COMPARISON OF (*R*)-(–)-6,6′-BIS(3,5-DINITROBENZAMIDO)BIPHENYL-2,2′-DICARBOXYLIC AND (*S*)-(+)-6,6′-BIS(3,5-DINITROBENZAMIDOMETHYL)BIPHENYL-2,2′-DICARBOXYLIC ACIDS AS CHIRAL HPLC SELECTORS

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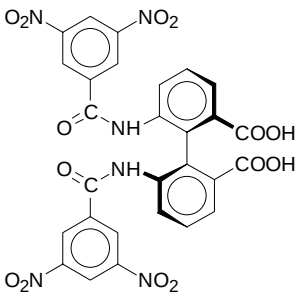
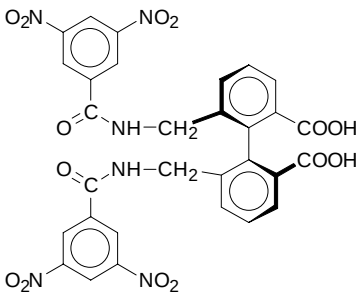
The title optically active diacids (*R*)-**I** and (*S*)-**II** of known absolute configuration were investigated as selectors in HPLC separation of enantiomers. With a standard set of benzamido alcohols and biaryl compounds, the separation was less efficient and less general than that found for selectors based on studied previously.

Key words: Chiral stationary phase; C_2 Symmetry; Biaryl.

In our previous communications[1–3] we have reported some chiral biaryl diacids of C_2 symmetry that proved to be efficient selectors for HPLC separation of enantiomeric acylamino alcohols and some axially chiral compounds.



(*R*)-**I**



(*S*)-**II**

In our continuing quest for other potent selectors of this type we extended our interest to biphenyl derivatives having 3,5-dinitrobenzamido groups in positions 6 and 6′, attached to the aromatic ring either directly or *via* a methylene group (acids (*R*)-**I** and (*S*)-**II**, respectively). As well known[4], the 3,5-dinitrobenzoyl group is a structural com-

ponent of many very effective Pirkle-type chiral stationary phases (CSPs). Comparison of the homologous acids **I** and **II** should give information on how the separation ability of the selector depends on the distance of the polar 3,5-dinitrobenzamide grouping from the chirality axis.

The preparation of the diacid (*R*)-**I** has already been published and its absolute configuration established[3], the diacid (*S*)-**II** was synthesized[5] from (*S*)-6,6′-dimethylbiphenyl-2,2′-dicarboxylic acid of known absolute configuration[6]. The selector acids (*R*)-**I** and (*S*)-**II** were ionically anchored on Separon SGX-NH_2 analogously as in our previous studies[1–3], the obtained phases being designated CSP 1 and CSP 2, respectively.

RESULTS AND DISCUSSION

Acylamino Alcohols

In contrast to analogous CSPs, based on 6,6′-dinitro substituted biphenyl-2,2′-dicarboxylic acids, which we studied previously[2], the separation of acylamino alcohols **1**–**24** (Scheme 1) on CSP 1 and CSP 2 is not so general. As seen from Table I, of simple cyclic amino alcohols mostly the *cis*-isomers were separated, more separations being achieved on CSP 2. Some compounds separable on CSP 1 were not separated on CSP 2 and *vice versa*.

Biaryl Compounds

With the biaryl derivatives (**25**–**44**, Scheme 2), most compounds resolved on one phase were resolved also on the other one (Table I). In some cases, CSP 1 and CSP 2 resolved compounds unresolvable on the previously studied columns[1,2]. Interestingly, compound **44** was successfully separated solely on CSP 1 out of about eight other CSPs tried (including modified celluloses, Pirkle-type selectors, chiral polymers *etc*.).

General Evaluation

As might be expected from the opposite absolute configurations of the selectors (*R*)-**I** and (*S*)-**II**, most enantiomers (but not all), eluted on CSP 1 as the first, were eluted on CSP 2 as the second, and *vice versa*. The obtained results also show that placing the amido functionality farther from the chirality axis has no dramatic or unequivocal effect on the separation ability. Generally, the CSPs based on acids **I** and **II** are less efficient (lower values of α and mostly no baseline separations) than those based on 6,6′-dinitrobiphenyl-2,2′-dicarboxylic, 4,4′,6,6′-tetranitrobiphenyl-2,2′-dicarboxylic and 2,2′-bipyridine-3,3′-dicarboxylic acids, studied previously.

TABLE I

Capacity factors, k_1, and separation factors, α, for HPLC of compounds **1–45** on stationary phases CSP 1 and CSP 2. The capacity factors k_1 refer to the first enantiomer eluted (with its sign of rotation), the separation factor α is the ratio of capacity factors of the enantiomers. No attempts were made to optimize the analytical conditions for the individual compounds. Mobile phase 10% 2-propanol in heptane, flow rate 0.8 ml/min. The optical activity of the eluates was monitored by a Chiralyser (Knauer) instrument.

