A New Chiral Stationary Phase for Gas Chromatography by Use of a Chiral Thiacalix[4]arene Derivative

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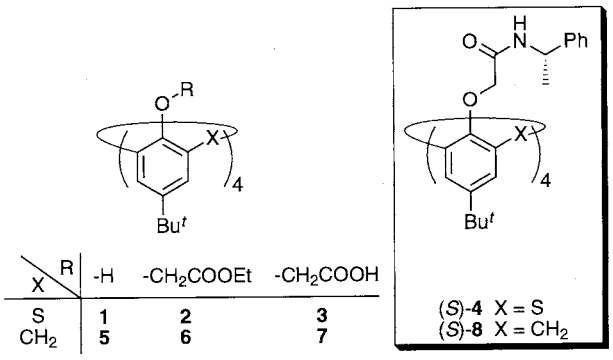
A new chiral stationary phase for capillary gas chromatography based on a chirally modified *p-tert*-butylthiacalix[4]arene with (*S*)-1-phenylethylamine was prepared to show good separations of enantiomeric amino acid, amine and alcohol derivatives, while the corresponding *p-tert*-butylcalix[4]arene counterpart did not differentiate the enantiomers.

In the last decade, a wide variety of chiral stationary phases (CSPs) have been developed for direct separation of enantiomers by gas chromatography (GC).[1] Among such CSPs, those based on variously modified cyclodextrins (CDs) have been most widely utilized because of their excellent chiral recognition as well as ready availability. This class of CSPs, however, suffer from several limitations inherent in the use of naturally occurring *d*-glucose as the chiral element; unavailability of the mirror image isomer of the chiral selector to reverse the elution order of a pair of enantiomers. Selectivity and stability of trifluoroacetylated-CD columns often diminish due to the hydrolysis of ester groups by moisture in sample.

Although calixarenes have macrocyclic structure like as CDs and have been one of the key compounds in molecular recognition chemistry,[2] they have, to the best of our knowledge, never been utilized for the construction of the chiral stationary phase for neither GC nor liquid chromatography.[3] Since we succeeded in a facile synthesis of *p-tert*-butylthiacalix[4]arene (TCA, **1**),[4] in which the bridging methylenes of the calix[4]arene (CA, **5**) are replaced by epithio groups, we have for some time been interested in the syntheses and properties of chirally modified TCAs. Herein, we report the preparation of an (*S*)-1-phenylethylamine-modified TCA [(*S*)-**4**] and CA [(*S*)-**8**] and their performances as chiral selectors for GC separation of enantiomers.



Cone-shaped tetraester **2**, which had been obtained from TCA **1** by treatment with ethyl bromoacetate and Na_2CO_3 in acetone,[5] was hydrolyzed to the tetracarboxylic acid **3** followed by conversion to the acid chloride and then treatment with (*S*)-1-phenylethylamine to give the tetramide (*S*)-**4**.[6] Starting from CA **5**, a sequence of similar transformations afforded the methylene analog (*S*)-**8**.[6] These chiral amides were coated on glass capillary columns as usual[7,8] and their gas chromatographic performances were examined for various samples of racemic amino acid, alcohol, and amine derivatives (Table 1, Figure 1).[9]

It can be seen that (*S*)-**4**-coated column showed not only good chemoselectivity but enantioselectivity for all racemic samples examined, while (*S*)-**8**-coated column did not indicate any enantioselectivity at all. As an α value (separation factor) of 1.02 or greater is considered to be of practical application in chiral discrimination by capillary GC, (*S*)-**4** demonstrated that TCA is an excellent skeleton to construct chiral selector for enantioseparation.

In terms of derivatization of analytes, non-derivatized alcohols and amines were poorly resolved on the (*S*)-**4** column possibly due to the insufficient retention and interaction with the CSP.[10]

