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Studies of the resolution of racemic 1,1′-bi-2-naphthol with a dipeptide chiral selector identified from a small library

Junmin Huang, Hui Chen, Tingyu Li *

Department of Chemistry, Box 9573, Mississippi State University, Mississippi State, MS 39762, USA

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Abstract

Several new stationary phases were prepared to study the structure–activity relationship of the chiral resolution of racemic 1,1′-bi-2-naphthol with a modified dipeptide Asn-Asn selector. The number of amino acid, the side chain protecting groups of the amino acid, and the Fmoc end-capping group all proved important for enantioselectivity. The linker also influenced enantioselectivity. Influence of the length of the linker appears to be related to the accessibility of chiral selectors. The bond through which the selector is attached to the linker proved important. Based on these results, it is postulated that hydrogen bonding interactions between one side chain amide group of one Asn and the oxygen on the backbone of another Asn with the two hydroxyl groups of the analyte play an important role in the resolution of racemic 1,1′-bi-2-naphthol with the modified dipeptide Asn-Asn selector.
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1. Introduction

Chiral separation is required in many areas of research. As enzymes and other biological receptor molecules possess chiral centers, enantiomers of a racemic compound may be absorbed, activated, and degraded by them in different manners. Due to this phenomenon, in many instances, two enantiomers of a racemic drug have very different pharmacological activities. In order to discern these differing effects, the biological activity of each enantiomer needs to be studied separately. This and other factors within the pharmaceutical industry have contributed significantly to the need for enantiomerically pure compounds and thus the need for chiral chromatography [1].

As a result, significant progress has been made in chiral stationary phase development in the past decades. Despite the progress, the mechanism of chiral recognition is still not well understood. Such studies could have been hampered by the complexity of the chiral stationary phases, nature of the weak interactions involved, and many possible modes of interaction due to the conformational flexibility of the stationary phases and analytes. To date, mechanism of the chiral recognition of only a few chiral recognition systems has been well studied. Among them, the chiral recognition mechanism of the modified quinine type chiral stationary phases has been investigated in depth [2–5]. Mechanistic investigation by variation of the chemical structure of the chiral stationary phases, NMR spectroscopy, and molecular modeling have all been utilized in these studies.

We have been interested in peptide-based chiral selectors. Recently, from a small dipeptide library [6], we developed a chiral selector that resolves 1,1′-bi-2-naphthol (Fig. 1) with a separation factor of 7.2, which is significantly higher than other separation factors reported for this well-studied analyte [7–13]. In order to gain an understanding of how this dipeptide-based chiral selector could resolve racemic 1,1′-bi-2-naphthol with such a high separation factor, we decided to perform a structure–activity study of this system. Simplicity of the chiral stationary phase and the large separation factor observed made such a study feasible. Our findings are reported in this article.

It should also be pointed out that efficient chiral resolution of 1,1′-bi-2-naphthol is also of significant practical importance. Optically active 1,1′-bi-2-naphthol (**1**) and its derivatives are frequently used as chiral auxiliaries and ligands in asymmetric synthesis [14]. Even though asymmetric synthesis of this compound has been reported, this important material is gener-

* Corresponding author. Tel.: +1 662 325 7613; fax: +1 662 325 7613.
E-mail address: TL45@ra.msstate.edu (T. Li).

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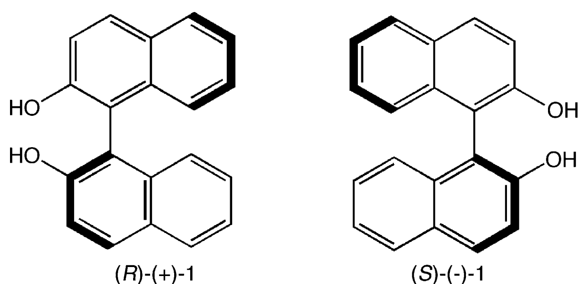

Fig. 1. R and S enantiomers of racemic 1,1′-bi-2-naphthol.

ally obtained in enantiomerically pure forms by the resolution of the racemic mixture. Of the resolution methods that have been reported, the popular procedure involves three steps: (1) the conversion of the racemic 1,1′-bi-2-naphthol to its phosphates; (2) resolution of the phosphates via its cinchonine salts; and (3) re-conversion of the resolved phosphate salts back to 1,1′-bi-2-naphthol [14]. Highly efficient enantioselective stationary phases could provide a viable alternative to the rather tedious derivative fractional crystallization procedure.

