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Synthesis of (1R-trans)-N,N'-1,2-cyclohexylenebisbenzamideoligodimethylsiloxane copolymers for use as chiral stationary phases for capillary supercritical fluid chromatography

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ABSTRACT

Eight new copolymers have been prepared as chiral stationary phases for capillary supercritical fluid chromatography (SFC) by the copolymerization hydrosilylation of α,ω-dihydromethyloligosiloxanes with four dialkene derivatives of (1R-trans)-N,N'-1,2-cyclohexylenebisbenzamide. This represents a novel approach to the synthesis of chiral stationary phases in that copolymers are formed from achiral α,ω-dihydrosiloxane and chiral diolefinic diamide monomers. The siloxane units ensure good general chromatographic performance (*e.g.*, high efficiency and thermal stability), while the chiral units facilitate enantioselectivity by providing specific interaction sites and selective chiral grooves or cavities. Several of these polymers are useful for the separation of enantiomeric diols.

INTRODUCTION

Recent advances in the analytical chromatographic separation of enantiomers can be attributed in part to the increasing interest in the resolution and enantiomeric purity of drugs [1]. It is well known that enantiomers can produce different biological activities according to their absolute configurations [1]. Approximately 40% of the pharmaceuticals obtained synthetically are chiral, however, only 10% of them are utilized as pure enantiomers, 90% being used in the racemic form [2]. This situation is expected to change as governmental drug regulatory agencies adopt more stringent standards relative to the enantiomeric purity of drugs. The development of accurate analytical tools is necessary for monitoring asymmetric syntheses and for assessing the enantiomeric purities of chiral drug substances. Chromatography using indirect methods (separations of diastereomers on achiral stationary phases) or direct methods using a chiral selecting agent in the mobile phase or on a chiral stationary phase (CSP) has proven to be the best technique for chiral separations [3].

Much effort has been expended in the development of CSPs for liquid chromatography (LC) and gas chromatography (GC) [3–5]. Since supercritical fluid chromatography (SFC) can be performed at lower temperatures than GC and it can produce higher practical efficiencies than LC, SFC is a potentially important technique for the resolution of enantiomers [6]. We have therefore initiated studies to develop CSPs capable of resolving enantiomers by SFC. CSPs for capillary SFC must have certain

characteristics: (a) these materials must be suitable for efficient coating and immobilization inside the fused-silica columns; (b) they must be resistant to thermal and chemical stress; (c) they must allow efficient diffusion of analytes and mobile phases; and (d) they must interact differentially with the two enantiomers of the chiral analyte. The first three characteristics are desirable properties of any good stationary phase. The fourth characteristic relates to their chiral recognition properties.

EXPERIMENTAL

Preparation of chiral starting materials

Preparation of (1R-trans)-N,N'-1,2-cyclohexyle-nebis(4-allyloxybenzamide) (**9**). Oxalyl chloride (4.3 g, 33.9 mmol) was added to a suspension of 5.09 g (28.1 mmol) of 4-allyloxybenzoic acid (prepared from allyl bromide and 4-hydroxybenzoic acid) in 70 ml of benzene at room temperature. The reaction mixture was stirred for 10 min at room temperature followed by refluxing until the acid dissolved (10–15 min). The solvent was removed under reduced pressure to give an oily residue which was dissolved in 60 ml of tetrahydrofuran (THF). 4-Methylmorpholine (3.4 g, 33.7 mmol) was added to the reaction mixture at 0°C under an argon atmosphere. A solution of 1.15 g (10.1 mmol) of (1R,2R)-*trans*-1,2-diaminocyclohexane (Fluka, Ronkonkoma, NY, USA) in 15 ml of THF was added to the reaction mixture at room temperature. The reaction mixture was stirred for 10 min at room temperature followed by refluxing for 2 h. The reaction mixture was evaporated under reduced pressure to give a solid residue which was then dissolved in 200 ml of chloroform. The chloroform solution was extracted with 100 ml of water, 100 ml of 1 M aqueous HCl, twice with 150-ml portions of 5% aqueous Na_2CO_3, and again with 100 ml of water to remove impurities. The chloroform layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a crude product, which was purified by preparative high-performance liquid chromatography (HPLC) (silica gel, chloroform–ethyl acetate = 3:1). The resulting white solid was recrystallized from ethyl acetate–hexane to give 2.47 g (56%) of product; m.p. 159–161°C; [α]$_D$ = -125.88° (c = 3.98, CH_2Cl_2); NMR (C^2HCl_3) δ 1.45 (m, 4 H), 1.82 (m, 2 H), 2.20 (m, 2 H), 4.0 (m, 2 H), 4.45 (dd, 4

H), 5.20–5.50 (dd, 4 H), 5.9–6.1 (m, 2 H), 6.75 (d, 4 H), 6.9 (m, 2 H), 7.65 (d, 4 H); IR (KBr) 3297, 3083, 1685, 841, 767 cm^{-1}.