Table 1. Capacity factor(k') and selectivity factor(α) of the enantiomers

Amino acids 		(*S*)-4		(*S*)-8	
-R (abbr.)	T / °C	k' (conf.)[a]	α	k'	α
-Me (Ala)	80	6.823 (*R*)	1.040	1.798	1.000
-Pr^i (Val)	80	9.100 (*R*)	1.050	5.075	1.000
-Bu^s (Ile)	90	9.050 (*R*)	1.037	3.939	1.000
-Pr (Nva)	90	9.215 (*R*)	1.037	3.196	1.000
-Bu^i (Leu)	90	12.83 (*R*)	1.038	3.756	1.000
-Bu (Nle)	90	15.83 (*R*)	1.032	5.197	1.000
$-CH_2CH_2SCH_3$ (Met)	100	9.454 (*R*)	1.013	3.783	1.000
-Ph (Phgly)	120	15.84 (*S*)	1.028	6.251	1.000
$-CH_2CO_2Pr^i$ (Gul-iPr)	130	16.25 (*R*)	1.015	6.989	1.000
$-CH_2$ Ph (Phe)	140	10.82 (*S*)	1.021	4.262	1.000
Alcohols		(*S*)-4		(*S*)-8	
-R	T / °C	k' (conf.)[a]	α	k'	α
-Me	140	10.314(*R*)	1.019	5.332	1.000
-Et	140	14.207	1.039	7.614	1.000
-Pr^i	140	16.126	1.026	8.826	1.000
-Pr	140	20.859	1.020	9.667	1.000
Amines		(*S*)-4		(*S*)-8	
-R	T / °C	k' (conf.)[a]	α	k'	α
-Me[b]	120	7.744 (*R*)	1.054	1.542	1.000
$-CH_2$-O-$COCF_3$	130	8.319 (*R*)	1.033		

Carrier gas: He (15 cm/s); Non-retained peak (CH_4) at 2.757 min; T: column temperature. [a]Configuration of the first-eluted enantiomer. [b]The chromatogram is given in the graphical abstract.

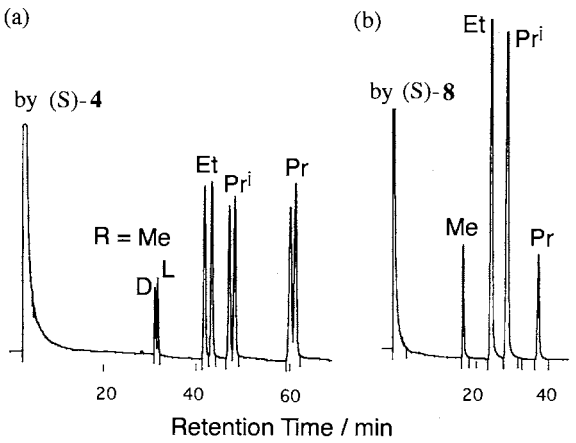


Figure 1. Typical chromatograms for the separation of 1-phenylalcohol isopropylcarbamate enantiomers by CSPs with (a) (*S*)-**4** and (b) (*S*)-**8**. Carrier gas: He (15 cm/s); column temperature: 140 °C.

The elution order is consistent in that, where the absolute stereochemistry of the analytes is known, the *R*-enantiomers were eluted prior to the *S*-counterparts, only two exceptions being the phenylglycine and phenylalanine derivative. Although further works should be done for elucidation of the chiral discrimination mechanism, stereoselective hydrogen bonding between the amide group of the analytes and (*S*)-**4** might play an important role for the chiral differentiation, as is suggested in the separation of enantiomers by chiral amide stationary phases derived from amino acids.[1]

The origin of the sharp contrast in the enantioselectivity between the two columns is not clear at present, while it may be, at least in part, ascribed to the difference in the melting points of the chiral selectors; amides (*S*)-**4** and (*S*)-**8** melted at 118 °C and 323 °C, respectively. Thus, it seems that amide (*S*)-**8** was in a solid state even in the OV-17 matrix at the operating temperature (~180 °C) and the chiral functional groups remained frozen to prevent effective interaction with the analytes. Judging from the pretreatment conditions used for the preparation of the (*S*)-**4** column, it may be safely used at least at 200 °C.[11]

In conclusion, we have shown here that TCA provides a hopeful basic unit for the construction of CSPs for GC separation of enantiomers. Systematic studies to develop superior chiral selectors to (*S*)-**4** and to clarify the separation mechanism are now under way by controlling the chiral moiety and the conformation of thiacalix[4]arene skeleton.

References and Notes

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3 Recently, chirally modified calix[4]arenes have been utilized as a *pseudo*stationary phase in capillary electrophoresis. See M. S. Peña, Y, Zhang, S. Thibodeaux, M. L. McLaughlin, A. M. de la Peña and I. M. Warner, *Tetrahedron Lett.*, **37**, 5841 (1996); M. S. Peña, Y, Zhang, and I. M. Warner, *Anal. Chem.*, **69**, 3239 (1997).

