Tetrahedron Letters, Vol. 34, No. 1, pp. 79-82, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

NOVEL CYCLODEXTRIN-OLIGOSILOXANE COPOLYMERS AND THEIR USE AS STATIONARY PHASES FOR SEPARATING ENANTIOMERS IN OPEN TUBULAR COLUMN SUPERCRITICAL FLUID CHROMATOGRAPHY

Jerald S. Bradshaw,*† Guoliang Yi,† Bryant E. Rossiter,† Shawn L. Reese,†
Patrik Petersson,‡ Karin E. Markides,‡ and Milton L. Lee*†
Department of Chemistry
Brigham Young University, Provo, UT 84602-1022, USA
and
Department of Analytical Chemistry
Uppsala University, Box 531, S-751 21 Uppsala, Sweden

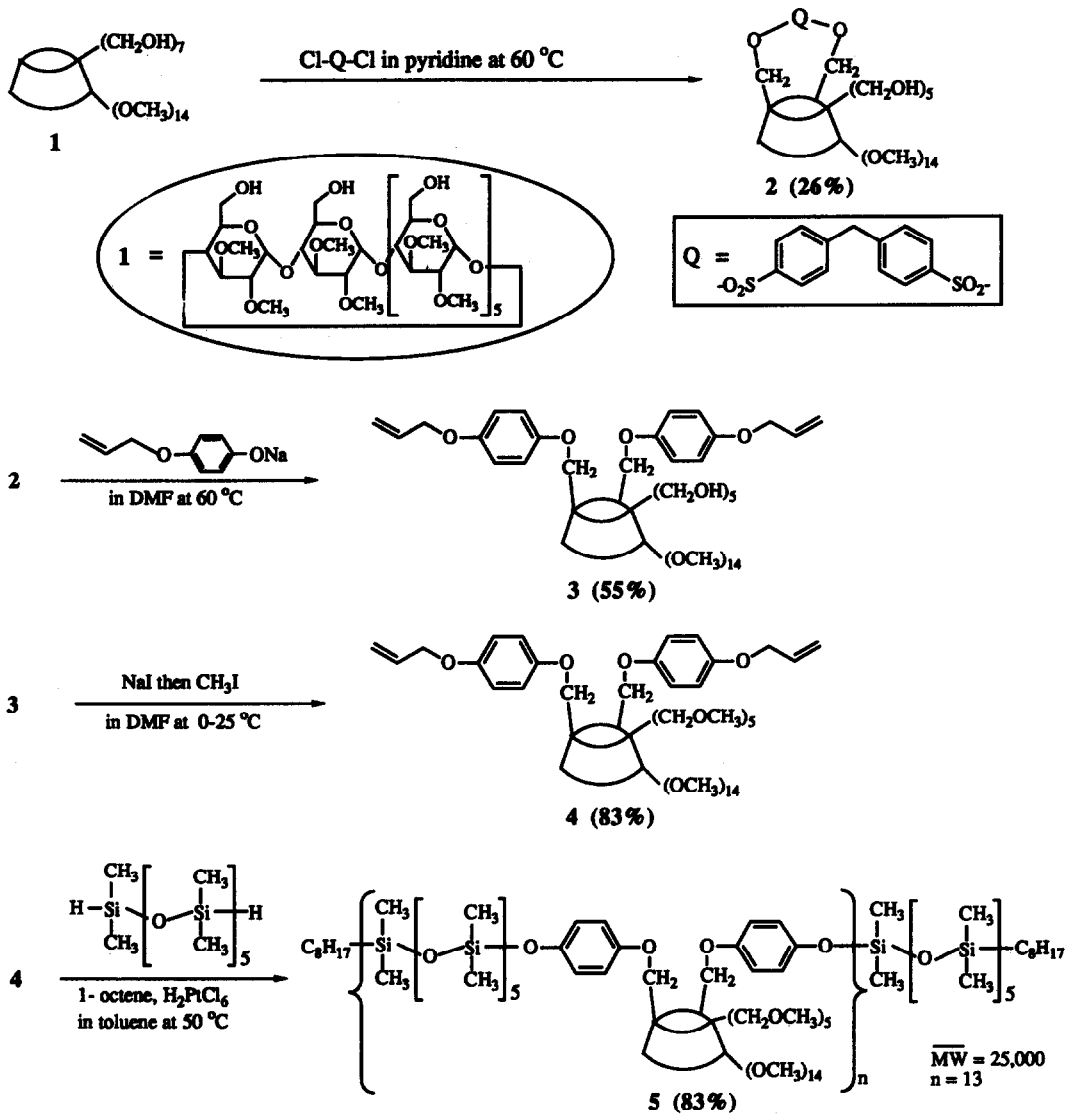
Summary: New stationary phases composed of cyclodextrin-oligosiloxane copolymers for open tubular column supercritical fluid chromatography have been developed. These phases allow the separation of enantiomers of a variety of chiral organic solutes.

