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Preparation and evaluation of chiral high-performance liquid chromatographic stationary phases of mixed character (π-donor and π-acceptor) for the resolution of racemic compounds

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ABSTRACT

Up to now, most stationary phases have had either π-acceptor or π-donor characteristics. In this study, the behaviour of stationary phases having mixed characteristics (π-donor and π-acceptor) was investigated and compared with that of silicas bonded either with the same π-acceptor group or with the same π-donor group. The chiral selectors, (*S*)-1-(α-naphthyl)ethylamine associated with (*S*)-phenylalanine and (*S*)-N-(3,5-dinitrobenzoyl)phenylalanine, were bound to a γ-aminopropylsilanized silica gel. Stationary phases possessing mixed character were obtained either by bonding the two chiral selectors on the same silica or by mixing two chiral silicas bonded with only one of two chiral selectors. The selectivity of these chiral stationary phases possessing π-donor and π-acceptor characters are similar; the α values are intermediate between those shown by the two chiral stationary phases with only π-donor or π-acceptor character. The results obtained in the resolution of a series of racemic compounds with either π-donor or π-acceptor character show that the chiral recognition mechanism is probably more complex than the conventional face-to-face π-interactions usually described.

INTRODUCTION

The resolution of racemic compounds by liquid chromatography using chiral stationary phases, consisting of silica gel bonded to small optically active compounds, has made notable advances in the last decade [1–4]. In addition to these stationary phases, the chiral identity of which is, in general, a molecule with a π-acceptor or a π-donor radical, more recently new stationary phases based on asymmetric natural (albumin, glycoproteins, cellulose derivatives, etc.) [5] or synthetic [6–8] macromole-

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cules have appeared. Even the noteworthy return of old asymmetric supports such as cellulose [9,10] and cellulose triacetate [11] cannot be forgotten.

Classical silica-bonded chiral stationary phases are easy to prepare and to use. Nevertheless, their scope of application is relatively limited when compared with that of stationary phases based on natural or synthetic macromolecules [12].

In order to obtain a wider range of application for these kinds of stationary phases we synthesized silicas carrying both a π-donor and a π-acceptor group. They were obtained in two different ways. First, we successively bonded the two chiral moieties carrying a π-donor group and a π-acceptor group on the same silica. Second, we explored the possibility of mechanically mixing a silica carrying a π-donor group with a silica carrying a π-acceptor group. We used (*S*)-N-(3,5-dinitrobenzoyl)phenylalanine as a π-acceptor group and (*S*)-1-(α-naphthyl)ethylamine associated with (*S*)-phenylalanine as a π-donor group. We then compared the chiral stationary phase CSP-AD1 (Fig. 1), made by successively bonding the two different groups, with the

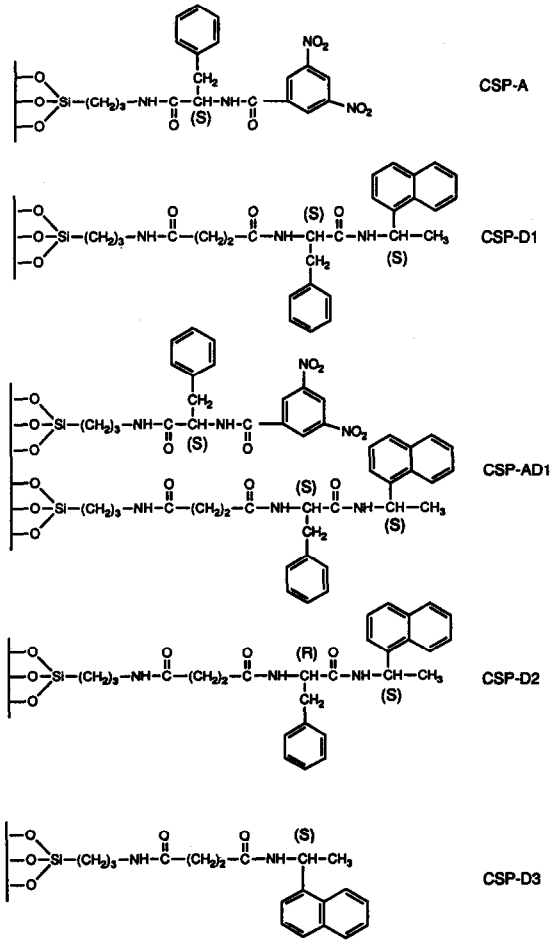

Fig. 1. Structures of chiral stationary phases.

