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Discrimination properties of tetraamidic branched selectors

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Abstract

A new class of tetraamidic selectors with arms derived from L-phenylalanine and spaced by a phenolic template was synthesized. These chiral compounds were used as stationary phases for analytical gas chromatographic resolution of racemic mixtures of volatile amino acid derivatives; ^{1}H NMR titration experiments were also performed. The experimental gas chromatographic and ^{1}H NMR data collected support the hypothesis of a cooperation of the two chiral arms in binding and recognition of amino acidic substrates. © 1998 Elsevier Science B.V.

Keywords: Enantiomer separation; Chiral selectors; Amino acids

1. Introduction

Since the seminal work of Gil-Av, Feibush and Charles-Sigler [1], a large number of chiral stationary phases (CSPs) for analytical resolution of racemic mixtures of volatile amino acid derivatives have been designed which show high efficiency in enantiomeric discrimination (for reviews, see Refs. [2–5]).

We have focused our attention on the properties of stationary phases for gas chromatographic analysis in which the chiral component is a branched amino acid-based tetraamidic selector [6]. The correlation between structure and activity of this type of molecule can be obtained from chromatographic data as well as from spectroscopic measures collected in solution.

In tetraamidic selectors, two chiral arms derived from L-phenylalanine are linked and spaced by a template. For similar types of selectors, a model of the interaction with *N*-trifluoroacetyl amino acid methyl ester (*N*-TFA amino acid Me ester) substrates has been proposed [7]. In this model, the two chiral arms interact with substrates through the formation of three hydrogen bonds and adopt a spatial arrangement that could be defined as an intermolecular three-stranded β-sheet (Fig. 1).

In this work we have designed and synthesized

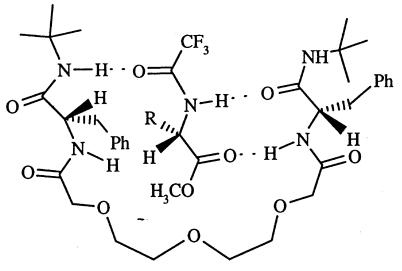

Fig. 1. Model of interaction proposed for selector Phe-3*O*-TA and *N*-TFA L-amino acid methyl esters substrate.

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different selectors varying the mobility and the length of aromatic templates as seen in Fig. 2. Selectors **2** and **3** are rather mobile whereas **1** is more conformationally constrained. Selector **4** with a single chiral arm was also synthesized as a reference compound. All selectors were tested as chiral components for gas chromatographic stationary phases in the resolution of racemates of *N*-TFA amino acid Me esters and values for the separation factors have been reported.

^{1}H NMR conformational studies on **1** and titration experiments for **1**–**4** with *N*-TFA-D, L-Phe Me esters have also been performed. This experimental data enables us to find partial answers to some important questions about the selector–selectand interaction: Do the chiral arms of **1**, **2** and **3** act cooperatively or separately in the binding and recognition of the substrate? Does the mobility and the length of template influence its capacity to discriminate between enantiomeric substrates?

2. Experimental

2.1. Preparation of dipeptide branched selectors

Reagents and solvents were purchased from Fluka or Aldrich and used without further purification. TLC was performed on silica gel plates, Merck 60 PF_{254}. Flash chromatography was performed with Merck silica gel 60 (40–63 mesh). ^{1}H NMR spectra were obtained on a Bruker-AC 300 MHz with tetramethylsilane as internal standard. Mass spectra