Preparation of (1R-trans)-N,N'-1,2-cyclohexyle-nebis(2-allyloxybenzamide) (**10**). Sodium metal (4.0 g, 0.17 mol) was dissolved in 100 ml of methanol under nitrogen, and 25.0 g (0.17 mol) of methyl 2-hydroxybenzoate were added. After addition of the ester, 39.7 g (0.33 mol) of allyl bromide was slowly dripped into the reaction mixture. The mixture was refluxed overnight, cooled and acidified with 6 M acetic acid. The methanol and excess allyl bromide were evaporated. The material was dissolved in 150 ml of diethyl ether and the ether solution was washed with 100 ml of water. The ether was dried over anhydrous $MgSO_4$ and distilled to give 21.1 g (67%) of the methyl 2-allyloxybenzoate; b.p. 71–83°C/0.12 mmHg. This ester was hydrolyzed to give 14.1 g (72%) of 2-allyloxybenzoic acid; m.p. 70–71°C.

2-Allyloxybenzoic acid (1.94 g, 0.011 mol) was treated as above with oxalyl chloride (1.66 g, 0.13 mol) to give 2-allyloxybenzoyl chloride; b.p. 71–71°C/0.065 mmHg. The acid chloride (1.85 g, 9.4 mmol) was reacted with (1R,2R)-*trans*-1,2-diamino-cyclohexane (1.01 g, 8.8 mmol) as above for the preparation of **9** to give 1.29 g (63%) of **10** after recrystallization from ether–hexane; m.p. 90–91°C; [α]$_D$ = -78.4° (c = 0.324, CHCl$_3$); NMR δ 1.15–1.5 (4 H, bm), 2.7–2.85 (2 H, bm), 2.15–2.3 (2 H, bm), 3.95–4.15 (2 H, bm), 4.6 (4 H, m), 5.2–5.4 (4 H, dd), 5.9–6.1 (2 H, m), 6.8–7.0 (4 H, m), 7.25–7.4 (2 H, m), 8.0–8.2 (4 H, m). Analysis for $C_{26}H_{30}O_4N_2$; calculated: C, 71.87; H, 6.96; found: C, 71.10; H, 7.17.

Preparation of (1R-trans)-N,N'-1,2-cyclohexyle-nebis(3-allyloxybenzamide) (**11**). 3-Hydroxybenzoic acid (3.90 g, 0.028 mol) was treated as above for the formation of 2-alkyloxybenzoic acid to give 1.60 g (32%) of 3-allyloxybenzoic acid after recrystallization from dichloromethane–hexane; m.p. 77–79°C.

3-Allyloxybenzoic acid (1.60 g, 9.0 mmol) was reacted with 1.37 g (0.011 mol) of oxalyl chloride as above for the formation of **9** to give 0.78 g (44%) of 3-allyloxybenzoyl chloride. As the acid chloride distilled, it began to decompose so that the vacuum fluctuated widely and no b.p. was obtained. The acid chloride (0.78 g, 4.0 mmol) was reacted with

0.22 g (1.9 mmol) of (1R,2R)-trans-1,2-diaminocyclohexane as above for the preparation of **9** to give 0.48 g (57%) of **11** after recrystallization from dichloromethane–hexane; m.p. 178–181°C; $[\alpha]_D$ = −42.2° (c = 0.694, CHCl$_3$); NMR δ 1.35–1.5 (4 H, m), 2.7–2.9 (2 H, m), 2.1–2.3 (2 H, m), 3.9–4.0 (2 H, m), 4.5 (4 H, d), 5.2–5.45 (4 H, dd), 5.9–6.1 (2 H, m), 6.6–6.8 (2 H, d), 6.9–7.0 (2 H, m), 7.2–7.3 (6 H, m). Analysis for C$_{26}$H$_{30}$O$_4$N$_2$; calculated: C, 71.87; H, 6.96; found: C, 72.00; H, 6.93.

