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Note

Preparative separation of enantiomers by flash chromatography

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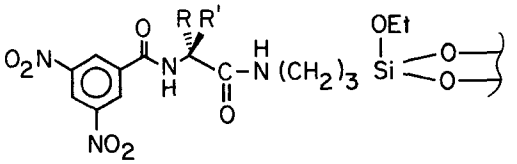
Chiral stationary phases (CSPs) developed in our laboratories are proving capable of separating the enantiomers of thousands of racemates[1]. For example, recent reports show the separation of the enantiomers of several phthalides[1] and an assortment of benzodiazepinones[2] to be so straightforward as to suggest that even modestly efficient chromatography systems might be satisfactory vehicles for some of these resolutions.

Flash chromatography is much used in synthetic laboratories as a rapid and inexpensive purification technique[3–5]. Since improved procedures have simplified the preparation of CSP 1 and 2 and since the development of increasingly selective CSPs can be anticipated, we felt it important to demonstrate just how easily many enantiomers may be separated.



1: R = Ph R′ = H 2: R′ = $(CH_3)_2CHCH_2$ R = H

We report here an improved procedure for the preparation of CSPs 1 and 2 on a multi-kilogram scale. We also comment on the advantages and limitations of flash chromatography for the resolution of racemates.

EXPERIMENTAL

Preparation of the aminopropyl silica gel

A slurry of 4 kg of Grace, grade 951, silica gel (58 μm) in 8 l of benzene, contained in a 22-l round bottomed flask, was dried by azeotropic distillation of water (Dean-Stark trap). When the collection of water had essentially ceased, 400 g of triethoxy-γ-aminopropyl silane (Petrarch) was added from an addition funnel over a 20-min period. Ethanol and additional (liberated) water were azeotropically removed. The mixture was kept at reflux overnight and after being allowed to cool, the supernatant liquid was removed by suction through a filter stick (a glass tube with a glass frit on its end). The solid was twice suspended in benzene and sucked

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dry. The resulting material was used, as such, in the preparation of the CSP. A portion, after washing with methanol and thorough drying, gave the following elemental analysis: C 3.61 N 0.55.

Preparation of the CSP 1

Solid (*R*)-N-3,5-dinitrobenzoylphenylglycine (346 g) (prepared as described in ref. 8) and 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), 300 g, were added to the aminopropyl silica gel (*ca.* 4 kg) described above. Enough methylene chloride was added (*ca.* 6 l) to suspend the solids when the flask was swirled. The reaction mixture turns dark in color as the reagents dissolve. The contents of the flask were periodically swirled over a 2-h period and the supernatant liquid was removed by suction. The CSP was then washed with six 2-l portions of methanol. Much longer reaction times or failure to remove the quinoline by methanol wash can lead to partial racemization of the CSP. Removal of the last traces of quinoline and dinitrobenzoylphenylglycine was achieved by washing the packed column with methanol prior to use. A thoroughly washed and dried portion of the chiral packing gave the following elemental analysis: N 1.15 C 5.36. The (*S*)-leucine derived CSP, 2, was prepared in an analogous way.

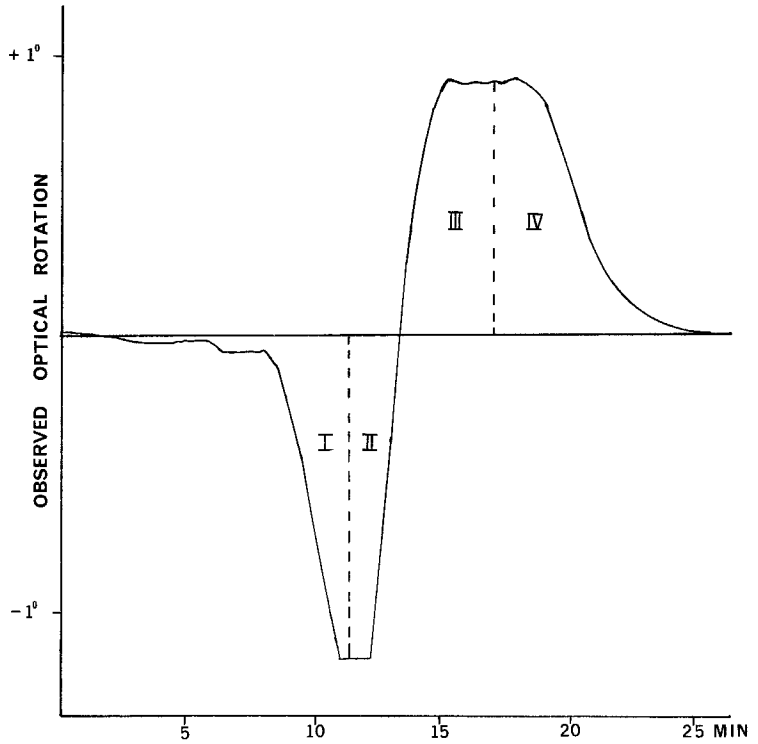


Fig. 1. Flash chromatogram of 4a (1 g on 300 g CSP 1) obtained using a Rudolph Autopol III polarimeter with a 20-cm flow cell. Enantiomeric purities of the four fractions were: I, 98% ee; II, 26% ee; III, 50% ee; IV, 74% ee.