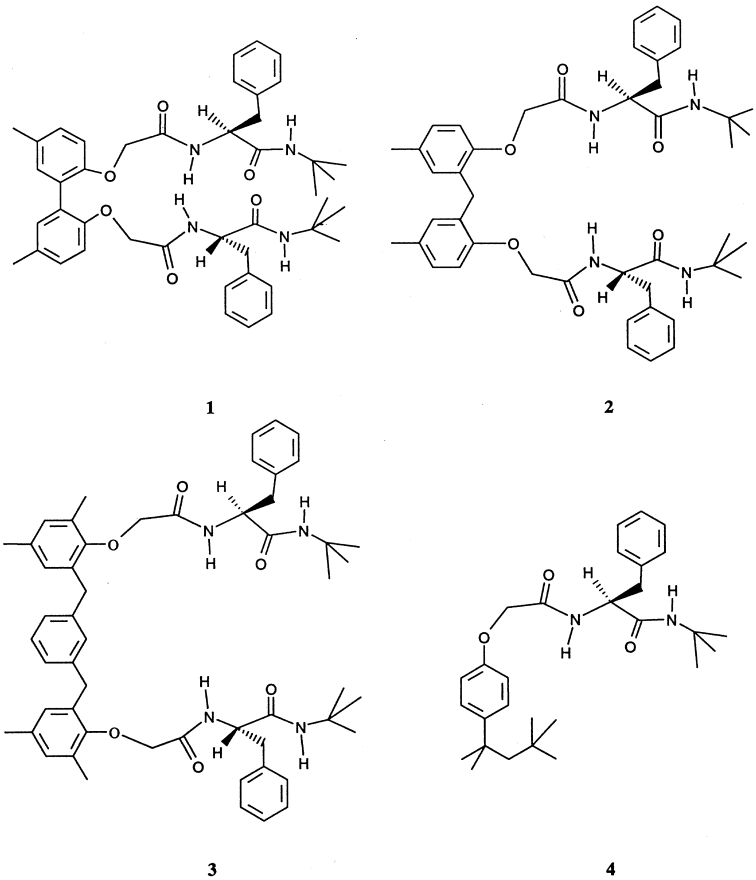

Fig. 2. Structure of selectors **1**, **2**, **3** and **4**.

were obtained by chemical ionisation with a FINNIGAN SSQ 710 spectrometer at 70 eV.

Phenol moieties of selectors **1**, **2** and **3** were obtained according to published procedures (respectively Refs. [8–10]) and their purity was >97% as determined by GC analysis; the *p-tert.*-octylphenol, commercially available, was purchased from Fluka.

All the selectors tested as phases for GC or used for ^{1}H NMR titration experiments in solution were purified by flash chromatography at more than 98% purity as indicated by analytical HPLC. For the analytical HPLC, a reversed-phase C_{18} column was used at a flow-rate of 1 ml/min using a water–acetonitrile gradient from 0 to 100% CH_3CN in 0.09% aqueous TFA in 30 min; UV detector (λ=215 nm).

2.2. General procedure for the synthesis of selectors

In the convergent strategy employed for the synthesis of selectors **1**–**4**, the *N*-bromoacetyl-L-Phe-*tert*-Bu-amide was condensed with phenol moieties as depicted in Fig. 3. The commercial Boc-L-Phe-OH (5.3 g, 0.02 mol) was dissolved in dry dioxane and the solution was cooled at 0°C. The 1,3-dicyclohexylcarbodiimide (4.12 g, 0.02 mol) and the *N*-hydroxysuccinimide (2.3 g, 0.02 mol) were added and the mixture was stirred for 14 h at room temperature. After filtering, the solution was cooled to 0°C and the *tert*-butylamine (2.1 ml, 0.02 mol) was added; the mixture was stirred at room temperature for 14 h and the crude was washed with water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and distilled off. The residue was purified with flash chromatography on silica gel with hexane–ethyl acetate mixture (50:50) to give *N*-Boc-L-Phe-*tert*-butyl amide as a white powder with 95% yield. This product (6.4 g, 0.02 mol) was dissolved in 50 ml of a 2:1 mixture of dichloromethane–trifluoroacetic acid and stirred at room temperature (30 min). The reaction mixture was washed with a saturated solution of $NaHCO_3$ and the residue was chromatogaphed on silica gel plates with the hexane–ethyl acetate mixture (50:50). The L-Phe-*tert*-butyl amide was obtained as a colourless oil with 95% yield. A solution of bromoacetyl chloride (1.66 ml, 0.02 mol) in dry dichloromethane (2 ml) was added dropwise at 0°C to L-Phe-*tert*-butyl amide (4.4 g, 0.02 mol) in the same solvent (10 ml). The reaction mixture was stirred at room temperature for 20 min then quenched with 10% aqueous HCl. The residue was extracted with ethyl acetate, the organic phase was dried on Na_2SO_4 and purified with flash chromatography with an hexane–ethyl acetate mixture (40:60). The final *N*-bromoacetyl-L-Phe-*t*Bu-amide was recovered as a white powder in 90% yield. The phenolic substrate was dissolved in dry dimethylacetamide; 1 equivalent of *N*-bromoacetyl-L-Phe-*t*Bu-amide and 4 equivalents of Cs_2CO_3 were

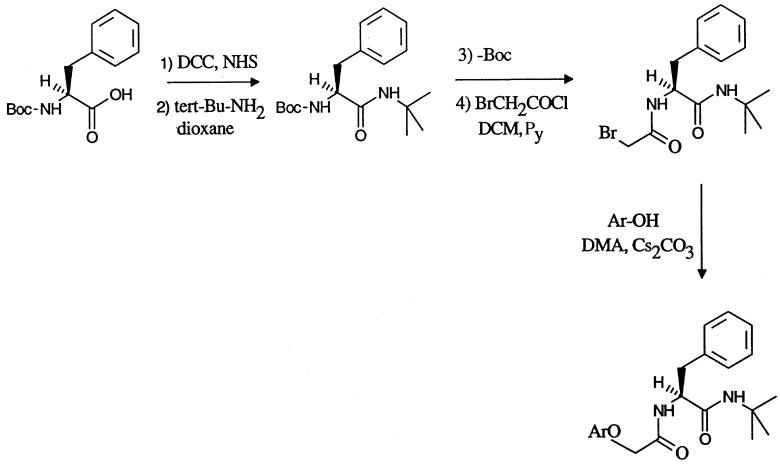

Fig. 3. Conditions for the synthesis of selectors.

added under nitrogen. The solution was stirred at 70°C for about 1 h. The reaction crude was filtered, washing the solid with dichloromethane. The solvent was distilled off under reduced pressure and the residue was chromatographed on silica gel plates with dichloromethane–ethyl acetate mixture (90:10) to give the products. Selectors were recovered as white powders with a yield of 91% for **1**, 60% for **2**, 98% for **3** and 71% for **4**.

