Enantioselective Liquid–Liquid Extraction of Underivatized Amino Acids with Simple Chiral Aminophenyl-Aldehyde

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The derivative of aminophenyl-aldehyde with an asymmetric carbon and an uryl group, (S)-2, was synthesized. The combination of (S)-2 and aliquat-336 in CDCl3 extracted underivatized amino acids in water layer by imine formation with enantioselectivities of 12/1 for Phe, 13/1 for Val, and 12/1 for Leu, which are comparable with those of previously reported binaphthol-based extractor (S)-1. The enantioselectivities of (S)-2 is remarkable considering the low molecular weight compared to (S)-1. Density functional theory computations and experimental data demonstrate that imine bond is strengthened by resonance-assisted hydrogen bond with the nearby —NH— group.

Keywords: Liquid–liquid extraction, Chiral extractor, Amino acid

Introduction

Enantioselective liquid–liquid extraction (ELLE) is a promising economical process due to a low energy consumption in the operation and convenience in scaling up.† Versatile chiral extractors of organic and metallo-organic compounds for ELLE have been developed.‡–§ Binol-based chiral aldehydes and ketones have been developed in our group for the extraction of underivatized amino acids through reversible imine bond formation,‡ which are quite remarkable considering that other extractors so far developed are usually applied to the extraction of derivatized amino acids based on weak noncovalent interactions.§ The imine bond is hydrolyzed in mild conditions by contact with aqueous acidic solution, which ensures the facile recovery of the extracted amino acids.⁶ Thus, chiral aldehydes might be efficient chiral extractors for underivatized amino acids, whose enantiomerically pure forms are widely used as intermediates in the synthesis of chiral pharmaceuticals.⁷

The molecular weights of binol-based aldehydes developed so far relatively large compared to those of amino acids.⁴ Simple molecules with low molecular weights will be more desirable in the sense of mass and cost efficiencies. Our group have previously reported salicyl-based chiral aldehydes, which has lower molecular weights compared to the binol-based aldehydes; however, they showed lower stereoselectivities than the binol-based ones.⁸ Thus our group gave efforts for developing simple extractor with low molecular weight and showing high enantioselectivity.

It is known that the imine bond produced by an amino acid and the binol-based aldehyde is stabilized by hydrogen bond with nearby —OH group, and such special hydrogen bond was known as resonance-assisted hydrogen bond (RAHB).⁹ It is quite likely that the replacement of the —OH group by —NH— group also enhances the stability of the imine bond.¹⁰ If —OH group is changed to —NH—, then a chiral unit can be directly attached to the —NH—, which would simplify the molecular structure and increase a chiral influence on the imine bond. In this context, the derivative of aminophenyl-aldehyde, (S)-2, was designed, whose molecular weight is 359.4 significantly lower than 538.6 of the previously developed binol-based aldehyde, (S)-1 (1). Here, the synthesis of compound (S)-2 and its stereoselectivities in the extraction of underivatized amino acids are reported.

Experimental

General. The reagents such as 2-aminobenzyl alcohol, phenyl isocyanate, and NaCN were purchased from Aldrich Korea or TCI Korea and used without further purification. ¹H and ¹³C NMR spectra were recorded on a Bruker AM 300 spectrometer in CDCl₃ or DMSO-d₆ solutions containing tetramethylsilane as an internal standard. Melting points
were measured with an Electrothermal IA 9000 digital. Optical rotations were measured on a DIP 360 polarimeter. Column chromatography was performed on silica gel of 230–400 mesh. HRMS were measured by electrospray ionization (ESI) with a Q-TOF analyzer.

**Synthesis of (2-Hydroxymethyl-Phenylamino)-Phenyl-Acetonitrile (4).** To a solution of dry MeOH (50 mL) and acetic acid (10 mL) were added 2-hydroxymethyl-aniline (3, 10.0 g, 81.3 mmol), phenyl aldehyde (6.8 mL, 73.8 mmol), and sodium cyanide (3.64 g, 73.8 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with ethyl acetate (EA) after the addition of aqueous sodium hydroxide solution (30 mL, 2.0 M). The organic layer was dried over Na2SO4, filtered off, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography by using an eluent of EA/hexane (2/1) to give 7.52 g of compound 4 (yield = 83%) as a colorless liquid. 1H NMR (300 MHz, CDCl3) δ = 7.65–7.61 (m, 2H), 7.52–7.41 (m, 3H), 7.33 (td, J = 7.8, 1.7 Hz, 1H), 7.15–7.11 (m, 1H), 6.95–6.85 (m, 2H), 5.56–5.47 (m, 2H), 4.67–4.66 (m, 2H), 1.89 (s, 1H); 13C NMR (75 MHz, CDCl3) δ = 144.4, 134.0, 129.7, 129.4, 129.3, 129.3, 127.1, 126.0, 118.4, 112.2, 64.5, 49.5; HRMS (ESI + H) calcd for C22H19N3O2, 362.1790; found, 362.1860.