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6 Preparations. A mixture of **2**[5] (1.07 g, 1.00 mmol) and potassium carbonate (2.76 g, 20.0 mmol) in DMSO-water (6:1, 35 cm^3) was heated at 120 °C for 12 h and then to the cooled mixture was added 2 M HCl (60 cm^3) in an ice-water bath. Precipitate was collected by filtration and washed with water, then dissolved in chloroform. After filtering off the solid residue, the filtrate was evaporated to dryness to obtain **3**, which was recrystalized form water-acetone to obtain a pure sample (840 mg, 87%). A mixture of **3** (0.96 g, 1.0 mmol) and thionyl chloride (10 cm^3) was refluxed for 2 h. After cooling, thionyl chloride was evaporated and further removed *in vacuo* at 80 °C for 1 h. The dichloromethane solution (20 cm^3) of the acid chloride was dropped to a dichloromethane solution (20 cm^3) of optically pure (*S*)-1-phenylethylamine (0.90 mg, 7.39 mmol) and triethylamine (0.68 mg, 6.69 mmol) at 0 °C. After dropping was complete, the mixture was stirred at room temperature for a further 1 h. The reaction was terminated by addition of HCl solution (2 M, 10 cm^3) at 0 °C. After extracting with chloroform (50 cm^3 × 3), the chloroform layer was evaporated to dryness to obtain crude product, which was purified by column chromatography (100 g silica gel, 1:4~1:1 ethyl acetate:chloroform) to obtain pure (*S*)-**4** (1.03 g, 76%). The compound (*S*)-**8** was obtained by a similar manner from **6**[5] *via* **7**. Properties. **3**: Mp 293.4~294.8 °C. Found: C, 60.48; H, 5.92; S, 13.46%. Anal. Calcd. for $C_{48}H_{56}O_{12}S_4$: C, 60.23; H, 5.70; S, 13.62%. ν(KBr)/cm^{-1} 3421 (OH), 2964 (CH), 1740 (CO). ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 36H, Bu^t), 5.08 (s, 8H, CH_2), 7.38 (s, 4H, Ar-H) ppm. (*S*)-**4**: Mp 117.8~119.1 °C. Found: C, 70.05; H, 6.85; S, 4.01%. Anal. Calcd. for $C_{80}H_{88}N_4O_8S_4$: C, 70.35; H, 6.79; S, 4.10%. ν(KBr)/cm^{-1} 3585~3317 (NH), 2964 (CH), 1668 (CO). ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 36H, Bu^t), 1.59 (d, *J* 7.0, 12H, Me), 4.77 (ABq, *J* 15.0, Δν 40 Hz, 8H, OCH_2CO), 5.14~5.21 (m, 4H, CH), 7.15~7.28 (m, 8H, Ar-H), 7.89 (d, *J* 8.0, 4H, NH) ppm. $[\alpha]_D^{29}$ -44.0° (c 1.02, C_2H_5OH). (*S*)-**8**: Mp 322.6~323.1 °C. ν(KBr)/cm^{-1} 3309 (NH), 2964 (CH), 1653 (CO). ^{1}H NMR ($CDCl_3$): δ 1.055 (s, 36H, Bu^t), 1.49 (d, *J* 7.0, 12H, Me), 3.03 (d, *J* 13.2, 4H, Ar-CH_2-Ar), 4.32 (d, *J* 13.2, 4H, Ar-CH_2-Ar), 4.34 (s, 8H, -OCH_2CO), 5.16 (t, *J* 7.45, 4H, CH), 6.68 (d, *J* 9.45, 8H, Ar-H), 7.23 (m, 20H, Ph), 7.51 (d, *J* 5.45, 4H, NH) ppm. $[\alpha]_D^{26}$ -36.1° (c 1.01, $CHCl_3$).

7 M. L. Lee and B. W. Wright, *J. Chromatogr.*, **184**, 235 (1980).

8 A glass capillary column (25 m × 0.25 mm i.d.) was leached with 6 M HCl at 170 °C for 12 h, deactivated with barium carbonate and statically wall-coated with a dichloromethane solutions of (*S*)-**4** (0.13% w/v) with OV-17 (0.08% w/v) or (*S*)-**8** (0.23% w/v) with OV-17 (0.17% w/v). Film thickness: 0.13 μm for (*S*)-**4** and 0.25 μm for (*S*)-**8** coated capillaries.

9 S. Ôi, Y. Ochiai, and S. Miyano, *Chem. Lett.*, **1991**, 1575, and literatures cited therein.

10 Retention data for 1-phenylethylalcohol: k' = 14.782, α = 1.012 at 90 °C. For 1-phenylethylamine: k' = 4.491, α = 1.000 at 100 °C. Each on (*S*)-**4**-coated column.

11 No direct comparison of the thermostability between (*S*)-**4**- and CD-coated columns has been attempted. The maximum allowable operating temperatures of commercially available CD columns range from 180 to 250 °C depending upon the functional groups introduced into CDs. See "CHIRALDEX™ Hand Book, A Guide to Using Cyclodextrin Bonded Phases for Chiral Separations by Capillary Gas Chromatography," 5th ed., Advanced Separation Technologies Inc., Whippany (1996).