stationary phase obtained by packing the column with a mixture (1:1) of CSP-A [13] and CSP-D1 (Fig. 1) (hereafter referred to as CSP-A + D1) and with the simple stationary phases CSP-A and CSP-D1. In order to test all the chiral stationary phases we used racemic compounds with either π-donor or π-acceptor character.

Silicas bonded to one chiral molecule with radicals possessing different character have already been described [14,15], but these are silicas bonded to a chiral molecule with both π-donor and π-acceptor radicals and, to our knowledge, no comparative study of the properties of a mixed stationary phase with those of two simple stationary phases with only one kind of radical has been undertaken. However, one example has been described [16] of γ-aminopropylsilanized silica on which a mixture of two chiral compounds was fixed by ionic bonding, but the two chiral compounds both had π-acceptor character.

We have studied the influence of the chiral centre of the phenylalanine moiety in CSP-D1 in which the naphthylethylamine group already has a chiral centre. Therefore, we prepared and tested two new chiral stationary phases, one of them by replacing (*S*)-phenylalanine with (*R*)-phenylalanine in CSP-D1 and the other by suppressing the amino acid (CSP-D2 and CSP-D3 [17], respectively, Fig. 1). We also tested a mixture (1:1) of CSP-A and CSP-D3 (hereafter referred to as CSP-A + D3).

EXPERIMENTAL

NMR spectra were measured at 200 MHz using a Bruker AC200 spectrometer. Tetramethylsilane (TMS) was used as the internal standard. Rotatory power was measured with a Perkin-Elmer Model 241 polarimeter. Elemental analyses were performed by the Service Central de Microanalyse du CNRS (Vernaison, France). The chromatographic experiments were carried out on an HP 1090 liquid chromatograph (Hewlett-Packard, Palo Alto, CA, U.S.A.) equipped with a PU4020 UV detector (Philips, Cambridge, U.K.) (254 nm). The chiral stationary phases were packed into stainless-steel tubes (100 mm × 4.6 mm I.D.) by the slurry method according to Coq *et al.* [18]. The volume of sample injected was of 5 μl. The flow-rate of the pump was 1 ml/min. The mobile phases consisted of various mixtures of *n*-heptane, chloroform and methanol.

Chemicals and reagents

Compounds **1–3** (Fig. 2) were obtained by treating the methyl ester of each amino acid with 3,5-dinitrobenzoyl chloride. Compound **6** was prepared by the method described previously [19]. All were identified by their ^{1}H NMR spectra and elemental analysis. Compounds **4**, **5** and **7–9** were purchased from Aldrich.

(S)-tert.-Butoxycarbonylphenylalanyl-(S)-1-(α-naphthyl)ethylamine (**10**) (Fig. 3). L-N-Boc-phenylalanine-N'-hydroxysuccinimide ester (Sigma) (5 g, 13.8 mmol) was dissolved in dichloromethane (120 ml) and cooled in an ice-bath. (*S*)-1-(α-naphthyl)ethylamine (2.4 g, 14.0 mmol) in dichloromethane (50 ml) was added over 10 min with magnetic stirring. The solution was stirred at 0°C for 1.5 h and left to stand at room temperature for 10 h. The solution was diluted with dichloromethane (200 ml) and washed with 1% orthophosphoric acid, 0.2 *M* potassium hydroxide and distilled water. After drying over magnesium sulphate, the solution was evaporated to dryness and the residue collected. Recrystallization from toluene gave 4.5 g (78%) of a white

