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Quaternized brucine as a novel chiral selector

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Abstract—A novel recognition scaffold for interfacial enantiomer recognition was synthesized via initial *N*-alkylation of brucine with 6-bromohexanoic acid followed by covalent attachment of the product to 3-aminopropyl silica; chromatographic tests demonstrated the participation of an anion-exchange interaction in the chiral recognition of 2,2′-dihydroxy-1,1′-binaphthyl-3-carboxylic acid derivatives with the resulting chiral stationary phase.

1. Introduction

Enantioselective recognition with synthetic and natural receptors is one of the major themes in supramolecular and analytical chemistry.[1,2] The key point for developing successful methodologies towards such selectors is the identification of a stable and readily accessible chiral building block suitable for chiral selective processes in solution and/or at the interface.

In our design successful chiral recognition relies on strong coulombic interaction (CI) even in highly competitive solvents. Despite the fact that CI itself is not spatially selective, as soon as a positively charged center is placed into the chiral environment (molecular, or supramolecular) the interaction with a negatively charged chiral analyte can be highly enantioselective, with CI stabilizing the resulting transient diastereomeric complex. Chiral recognition is then achieved through simultaneous cooperation of CI with other site-directed binding modes, namely H-bonding, π–π stacking, steric modes and molecular scaffold. The validity of this approach has already been proved by using chiral sapphyrin dimers,[3] cinchonan carbamates[4] and bicyclic guanidines[5–7] for enantioselective recognition.

Herein, we present results obtained with a novel recognition unit, quaternized brucine **1** (work on other alkaloids are in progress). Brucine was chosen because its structure seems to be well suited to provide different interaction modes with chiral analytes. The main question we wished to address was whether enantioselective recognition could be achieved with this novel chiral system.

A chiral stationary phase (CSP) for high-performance liquid chromatography **2** based on covalently bonded quaternized brucine was prepared and characterized. The synthetic protocol (Fig. 1) includes *N*-alkylation leading to quaternization of brucine in the first step followed by the covalent attachment of the resulting carboxylated product **1** to 3-aminopropyl silica. The synthetic procedure represents an innovative and general approach to the development not only of alkaloid based separation media but also of homogeneous and heterogeneous catalytic systems and optical chemical sensors operating in an enantioselective fashion as well as novel sol-gel forming systems.[8]

Raman spectroscopy, a powerful analytical tool capable of providing valuable information on the presence of functional groups on solid surfaces, was used for the characterization of the reaction products. Successful immobilization of the quaternary salt **1** on silica was proved by the emergence of the characteristic vibrations of **1** (e.g. 1652, 1609, 1451, 1415, 760 cm^{-1}) in the spectrum of the resulting CSP **2**. Finally, the unreacted amino groups of the starting 3-aminopropyl silica were shielded by end-capping with acetyl chloride. Generally, this step can also be monitored by Raman spectroscopy. However, in the case of brucine, which itself contains two methoxy groups, the reaction with acetyl chloride results only in increased intensity of the valence vibration signal of the methyl group at 2960 cm^{-1}. The sorbent was also subjected to elemental analysis and the surface coverage of **1** was calculated to be about 3.3 μmol m^{-2}. The end-capped sorbent was packed into a stainless steel column (100×4 mm ID) by the down-fill slurry method for chromatographic tests.

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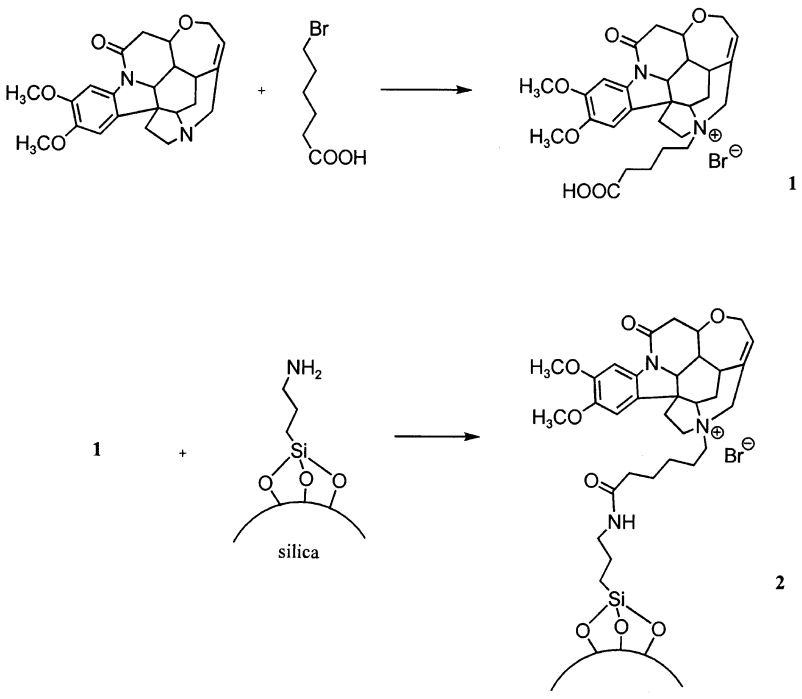
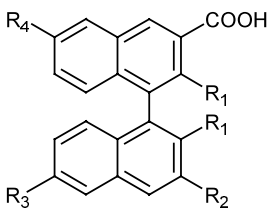