2.3. Characterization of the selectors

2.3.1. Selector *1*

^{1}H NMR (CD_2Cl_2, 300 MHz, T=313K): δ (ppm) 1.16 (s, 18H, 2$(CH_3)_3C$), 2.36 (s, 6H, 2CH_3), 2.72 (dd, 2H, 2×1/2 CH_2, J=13.6 and 6.9 Hz), 2.83 (dd, 2H, 2×1/2 CH_2, J=13.6 and 7.6 Hz), 4.33 (d, 2H, 2×1/2 OCH_2CO, J=15.0 Hz), 4.4–4.6 (m, 2H, 2CH), 4.40 (d, 2H, 2×1/2 OCH_2CO, J=15.0 Hz), 5.58 (s, 2H, 2 NHC$(CH_3)_3$), 6.90 (d, 2H, H-6 and H-6′, J=8.3 Hz), 6.95 (s, 2H, 2 CONHCH_α), 7.00 (dd, 2H, H-5 and H-5′, J=8.3 and 1.9 Hz), 7.12 (d, 2H, H-3 and H-3′, J=1.9 Hz), 7.3–7.5 (m, 10H, 10 H_{arom}). MS: 735 (M^++1, 100%), 663 (8%), 635 (12%); IR (KBr) ν (cm^{-1}): 3328, 1662. *Mp*=98°C.

2.3.2. Selector *2*

^{1}H NMR ($CDCl_3$, 300 MHz, T=300K): δ (ppm) 1.16 (s, 18H, 2$(CH_3)_3C$), 2.25 (s, 6H, 2CH_3), 2.84 (dd, 2H, 2×1/2 CH_2-Ph, J=13.6 and 8.6 Hz), 2.95 (dd, 2H, 2×1/2 CH_2-Ph, J=13.6 and 6.5 Hz), 3.96 (s, 2H, Ar-CH_2-Ar), 4.42 (d, 2H, 2×1/2 OCH_2CO, J=14.9 Hz), 4.4–4.5 (m, 2H, 2CH), 4.51 (d, 2H, 2×1/2 OCH_2CO, J=14.9 Hz), 5.3 (bs, 2H, 2 NHC$(CH_3)_3$), 6.69 (d, 2H, H-6 and H-6′, J=8.2 Hz), 6.85 (d, 2H, H-3 and H-3′, J=1.7 Hz), 6.98 (dd, 2H, H-5 and H-5′, J=8.2 and 1.7 Hz), 7.0–7.3 (m, 12H, 10 H_{arom} and 2 CONHCH_α). MS: 749 (M^++1, 100%), 677(8%), 501 (7%); IR (KBr) ν (cm^{-1}): 3306, 1653.

2.3.3. Selector *3*

^{1}H NMR ($CDCl_3$, 300 MHz, T=300K): δ (ppm) 1.20 (s, 18H, 2$(CH_3)_3C$), 2.14 (s, 6H, 2CH_3), 2.20 (s, 6H, 2CH_3), 3.00 (dd, 2H, 2×1/2 CH_2, J=13.5 and 8.3 Hz), 3.13 (dd, 2H, 2×1/2 CH_2, J=13.5 and 6.4 Hz), 3.84 (s, 4H, 2 Ar-CH_2-Ar), 3.94 (d, 2H, 2×1/2 OCH_2CO, J=14.9 Hz), 4.02 (d, 2H, 2×1/2 OCH_2CO, J=14.9 Hz), 4.5–4.7 (m, 2H, 2CH), 5.57 (s, 2H, 2 NHC$(CH_3)_3$), 6.69 (s, 2H, H-3 and H-3″ or H-5 and H-5″), 6.82 (2, 2H, H-5 and H-5″ or H-3 and H-3″), 6.94 (dd, 2H, H-4′ and H-6′, J=7.5 and 1.3 Hz), 7.15 (t, 1H, H-5′, J=7.5 Hz), 7.2–7.3 (m, 11H, H-2′ and 10 H_{arom}), 7.55 (d, 2H, 2 CONHCH, J=8.1 Hz). MS: 867 (M^++1, 100%), 635 (16%), 608 (87%); IR (KBr) ν (cm^{-1}): 3316, 1657. *Mp*=100°C.

