Preparation of a Chiral Stationary Phase for the Liquid Chromatographic Separation of Enantiomers

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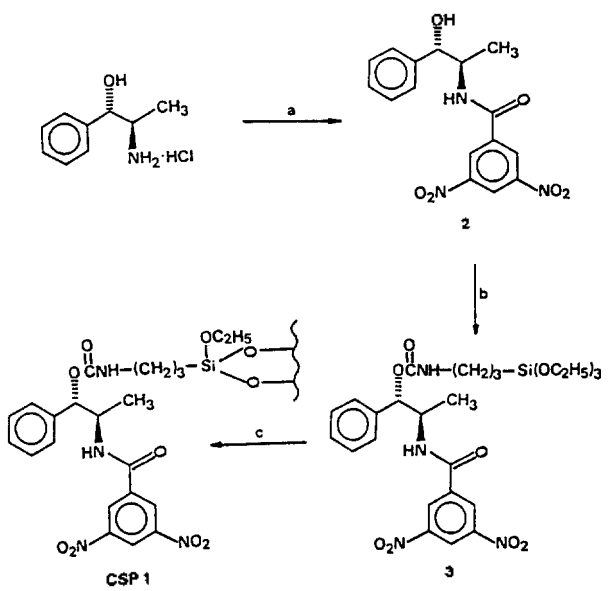
Recently, the liquid chromatographic direct separation of enantiomers on chiral stationary phases (CSPs) has been recognized to be the most promising technique for the determination of enantiomeric composition of optically active materials. During the last decade, various efforts have been devoted to the development of new chiral stationary phases for the liquid chromatographic resolution of enantiomers and, as results, various CSPs have been introduced[1]. In this area, our efforts have resulted in the development of various CPSs which discriminate between enantiomers through the $\pi-\pi$ interaction between CSPs and racemic analytes[2].

In this communication, we want to report the preparation of a new CSP by connecting N-3,5-dinitrobenzoyl-(1S,2R)-norephedrine to silica gel. (1S,2R)-norephedrine is attractive as a candidate for CSPs because (1S,2R)-norephedrine is readily avaiable as an optically active form with a reasonable price. The conformational flexibility of (1S,2R)-norephedrine also attracts our interest because CSP derived from (1S,2R)-norephedrine is expected to show a certain degree of conformational flexibility. One the other hand, Pirkle type CSPs derived from N-3,5-dinitrobenzoylamino acids are conformationaly quite rigid because of the intramolecular hydrogen-bonding[3]. Therefore, comparison of the resolution behaviour on CSPs which have different conformational flexibility may provide insights into the role of the conformational rigidity or flexibility of CSPs on the chiral recognition.



Scheme 1. [a](a) 3,5-dinitrobenzoyl chloride, triethylamine, CH_2Cl_2, R. T.; (b) isocyanatopropyltriethoxysilane, triethylamine, toluene, reflux; (c) 10 μm Spherisorb silica gel, benzene, reflux, Dean-Stark trap.

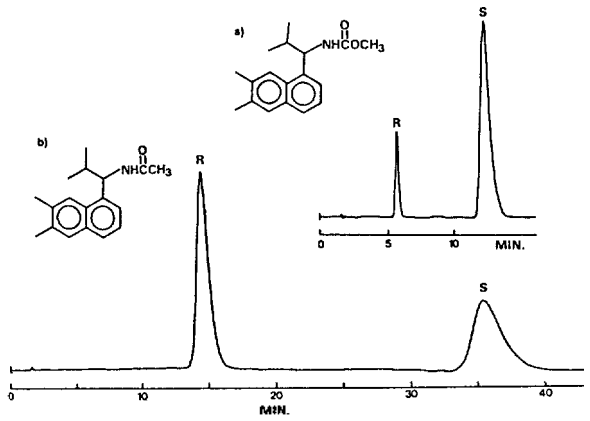


Figure 1. Liquid chromatographic resolutions of a) N-carbomethoxy and b) N-acethyl-1-[1-(6,7-dimethylnaphthyl)]-1-amino-2-methylpropane on CSP 1. The chromatographic system used consists of Waters Model 510 pump, Waters Model U6k Liquid Chromatographic Injector, Waters Model 441 Absorbance Detector and Waters Model 740 data Module Recorder. Chromatograms were obtained by using 10% isopropyl alcohol in n-hexane as a mobile phase with flow rate of 2 ml/min at 254 nm UV. The separability factors, α, for a) and b) are 2.71 and 2.70 while the capacity factors for the first eluted enantiomers are 2.73 and 8.78 respectively.

Preparation of CSP 1 is summarized in Scheme 1[4]. As shown in Scheme 1, the method is quite simple and involves only three steps: i) N-3,5-dinitrobenzoylation, ii) formation of triethoxysilylcarbamate and iii) bonding to silica gel. CSP 1 thus prepared contains a strong π-acidic site such as 3,5-dinitrobenzoyl group. Therefore CSP 1 may be used for the resolution of racemates containing π-basic functional groups.

