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Assessing chiral self-recognition using chiral stationary phases

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ABSTRACT

Chiral stationary phases were synthesized and their ability to separate racemic precursors from which they were derived was assessed. Taken in conjunction with homochiral recognition previously observed in the solid state, the results of this study reveal that a geometrically controlling π–π interaction has a profound influence on molecular recognition.

1. Introduction

An important but relatively unexplored area of small-molecule chiral recognition involves enantioselective self-assembly, often referred to as self-recognition.[1–8] Several important examples of weak small-molecule chiral self-recognition in solution involving hydrogen-bonded dimers have been reported.[9] For instance, Hara has shown that an enantioenriched sample of *N*-acetyl-*S*-valine *tert*-butyl ester exhibits self-induced NMR nonequivalence, the intensity of the signals is reflective of the enantiomeric ratio in solution.[10] Furthermore, chiral stationary phases (CSPs) derived from *N*-acetyl-*S*-valine *tert*-butyl ester and several related amino acid esters were used to show that chiral self-recognition can be used for chiral chromatographic separations, albeit with weak enantiodiscrimination.[11–13] In contrast to the weak self-association of small molecules, significant levels of enantioselective self-assembly have been reported for supramolecular constructs, such as hydrogen-bonded assemblies,[14–19] metal/ligand complexes,[20–23] and supramolecular polymers.[24] This difference reflects the larger number of intermolecular interactions composing the supramolecular assemblies relative to the small-molecule complexes.

In the course of our studies on small-molecule chiral chromatography, we have observed that several of our and related CSPs derived from amide and ester derivatives of 3,5-dinitrobenzoyl (DNB) amino acids can effectively separate the racemic precursors of these CSPs.[25,26] In all cases, the enantiomer forming the homochiral diastereomeric complex with the CSP is more retained on the chromatography column. Furthermore, enantiomerically enriched samples of the DNB-leucine amides show self-induced chemical shift nonequivalence.[27] Based on these studies, we proposed that a chiral recognition mechanism exists in solution involving three essential points of interaction: two hydrogen-bonding interactions and a controlling multipoint offset π–π interaction between the aromatic moieties. Recently, we have provided strong evidence to confirm this hypothesis through X-ray crystallographic analysis (Fig. 1).[28]

Significantly, the model not only explains the high level of chiral self-association but also reveals that the offset π–π interaction can play a prominent role in the chiral recognition of small chiral molecules. Herein, we explore the chiral self-recognition phenomenon further through chiral chromatographic analysis. The difference in free energy ($\Delta\Delta G$) of association between the homochiral complex and the heterochiral complex can be derived simply from chromatographic separation factors (α).[3] Hence, chiral chromatography provides an effective means of studying self-recognition. Although dual hydrogen bonding drives the dimerization of 'like' molecules, we postulate that the presence of

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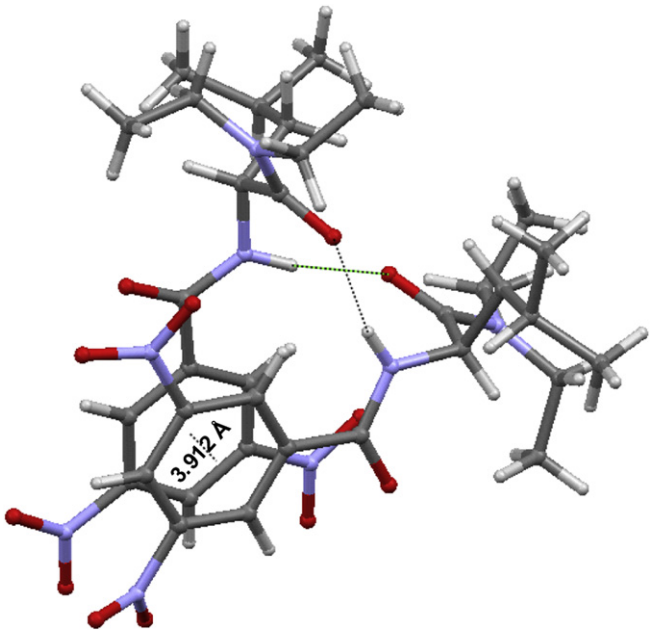


Fig. 1. X-ray structure of the diethyl amide of DNB leucine. Two hydrogen-bonding interactions and an offset π–π interaction account for the chiral recognition.[28]

the offset π–π interaction orients the molecules and promotes strong enantioselectivity. The results of these studies have important implications for future CSP and catalyst design as the offset π–π interaction is much more general than the π-stacking interaction between a π-acid and a π-base, an interaction designed into the majority of selector/substrate complexes.[3–5] Moreover, the results can potentially be applied to rational drug design.