The analytical chromatographic separation of enantiomers has become extremely important in light of the more stringent requirements for the enantiomeric purity of drugs.[1] Direct chromatographic separation using chiral stationary phases (CSPs) is the most convenient and reliable method to determine enantiomeric purity.[2]

We have recently reported new chiral stationary phases composed of copolymers of chiral organic and dimethyloligosiloxane units for open tubular column supercritical fluid chromatography (SFC).[3] These materials provide complete separation of a variety of chiral organic solutes. In view of the superior ability of the cyclodextrins to separate chiral molecules,[4] we have prepared cyclodextrin-oligosiloxane copolymeric stationary phases for open tubular column SFC. Two of these novel phases (**5** in Scheme I and **6**) exhibit noteworthy enantiomeric separation of a variety of chiral organic solutes (see Figure 1).

†Brigham Young University
‡Uppsala University

Scheme I. Preparation of β-Cyclodextrin-dimethylsiloxane Copolymer



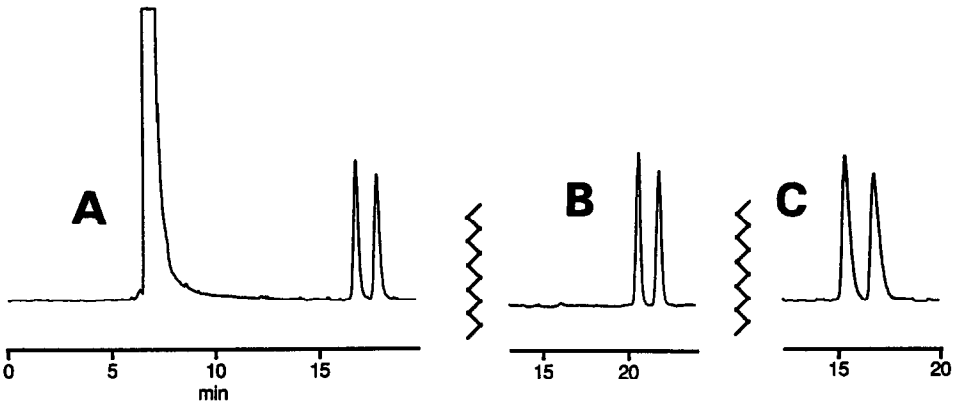


Figure 1. SFC separation of the enantiomers of diethyl tartrate (A) and *t*-2-phenylcyclohexanol (B), on phase **5** and ibuprofen (C) on phase **6**. Conditions are given in the text.

Copolymer **5** was prepared by the multi-step sequence shown in Scheme I. Heptakis(2,3-di-O-methyl)-β-cyclodextrin (**1**) was prepared as reported,[5] except that ammonium fluoride was used to remove the silyl protecting groups[6] rather than tetrabutylammonium fluoride. Bissulfonate ester **2** was prepared using *p,p'*-methylenebis(benzenesulfonyl chloride) as was reported for β-cyclodextrin.[7,8] Compound **2** was reacted with an excess of sodium *p*-allyloxyphenoxide to give the bis(*p*-allyloxyphenoxy)-substituted heptakis(2,3-di-O-methyl)-β-cyclodextrin (**3**). We have previously found that the allyloxyphenyl group is one of the best alkenes for the hydrosilylation reaction.[3b] Allyloxy-substituted **3** was further methylated to give permethylated diene **4**.[8] Copolymer **5** was prepared by the hydrosilylation of **4** with dodecamethylhexasiloxane in a manner similar to that reported.[3b] Copolymer **6** was prepared in the same manner as **5** except one part dihexyldimethylsiloxane and three parts dodecamethylhexasiloxane were used, giving a polymer with some hexyl substituents.

Copolymers **5** and **6** were coated on 5-M x 50-μM i.d. fused silica columns with a film thickness of about 0.25 μM as reported.[3c] Preliminary testing of these phases has been done using SFC at 60°C (polymer **5**) and 65°C (polymer **6**) with CO_2 as the carrier. The columns were density programmed from 0.30 g mL^{-1} at 0.010 g mL^{-1} min^{-1} after a 1-min isopycnic period (**5**) or from 0.40 g mL^{-1} at 0.005 g mL^{-1} min^{-1} after a 1-min isopycnic period (**6**). Enantiomer separations were observed for chiral diols and monoalcohols, ketones and carboxylic acids containing aromatic substituents. For example, Figure 1 shows the separations of diethyl tartrate (A) and *t*-2-phenylcyclohexanol (B) using phase **5** and 2-(*p*-isobutylphenyl)propanoic acid (ibuprofen) (C) using phase **6**. Numerous other enantiomeric pairs have been resolved using these phases,[9] indicating a significantly broader application range than observed using the more conventional three-point interactive phases.