2.3.4. Selector *4*

^{1}H NMR ($CDCl_3$, 300 MHz, T=300K): δ (ppm) 0.67 (s, 9H, $CH_2C(CH_3)_3$), 1.14 (s, 9H, NHC$(CH_3)_3$), 1.26 (s, 6H, $(CH_3)_2$CAr), 1.62 (s, 2H, $CH_2C(CH_3)_3$), 2.92 (dd, 1H, CH_2, J=13.1 and 8.7 Hz), 3.16 (dd, 1H, 1/2 CH_2, J=13.1 and 5.6 Hz), 4.42 (d, 1H, 1/2 OCH_2CO, J=14.7 Hz), 4.4–4.6 (m, 1H, CH), 4.52 (d, 1H, 1/2 OCH_2CO, J=14.7 Hz), 5.2 (bs, 1H, CONHCH), 5.3 (bs, 1H, NHC$(CH_3)_3$), 6.80 (d, 2H, H-2 and H-6, J=8.6 Hz), 7.10 (d, 2H, H-3 and H-5, J=8.6 Hz), 7.2-7.4 (m, 5H,). MS: 467 (M^++1, 100%); IR (KBr) ν (cm^{-1}): 3317, 1650. *Mp*=99°C.

2.3.5. Preparation of capillary columns

Dynamic coating was performed on untreated 0.25 mm I.D. fused-silica capillary columns from Supelco (USA), with 0.4% dichloromethane solutions of the chiral selector mixed 1/1 (w/w) with Carbowax 20M.

Gas chromatograms were obtained under isothermal conditions for separation factor determination at 80°C and 100°C for phases containing selectors **1**, **2** and **4**; 110°C and 140°C for selector **3** as this phase crystallized below 100°C. In order to compare the efficiency of selectors **3** and **4** at the same temperature, we calculated for selector **4**, the α values at 110°C and 140°C.

The injector was kept at 280°C while the helium gas flow-rate was approximately 0.8 ml/min.

Capillary columns with tetraamide phases **1**, **2** and **3** show low bleeding up to 220°C and can be used to separate D,L-amino acid derivatives without bonding procedures. Phase **4**, with a lower molecular weight, showed bleeding for temperatures higher than 180°C. Upper working temperatures are estimated at about 200°C for tetraamidic phases and about 160°C for the diamidic phase.

2.3.6. Derivatisation of D,L-amino acid substrates

N-Trifluoroacetyl-L-phenylalanine methyl ester as the *N*-trifluorocetyl methyl esters of other D- and L-amino acids were used as volatile selectands in gas chromatography as well as soluble substrates in ^{1}H NMR titration experiments in chloroform-*d*. The D- and L-amino acids were derivatised as previously described [6].

2.3.7. ^{1}H NMR titration experiments

To a 500 μl volume of a 0.1 *M* solution of the selector in anhydrous chloroform-*d* were successively added volumes of 35 μl of a solution of 0.3 *M* *N*-trifluoroacetyl-L-phenylalanine methyl ester in the same solvent until a ratio 4:1 between substrate and selector was reached. The experiments were performed at 300 K with a Bruker-AC 300 MHz.

The self-association of each selector was studied in the same range of concentration covered in the titration, to calculate the $\Delta\delta$ values reported in the plots as described in the Section 3.

3. Results and discussion

Selectors **1**–**4** were tested as chiral components of gas chromatographic stationary phases in the resolution of a mixture of racemic Ala, Val, Thr, Ile, Leu, Nle, Pro, Asp, Glu, Phe *N*-trifluoroacetyl methyl esters. Two typical gas chromatograms obtained in isothermal conditions using a column filled with selector **1**/Carbowax 20M are shown in Fig. 4.

The characteristics of the capillary columns and the separation factors α, calculated from the retention times of the enantiomers are reported in Table 1. The difference of the free energy of the enantiomer differentiation is derived according to Eq. (1):

$$-\Delta_{R,S}(\Delta G) = RT \ln \alpha \quad (1)$$

Values of $-\Delta_{R,S}(\Delta G)$ are shown in Table 2. From this set of thermodynamic data, the selector **2** bringing a methylene bridge between the two aromatic rings in the template, seems to be the most efficient in the enantiomeric discrimination of substrates with the largest values of α so far recorded with similar tetraamidic selectors. The existence of an optimal distance between the two chiral arms at which they seem to cooperate with a positive synergic effect was also observed for selectors in which the two diamidic arms are spaced by a polyether-based template [6,7].