Figure 1. Reaction sequence for preparation of **1** and chiral sorbent **2**.

The type of immobilization of quaternized brucine presented herein provides the chiral stationary phase carrying a permanent positive charge. Several chiral derivatives of 1,1′-binaphthyl-3-carboxylic acid **3**–**6** (Fig. 2) were chosen as potentially separable candidates on the quaternized brucine-based sorbent.

Electrostatic coulombic cation–anion attraction is supposed to be one of the main types of interactions indispensable to obtaining enantioseparation in this system. For this purpose, reversed phase conditions with mixtures of methanol and aqueous buffers were used as mobile phase. The effect of buffer pH, buffer anion type and its concentration as well as the amount of methanol in the mobile phase was studied.

The observed retention factors k and enantioselectivity factor values (α) of the enantiomers of **3**–**6** in mobile phases composed of mixtures of 20 mmol L^{-1} sodium phosphate buffer/methanol are summarized in Table 1. Decreasing pH and/or amounts of methanol in the mobile phase lead to a drop in the elution strength of the mobile phase and hence to a significant increase in the retention times for both enantiomers of compounds **3**–**6**. Nevertheless, the α values for the enantiomers of derivatives **3** and **4** remained relatively high even at pH 7.0 and 8.7 (Fig. 3). This indicates that the separation ability of the sorbent is practically independent of the pH of the mobile phase in the pH range tested and the enantiomers of the acids are separated in anionic form. This finding is consistent with the idea that the CI between the deprotonated carboxylic group of the separated analytes and the positively charged brucine moiety of the CSP participate in chiral recognition processes taking part on the sorbent. The type of anion present in the buffer used was also found to be important. Besides the phosphate buffer, triethylaminacetate (TEAA) and 2-[4-(2-hydroxyethyl)-1-piperazino]-ethanesulfonate (HEPES) were tested (Table 1). Again, only compounds **3** and **4** with carboxylic groups gave measurable separation of the individual enantiomers. The shift of the appropriate retention factors k to higher values with respect to the phosphate buffer of the same pH can be easily interpreted as a consequence of the higher elution strength of the latter mobile phase. A selectivity factor $\alpha = 1.60$ in TEAA buffer for **3** is the highest we achieved, the other α values obtained are comparable with data measured for the phosphate buffer.



	R_1	R_2	R_3	R_4
3	-OH	-H	-tBut	-H
4	-OH	-H	-H	-tBut
5	$-OCH_3$	-H	-H	-H
6	$-OCH_3$	$-CO_2H$	-tBut	-tBut

Figure 2. Structure of separated derivatives **3**–**6**.

For satisfactory separation of the enantiomers of 1,1′-binaphthyl derivatives, several structural prerequisites must be fulfilled. Firstly, in our preliminary experiments it was found that the carboxylic group at position 3 must be present: no asymmetric recognition of racemic 1,1′-binaphth-2,2′-diol and methyl 1,1′-binaphth-2,2′-diol-3-methylcarboxylate was achieved on the brucine CPS. Secondly, the hydroxyl groups of

Table 1. Retention factors k and enantioselectivity α of the enantiomers of **3–6** at various pH values of 20 mmol L^{-1} sodium phosphate buffer, triethylaminacetate (TEAA) and [4-(2-hydroxyethyl)-1-piperazino]ethanesulfonate (HEPES) and the amount of methanol in mobile phase composed of buffer/methanol mixture