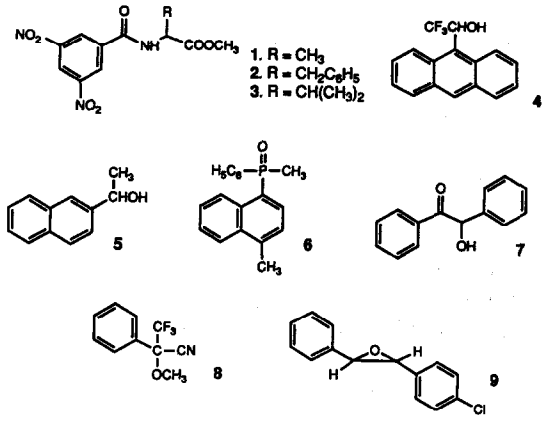

Fig. 2. Structures of test compounds.

solid, m.p. 145°C. ^{1}H NMR (200 MHz): δ ($CDCl_3$) 1.36 (s, 9H, *t*-Bu), 1.58 (d, 3H, CH_3), 3.01 (m, 2H, CH_2Ar), 4.38 (m, 1H, CH_3CH), 5.95 (m, 1H, NCHCO), 7.0–8.2 ppm (m, 12H, ArH). ^{13}C NMR (50.3 MHz): δ ($CDCl_3$) 20.9 (CH_3), 28.1 [$(CH_3)_3$], 38.4 (CH_2), 44.6 (CH_3CH), 56.0 (NCHCO), 80.1 (C_q), 130.9, 133.8, 136.4 and 137.9 (C_q aromatic), 155.2 (O–CO–N), 170.0 ppm (CO–N). $[\alpha]_D^{23} = -3.6°$ (c = 1, dichloromethane). Analysis: calculated for $C_{26}H_{30}N_2O_3$, C 74.61, H 7.22, N 6.69; found, C 74.08, H 7.16, N 6.66%.

(R)-tert.-Butoxycarbonylphenylalanyl-(S)-1-(α-naphthyl)ethylamine (**11**). Analogously to **10**, compound **11** was obtained from D-N-Boc-phenylalanine-N′-hydroxysuccinimide ester. Recrystallization from toluene gave 5 g (86%) of a white solid, m.p. 154°C. ^{1}H NMR (200 MHz): δ ($CDCl_3$) 1.36 (s, 9H, *t*-Bu), 1.47 (d, 3H, CH_3), 3.06 (m, 2H, CH_2Ar), 4.38 (m, 1H, NCHCO), 5.90 (m, 1H, CHN), 7.2–8.1 ppm (m, 12H, ArH). ^{13}C NMR (50.3 MHz): δ ($CDCl_3$) 20.8 (CH_3), 28.2 [$(CH_3)_3$], 38.5 (CH_2), 44.8 (CH_3CH), 56.1 (NCHCO), 79.9 (C_q), 130.8, 133.8, 136.7 and 138.0 (C_q aromatic), 154.5 (O–CO–N), 169.9 ppm (CO–N). $[\alpha]_D^{23} = +33.0°$ (c = 1.4, dichloromethane). Analysis: calculated for $C_{26}H_{30}N_2O_3$, C 74.61, H 7.22, N 6.69; found, C 74.83, H 7.28, N 6.73%.