Preparation of (1R-trans)-N,N'-1,2-cyclohexylenebis[4-(3-butenyl)benzamide] (**12**). 4-Allylbromobenzene (3.00 g, 0.015 mol) (Aldrich) dissolved in HPLC-grade THF was slowly added to 0.38 g (0.16 mol) of magnesium in 100 ml of HPLC-grade THF. The Grignard was allowed to form and then a gas dispersion tube was placed in the Grignard mixture. Carbon dioxide was passed through a drying tube filled with Drierite before it entered the reaction. The mixture was stirred at −10°C for 1 h and for 1 h at room temperature while carbon dioxide was bubbled into the reaction mixture. The THF was evaporated and 50 ml of water were added. The reaction was acidified with glacial acetic acid. The aqueous solution was extracted twice with 50-ml portions of chloroform and with 50 ml of diethyl ether. The chloroform and ether layers were each washed with water until neutral and then combined and dried over anhydrous MgSO$_4$. The solvents were evaporated and the product was chromatographed on 20 g of silica gel with 100 ml of hexane and then hexane–acetic acid (10:0.1) as eluents. The 4-allylbenzoic acid (0.5 g, 20%) was isolated by recrystallization from ether–hexane. Even after column chromatography, there was some type of aromatic impurity. This material was used in the next step without further purification.

4-Allylbenzoic acid (0.50 g, 3.1 mmol) was treated as above with 0.51 g (4.0 mmol) of oxalyl chloride to give 4-allylbenzoyl chloride which was not purified but used directly with 0.17 g (1.5 mmol) of (1R,2R)-trans-1,2-diaminocyclohexane as above for the preparation of **9** to give 0.22 g (37%) of **12**. Compound **12** was purified by column chromatography on 5 g of silica gel with toluene–acetic acid (10:0.2) as eluent and then on 5 g of silica gel with hexane–acetic acid (10:0.2) as eluent. The product was recrystallized from dichloromethane–hexane; m.p. 207.5–209°C; $[\alpha]_D$ = −136° (c = 0.184,
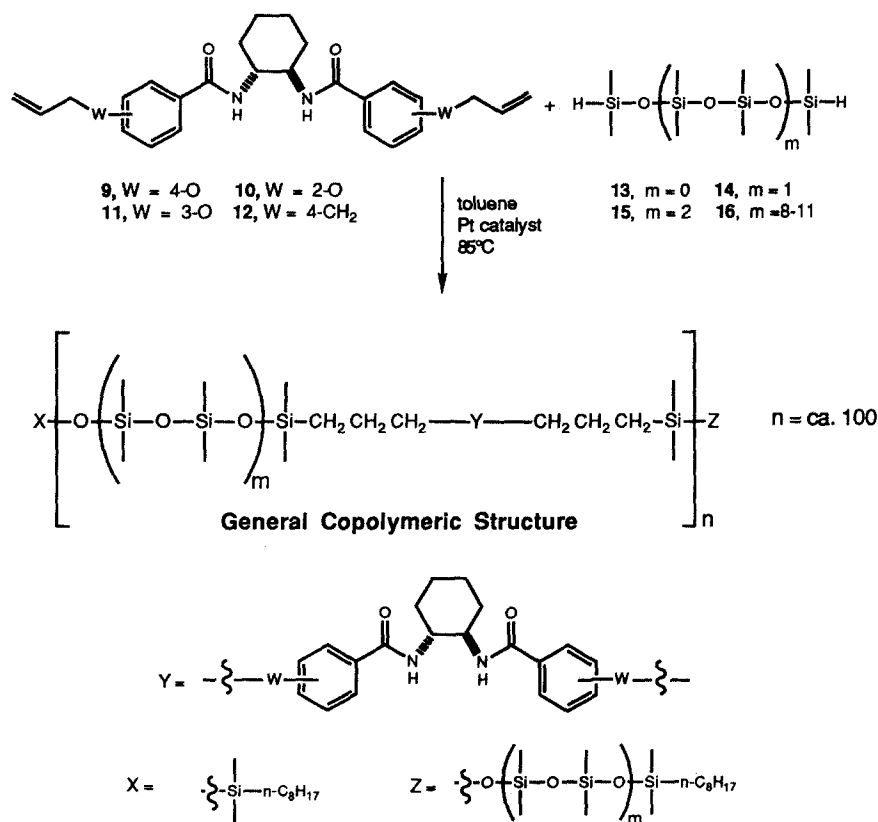
CHCl$_3$); NMR δ 1.2–1.65 (4 H, bm), 2.7–2.9 (2 H, bm), 2.1–2.35 (2 H, bm), 3.3–3.5 (4 H, m), 3.85–4.1 (2 H, m), 5.0–5.2 (3 H, m), 5.8–6.0 (2 H, m), 7.7–7.9 (2 H, m), 7.1–7.3 (4 H, m), 7.4–7.8 (4 H, bm). Analysis for C$_{26}$H$_{30}$O$_2$N$_2$ · 1.5 H$_2$O; calculated: C, 72.71; H, 7.04; found: C, 72.63; H, 6.93.