2. Results and discussion

The structures of the CSPs and the racemic analytes used in this study are shown in Fig. 2. Notably, single enantiomers from the racemates in Fig. 2 are precursors to the four CSPs shown, requiring hydrosilyation prior to tethering to the silica support. Preparations of three commercially available CSPs (**1**, **2**, and **4**)[29,30] and compounds **5**–**10**[31] have been described earlier. The synthesis of (*S*)-CSP **3** is shown in Scheme 1. All four CSPs were initially designed to separate the enantiomers of π-basic racemic analytes suspected to interact with the CSPs through a well-established chiral recognition mechanism.[31] In each case, the essential functionalities thought to be responsible for chiral recognition are located in similar places on the backbone. CSPs **2** and **3**, derived from *tert*-butyl β-lactam and ε-caprolactam, respectively, are cyclized versions of CSPs **1** and **4** and were designed to provide a more conformationally rigid backbone, thus removing a degree of freedom at the stereocenter. Prior studies indicate that CSP **2** and CSP **4** give the highest enantioselectivities for separation of a series of π-basic racemic analytes including napthylenecarboxamides, naproxen derivatives, and benzodiazepines, while CSP **3** shows the poorest performance in all cases.[25]

The four π-acidic CSPs shown in Fig. 2 are also capable of separating the enantiomers of all of the π-acidic analytes used in this study. Chromatographic (HPLC) analysis was performed on each of the four π-acidic CSPs using a mobile phase of 20% 2-propanol in hexane (flow rate 2 mL/min). Chromatographic separation factors (α) for these racemic analytes are displayed in Table 1, with entries involving chiral self-recognition marked in bold. In all cases, the enantiomer forming the homochiral adsorbate is the more retained on the column. The butyl ester of DNB-leucine (±)-**6** shows significantly reduced α values relative to its secondary amide

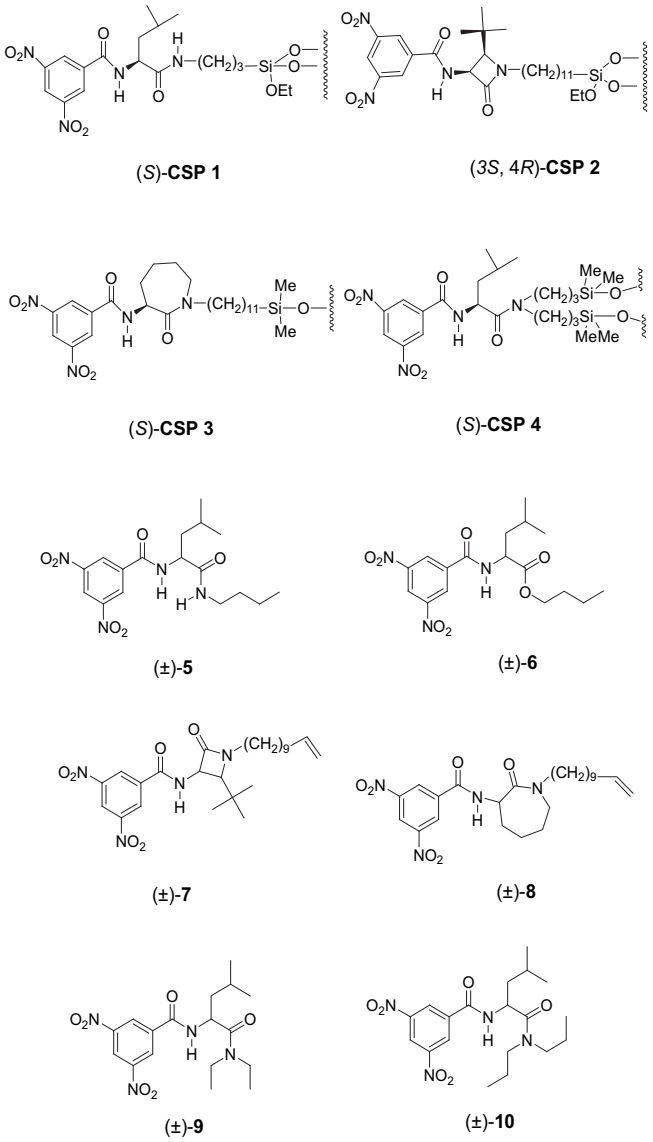
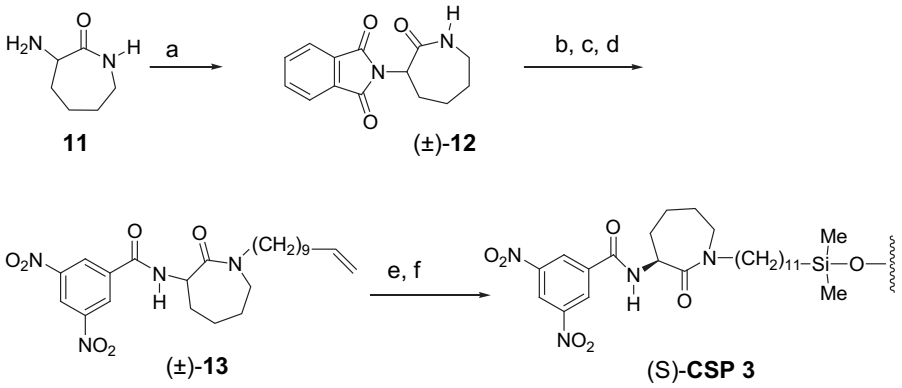