Succinyl-(S)-phenylalanyl-(S)-1-(α-naphthyl)ethylamine (**12**). A 4.2-g (10-mmol) amount of **10** was dissolved in glacial acetic acid (45 ml) and cooled in an ice-bath. Hydrogen chloride was passed through for 40 min and the solution was left to stand at room temperature for 3 h. The solvent was removed *in vacuo* and the residual solid washed with diethyl ether. The solid was then dissolved in pyridine (12 ml) and succinic anhydride (1.1 g, 11 mmol) was added. After stirring for 24 h at room temperature, the mixture was evaporated to dryness and the residue treated with 5% orthophosphoric acid (120 ml) and distilled water. Recrystallization from ethanol–water gave 3.5 g (83%) of a white solid, m.p. 155°C ^{1}H NMR (200 MHz): δ (acetone-d_6) 1.54 (d, 3H, CH_3), 2.45–2.58 (m, 4H, CH_2CH_2), 2.68 and 3.10 (m, 2H, CH_2Ar), 4.73 (dq, 1H, CH_3CH), 5.85 (m, 1H, NCHCO), 7.1–8.3 ppm (m, 12H, ArH). ^{13}C NMR (50.3 MHz): δ (acetone-d_6) 22.0 (CH_3), 29.7 and 31.1 (CH_2CH_2), 38.7 (CH_2Ar), 45.6 (CH_3CH), 55.5 (NCHCO), 131.7, 134.8, 138.6 and 140.8 (C_q

aromatic), 170.9, 172.4 and 174.5 ppm (CO). $[\alpha]_D^{23} = -20.5°$ ($c = 2$, pyridine). Analysis: calculated for $C_{25}H_{26}N_2O_4$, C 71.75, H 6.26, N 6.69; found C 71.41, H 6.11, N 6.68%.

Succinyl-(R)-phenylalanyl-(S)-1-(α-naphthyl)ethylamine (**13**). Analogously to **12**, compound **13** was obtained from **11**. Recrystallization from ethanol–water gave 3.8 g (90.5%) of a white solid, m.p. 156°C. ^{1}H NMR (200 MHz): δ ($CDCl_3$–DMSO-d_6) 1.36 (d, 3H, CH_3), 2.20–2.50 (m, 4H, CH_2CH_2), 2.93 (m, 2H, CH_2Ar), 4.60 (q, 1H, CH_3CH), 5.70 (m, 1H, NCHCO), 7.0–8.1 ppm (m, 12H, ArH). ^{13}C NMR (50.3 MHz): δ ($CDCl_3$–DMSO-d_6) 20.8 (CH_3), 29.2 and 30.5 (CH_2CH_2), 37.6 (CH_2), 44.4 (CH_3CH), 54.1 (NCHCO), 130.5, 133.4, 136.8 and 138.6 (C_q aromatic), 169.7, 171.7 and 174.5 ppm (CO). $[\alpha]_D^{23} = +52.5°$ ($c = 2$, pyridine). Analysis: calculated for $C_{25}H_{26}N_2O_4$, C 71.75, H 6.26, N 6.69; found, C 71.56, H 6.26, N 6.66%.

Chiral stationary phases

General procedure. To a solution of 3.1 mmol of the appropriate chiral acidic moiety in 60 ml of tetrahydrofuran (THF), 3.5 g of γ-aminopropylsilanized silica, obtained from a spherical silica (5 μm, 100 Å, Nucleosil 100-5; Macherey, Nagel & Co.) according to the method of Pirkle *et al.* [1] (analysis: C 3.10, H 1.05, N 0.90%) and a solution of 0.93 g (3.7 mmol) of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) in 15 ml of THF were added successively while stirring at room temperature. The mixture was allowed to react overnight. The resulting bonded silica was collected by filtration and washed exhaustively with THF, ethanol, water, acetone and diethyl ether and dried *in vacuo* at room temperature. All elemental analyses are given in Table I.

Phase CSP-AD1. This CSP was prepared in two steps according to the above-described general procedure. First, 3 g of γ-aminopropylsilanized silica were treated with a solution of 150 mg of **12** in 150 ml of THF and 120 mg of EEDQ in 10 ml of THF. In the second step, 2.5 g of the previously obtained silica (analysis: C 5.18, H 1.43, N 1.33%) was treated with a solution of 1 g of (*S*)-N-(3,5-dinitrobenzoyl)phenylalanine in 40 ml of THF. CSP-AD1 was collected by filtration and washed as usual.