Comparing α and $-\Delta_{R,S}(\Delta G)$ values of selectors **1**, **2** and **3** with those of selector **4**, we can conclude that the two-armed receptors are more efficient than the single-armed one for discrimination of antipode pairs. A cooperative action of the two chiral arms could be postulated. In this sense, our receptors confirm the selector–selectand interaction model in which a three-stranded intermolecular β-sheet structure is formed. The 1:1 stoichiometry of the complex between selector **2** and *N*-trifluoroacetyl-L-phenylalanine methyl ester was obtained by the method of continuous variations; the Job plot has a maximum at a mole fraction of 0.5 which is indicative of a 1:1 complex [11,12].

In the complex between selector **2** and *N*-trifluoroacetyl phenylalanine methyl ester, the arms of the receptor probably hold the substrate assuming a tweezer-like arrangement induced from the substrate binding.

From gas chromatographic data we can conclude that selector **1** is slightly less efficient than **2** in the discrimination of the enantiomers with the remarkable exception of the antipodes of proline that are resolved only with selector **1**. Selectors **2**, **3** and **4** as well as the tetraamidic selectors previously tested do not separate proline enantiomers [6]. This result shows that very specific selector–selectand interactions are required in the case of proline to separate enantiomers. The conformationally-constrained selector **1** could interact tighter than other selectors with this amino acid. Selector **1** is conformationally constrained because of the steric hindrance of the two chiral arms that can also interact with each other via hydrogen bonding.

In the ^{1}H NMR spectrum of selector **1** recorded at 238 K, two sets of signals are present corresponding to two diastereomeric conformers with different orientation of aromatic rings of the template. The two conformers **1a** and **1b** are schematically represented in Fig. 5. The spectra of selector **1** in dichloromethane-d_2 at 313 and 238 K are compared in Fig. 6. Collecting proton NMR spectra in dichloromethane-d_2 at different temperatures, we

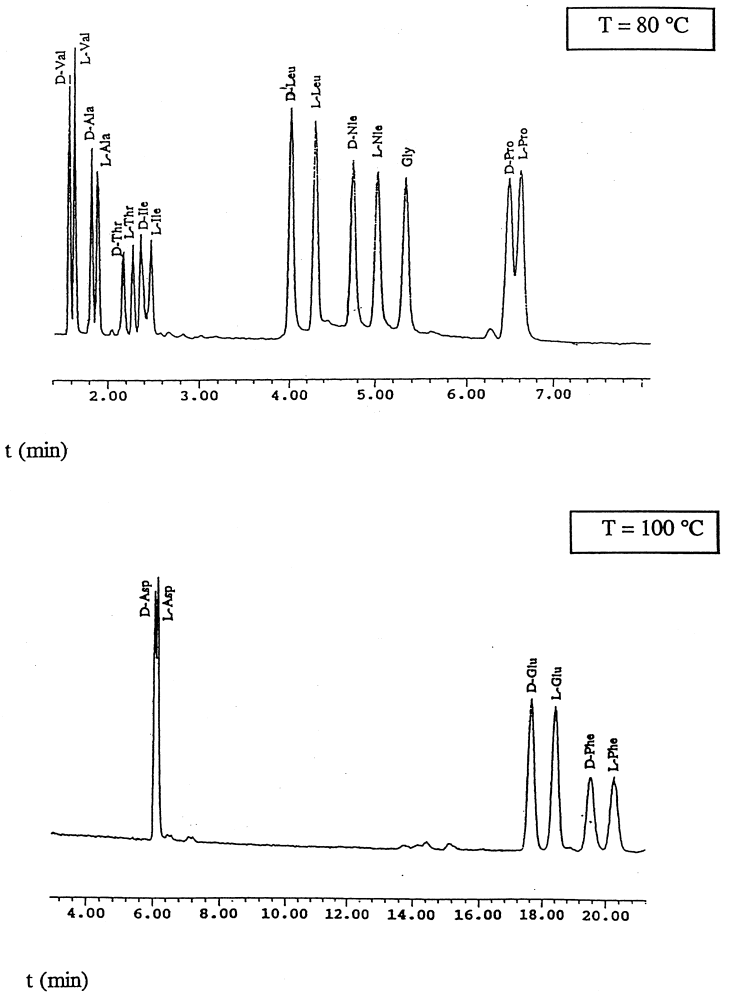

Fig. 4. Gas chromatograms at $T=80$°C and $T=100$°C obtained with a 0.25-mm I.D. fused-silica capillary column with selector **1** as chiral component of stationary phase.

Table 1
Characteristics of capillary columns and separation factors for chiral stationary phases containing selectors **1**, **2**, **3** and **4**

Column[a]	L (m)	I.D. (mm)	T_1 (°C)	Separation factors α at $T=T_1$							T_2 (°C)	α at $T=T_2$		
				Val	Ala	Thr	Ile	Leu	Nle	Pro		Asp	Glu	Phe
1/CW	15	0.25	80	1.05	1.05	1.07	1.07	1.08	1.07	1.02	100	1.02	1.05	1.04
2/CW	15	0.25	80	1.10	1.08	1.12	1.12	1.12	1.08	1.00	100	1.02	1.06	1.05
3/CW	15	0.25	110	1.05	1.04	1.06	1.06	1.05	1.06	1.00	140	1.01	1.01	1.02
4/CW	15	0.25	110	1.02	1.01	1.05	1.04	1.03	1.02	1.00	140	1.00	1.01	1.01
4/CW	15	0.25	80	1.04	1.03	1.07	1.06	1.06	1.04	1.00	100	1.00	1.02	1.02

[a] Fused-silica columns with Carbowax 20M added to chiral phase (ratio 1:1, w/w).