Compound	Amount of methanol (%, v/v)	pH of phosphate							
		2.9		4.7		7.0		8.7	
		k_1	α	k_1	α	k_1	α	k_1	α
3	20	–	–	–	–	–	–	14.1	1.18
	40	43.4	1.02	33.0	1.19	10.2	1.20	3.0	1.18
	60	10.3	1.17	7.4	1.17	2.4	1.14	0.8	1.03
	80	6.5	1.12	1.5	1.10	1.0	1.10	0.5	1.00
4	20	–	–	–	–	–	–	17.5	1.14
	40	49.7	1.19	35.9	1.16	12.8	1.18	3.1	1.11
	60	11.3	1.19	6.9	1.13	2.4	1.12	0.9	1.00
	80	4.6	1.08	1.8	1.01	0.7	1.00	0.4	1.00
5	20	–	–	–	–	–	–	1.7	1.00
	40	3.1	1.00	5.0	1.00	1.5	1.00	0.4	1.00
	60	1.4	1.00	2.0	1.00	0.5	1.00	0.2	1.11
	80	1.3	1.00	0.6	1.00	0.3	1.00	0.1	1.00
6	20	–	–	–	–	19.5	1.00	1.5	1.00
	40	17.6	1.00	–	–	3.3	1.00	0.4	1.00
	60	7.0	1.00	15.3	1.00	1.1	1.00	0.1	1.12
	80	8.2	1.00	1.9	1.00	0.6	1.00	0.1	1.00

		pH value			
		4.7 (TEAA)		7.0 (HEPES)	
		k_1	α	k_1	α
3	60	15.8	1.60	11.2	1.13
4	60	14.1	1.11	14.1	1.03

k_1 is retention factor of the less retained enantiomer ($k_1=(t_{R1}-t_0)/t_0$, where t_{R1} and t_0 are retention times of the first eluted enantiomer and dead time of the column, respectively; α is separation factor of the enantiomeric pair ($\alpha=k_2/k_1$), where k_2 is retention factor of the more strongly retained enantiomer; the pH of phosphate buffers was adjusted before the addition of methanol into the buffer solution.

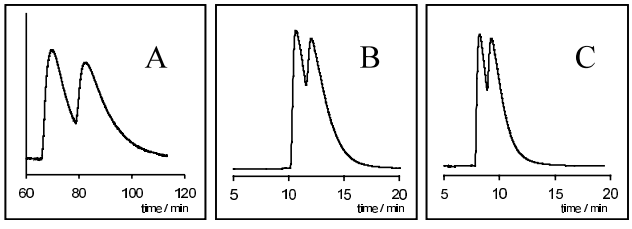


Figure 3. Separation of enantiomers of **3** in the mobile phase composed of 40% methanol–60% phosphate buffer (20 mmol L^{-1}) at different pH values: 4.7 (A), 7.0 (B), 8.7 (C).

1,1′-binaphth-2,2′-diol-3-carboxylic acid seem to be essential for chiral recognition. Thirdly, as the enantioseparation is feasible in the wide pH range of the mobile phase under the circumstance of full deprotonation of the carboxylic group of the analytes, an active role of the CI in the chiral recognition process can be assumed.

In conclusion, our results show the value of this concept, where directionally non-selective strong CI can be used advantageously to stimulate enantioselective recognition if applied to an appropriate chiral environment providing additional spatial selective interaction modes. Currently, we are testing other quaternized alkaloids, yohimbine and quinine, for chiral recognition applications. Our preliminary results with these compounds are consistent with the chiral recognition concept mentioned above (unpublished results).

2. Experimental

2.1. General

2.1.1. Raman spectroscopy. Raman spectra were collected using a Fourier-transform near-infrared (FT-NIR) spectrometer Equinox 55/S (Bruker, Germany) equipped with an FT Raman module FRA 106/S (Bruker). The focused laser beam (250 mW) of Nd:YAG laser (1064 nm, Coherent) irradiated the samples of sorbents in glass vials placed on motorized X–Y–Z sample stage. Scattered light was collected in the backscattering geometry. Interferograms were

obtained with a quartz beamsplitter and a Ge detector (liquid N_2 cooled). Typically 128 of accumulated interferograms were processed by the Fourier transformation with Blackman–Harris 4-term apodization and a zerofilling factor of 8 in order to obtain individual FT Raman spectra with a 4 cm^{-1} resolution.