TABLE I

ELEMENTARY ANALYSES OF CHIRAL STATIONARY PHASES

Chiral stationary phase	Elemental analysis (%)			Ratio of carbon atoms per nitrogen atom		Bonded chiral moieties per gram of stationary phase (mmol)[a]	
	C	H	N	Analytical	Theoretical[a]	From %C	From %N
CSP-A	10.93	1.76	2.69	4.74	4.75	0.48	0.48
CSP-D1	15.53	2.02	2.01	9.01	9.33	0.46	0.48
CSP-AD1	11.80	1.80	2.40	5.74	6.71	0.42	0.49
CSP-D2	10.65	1.79	1.77	7.02	9.33	0.32	0.42
CSP-D3	9.41	1.65	1.54	7.13	9.50	0.41	0.55

[a] Calculations made with regard to organic moiety structures in each stationary phase. The remaining free NH_2 groups were not considered. In CSP-AD1 a ratio of 1:1 between both kinds of chiral moieties was considered.

TABLE II

CAPACITY FACTORS, k'_1, OF FIRST-ELUTED ENANTIOMER AND SELECTIVITY FACTORS, α, IN THE COLUMNS TESTED

Chiral stationary phase	Compound 1		2		3		4		5		6		7		8		9	
	k'_1	α	k'_1	α	k'_1	α	k'_1	α	k'_1	α	k'_1	α	k'_1	α	k'_1	α	k'_1	α
CSP-A	1.84(*R*)[a]	1.19	0.74(*R*)	1.24	1.03(*R*)	1.22	2.18(*S*)	1.19	8.10	1.06	19.17	1.13	6.59	1.04	0.35	1.27	0.52	1.60
CSP-D1	1.73(*R*	1.42	0.38(*R*)	1.39	0.71(*R*)	1.51	2.72	1.00	3.88	1.00	3.73	1.00	2.73	1.00	0.19	7.93	0.21	1.53
CSP-AD1	2.97(*R*)	1.23	1.11(*R*)	1.29	1.47(*R*)	1.35	3.59(*S*)	1.13	8.51	1.00	19.06	1.04	7.14	1.00	0.33	1.00	0.50	1.66
CSP-A + D1	2.43(*R*)	1.21	1.00(*R*)	1.27	0.89(*R*)	1.32	2.39(*R*)	1.13	7.73	1.00	7.87	1.00	5.14	1.09	0.29	2.23	0.34	1.68
CSP-D2	4.37(*R*)	1.07	1.87(*S*)	1.02	1.78(*R*)	1.06	3.49	1.00	4.55	1.00	2.29	1.00	3.14	1.00	0.25	10.00	0.18	1.04
CSP-D3	3.40(*R*)	1.46	1.11(*R*)	1.30	0.59[b](*R*)	1.76	3.00	1.09	4.50	1.00	2.34	1.00	2.43	1.00	0.23	9.24	0.21	1.44
CSP-A + D3	2.02(*R*)	1.34	0.78(*R*)	1.23	0.59[b](*R*)	1.33	2.74(*S*)	1.14	6.71	1.02	10.52	1.00	4.04	1.00	0.30	2.46	0.37	1.55
Mobile phase, chloroform + 0.5% methanol–heptane	70:30		80:20		70:30		70:30		25:75		50:50		25:75		10:90		25:75	

[a] Absolute configuration of first-eluted enantiomer.
[b] Composition of mobile phase 80:20.

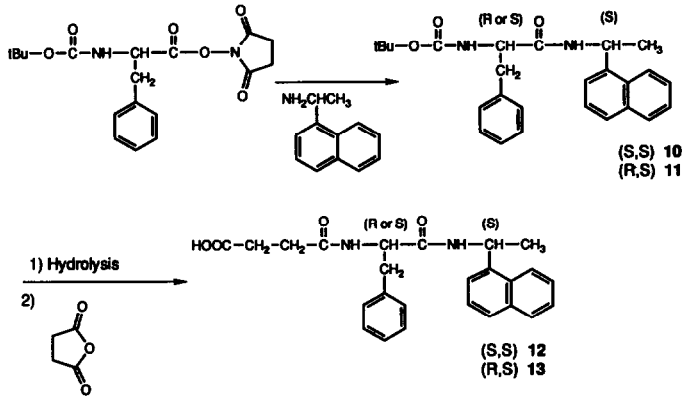

Fig. 3. Synthetic scheme for the preparation of **12** and **13**.