Table 2
$-\Delta_{R,S}(\Delta G)$ values in cal/mol calculated according to Eq. (1)

Selector	Val	Ala	Thr	Ile	Leu	Nle	Pro	Asp	Glu	Phe
1	34	34	47	47	53	47	13	14	36	29
2	66	53	79	79	79	53	0	14	43	36
3	37	29	44	44	37	44	0	8	8	16
4a	15	7	37	30	22	15	0	0	9	9
4b	27	20	47	40	40	27	0	0	14	14

$T=T_1$ for Val, Ala, Thr, Ile, Leu, Nle, Pro and $T=T_2$ for Asp, Glu and Phe. In the case of selector **4**: in **4a** $T_1=110$°C and $T_2=140$°C, in **4b** $T_1=80$°C and $T_2=100$°C.

followed the signal of six protons of *para*-methyl groups in biaryl that is a singlet at $T=300$ K ($\delta=$ 2.36 ppm) and splits in two singlets at temperatures lower than 263 K. From the coalescence temperature of 263 K relative to these protons, we calculated an energetic barrier of 13.5 Kcal/mol for the interconvertion of the two conformers [13].

During the ^{1}H NMR titrations of selectors **1**–**4** with *N*-trifluoroacetyl phenylalanine methyl ester at 300 K in chloroform-*d*, the protons of *tert*-butyl amide moiety of chiral arms are shifted downfield when the selectands are added. The downfield shift is an indication of the involvement of these protons in hydrogen bond formation with amino acidic selectands as proposed for tetraamidic receptors [6].

In Figs. 7–10, the ^{1}H NMR titration curves of selectors **1**, **2**, **3** and **4** with *N*-TFA-D, L-Phe Me esters are reported. Downfield shifts of *tert*-butyl amidic protons of selectors are corrected taking into account the dilution and $\Delta\delta=\delta_{obs}-\delta_{free}$ values are plotted against molar ratio substrate-selector; the δ_{obs} is the observed chemical shift in the mixture and the δ_{free} is the chemical shift of the free ligand at the same concentration as in the mixture. The experimental procedure of the titration experiments was as reported in Ref. [7]. In these conditions the experimental error on $\Delta\delta$ values is about 0.003 ppm or less as determined by measurements on three independent samples.

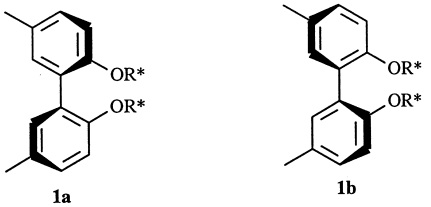

Fig. 5. Equilibrium between conformers **1a** and **1b** in selector **1**.

Attempts to determine binding constants fitting these titration curves with iterative least-squares programs gave small and nonreproducible values of K_{ass} due to the lability of the selector–substrate complex. Moreover, a very high concentration of selectands should be used in order to obtain reliable results [14]. Indeed, it is a characteristic of this type of selectors to exhibit weak binding (low K_{ass}) with the substrate; this allowed avoidance of long retention times and peak broadening in GC analysis. Qualitative indications from ^{1}H NMR titration curves are consistent with conclusions that we derived from gas chromatographic experiments. Curves obtained for selector **2** with D- and L-*N*-TFA-Phe Me esters present the largest gap in the $\Delta\delta$ values of two enantiomers whereas curves of selector **4** with the same selectands present lowest separation among all selectors.

4. Conclusions

The experimental gas chromatographic and ^{1}H NMR data collected in this work support the hypothesis of a cooperation of the two chiral arms of selectors **1**–**3** in binding and recognition of amino acidic substrates. Indeed, the efficiency in enantiomeric discrimination of mono-branched selector **4** is lower than that one of dibranched selectors. The 1:1 stoichiometry of the selector–substrate complex found for selector **2** in the Job plot is in agreement with this conclusion. Selector **1** could assume a tweezer-like arrangement because it is relatively constrained; in selectors **2** and **3** we can imagine that