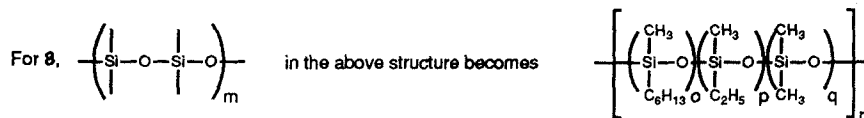*Preparation of (1R-trans)-N,N'-1,2-cyclohexylene-bisbenzamideoligodimethylsiloxane copolymer phases*

The chiral stationary phases were prepared according to Fig. 1. Specific details for these syntheses are outlined as follows.

Preparation of (1R-trans)-α-(dimethyloctylsilyl)-ω-[(dimethyloctylsiloxanyl)oxy]poly[oxy(dimethylsilanediyl)-1,3-propanediyloxy-1,4-phenylenecarbonylimino-1,2-cyclohexyleneiminocarbonyl-1,4-phenyleneoxy-1,3-propanediyl(dimethylsilylene)] (**1**) (Fig. 1). Chiral monomer **9** (0.34 g, 7.8 mmol), 11.0 μl of 1-octene (for endcapping) and tetramethyldisiloxane (**13**) (Aldrich, Milwaukee, WI, USA) (0.11 g, 8.5 mmol) were placed in a 50-ml PTFE centrifuge tube and dissolved in 20 ml of toluene. Chloroplatinic acid (15 μl, 1%) was added, and the vial was capped and placed in a sonic bath at 50°C for ca. 36 h. The polymer was dissolved in 10 ml of dichloromethane and precipitated by a mixture of 5 ml of methanol and 5 ml of water. The solvents were decanted and the polymer was again dissolved and precipitated three more times. This process separated the polymer from low-molecular-weight impurities. The polymer was again dissolved in 10 ml of dichloromethane and filtered through a 0.2-μm filter to remove high-molecular-weight material. The dichloromethane was evaporated and the polymer was dried under vacuum at 60°C for 15 h to give 0.38 g (86%) of a brown crystalline polymer (**1**). The NMR spectrum showed that there was still alkene present in the polymer. This polymer was crystalline and was not studied further.

Preparation of (1R-trans)-α-(dimethyloctylsilyl)-ω-[(1,1,3,3,5,5-hexamethyl-5-octyltrisiloxanyl)oxy]poly[oxy(1,1,3,3,5,5-hexamethyltrisiloxane-1,5-diyl)-1,3-propanediyloxy-1,4-phenylenecarbonylimino-1,2-cyclohexyleneiminocarbonyl-1,4-phenyleneoxy-1,3-propanediyl(dimethylsilylene)] (**2**) (Fig. 1). Compound **9** (0.34 g, 7.8 mmol), 7 μl of 1-octene (for endcapping) and 0.23 g (8.3 mmol) of octamethyltetrasiloxane (**14**) (Aldrich) were placed

9, W = 4-O 10, W = 2-O
11, W = 3-O 12, W = 4-CH₂

toluene
Pt catalyst
85°C

13, m = 0 14, m = 1
15, m = 2 16, m = 8-11

n = ca. 100

General Copolymeric Structure

Copolymer	m	W
1	0	4-O
2	1	4-O
3	2	4-O
4	8-11	4-O
5	1	2-O
6	1	3-O
7	1	4-CH₂

For 8, in the above structure becomes

where o = 2, p = 2, q = 3.3 and r = 1.3

Fig. 1. Preparation of copolymer phases 1-8.