Phase CSP-D3. This has already been described by Ôi *et al.* [17] and was prepared by our general procedure.

Phases CSP-A + D1 and CSP-A + D3. These were prepared by mechanically mixing either CSP-A and CSP-D1 or CSP-A and CSP-D3 phases (50:50, w/w).

RESULTS AND DISCUSSION

The chemical structures of the racemic compounds used as test compounds are shown in Fig. 2. The results obtained after testing the chiral stationary phases are given in Table II.

It appears clearly that racemic products **1**, **2** and **3**, N-(3,5-dinitro)benzoyl derivatives of amino acids, therefore having a π-acceptor character, can be separated by all the stationary phases tested, even CSP-A, a chiral stationary phase with the same π-character. The racemic compound **4**, usually used as a test compound for testing the chromatographic behaviour of chiral stationary phases and itself having a π-donor character, is only resolved by chiral stationary phases having a π-acceptor or a mixed character. On the other hand, **5**, **6** and **7** are not resolved by most of the chiral stationary phases tested. Compounds **8** and **9** are weakly retained by our chiral phases but, in general, they are well resolved. However, **8** shows an unexpected behaviour. It is not resolved by CSP-AD1. Moreover, one of the enantiomers of **8** interacts very weakly with the other chiral phases while the second enantiomer is strongly retained. Therefore compound **8** seems appropriate for the study of chiral recognition mechanisms.

As several racemic products (**1**, **2** and **3**) are resolved in the same way by silicas with either a π-acceptor or a π-donor group, the need for these groups may be questioned. We synthesized and tested a chiral stationary phase in which the nitrobenzoyl radical in CSP-A has been replaced with an acetyl radical (CSP-0, Fig. 4). The selectivity values in this case, for the same elution strength, are 1.02 (k' = 1.13) for **1**, 1.00 (k' = 0.35) for **2** and 1.00 (k' = 0.42) for **3**. According to these clearly low values, it can be deduced that an electronic interaction between CSP-A and compounds **1**–**3** is

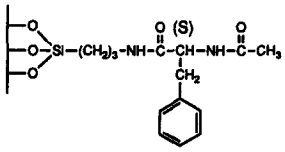

Fig. 4. Structure of CSP-0.

established by dinitrobenzoyl groups. Therefore, in certain instances, a non-classical electronic interaction between π-acceptor groups [20,21] instead of the classical charge-transfer interaction between a π-acceptor and a π-donor group exists. This could be the origin of the known easy separation of compounds with a dinitrobenzoyl group [4] and that of the wide field of application of chiral stationary phases bearing that group, even showing a good resolving power for compounds containing the same group [22]. We can draw the same conclusion when we consider that a number of racemic compounds containing a 3,5-dinitrobenzoyl radical are separated by chiral stationary phases bearing a π-donor group as weak as a C–C double bond [23]. These results suggest that solute–chiral entities in the stationary phase interactions, which take part in the chiral recognition mechanism, are probably more complex than the standard face-to-face π-system interactions considered by most workers.

Comparison between CSP-A and CSP-D1

CSP-A itself has a large separation capacity. It separates compounds that can be considered to be π-donors in addition to π-acceptors.

We tried to improve its selectivity further by blocking the remaining NH_2 groups with 3,5-dinitrobenzoyl chloride, thus increasing the number of π-acceptor interaction sites. In fact, we established that the retention values increase but the selectivity is slightly lower (**1**, $k' = 4.59$, $\alpha = 1.14$; **4**, $k' = 2.38$, $\alpha = 1.10$). Therefore, the resulting bonded silica does not show any improvement over CSP-A for the same elution strength.