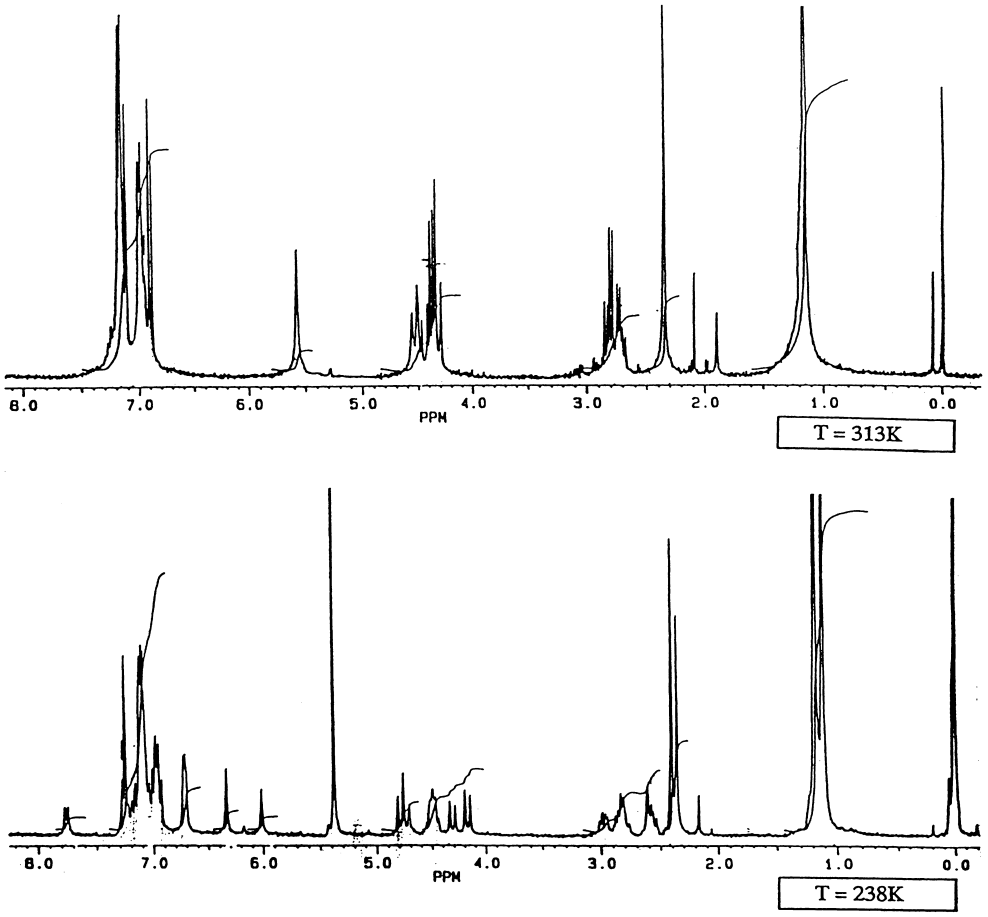

Fig. 6. ^{1}H NMR spectra of selector **1** at 313 and 238 K in dichloromethane-d_2 (300 MHz).

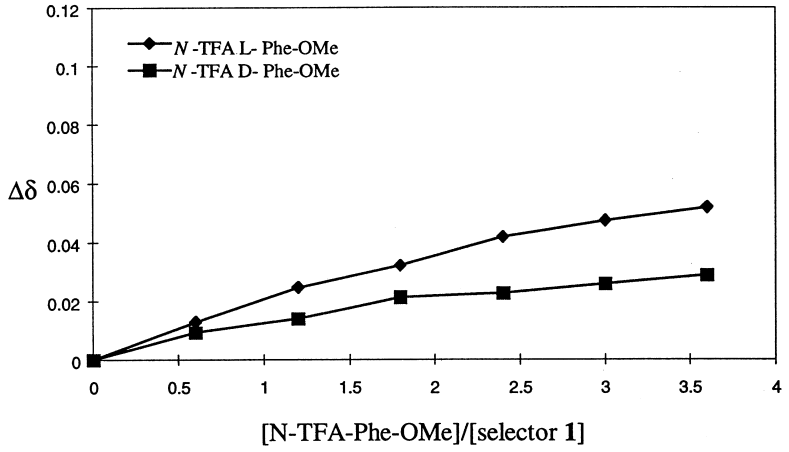

Fig. 7. Chemical shift variation ($\Delta\delta$) of the NH-Bu^t of selectors **1**, **2**, **3** and **4** induced by addition of D- and L-*N*-TFA Phe Me esters.

