CSP **2** are 1.00, 1.33, 1.17, respectively. The chromatograms on CSP **2** are shown in Figure 2 (d)–(f).[10] The OH type CSP **1** exhibited excellent enantiomer-separation of all amines employed here using the normal mobile phase without addition of an acid additive.

Next, the enantiomer-selectivities of selectors **3** and **4** in solution were examined. The binding constants of **3** with chiral amines, **11**–**13** were determined in chloroform-*d* by ^{1}H NMR spectroscopic method.[11] Those of **4**

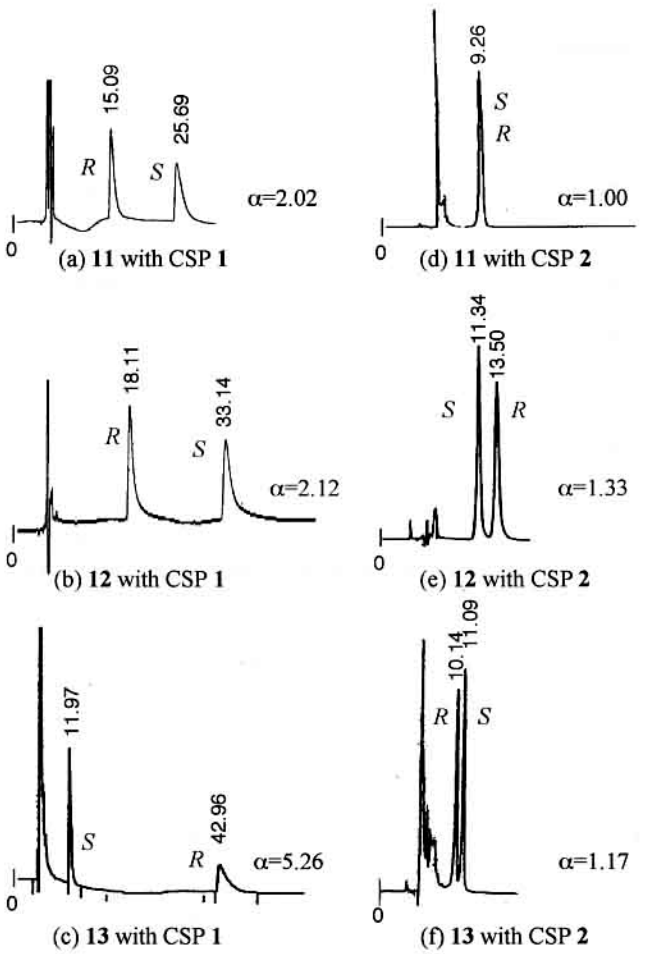

Figure 2. Chromatograms for the resolution of **11**–**13** on CSP **1** and on CSP **2** using normal mobile phase. Chromatographic conditions: flow rate = 0.7 ml/min, 25°C, hexane/EtOH/TEA = 70/30/0.2 for **11**, **12** on CSP **1**, hexane/EtOH/TEA = 60/40/0.5 for **13** on CSP **1**, hexane/EtOH/TFA/H_2O = 70/30/0.5/0.2 for **11**–**13** on CSP **2**. The scale of the abscissa is presented in min.

Table 1. Binding constants and enantiomer-selectivities of selectors **3**, **4** at 303 K and separation factors (α) of corresponding CSPs **1**, **2**

Selector	Substrate	K_R/M^{-1}	K_S/M^{-1}	K_R/K_S	α^c
	11	1.1[d]	4.8[d]	0.23	2.02
3[a]	**12**	0.54[d]	2.8[d]	0.20	2.12
	13	72	7.7	9.3	5.26
	11·HCl	25	25	1.0	1.00
4[b]	**12**·HCl	38	27	1.4	1.33
	13·HCl	16	15	1.0	1.17

[a] In $CDCl_3$.
[b] In $CDCl_3/CD_3OD = 7/3$.
[c] From chromatography for the corresponding substrate, see Figure 2.
[d] Obtained by an extrapolation according to the van't Hoff relation.

were determined with the corresponding ammonium hydrochloride in methanol-d_4–chloroform-d (v/v = 3/7) mixed solvent. The results are listed in Table 1 where the enantiomer-selectivity of the selectors are shown by the ratio of binding constants (K_R/K_S) with the separation factor (α) of corresponding CSP. The binding constants of amines **11**–**13** with selector **3** range from 0.54 to 72 M^{-1}. The enantiomer selectivities are large ($K_R/K_S = 0.23$, 0.20, 9.3). The enantiomer-selectivities of **4** were smaller than those of **3**. Clear selectivity was observed when **12**·HCl was employed ($K_R/K_S = 1.4$). The chromatogram for the resolution of **12** on CSP **2** using an acid additive showed a separation factor $\alpha = 1.33$ where the baseline separation was performed (Fig. 2 (e)). In the case of **13**·HCl, the enantiomer-selectivity (K_R/K_S) was small with selector **4** in solution, but the enantiomer separation using the corresponding CSP **2** was clearly observed (Fig. 2 (f), $\alpha = 1.17$). In general, the enantiomer which has larger retention time in chromatogram has larger binding constant in complexation of the corresponding model compounds. Since there exists a correlation between the enantiomer-selectivities in chiral chromatography and that of the corresponding model compounds of the selectors in solution, it is deduced that the chiral separation arose from chiral recognition in host–guest interaction.

In conclusion, we have prepared OH type CSP **1**, and OMe type CSP **2** in which selectors were immobilised on silica gel covalently. On both CSPs **1** and **2**, clear chromatographic enantiomer-separations of chiral amines were observed using normal mobile phases.[12] Especially, the chromatography on CSP **1** exhibited excellent enantiomer-separations using a normal mobile phase without acid additives. A correlation between the enantiomer-selectivities in chiral chromatography and that of the corresponding model compounds of the selectors in solution was observed, implying that the chiral separation arose from chiral recognition in host–guest interaction. Currently, we are investigating the enantiomer separations of a wide range of amino compounds in order to clarify the characteristics of substrates which can be separated using these CSPs.

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12. The CSPs **1** and **2** can be used for the separation of other primary amines and amino acids, such as norephedrine, phenylalanine, and alaninol, which exhibit separation factors (α) 1.32, 1.24, 1.07 on CSP **1** and 1.47, 1.45, 1.18 on CSP **2**, respectively. Chromatographic conditions: flow rate = 0.7 ml/min, 25°C, hexane/*iso*-PrOH/MeOH/TFA = 80/15/5/0.5 for the separation of alaninol, hexane/EtOH/TFA = 70/30/0.5 for the separation of other amines.