Fig. 2. CSPs and racemic analytes utilized in this study.

counterpart (±)-**5**, consistent with many of the previous studies involving π-donor/π-acceptor systems.[31] This result implicates the carbonyl oxygen as a hydrogen bonding acceptor in the chiral recognition mechanism owing to the increased basicity of the amide carbonyl oxygen relative to the carbonyl oxygen of the butyl ester. Furthermore, the DNB tertiary amides (±)-**9** and (±)-**10** give larger α values than the secondary *n*-butyl amide (±)-**5**. In the later case, an additional hydrogen-bonding interaction from the secondary amide hydrogen may provide a competing achiral mode of interaction that increases retention and thus diminishes enantioselectivity. The length of the alkyl chains on the *N*,*N*-dialkyl amides also affects enantioselectivity showing a modest increase from the diethyl amide (±)-**9** to the dipropyl amide (±)-**10** but then decreasing as the alkyl chains are lengthened further (data not shown). Similar effects of the length of alkyl substituents on enantioselectivity have been noted earlier and attributed to intercalation of these groups between the strands of bonded phase.[32] Separations of other racemic DNB amino acids can be accomplished on all four CSPs.

Interestingly, the ε-caprolactam derived (*S*)-CSP **3** generally outperforms the other CSPs for chromatographic resolutions of the π-acidic racemates shown in Fig. 2, despite typically giving the



Scheme 1. Synthesis of (*S*)-CSP **3**. Reagents and conditions: (a) Phthalic anhydride, cat.Uncap triethylamine, reflux (b) Sodium hydride, 10-undecenyl mesylate (c) Ethanolic hydrazine solution, reflux (d) 3,5-Dinitrobenzoyl chloride, triethylamine (e) Resolution on (*S*)-*N*-(1-naphthyl)leucine(siloxyundecylester) column (f) Hydrosilylation and bonding to silica.

Table 1
Examples of chiral self-recognition of racemic analytes on several amino acid derived CSPs