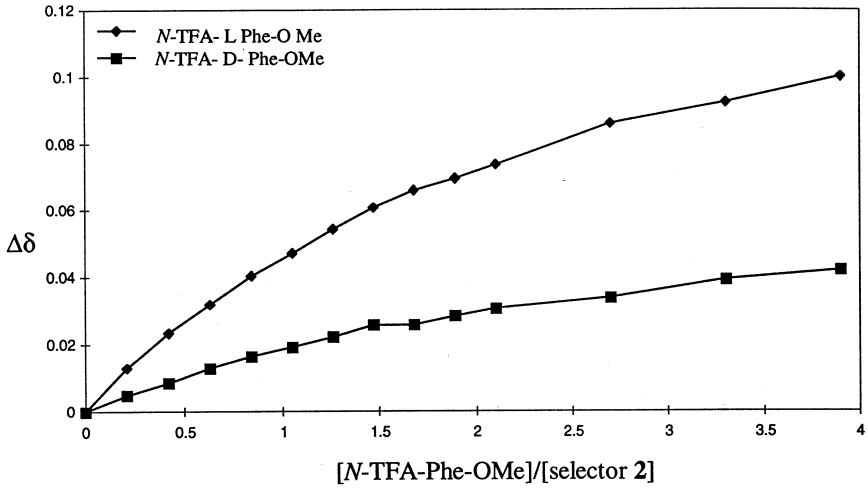

Fig. 8. Chemical shift variation ($\Delta\delta$) of the NH-Bu^t of selectors **1**, **2**, **3** and **4** induced by addition of D- and L-*N*-TFA Phe Me esters.

a tweezer disposition of chiral arms is induced from the binding with substrate.

The possibility of synthesizing a large variety of aromatic polyphenolic structures makes our approach promising for the prospect of designing templates bringing functional groups in the *para* position of phenolic moieties. The hydroxy phenolic groups of the templates could be derivatized with chiral arms for the discrimination of selectand molecules. The functional groups in the *para* position could be utilized to link the selector to a solid support in order to obtain a new class of covalently-linked chiral stationary phases.

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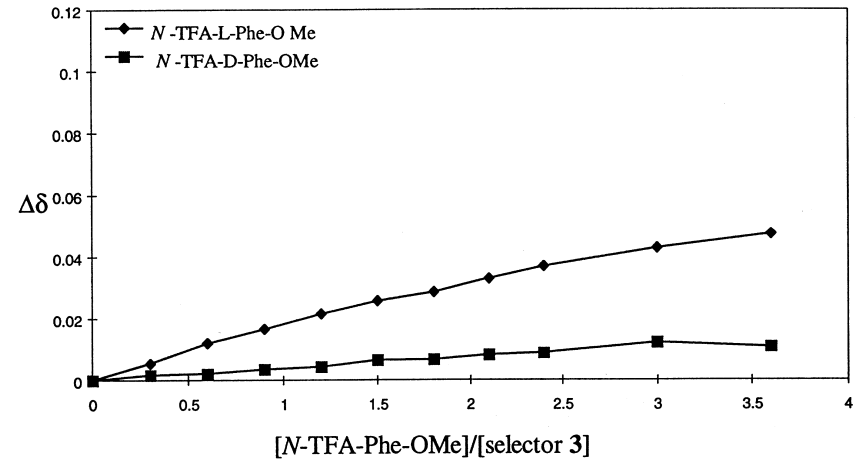

Fig. 9. Chemical shift variation ($\Delta\delta$) of the NH-Bu^t of selectors **1**, **2**, **3** and **4** induced by addition of D- and L-*N*-TFA Phe Me esters.

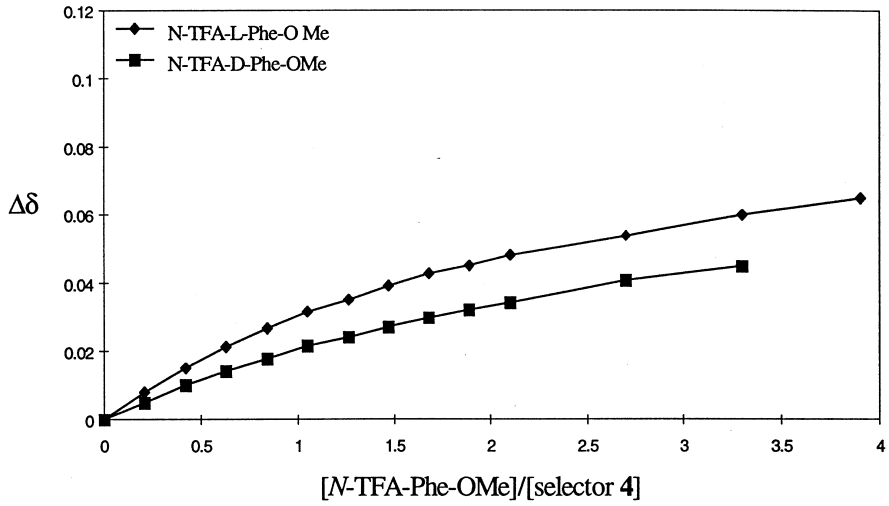

Fig. 10. Chemical shift variation ($\Delta\delta$) of the NH-Bu^t of selectors **1**, **2**, **3** and **4** induced by addition of D- and L-*N*-TFA Phe Me esters.

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