The resolution of N-acetyl and N-carbomethoxy-1-[1-(6,7-dimethyl-naphthyl)]-1-amino-2-methylpropane on CSP 1 are shown in Figure 1. As shown in the Figure, the optical resolutions on CSP 1 are quite excellent and even better than those on the CSP derived from (R)-3,5-dinitrobenzoylphenylglycine[5]. The analytes shown in Figure 1 have appreciable conformational control engendered by their peri-hydrogen and the steric bulk of the isopropyl group on the chiral center. However, resolutions of analytes such as N-acyl-1-(1-naphthyl)ethylamines which are conformationally less rigid than those shown in Figure 1 on CSP 1 were found to be worse than those on CSP derived from 3,5-dinitrobenzoylphenylglycine.[6]

To explain the chiral recognition mechanism exerted by CSP 1, we need to collect more data. However, at this stage, we suspect that a conformationally flexible CSP may show better chiral recognition for conformationally rigid analytes than a conformationally rigid CSP while a rigid CSP may show better chiral recognition for flexible analytes than a flexible CSP. The chiral recognition by a CSP has been known to require a minimum of three simultaneous interactions with at least one of the two enantiomers.[7] It is plausible to imagine that a rigid CSP which has three interaction sites in a distinct geometric array can best discriminate between enantiomers which have three complimentary interaction sites at the proper position. However, if the three interaction

sites of analytes are not arranged properly to contact with the three interaction sites of a rigid CSP, the analyte conformation should be altered in order to interact with the rigid CSP. In consequence, a rigid CSP may show better chiral recognition for flexible analytes than a flexible CSP and vice versa. To the best of our knowledge, this is the first time to propose the role of the conformational flexibility of CSPs in the resolution of rigid analytes even though Pirkle previously suggested the role of the rigidity of CSPs in chiral recognition.[8] However, it should be noted that the structural differences between the two CSPs which have different conformational rigidity may also be responsible for the different chiral recognition behaviors. The efforts to elucidate the chiral recognition mechanism concerning the role of the second stereogenic center of CSP 1 and to generalize the assumption described above are still under progress in our laboratory.

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References

1. For reviews, see (a) W. H. Pirkle and T. C. Pochapsky, *Chem. Rev.* **89**, 347 (1989); (b) W. H. Pirkle and G. S. Mahler in "Synthesis and Separation using Functional Polymers", D. C. Sherrington and P. Hodge, Eds., John Wiley and Sons Ltd., New York, 1988; Chap. 9; (c) Y. Okamoto, *Chemtech*, 176 (1987).
2. (a) W. H. Pirkle and M. H. Hyun, *J. Org. Chem.* **49**, 3043 (1984); (b) W. H. Pirkle, M. H. Hyun and B. Bank, *J. Chromatogr.* **316**, 585 (1984); (c) W. H. Pirkle and M. H. Hyun, *J. Chromatogr.* **322**, 295 (1985); (d) W. H. Pirkle and M. H. Hyun, *J. Chromatogr.* **322**, 309 (1985); (e) M. H. Hyun and W. H. Pirkle, *J. Chromatogr.* **393**, 357 (1987).
3. (a) W. H. Pirkle, C. J. Welch and M. H. Hyun, *J. Org. Chem.* **48**, 5022 (1983); (b) P. Macaudiere, M. Lienne, A. Tambute and M. Caude in "Chiral Separation by HPLC: applications to pharmaceutical compounds", A. M. Krstulovic, Ed., Ellis Horwood LTD., Chichester, 1989; Chap. 14.
4. The spectroscopic and the physical data of compounds 2 and 3 and the microanalysis data for CSP 1 are as following; (compound 2) yield: 83%, m.p.: 181–183 °C, 1H NMR ($CDCl_3$, DMSO) δ 1.10 (d, 3H), 4.32 (m, 1H), 4.82 (d, 2H), 7.21 (d, 5H), 8.54 (d, 1H), 8.88 (d, 2H), 9.05 (s, 1H), IR(KBr): cm^{-1} 3380, 3350, 1660, 1550 (compound 3) yield: 68%, m.p.: 168–170 °C, ^1H NMR ($CDCl_3$) δ 1.15 (m, 20H), 3.75 (q, 6H), 5.85 (broad, 2H), 7.20 (d, 5H), 8.85 (s, 2H), 8.95 (d, 1H), IR (KBr) cm^{-1} 3310, 2900, 1700, 1660, 1550; (CSP 1) Anal. Found: C, 3.45; N, 0.47; H, 0.61. Calcd.: 0.11 mmol/g (based on N); 0.13 mmol/g (based on C).
5. see 3. (a).
6. For example, the α value for the resolution of N-acethyl-1-[1-(6,7-dimethyl naphthyl)]-1-aminoethane on CSP 1 under the chromatographic condition shown in Figure 1 was 1.50 while it was 2.20 on the CSP derived from 3,5-dinitrobenzoylphenylglycine (see Ref. 3a).
7. This has been known as "the Three Point Interaction Model"; see C. E. Dalgleish, *J. Chem. Soc.* 3940 (1952) and the review articles cited in reference 1.
8. W. H. Pirkle, T. C. Pochapsky, G. S. Mahler and R. E. Field, *J. Chromatogr.* **348**, 89 (1985).