Compound	CSP 1		CSP 2	
	k_1	α	k_1	α
		Acylamino alcohols		
1a *cis*	8.8 (–)	1.11	7.4 (+)	1.11
1a *trans*	18.0	1.00[a]	15.6	1.00[a]
2b *cis*	7.8	1.00[a]	7.2	1.00[a]
2a *trans*	8.4 (–)	1.05	8.2	1.00[a]
3a *cis*	6.8	1.00[a]	6.2	1.00[a]
3a *trans*	6.6	1.09[a]	5.6	1.00[a]
4a *cis*	5.4	1.00[a]	4.8 (+)	1.08
4a *trans*	4.6	1.00[a]	4.4	1.00[a]
5a *cis*	4.2	1.00[a]	4.00 (+)	1.00[a]
5a *trans*	4.0	1.00[a]	3.4	1.00[a]
6a *cis*	3.6	1.00[a]	4.4 (+)	1.09
6a *trans*	3.0	1.00[a]	2.8	1.00[a]
7a *cis*	3.0	1.00[a]	2.8 (+)	1.00[a]
7a *trans*	2.4	1.00[a]	2.2	1.00[a]
8a *cis*	4.4	1.00[a]	4.0	1.00[a]
8a *trans*	4.6	1.00[a]	4.6	1.00[a]
9b *erythro*	15.4	1.00[a]	14.8 (+)	1.08
10b *threo*	7.6	1.00[a]	7.1 (+)	1.08
10b *erythro*	7.4	1.00[a]	7.2 (+)	1.17
11a *threo*	3.8	1.00[a]	4.2	1.00[a]
11a *erythro*	4.0	1.00[a]	4.0	1.00[a]
12a *threo*	16.8 (+)	1.07	12.8	1.00[a]
12a *erythro*	13.6	1.00[a]	10.2	1.00[a]
13b	27.2	1.00[a]	24.4 (–)	1.05
14b	9.2 (+)	1.11	9.4 (–)	1.21
15b	9.8	1.00[a]	9.4 (+)	1.15
16b	9.8 (–)	1.12	9.8 (–)	1.10
17 *cis*	6.6	1.00[a]	5.8	1.00[a]
17 *trans*	17.6	1.00[a]	14.4	1.00[a]
18a	13.4	1.00[a]	9.8 (–)	1.-08
19a	7.4	1.00[a]	5.8	1.00[a]
20b	7.4	1.00[a]	7.6 (+)	1.29
21a	7.4	1.00[a]	6.2	1.00[a]
22a	7.4	1.00[a]	6.4	1.00[a]
23a	16.2 (+)	1.13	14.4	1.00[a]
24a	19.0 (+)	1.08	14.6 (–)	1.16

TABLE I
(*Continued*)

Compound	CSP 1		CSP 2	
	k_1	α	k_1	α
	Biaryl derivatives			
25	8.8 (+)	1.18	7.8 (–)	1.10
26	3.8 (–)	1.47	3.2	1.00[a]
27	[c]		4.6	1.00[a]
28	[c]		24.4	1.00[a]
29	9.4	1.00[a]	4.2	1.00[a]
30	2.4	1.00[a]	1.4	1.00[a]
31	1.8	1.00[a]	1.6	1.00[a]
32[b]	1.7	1.00[a]	1.0	1.00[a]
33[b]	1.6	1.00[a]	1.4[b]	1.00[a]
34	3.8	1.00[a]	2.4	1.00[a]
35	3.8 (+)	1.15	3.0 (–)	1.2
36	17.8 (+)	1.17	12.0 (–)	1.07
37	1.6	1.00[a]	1.2	1.00[a]
38	2.3 (+)[b]	1.22	1.4	1.00[a]
39	17.2 (+)	1.15	14.7 (–)[b]	1.09
40	10.6 (+)	1.06	7.4 (+)	1.08
41	5.0 (+)	1.12	3.8 (–)	1.16
42[b]	2.3 (+)	1.19	1.6	1.00[a]
43	5.2	1.00[a]	2.8	1.00[a]
44	3.6 (–)[b]	1.14	3.1[b]	1.00[a]
45	18.0 (sh)	1.04	16.8 (+)	1.11

[a] No separation. [b] Flow rate 0.5 ml/min. [c] Strong adsorption on the column under the conditions applied.

EXPERIMENTAL

The preparation of the acid (*R*)-**I** and the corresponding CSP 1 has already been described in our previous communication[3].

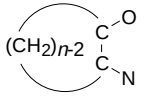
(+)-(*S*)-6,6′-Bis(3,5-dinitrobenzamidomethyl)biphenyl-2,2′-dicarboxylic Acid ((*S*)-**II**)