Analyte	(*S*)-CSP **1**	(3*S*,4*R*)-CSP **2**	(*S*)-CSP **3**	(*S*)-CSP **4**
	α,[a] k'_1[b] $[\alpha]_D$[c]	α,[a] k'_1[b] $[\alpha]_D$[c]	α,[a] k'_1[b] $[\alpha]_D$[c]	α,[a] k'_1[b] $[\alpha]_D$[c]
(±)-**5**	**1.50**, 0.96, (***S***)	2.03, 1.33, (*S*)	3.32, 0.66, (*S*)	3.04, 1.37, (*S*)
(±)-**6**	**1.29**, 0.99, (***S***)	1.57, 1.61, (*S*)	1.89, 1.26, (*S*)	2.21, 1.06, (*S*)
(±)-**7**	1.88, 1.41, (3*S*,4*R*)	**3.73**, 1.41, (**3*S*,4*R***)	7.11, 1.55, (3*S*,4*R*)	3.72, 1.54, (3*S*,4*R*)
(±)-**8**	2.48, 2.41, (*S*)	4.03, 3.73, (*S*)	**2.54**, 2.33, (***S***)	4.05, 2.32, (*S*)
(±)-**9**	2.04, 1.38, (*S*)	3.02, 1.61, (*S*)	4.34, 1.00, (*S*)	**5.39**, 2.01, (***S***)
(±)-**10**	2.21, 1.01, (*S*)	3.60, 1.53, (*S*)	4.63, 0.83, (*S*)	**6.05**, 2.22, (***S***)

[a] Chromatographic separation factor.
[b] Retention factor (see experimental) for the first eluted enantiomer using 20% 2-propanol/80% hexane as the mobile phase at a flow rate of 2 mL/min.
[c] Absolute configuration of the more strongly retained enantiomer.
Entries involving chiral self-recognition are marked in bold.

poorest performance for resolution of π-basic racemates.[25] A striking example in Table 1 involves the resolution of (±)-**7**, which has an α value of 7.11 on CSP **3**, nearly twice that of CSP **2** and CSP **4**. The chiral recognition mechanisms are clearly different in each case. The large enantioselectivity indicates that the molecular surfaces of (*S*)-CSP **3** and (3*S*,4*R*)-**7** display a high degree of complementarity. Conformational rigidity of a CSP will enhance enantioselectivity when one enantiomer of the analyte closely conforms to the molecular shape of the CSP. A rigid backbone reduces the likelihood of multiple conformations contributing to the chiral recognition process.

On the other hand, a rigid CSP will impose severe steric requirements on chiral recognition, particularly when the interacting surfaces are not well suited to each other. These opposing factors likely explain the disparity between π-basic and π-acidic analytes on CSP **3**. The results presented here suggest that shape complementarity plays a critical role in self-recognition and, more generally, in chiral discrimination.

Despite several reports of weak small-molecule self-recognition through hydrogen-bonded dimers (see Introduction),[9] the preference for the homochiral dimer has not been explained sufficiently. Hara's proposed chiral recognition mechanism for self-discrimination of *N*-acyl amino acid esters involves two parallel edge-to-edge hydrogen-bonding interactions in a head-to-tail approach generating a anti-β-sheet-like structure.[33] The head-to-tail alignment does not satisfy the minimized steric repulsion interaction between substituents on the stereogenic center and hence fails to explain the stability differences between the diastereomeric complexes. Alternatively, a head-to-head approach from cross, dual hydrogen bonding (Fig. 1) minimizes steric interactions between the two alkyl substituents on the stereogenic centers. This cross hydrogen bonding is sufficient to explain dimerization of DNB leucine amides in solution[27,34] and in the solid state.[28] Furthermore, the offset π–π interaction between aromatic rings controls enantioselective dimerization by providing a third point of interaction and orienting the molecules with respect to each other. The offset π–π interaction is not as geometrically restricted as the π-stacking interaction seen in many CSP/analyte interactions, hence providing a larger degree of rotational and translational space for the molecules to move while still maintaining the essential three points of interaction. These added degrees of freedom might explain the surprisingly high separation factors of the racemic DNB analytes on the conformationally rigid and sterically cumbersome CSP **3**.

3. Conclusion

We have described the chromatographic resolution of a series of racemic amino acids derivates containing an electron-deficient aromatic ring. Consistent with results obtained in the solid state, the results presented here provides evidence suggesting that the origin of homochiral enantioselective control is determined by head-to-head dual hydrogen bonding and a geometrically controlling offset π–π interaction. Factors, such as rigidity and shape complementarity also appear to affect the magnitude of enantioselective discrimination.