in a 50-ml PTFE centrifuge tube and dissolved in 7 ml of toluene. A few small crystals of dicyclopentadienyl platinum were added to the reaction mixture which was then capped and placed in the sonic bath at 50°C and allowed to react until all the alkene was gone. The toluene was evaporated and then the polymer was treated as above for **1** with dichloromethane, methanol and water to give 0.53 g (64%)

of 2. The polymer was a brown crystalline material; $[\alpha]_D = -63.1°$ ($c = 4.52$, CH_2Cl_2).

Preparation of (1R-trans)-α-(dimethyloctylsilyl)-ω-[(1,1,3,3,5,5,7,7,9,9-decamethyl-9-octylpentasiloxanyl)oxy]poly[oxy(1,1,3,3,5,5,7,7,9,9-decamethylpentasiloxane-1,9-diyl)-1,3-propanediyloxy-1,4-phenylenecarbonylimino-1,2-cyclohexyleneiminocarbonyl-1,4-phenyleneoxy-1,3-propanediyl (dimethylsilylene)] (3) (Fig. 1). Dodecamethylhexasiloxane (15) was first prepared by placing 3.00 g (0.010 mol) of 14 and 1.41 g (0.011 mol) of 13 in a 50-ml PTFE centrifuge tube with a magnetic stir bar. The silanes were stirred for 5 min to give a homogenous mixture and then one drop of triflic acid was added. The reaction was stirred at room temperature for 2 min and then 10 drops of hexamethyldisilazane (HMDS) were added. An aliquot of 10 ml of dichloromethane was added and the polymer was washed 4 times with 10 ml of water. The dichloromethane was evaporated and the product was distilled to give 1.43 g (33%) of 15; b.p. 45–51°C/0.70 mmHg. A GC–mass spectrometric (MS) analysis of 15 showed one peak with a parent mass of 431.

Siloxane 15 (0.40 g, 0.9 mmol), 0.40 g (0.9 mmol) of 9 and 8 µl of 1% chloroplatinic acid were placed in a 50-ml PTFE centrifuge tube and dissolved in 10 ml of toluene. The vial was capped and placed in the sonic bath at 50°C for 16 h, and then 10 µl of 1-octene were added for endcapping purposes. The reaction was carried out until the Si–H band in the IR spectrum was gone. The toluene was evaporated and the polymer was treated as above for 1 with dichloromethane, methanol and water to give 0.62 g (78%) of 3 as a viscous light tan liquid.

Preparation of copolymer 4 (Fig 1). Polysiloxane 16 was first prepared by placing 1.50 g (5.1 mmol) of 14 and 0.21 g (1.6 mmol) of 13 in a 50-ml PTFE centrifuge tube with a magnetic stir bar. The mixture was stirred for 3 min at room temperature and then 10 mg of triflic acid were added. The vial was capped and the reaction was stirred overnight at room temperature. The reaction was neutralized with 15 drops of HMDS, and then 10 ml of dichloromethane were added. The polymer solution was washed 3 times with 10-ml portions of water and then filtered through a 0.2-µm filter. The solvent was evaporated and the polymer was dried under vacuum at 80°C for 24 h. The NMR spectrum of 16

indicated the structure shown in Fig. 1.

Siloxane 16 (0.66 g, 0.51 mmol) and 0.20 g (0.46 mmol) of 9 were placed in a 50-ml PTFE centrifuge tube and dissolved in 15 ml of toluene. Chloroplatinic acid (15 µl, 1%) was added to the reaction, and a condenser was fitted into the top of the vial. The toluene level eventually dropped to about 3 ml. At this point hydrosilylation began. When all of the alkene had reacted, 10 ml of dichloromethane were added and the polymer was treated as 1 above except the dichloromethane solution was also filtered through a 2-inch column of Superlig VIII (IBC Advanced Technologies, Provo, UT, USA) to remove residual platinum. The solvent was evaporated to give 0.60 g (75%) of 4 as a cream colored viscous liquid; $[\alpha]_D = -31.1°$ ($c = 0.238$, $CHCl_3$).