2.1.2. Chromatography. Perkin–Elmer HPLC Station Series 200 equipped with quaternary pump, autosampler and diode-array detector was used. Data were collected and processed in Turbochrom Workstation 6.0 integrator.

2.2. Preparation of 3-aminopropylsilica

Silica (Separon SGX 500, 7 μm; pore diameter: 50 nm; pore volume: 0.4 mL/g; specific surface 150 m^2/g, Tessek, Czech Republic) (5.5 g) was dried under high vacuum (140°C, 24 h). The dried silica was suspended in dry toluene (molecular sieves 3 Å; 200 ml) and (3-aminopropyl)triethoxysilane (3 ml) was added. The suspension was heated under reflux for 8.5 h. The resulting derivatized silica was filtered off, washed with hot toluene (150 mL), dry acetone (150 mL) and dry methanol (200 mL) and dried under high vacuum (100°C, 1 h).

2.3. Synthesis of *N*-(5-carboxypentyl)brucinium bromide, 1

Brucine free base (0.509 g, 1.3 mmol) and 6-bromohexanoic acid (0.253 g, 1.3 mmol) were dissolved in dry acetonitrile and the mixture heated under reflux for 3 days. After cooling down to room temperature the product was filtered off as a white precipitate, washed with diethyl ether (50 mL) and dried under high vacuum (40°C, 3 h). Analysis of the reaction mixture/of the product: TLC ($CHCl_3$–MeOH, 8:3): R_f (product) = 0; R_f (brucine) = 0.5; R_f (6-bromohexanoic acid) = 1. Yield 0.41 g (54%): $[\alpha]_D^{25}$ +26.8 ($c = 1.0$ g L^{-1}, $d = 1$ dm, methanol); elemental analysis for $C_{29}H_{37}BrN_2O_6$ (589.51): calcd: Br, 13.55; C, 59.08; H, 6.33; N, 4.75%. Found: Br, 13.61; C, 58.38; H, 6.61; N, 5.15%. Mass spectroscopy (FAB; M^+–Br = 509.3): 509 (100%), 435 (50%), 231 (68%), 213 (80%); ^{1}H NMR (300 MHz; DMSO-d_6; TMS) δ (ppm): 12.09 (s, 1H), 7.64 (s, 1H), 7.30 (s, 1H), 6.34 (s, 1H), 4.4 (m, 1H), 4.2–4.1 (m, 1H), 4.09 (m, 2H), 3.84 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.61 (bs, 2H), 3.3 (m, 1H), 2.91 (m, 2H), 2.6 (m, 3H), 2.30 (t, $J = 7.1$, 2H), 2.12 (m, 2H), 1.84 (m, 4H), 1.60 (m, 3H), 1.41 (m, 3H); ^{13}C NMR (75 MHz; DMSO-d_6; TMS) δ (ppm): 218.1, 179.7, 174.1, 168.3, 154.9, 151.3, 149.4, 145.7, 140.8, 140.7, 135.3, 132.9, 120.0, 107.6, 81.3, 78.6, 70.8, 68.7, 65.9, 64.0, 62.0, 61.2, 57.4, 51.7, 45.0, 39.0, 34.6, 29.6, 28.2.

2.4. Synthesis of the chiral brucine-based sorbent, 2

3-Aminopropylsilica was deprotonated with 1% (v/v) triethylamine solution in acetonitrile for 30 min. The sorbent was washed with pure acetonitrile. A solution of **2** (0.175 g) in dry acetonitrile (30 mL) was prepared and the deprotonated 3-aminopropylated silica (1.1 g) was added. The suspension was heated under reflux for 5 days. Then the sorbent was filtered off, washed with acetonitrile, methanol, methanol–water, methanol and dichloromethane and dried under high vacuum (40°C, 2 days). A mixture of acetyl chloride (0.5 mL) and triethylamine (0.5 mL) in dry acetonitrile (20 mL) was added to the suspension of the sorbent in dry acetonitrile (30 mL). The reaction mixture was occasionally stirred and kept at room temperature for 2 days. The resulting end-capped sorbent was filtered off, washed with acetonitrile, acetonitrile–water, acetonitrile, dichloromethane and dried in vacuum (40°C, 2 days).

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