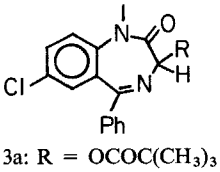
Chromatographic procedure

The standard procedure for flash chromatography was used as far as apparatus, packing, sample application etc. are concerned[3]. Mixtures of 2-propanol (2–5%) and hexane were used as the mobile phase. An overpressure of nitrogen was adjusted to give a linear flow velocity of *ca.* 50 mm/min (ref. 3). Fractions of 20 ml were collected[3]. The contents of the fractions were monitored by thin-layer chromatography (TLC) (silica gel, E. Merck, 60 F254)[3]. When complete (or near complete) separation of the enantiomers was achieved, this was obvious from the TLC evaluation. If but partial separation is obtained, other detection methods are more useful. A polarimeter equipped with a flow cell can give visual indication as to when fractions should be collected. (Fig. 1). Commercially available chiral high-performance liquid chromatography (HPLC) columns containing CSP 1 or 2 may be used for fraction evaluation; this method was employed in several of the described experiments. Finally, chiral TLC plates[9] might be used for fraction evaluation. We have not used this approach but it is, in principle, sound. However, visualization of the spots against the CSP background might be troublesome in some cases.

RESULTS AND DISCUSSION

Using a 150 × 40 mm bed (120 g) of CSP 1, a 200-mg sample of racemic benzodiazepinone 3a was completely resolved into its enantiomers. Similar results were achieved in the case of compounds 3b and 3c. Attempts to resolve 1 g of each of 3b and c and 4a and b on a 200 × 60 mm bed (300 g) of CSP 2 afforded incomplete separation. Nevertheless, it was found for each of the above compounds that the fractions containing the first and last thirds of the applied material were enantiomerically pure. Thus *ca.* 300 mg of each pure enantiomer were obtained.

(3)



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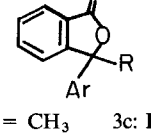

3a: R = $OCOC(CH_3)_3$ 3b: R = CH_3 3c: R = $CH(CH_3)_2$
4a: Ar = 1-(3,7-dimethylnaphthyl), R = CH_3
4b: Ar = 1-(4,7-dimethylnaphthyl), R = n-C_4H_9

Thus were obtained: 3b (*R*)-enantiomer, m.p. = 201–204°C, $[\alpha]_D^{25} = -152.3$ (C 2.36, $CHCl_3$); (*S*)-enantiomer, m.p. 203–205°C, $[\alpha]_D^{25} = +155.4$ (C 1.90, $CHCl_3$); 3c (*R*)-enantiomer, m.p. 190–191°C, $[\alpha]_D^{25} = -110.0$ (C 2.14, $CHCl_3$), (*S*)-enantiomer, m.p. 189–191°C, $[\alpha]_D^{25} = +113.2$ (C 1.53, $CHCl_3$); 4a (+)-enantiomer, m.p. 89–91°C, $[\alpha]_D^{25} = +428.4$ (C 1.32, $CHCl_3$), (−)-enantiomer, m.p. = 94–95°C, $[\alpha]_D^{25} = -434.3$ (C 1.41, $CHCl_3$); 4b (+)-enantiomer m.p. = 118–120°C, $[\alpha]_D^{25} = +474.6$ (C 1.32, $CHCl_3$), (−)-enantiomer m.p. = 118–120°C, $[\alpha]_D^{25} = -466.1$ (C 1.28, $CHCl_3$).

The preceding resolutions were each conducted in *ca.* 20 min and succeed owing to the high separability factors ($\alpha > 2$) encountered. A wide variety of racemates show high separability factors when chromatographed on CSPs 1 and 2[1]. For those racemates which show small separability factors, flash chromatography is of

reduced utility unless one is only interested in obtaining a relatively small amount of enantiomerically pure material from the racemate. For example, the enantiomers of 2,2,2-trifluoro-1-(-9-anthryl)-ethanol have a separability factor of 1.2 on CSP 2. The early and late fractions resulting from chromatography of 1 g of this material on 300 g of CSP 2 afforded 50 mg of each enantiomer (optical purity > 98%), an amount of this useful NMR chiral solvating agent[6] adequate for several spectra. Using a larger MPLC column (900 g of an ionically bonded CSP resembling 1) containing a packing affording an α of 1.33, 1 g of this alcohol was completely resolved, a situation that persists up to a sample load of *ca.* 3 g[7].

CONCLUSION

Although the performance of flash chromatography is lower than that of larger MPLC systems, the simplicity and economy of the technique commends it to many. When used in combination with readily available chiral packings, flash chromatography, offers a quick and inexpensive approach to the resolution of many racemates. For example, the study of chiral type 3 benzodiazepinones[10,11] (Valium® analogues, known to exhibit enantiodependent physiological activity), for many of which no other satisfactory method for resolving the racemate is known, should be now greatly facilitated.

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