Preparation of (1R-trans)-α-(dimethyloctylsilyl)-ω-[(1,1,3,3,5,5-hexamethyl-5-octyltrisiloxanyl)oxy]poly[oxy(1,1,3,3,5,5-hexamethyltrisiloxane-1,5-diyl)-1,3-propanediyloxy-1,2-phenylenecarbonylimino-1,2-cyclohexyleneiminocarbonyl-1,2-phenyleneoxy-1,3-propanediyl(dimethylsilylene)] (5) (Fig. 1). Alkene 10 (0.41 g, 0.94 mmol) and 0.28 g (1.0 mmol) of siloxane 14 were placed in a 50-ml PTFE centrifuge tube with a magnetic stir bar and dissolved in a mixture of 3 ml of toluene and 2 ml of dichloromethane. 1% Chloroplatinic acid (15 µl) was added and a reflux condenser was fitted into the top of the vial. The reaction was heated at 85°C until the alkene was gone. The toluene was evaporated and the polymer was treated as above for 1 to give 0.59 g (88%) of 7 as a light brown viscous liquid; $[\alpha]_D = -73.8°$ ($c = 0.496$, $CHCl_3$).

Preparation of (1R-trans)-α-(dimethyloctylsilyl)-ω-[(1,1,3,3,5,5-hexamethyl-5-octyltrisiloxanyl)oxy]poly[oxy(1,1,3,3,5,5-hexamethyltrisiloxane-1,5-diyl)-1,3-propanediyloxy-1,3-phenylenecarbonylimino-1,2-cyclohexyleneiminocarbonyl-1,3-phenyleneoxy-1,3-propanediyl(dimethylsilylene)] (6) (Fig. 1). Copolymer 6 was prepared in the same manner as 5 using 0.14 g (0.32 mmol) of 11 and 0.10 g (0.35 mmol) of siloxane 14 in 3 ml of toluene and 2 ml of dichloromethane. The polymer was purified as described for 5 above to give 0.14 g (58%) of 6 as a white glassy polymer; $[\alpha]_D = -18.7°$ ($c = 0.230$, $CHCl_3$).

Preparation of copolymer (1R-trans)-α-(dimethyloctylsilyl)-ω-[(1,1,3,3,5,5-hexamethyl-5-octyltrisiloxanyl)oxy]poly[oxy(1,1,3,3,5,5-hexa-
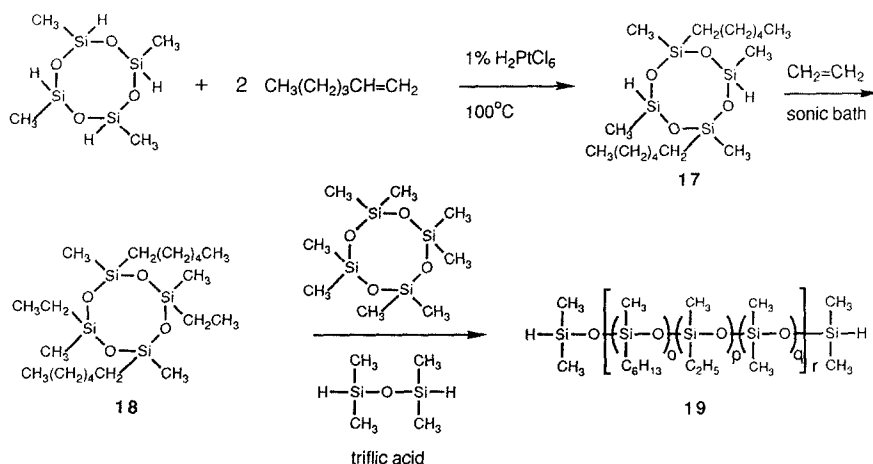
Fig. 2. Preparation of cross-linkable oligosiloxane **19**.

methyltrisiloxane-1,5-diyl)-1,4-butanediyl-1,4-phe-nylenecarbonylimino-1,2-cyclohexyleneiminocarbo-nyl-1,4-phenylene-1,4-butanediyl(dimethylsilyl-ene)](7) (Fig. 1). This copolymer was synthesized following the procedure described for **5** above using 0.22 g (0.55 mmol) of dialkene **12** and 0.16 g (0.58 mmol) of siloxane **14** to give 0.34 g (92%) of **7**; $[\alpha]_D = -61.0°$ ($c = 0.184$, CHCl$_3$).