Cyclodextrin-based stationary phases have been used in liquid chromatography (LC), gas chromatography (GC), and SFC.[10] It is believed that in aqueous media, as is often used in LC, the predominating mechanism for chiral recognition is the formation of molecular inclusion complexes of the enantiomeric solutes in the cyclodextrin cavity.[11]

The recognition mechanism in GC and SFC columns, where relatively nonpolar mobile phases are used, is not well established.[12] Inclusion complexation is possible in GC since the carrier gas does not compete with the sample solutes for complexation in the cyclodextrin cavity.[13] Regarding the relative roles of different types of forces on inclusion complexation and recognition, Schürig and co-workers and Armstrong and co-workers suggested that both weak and strong interactions might be involved and that chiral recognition might even take place on the outer surface of the cyclodextrin toroid.[10,14] From this study, it is believed that in SFC when carbon dioxide is used as the mobile phase, solute inclusion in combination with dipolar interactions with the ether groups of the CD are involved in the recognition process.

Acknowledgment

This work was supported by a grant from Supelco.

References

1 (a) *Chem. Eng. News* **1990**, *68*, 38 (March 19, 1990); (b) Stevensen, D.; Wilson, I.D. (Eds) *Chiral Separations* **1988**, Plenum Press, New York; (c) DeCamp, W.H. *Chirality* **1989**, *1*, 2.
2 Allenmark, S.G. *Chromatographic Enantioseparation* **1988**, Ellis Norwood, Chichester, England, Chapter 3.
3 (a) Rossiter, B.E.; Petersson, P.; Johnson, D.F.; Eguchi, M.; Bradshaw, J.S.; Markides, K.E.; Lee, M.L. *Tetrahedron Lett.* **1991**, *32*, 3609; (b) Johnson, D.F.; Bradshaw, J.S.; Eguchi, M.; Rossiter, B.E.; Lee, M.L.; Petersson, P.; Markides, K.E. *J. Chromatogr.* **1992**, *594*, 283; (c) Petersson, P.; Markides, K.E.; Johnson, D.F.; Rossiter, B.E.; Bradshaw, J.S.; Lee, M.L. *J. Microcol. Sep.* **1992**, *4*, 155.
4 (a) Armstrong, D.W.; Li, W.-Y.; Chang, C.-D.; Pitha, J. *Anal. Chem.* **1990**, *62*, 914; (b) Bicchi, C.; Artuffo, G.; D'Amato, A.; Nano, G.N.; Galli, A.; Galli, M. *J. High Resolut. Chromatogr.* **1991**, *14*, 301; (c) Keim, W.; Köhnes, A.; Meltzow, W.; Römer, H. *J. High Resolut. Chromatogr.* **1991**, *14*, 507.
5 Takeo, K.; Mitoh, H.; Uemura, K. *Carbohydr. Res.* **1989**, *187*, 203.
6 Zhang, W.-J.; Robins, M.J. *Tetrahedron Lett.* **1992**, *33*, 1177.
7 Tabushi, I.; Shimokawa, K.; Shimizu, N.; Sherakata, H.; Fujita, K. *J. Am. Chem. Soc.* **1976**, *98*, 7855.
8 Satisfactory elemental analyses and ^{1}H and ^{13}C NMR spectra were obtained on all new momeric cyclodextrin derivatives.
9 Petersson, P.; Markides, K.E.; Yi, G.-L.; Rossiter, B.E.; Bradshaw, J.S.; Lee, M.L., in preparation.
10 (a) Schürig, V.; Nowotny, H.-P. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 939; (b) Schmalzing, D.; Nicholson, G.J.; Jung, M.; Schürig, V. *J. Microcol. Sep.* **1992**, *4*, 23; (c) Schürig, V.; Juvancz, Z.; Nicholson, G.J.; Schmalzing, D. *J. High Resolut. Chromatogr.* **1991**, *14*, 52.
11 Menges, R.A.; Armstrong, D.W. *Chiral Separations by Liquid Chromatography* **1991**, S. Ahuja ed., ACS Symposium Series 471, American Chemical Society, Washington D.C., USA, p. 67.
12 Kano, K.; Yoshiyasu, K.; Hashimoto, S. *J. Chem. Soc. Chem. Commun.* **1989**, 1278.
13 Armstrong, D.W.; Li, W.Y.; Stalcup, A.M.; Secor, H.V.; Izac, R.R.; Seeman, J.I. *Anal. Chim. Acta* **1990**, *234*, 365.
14 Berthod, A.; Li, W.-Y.; Armstrong, D.W. *Anal. Chem.* **1992**, *64*, 873.

(Received in USA 16 September 1992)