On the other hand, as would be expected, CSP-D1 acts by separating almost exclusively compounds with a manifest π-acceptor character. Nevertheless, the very good separation of **8** and **9**, compounds possessing neither pronounced π-donor nor π-acceptor character, can be noted.

Comparison between CSP-AD1 and CSP-A + D1

In CSP-AD1 we find, except for **8** (loss of separation), a small decrease when we compare it to the individual performances of CSP-A and CSP-D1. This decrease in α can result from the dilution of each chiral moiety in the other.

A π-character interaction between the 3,5-dinitrobenzoyl group in one of the chiral moieties and the naphthylethylamine group in the other can be postulated in CSP-AD1. The absence of resolution for **8** may be produced by the mutual inhibition that these π-characters interactions can produce between the chiral moieties as they can block the interaction of this racemic compound with the chiral stationary phase. As **8** is the least retained of all the tested compounds, it is the most affected by this phenomenon. Moreover, it can be said that this interference can only be established at short distances, as it does not exist with CSP-A + D1.

CSP-A + D1, prepared by mechanically mixing CSP-A and CSP-D1 (1:1, w/w), shows a chromatographic behaviour similar to that of CSP-AD1: the α values are intermediate between those for CSP-A and CSP-D1 before mixing. This mixed stationary phase is constituted of silica particles with only one of two different chiral entities. Thus, the foregoing hypothesis of interaction between chiral moieties having different character cannot be applied. In this instance, the reduction in α comes from a decrease in the mixed stationary phase of the amount of chiral silica suitable for each racemic compound. Although CSP-A + D1 and CSP-AD1 show similar performances, one of the main advantages of the chiral stationary phase over CSP-AD1 is the ease of preparation. Moreover, the mixing of different kinds of bonded silica particles avoids interferences due to the proximity of chiral moieties.

Effect of chiral centres on CSP-D selectivity

In CSP-D1 there are two asymmetric centres because the choosen π-donor group itself is a chiral entity. Previous papers [23–27] have shown that the performances of chiral stationary phases remain the same or are slightly improved on going from one to two asymmetric centres in the chiral moiety. However, we have seen that interferences could exist between two chiral entities in the same bonded silica. It can be considered that the same phenomenon can exist in a chiral moiety possessing two different chiral centres. To study the existence of this effect, we synthesized and tested CSP-D2 and CSP-D3.

CSP-D2 differs from CSP-D1 in the absolute configuration of the phenylalanine moiety. Surprisingly, the α values decrease considerably in all instances (except for **8**, which is very well resolved). Thus, CSP-D2 gives α values near unity even with π-acceptor compounds that are well separated by CSP-D1. These results seem to show the importance of the absolute configuration in the phenylalanine asymmetric center. However, when it is eliminated (CSP-D3), the α values recover their previous magnitude. Hence, a competition between the stereoisomers of racemic compounds and the two asymmetric centres, located here in the sole chiral entity (CSP-D1 or CSP-D2), must exist. Therefore, in general, the existence of two or more chiral centres in a chiral stationary phase does not improve the separation but, depending on the configuration of these centres and the relative affinity of the two enantiomers for them, it can seriously interfere with the selectivity.

As a consequence of data obtained from CSP-D3, we also tested its mixture with CSP-A (1:1, w/w) (CSP-A + D3). As with CSP-A + D1, we obtained α values intermediate between those of CSP-A and CSP-D3 and an overall chromatographic behaviour resulting from the addition of their individual behaviours. Hence, it can be considered that mixtures of bonded silicas with different chromatographic behaviours can be useful for increasing the performances of the individual components.

CONCLUSION

The performances of two different stationary phases can be combined by packing the same column with a mixture of the two components. This stationary phase preparation method is better than bonding successively the different chiral entities whose characteristics we wish to combine.

Two different chiral asymmetric centres in the same stationary phase can, depending on their configuration, lead to bad selectivity.

According to our results, the validity of the recognition models proposed previously and based in π-acceptor–π-donor interactions may be questioned.

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