Preparation of copolymer **8** (Fig. 1). Oligosiloxane **19** was first prepared (Fig. 2) by placing 2,4,6,8-tetramethylcyclotetrasiloxane (7.0 g, 0.12 mol) and 4.90 g (0.058 mol) of 1-hexene in a flask along with 15 μl of 1% chloroplatinic acid. The reaction mixture was heated overnight at 100°C to give **17** which was then transferred to a 50-ml PTFE centrifuge tube. Ethylene was bubbled into the mixture for 2 h and then the vial was capped and placed in a sonic bath. The reaction was continued until there was no Si–H band in the IR spectrum. The products were vacuum distilled to give 2.19 g of tetramethyldihex-yldiethylcyclotetrasiloxane (**18**) (b.p. 105–125°C/0.055 mmHg) and 1.52 g of by-product te-tramethyltrihexylethylcyclotetrasiloxane (b.p. 125–140°C/0.055–0.1 mmHg).

Compound **18** (0.39 g, 0.84 mmol) was combined with 0.25 g (0.84 mmol) of octamethylcyclotetrasi-loxane **14** and 0.17 g (1.27 mmol) of siloxane **13** (for endcapping) in a 50-ml PTFE centrifuge tube. The siloxanes were stirred together with a magnetic stir bar for 5 min and one drop of triflic acid was added. The reaction was continued for 2 min and 1.5 ml of

hexane were added and the mixture was stirred for an additional 10 min. HMDS (15 drops) was used to stop the reaction. The polymer was dissolved in 10 ml of dichloromethane and washed four times with 10-ml portions of water. The dichloromethane was evaporated and the polymer was dissolved in 10 ml of diethyl ether and filtered through a 0.2-μm filter to remove a white precipitate. The ether was evaporated to give 0.39 g (52%) of **19**. An NMR spectrum indicated the structure shown in Fig. 2.

Siloxane **19** (0.39 g, 0.45 mmol) and 0.18 g (0.41 mmol) of **9** were dissolved in 3 ml of toluene. Chloroplatinic acid (10 μl, 1%) was added and a condenser was placed in the top of the vial. The reaction was heated and stirred at 85°C under nitrogen until all of the alkene reacted. The polymer was treated as above for **4** to give 0.45 g (83%) of **8**; $[\alpha]_D = -31.3°$ ($c = 0.418$, CHCl$_3$).

RESULTS AND DISCUSSION

The typical chiral polysiloxane stationary phases for GC contain chiral moieties attached to a polymethylsiloxane backbone [4]. The chiral phases prepared in this study are different in that the polymers are composed of alternating chiral hydrocarbon and achiral polysiloxane units (Fig. 1). They were synthesized by a polymeric hydrosilylation of a bis (hydrosiloxane) and a dialkene-containing bisbenz-amide as shown.

The (1R,2R)-*trans*-1,2-diaminocyclohexane was

chosen as the chiral organic moiety because it is commercially available, has C_2 symmetry, and the amine groups are held in a semi-rigid position. The allyloxybenzoic acid portion of monomers 9–12 were used as the dialkene source (see Fig. 1) because they hydrosilylate well onto hydrosiloxanes and they are chemically and thermally stable under chromatographic conditions [7].

Once the chiral portion of the copolymer had been selected, the achiral bis(hydrosiloxane) monomers were chosen to study the effect of the length of the siloxane oligomer on the selectivity and efficiency of the chiral stationary phase. The original tetramethyldisiloxane spacer (13) reacted with 9 to give a highly crystalline material (1). Because of its high crystallinity, this copolymer was difficult to coat inside the fused-silica capillary column and manifested poor overall chromatographic properties. We felt that we could remedy this by increasing the number of siloxane units in the achiral spacer. Octamethyltetrasiloxane (14) was used to give polymer (2) which was still crystalline, but gave much better solute diffusion in the phase. Phase 2 proved to be an efficient stationary phase for the enantiomeric separation of a number of chiral diols [8,9].