4. Experimental section

4.1. General methods

J values are given in hertz. The various CSPs and racemic analytes used in this study were previously described unless otherwise noted.[30–34] CSP **1** was obtained from Regis Technologies (Morton Grove, IL). The ^{1}H NMR spectra were obtained on a Varian XL-200 using tetramethylsilane as an internal reference. Low-resolution mass spectra were obtained on a Varian MAT CH-5 mass spectrometer with 70 eV electron impact ionization. High-resolution mass spectra were obtained on a Varian 731 mass spectrometer. Microelemental analyses were performed by the University of Illinois Microanalytical Service. Optical rotations were determined at room temperature with a Rudolph Autopol III polarimeter and a 1 dm polarimetric cell. Chromatography was performed using a Rainin HPX solvent delivery system and pressure monitor, a Rheodyne 7125 injector with a 20 μl sample loop, a Milton Roy LDC Monitor D fixed wavelength detector opening at 254 nm and a Kipp and Zonen BD 41 recorder. Chromatographic runs were conducted at ambient temperature with a flow rate of 2 mL/min. The void volume was determined by using 1,3,5-*tert*-butylbenzene. The

retention factor ($k'1$) was calculated using the following equation: $k'1=(tn-t0)/t0$ where tn is the retention time of the analyte and t0 is the retention time of 1,3,5-*tert*-butylbenzene. The separation factor (α) is a ratio of the retention factors of the two enantiomers.

4.2. Detailed synthetic protocols

*4.2.1. (N-3,5-Dinitrobenzoyl)-3-amino-N-10-undecenyl-ε-caprolactam (**13**).* Compound **11** was purchased from (Sigma, St. Louis MO), and **12** was synthesized as described previously.[35] Sodium hydride (60%) dispersion in mineral oil, 506 mg (12.6 mmol), in 50 mL of dry benzene and 3.8 mL of dry DMSO were stirred with the phthalimido-ε-caprolactam (**12**) at 60 °C for 20 min. A mixture of 10-undecenyl mesylate, 3.16 g (12.7 mmol), and tetrabutylammonium bromide, 0.750 g (2.33 mmol), in dry benzene were added to the reaction mixture at room temperature. After refluxing for 7 h, the benzene was evaporated the product was diluted with 100 mL of dichloromethane. After washing with 100 mL (3×) of water, the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography to afford 3.68 g of pure product. An ethanolic 1 M solution of hydrazine hydrate (8.8 mL) was added to *N*-alkylated-ε-caprolactam, 3.3 g (8.0 mmol), suspended in 100 mL of 95% ethanol. After refluxing for 6 h, the solvent was evaporated and the contents were diluted with dichloromethane. After removal of the insoluble solid by filtration, 2.26 g of 3-amino-10-undecenyl-ε-caprolactam (crude oil product) was isolated and used without further purification. In the next step, 3,5-dinitrobenzoyl chloride, 2.42 g (9.5 mmol), in 20 mL of dry dichloromethane was added to a dichloromethane solution (40 mL) of the 3-amino-10-undecenyl-ε-caprolactam, 2.26 g (8.0 mmol), and triethylamine, 1.5 mL (10.8 mmol), in an ice-bath. The reaction mixture was stirred at room temperature for 30 min and washed twice with 40 mL of 2 N NaOH and 50 mL of brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was chromatographed on silica gel to afford (3.6 g, 94%) of the pure product. R_f=0.3 (hexane/ethyl acetate=3/1); Mp: 102–104 °C; ^{1}H NMR ($CDCl_3$): δ 1.20–1.50 (br s, 12H), 1.40–1.70 (m, 2H), 1.80–2.30 (m, 7H), 3.05–3.70 (m, 5H), 4.72–4.85 (m, 1H), 4.87–5.07 (m, 2H), 5.70–5.92 (m, 1H), 8.64 (d, J=6.4 Hz, 1H), 8.99 (d, J=2.4 Hz, 2H), 9.15 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 27.461, 28.171, 28.346, 28.544, 29.460, 29.636, 29.941, 29.956, 30.025, 32.147, 32.344, 49.463, 49.783, 53.805, 114.720, 121.462, 127.831, 138.446, 139.736, 149.214, 161.929, 172.613; ν_{max}/cm^{-1} (KBr): 3257.57 (N–H), 3080.26 (C=C), 2926.85 (C=C arom.), 2853.75 (NO_2), 2854 (C=O), 1627.67 (*meta*-benzene), 1659 (NO_2 arom.), 1300.21, 1265.25 (NO_2); mass spectrum: m/z (relative intensity) 474 (55.9%), 307 (73.7), 195 (98.8), 149 (49.1), 97 (70.2), 55 (98,8), 41 (100); (found: C, 60.66; H, 7.22. $C_{24}H_{34}N_4O_6$ requires: C, 60.74; H, 7.22).