A solution of (*S*)-6,6′-bis(aminomethyl)biphenyl-2,2′-dicarboxylic acid[5] ($[\alpha]_D$ +240.8° (*c* 0.5, H_2O); 600 mg, 2 mmol) in 0.20 M NaOH (41 ml, 8.2 mmol) was stirred with finely ground 3,5-dinitrobenzoyl chloride (1.110 g, 4.8 mmol) until it dissolved. Another portion of 0.20 M NaOH (about 3 ml) was added to keep the solution slightly alkaline. After standing overnight, the solution was acidified with dilute (1 : 5) hydrochloric acid, stirred for 2 h and the product was collected, washed with water and dried in vacuo. Yield 1.30 g (91%) of fine powder which melted at 160–165 °C, resolidified and melted again at 274–284 °C; $[\alpha]_D$ +296.2° (*c* 0.5, 0.1 M NaOH). For $C_{30}H_{20}N_6O_{14}$. 0.5 H_2O (697.5)

calculated: 51.65% C, 3.03% H, 12.05% N; found: 51.63% C, 2.93% H, 12.11% N. ^{1}H NMR spectrum (200 MHz, $(CD_3)_2SO$, standard TMS): 9.54 t, 2 H, J(NH,CH_2) = 5.3 (NH); 9.05–9.63 m, 6 H (3,5-dinitrobenzoyl); 7.48–7.86 m, 6 H (H arom); 4.16 m, 4 H (CH_2).

(*RS*)-6,6′-Bis(3,5-dinitrobenzamidomethyl)biphenyl-2,2′-dicarboxylic Acid ((*RS*)-**II**)

The racemic diacid (*RS*)-**II** was prepared from racemic 6,6′-bis(aminomethyl)biphenyl-2,2′-dicarboxylic acid[5] in 86% yield, exactly as described for the optically active acid (*S*)-**II**; m.p. 297–298 °C. For $C_{30}H_{20}N_6O_{14}$ (688.5) calculated: 52.33% C, 2.93% H, 12.21% N; found: 52.55% C, 2.98% H, 12.17% N. ^{1}H NMR spectrum: same as for (*S*)-**II**.



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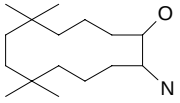
3, n = 9
4, n = 13
5, n = 16
6, n = 20
7, n = 26



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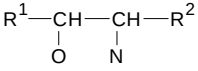
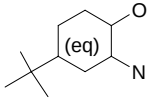
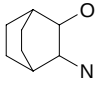


9, $R^1 = R^2 = CH_3$
10, $R^1 = R^2 = C_4H_9$
11, $R^1 = R^2$ = cyclohexyl
12, $R^1 = C_6H_5$; $R^2 = CH_3$

a, N = $NHCOC_6H_5$; O = OH
b, N = $NHCOC_6H_4NO_2(p)$; O = OH



13, O(ax), N(ax)
14, O(eq), N(eq)
15, O(ax), N(eq)
16, O(eq), N(ax)



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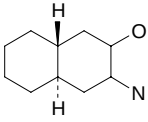
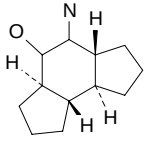
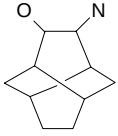


18, O(ax), N(ax)
19, O(eq), N(ax)



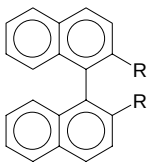
20, O(eq), N(eq)



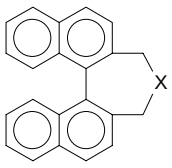
21, O(*endo*), N(*endo*); 30°
22, O(*exo*), N(*exo*); 30°
23, O(*endo*), N(*exo*); 90°
24, O(*exo*), N(*endo*); 120°

Expressions (ax) and (eq) for the conformationally homogeneous compounds **13–16** and **18–20** denote the respective axial and equatorial positions of the substituents; for compounds **21–24** torsion angles between substituents are given

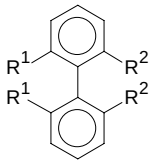
SCHEME 1



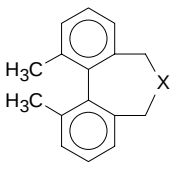
	R
25	CH_2OH
26	CO_2CH_3
27	$CH_2NHCOCH_3$
28	CH_2CN
29	$CH_2CH(CO_2C_2H_5)_2$



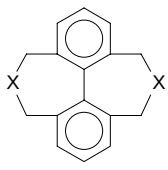
	X
30	$C(CO_2C_2H_5)_2$
31	$CHCO_2CH_3$
32	S
33	O
34	C=O
35	C=N-OH
36	CO-NH



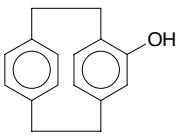
	R^1	R^2
41	CH_2OH	CH_3
42	CO_2CH_3	CH_3



	X
37	C=O
38	C=N-OH
39	CO-NH
40	$C(CO_2C_2H_5)NHCOCH_3$



43, X = $C(CO_2C_2H_5)_2$



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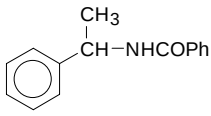

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SCHEME 2

Preparation of CSP 2

A solution of diacid (*S*)-**II** (1.1109 g, 1.614 mmol) in methanol (25 ml) was added to a suspension of Separon SGX-NH_2 (Tessek; 3.00 g) in methanol (10 ml). After standing for 24 h with intermittant gentle stirring, the mixture was filtered, the adsorbent washed with methanol and acetone (50 ml each) and dried in vacuo. Evaporation of the filtrate recovered 261.2 mg of the acid; thus 849.7 mg of the acid was anchored and the selector content was 0.32 mmol/g phase.

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