Because phase 2 was still crystalline, a phase containing a dodecamethylhexasiloxane spacer (3) was synthesized as shown in Fig. 1. Dodecamethylhexasiloxane (15) needed for the preparation of phase 3 was prepared by equilibrating octamethylcyclotetrasiloxane (14) with tetramethyldisiloxane (13) using triflic acid. Equilibrium favoring higher-molecular-weight polysiloxanes occurs very rapidly in this reaction. In the first reaction to form 15, very little of the desired product was formed when the siloxanes and triflic acid were stirred overnight. The desired material could be isolated after allowing the reaction to run for only 4.5 min. GC, MS and NMR spectroscopy were used to characterize siloxane 15. We have since found the procedure of Uchida et al. [10] to be a convenient source of this dihydrosiloxane. The dodecamethylhexasiloxane (15) was distilled and reacted with alkene 9 to form phase 3 as a viscous liquid.

Phases 5 and 6 were prepared to determine the effect on enantiomeric selection of altering the position of the allyloxy group on the benzamide portion of the chiral monomer. Phase 5 has the ortho orien-

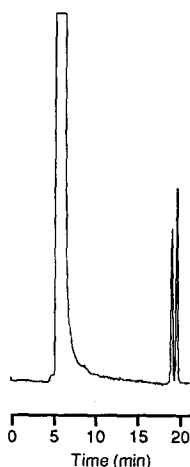Fig. 3. SFC separation of the enantiomers of cis-1,2-dihydroxycyclohexyl methyl ketone using a column coated with copolymer 6. Conditions: CO_2 at 60°C, 5 m × 50 μm I.D. fused-silica column (film thickness ≈ 0.20 μm), density programmed from 0.30 to 0.55 g ml^{-1} at 0.01 g ml^{-1} min^{-1} after an initial 5-min isopycnic period.

tation of the alkoxy and carboxamide moieties on the benzene rings and 6 has the meta orientation. Fig. 3 illustrates the excellent efficiency and selectivity obtained using a column coated with phase 6 for the separation of the cis-1,2-dihydroxycyclohexyl methyl ketone enantiomers.

An NMR–molecular modelling study involving alkene 9 and (+)- and (−)-diethyl tartrate indicated that the tartrate might be hydrogen bonding with the ether oxygen of the p-allyloxy group [11]. (1R-trans)-1,2-Cyclohexylenebis(4-butyl)benzamide was prepared for molecular modelling studies with (+)- and (−)-diethyl tartrate. It was predicted from these studies [11] that a phase containing a chiral monomer with no ether oxygen atoms could provide even better resolution of chiral diol enantiomers. To test this prediction we synthesized copolymer 7.

One of the requirement of a stationary phase for SFC is that it must be insoluble in the supercritical fluid over the density programming range. This can be accomplished by cross-linking the phase using azo-tert.-butane (ATB) or dicumyl peroxide (DCP) [12]. Phase 2 does not contain any vinyl or octyl groups which are normally added to aid cross-linking. When this phase was tested before and after free radical cross-linking, it showed a marked de-
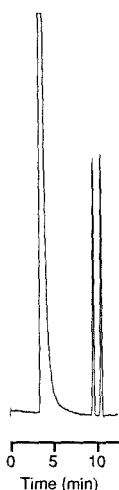
Fig. 4. SFC separation of an anticonvulsant drug (±-mepheny-toin) using a column coated with copolymer **8**. Conditions: CO_2 at 80°C, 5 m × 50 μm I.D. fused-silica column, density programmed from 0.50 to 0.80 g ml^{-1} min^{-1} after an initial 5-min isopycnic period.

crease in efficiency and selectivity. To overcome this problem, the cross-linkable phase **8** was prepared as shown in Fig. 1. The α,ω-dihydrosiloxane **19** containing hexyl and ethyl substituents was prepared as shown in Fig. 2. Preliminary work showed that phase **8** bled heavily from the column before cross-linking at 0.50 g ml^{-1} at 60°C, but after cross-linking, the phase did not bleed until 0.85 g ml^{-1} at 60°C. The ATB initiated cross-linking of **8** resulted in a phase with poor selectivity and efficiency while the phase cross-linked with DCP gave good chromatographic performance. Fig. 4 is a chromatogram showing the enantiomeric separation of the anticonvulsant drug (±)-mephenytoin on a DCP cross-linked phase (**8**).

Details of the preparation and chromatographic characterization of columns coated with these polymers are reported elsewhere [9]. Development of similar copolymers containing other chiral organic moieties is presently underway.

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