*4.2.2. (+)-(S)-(N-3,5-Dinitrobenzoyl)-3-amino-N-10-undecenyl-ε-caprolactam ((S)-**13**).* Enantiomerically pure samples of **13** were obtained by preparative medium pressure liquid chromatography of the respective enantiomers on a 1″×30″ column containing a (*S*)-*N*-(1-naphthyl)leucine-derived CSP bonded to 60 μm irregular silica.[25] The (+)-(*S*)-(*N*-3,5-dinitrobenzoyl)-3-amino-*N*-10-undecenyl-ε-caprolactam elutes second, the enantiomeric purity being greater than 99%. The NMR spectrum is identical to that of the racemate. $[\alpha]_D$ +55.04 (*c* 4.98 in CH_2Cl_2). The solvent choice for the specific rotation was based solely on solubility.

*4.2.3. (+)-(S)-N-11-Dimethylethoxyundecyl-(N-3,5-dinitrobenzoyl)-3-amino-ε-caprolactam (CSP-**3**).* Compound (*S*)-**13**, 0.93 g (2.0 mmol), and 15 mL of dimethylchlorosilane were dissolved in 15 mL of dry dichloromethane. After addition of chloroplatinic acid (44 mg), the reaction mixture was heated to reflux under a nitrogen atmosphere. After 100 min, an aliquot of the reaction mixture showed (NMR analysis) no remaining vinyl group on the starting material. The excess of dimethylchlorosilane was removed by distillation. Residual dimethylchlorosilane was removed by three successive distillations after the addition of small portions of dichloromethane. A mixture of 2 mL of dry triethylamine and 3 mL of absolute ethanol was added to the crude chlorosilane with 15 mL of dry dichloromethane at 0 °C and the reaction mixture was stirred for 30 min at room temperature. After concentration of the reaction mixture, 10 mL of anhydrous diethyl ether was added. The insoluble triethylamine hydrochloride was removed by filtration, and the filtrate was evaporated. The crude product was purified on silica gel producing pure ethoxysilane oil (762 mg, 86.4%). $[\alpha]_D$ +62.90 (*c* 0.97 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 0.03 (s, 6H), 0.47–0.60 (m, 2H), 1.05–1.35 (br s, 16H), 1.12 (t, J=6.9 Hz, 3H), 1.40–1.65 (m, 2H), 1.80–2.20 (m, 5H), 3.20–3.50 (m, 4H), 3.50–3.70 (m, 1H), 3.60 (q, J=7.0 Hz, 2H), 4.83 (dd, J=10 and 6.4 Hz, 1H), 8.66 (d, J=6.2 Hz, 1H), 8.90 (d, J=1.8 Hz, 2H), 9.06 (t, J=2.1 Hz, 1H); mass spectrum: m/z (relative intensity) 578 (2.59%), 459 (29.0), 307 (30.8), 195 (51.0), 103 (100), 75 (76.3), 55 (61.6), 44 (96.0); HR-MS (FAB) (found: $[M+H]^+$, 578.3137. $C_{28}H_{46}N_4O_7Si$ requires m/z 578.3136). *Chiral stationary phase* (+)-(*S*)-*N*-11-*Dimethylethoxyundecyl*-(*N*-3,5-*dinitrobenzoyl*)-3-*amino*-ε-*caprolactam*. The ethoxysilane (762 mg) from the previous step was added to dichloromethane slurry of 4.4 g of Rexchrom silica (5 μm, 100 Å) from Regis Technologies that had been previously dried by azeotropic water removal with benzene. The resulting slurry was evaporated to dryness under reduced pressure, then mechanically rocked in a Kügelrohr oven under reduced pressure (0.3 Torr) at 100 °C for 30 h. The modified silica was washed with methanol and packed into a 4.6×250 mm stainless steel HPLC column by conventional methods. The residual silane groups were endcapped using 2 mL of hexamethyldisilazane in 50 mL of dichloromethane.

Acknowledgements

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