2. Experimental

2.1. Abbreviations

DIC, diisopropylcarbodiimide; HOBt, 1-hydroxybenzotriazole; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; TFA, trifluoroacetic acid; DIPEA, *N*,*N*-diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; NMM, *N*-methylmorpholine; DMF, *N*,*N*-dimethylformamide; DCM, dichloromethane; IPA, 2-propanol; THF, tetrahydrofuran; Ac, acetyl; NEC, naphthylethyl carbamate; Trt, trityl; CBZ, benzyloxycarbonyl; Fmoc, 9-fluorenylmethoxycarbonyl; Boc, *tert*-butyloxycarbonyl; Fmoc-Ahx-OH, 6-[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino hexanoic acid; Fmoc-Abu-OH, 4-[(9*H*-fluoren-9-ylmethoxy) carbonyl]amino butyric acid; Fmoc-Aun-OH, 11-[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino undecanoic acid; Fmoc-Gly-OH, *N*-α-Fmoc-glycine; Fmoc-Asn(Trt)-OH, *N*-α-Fmoc-*N*-β-trityl-L-asparagine; Fmoc-Gln(Trt)-OH, *N*-α-Fmoc-*N*-γ-trityl-L-glutamine; Boc-Asn(Trt)-OH, *N*-α-*t*-Boc-*N*-β-trityl-L-asparagine; Z-Asn(Trt)-OH, *N*-α-CBZ-*N*-β-trityl-L-asparagine; Fmoc-Asn-OH, *N*-α-Fmoc-L-asparagine.

2.2. General supplies and equipment

All reagents were used as received except as noted. Amino acid derivatives were purchased from NovaBiochem (San Diego, CA, USA). All other chemicals and solvents were purchased from Aldrich (Milwaukee, WI, USA), Fluka (Ronkonkoma, NY, USA), or Fisher Scientific (Pittsburgh, PA, USA). HPLC grade silica gel (particle size 5 μm, pore size 100 Å, and surface area 298 m^2/g) was obtained from Akzo Nobel (Kromasil, EKA Chemicals, Bohus, Sweden). Selecto silica gel (32–63 μm) from Fisher Scientific was used for flash column chromatographic purification of target compounds. Thin-layer chromatography was completed using EM silica gel 60 F-254 TLC plates (0.25 mm; E. Merck, Darmstadt, Germany). Proton NMR data were recorded at 300 MHz and referenced to TMS. Coupling constants were calculated from chemical shifts and reported as absolute values in Hz. Elemental analyses were performed by Atlantic Microlabs (Norcross, GA, USA). HPLC analyses were completed with a Beckman analytical gradient system (System Gold). UV spectra were obtained with a Shimadzu UV 201 spectrometer (cell volume 3 mL; cell pass length 10 mm).

2.3. Preparation of the chiral stationary phase **2**

To 0.80 g of NH_2-$(CH_2)_5$CO-APS (H-Ahx-APS) prepared previously [6] (the surface amino concentration was 0.60 mmol/g) were added mixtures of Fmoc-Asn(Trt)-OH (3 equiv., 0.86 g), HATU (3 equiv., 0.55 g), and DIPEA (3 equiv., 0.19 g) in 8 mL of DMF. After agitating for 6 h, the resulting silica was filtered and washed with DMF, methanol, and DCM. The surface Asn(Trt) concentration was determined to be 0.51 mmol/g-based on the Fmoc cleavage method. After that, the remaining unreacted free amine groups in the coupling reactions were end-capped by reacting with acetic anhydride and pyridine in DCM, then filtered and washed with DMF, methanol, and DCM to yield the desired chiral selector on the silica gel.

2.4. Preparation of the chiral stationary phase **3**

To 0.80 g of NH_2-$(CH_2)_5$CO-APS (H-Ahx-APS) (the surface amino concentration was 0.60 mmol/g) were added mixtures of Fmoc-Asn-OH (3 equiv., 0.51 g), HATU (3 equiv., 0.55 g), and DIPEA (3 equiv., 0.19 g) in 8 mL of DMF. After agitating for 6 h, the resulting silica was filtered and washed with DMF, methanol, and DCM. The surface Asn concentration was determined to be 0.52 mmol/g-based on the Fmoc cleavage method. The Fmoc protecting group was then removed by treatment of the silica with 10 mL of 20% (v/v) piperidine in DMF for 1 h. The deprotected silica, H-Asn-Ahx-APS, was collected by filtration and washed with DMF, methanol, and DCM. Then another module, Fmoc-Asn-OH, was coupled to the resulting silica following an identical reaction sequence. The surface Fmoc concentration was determined to be 0.42 mmol/g-based on the Fmoc cleavage method. After that, the remaining unreacted free amine groups in the coupling reactions were end-capped by reacting with acetic anhydride and pyridine in DCM, then filtered and washed with DMF, methanol, and DCM to yield the desired chiral selector on the silica gel.

2.5. Preparation of the chiral stationary phase **4**

The Fmoc protecting group of CSP **1** was removed by treatment of the silica with 10 mL of 20% (v/v) piperidine in DMF to yield CSP **4**.

2.6. Preparation of the chiral stationary phase **5**

To 0.80 g of NH_2-$(CH_2)_5$CO-APS (H-Ahx-APS) (the surface amino concentration was 0.60 mmol/g) were added mixtures of

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