**Synthesis of (2-Formyl-Phenylamino)-2-Phenyl-Ethylamine (5).** Compound 4 (6.5 g, 27.7 mmol) was added slowly to a solution of NaBH4 (3.93 g 104 mmol) and acetonitrile (4). To a solution of dry MeOH (50 mL) and sodium cyanide (3.64 g, 73.8 mmol) at 0 °C, and the resulting mixture was stirred at room temperature, evaporated to dryness, and extracted with EA. The organic layer was washed with water and dried over Na2SO4, filtered off, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography with an eluent of EA/hexane/MC (2/1/10) to give 4.67 g of compound 5 (yield = 30%). 1H NMR (300 MHz, CDCl3) δ = 8.67 (s, 1H), 7.45–7.31 (m, 6H), 7.20–7.16 (m, 1H), 7.03 (m, 1H), 6.93–6.88 (m, 2H), 6.51 (t, J = 9 Hz, 1H), 6.37–6.30 (m, 2H), 5.75 (d, J = 9 Hz, 1H), 5.19 (t, J = 6 Hz, 1H), 4.62–4.47 (m, 3H), 3.46–3.35 (m, 2H); 13C NMR (75 MHz, CDCl3) δ = 156.2, 145.7, 142.6, 140.7, 129.1, 128.9, 128.1, 127.7, 127.4, 127.0, 126.5, 126.1, 118.1, 116.1, 111.0, 61.7, 58.3, 46.5; HRMS (ESI + H) calcd for C22H21N3O2, 362.1790; found, 362.1860.

**Result and Discussion**

As shown in Scheme 1, commercially available 2-aminobenzyl alcohol (3) was subjected to Strecker reaction with phenylaldehyde and cyanide anion, which led to the formation of a nitrile compound 4. The reduction of 4 in the presence of NaBH4 followed by the reaction with phenyl isocyanate produced the ureyl-pendant alcohol, 6. Subsequent oxidation of the alcohol with manganese dioxide in MC obtained the desired aldehyde, 2. The optically pure form of 2 was prepared by a commercial preparative procedure.
A representative experiment of ELLE with (S)-2 was carried out for phenylalanine. The organic layer was prepared by dissolving (S)-2 (30 mM) together with aliquat-336 (60 mM) in CDCl$_3$ (2 mL) and the aqueous layer by dissolving phenylalanine as a sodium salt (0.75 M) in water (2.0 mL). The two layers were stirred at room temperatures.

Figure 1(a) shows partial $^1$H NMR spectra of (S)-2 mixed with aliquat-336 in CDCl$_3$ before the ELLE experiment. The signal at 9.83 ppm was assigned to the imine proton, which is much higher than that expected by the $^1$H NMR. This experiment proves that (S)-2 is a highly enantioselective chiral extractor for underivatized phenylalanine.

The optical purity of D-phenylalanine that was obtained by the hydrolysis of the organic layer shown in Figure 1(d) was measured by HPLC to be 97%, whose purity was slightly higher than that expected by the $^1$H NMR. This experiment proves that (R)-2 is a highly enantioselective chiral extractor for underivatized phenylalanine.

<table>
<thead>
<tr>
<th>Amino acid</th>
<th>D/L ratio$^5$</th>
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<tr>
<td>Phenylalanine</td>
<td>12</td>
</tr>
<tr>
<td>Methionine</td>
<td>6.0</td>
</tr>
<tr>
<td>Serine</td>
<td>9.0$^6$</td>
</tr>
<tr>
<td>Valine</td>
<td>13</td>
</tr>
<tr>
<td>Leucine</td>
<td>12</td>
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$^a$ Amino acids of 0.75 M in aqueous layers were extracted into the organic layer containing (S)-2 (30 mM) and Aliquat 336 (60 mM).

$^b$ The D/L ratios were determined by the integration of NH signals of their $^1$H NMR spectra (Appendix S1, Supporting Information).

The geometries and energies of the imines of (S)-2 and several amino acids were obtained by the density functional theory (DFT) calculations to understand the basis of the enantioselectivities. Generally, the stable conformations of (S)-2-D-AA and (S)-2-L-AA (where AA = an amino acid)
were initially searched by molecular dynamics run at the density functional tight binding (DFTB) level of theory using the DFTB+ 1.2 program and a few low energy conformers were optimized further at the B3LYP/6-311G (d) level of theory using Gaussian 09 program. The optimized structures for (S)-2-D-Phe and (S)-2-L-Phe are shown in Figure 2 as a representative. The calculations predict that the former is more stable than the latter by 2.1 kcal/mol in accordance with the experimental result.

The calculations on (S)-2-L-Ala and (S)-2-D-Ala predict that the latter is more stable than the former only by 0.21 kcal/mol, which suggests a low enantioselectivity of the (S)-2 for alanine. The energy differences between the imine diastereomers are expected to be 2.3 and 2.4 kcal/mol for valine and leucine, respectively.

Conclusion

We have synthesized an extractor, (S)-2, for ELLE of underivatized amino acids, which has significantly lower molecular weight compared to the previously reported binaphthol-based one, and much higher enantioselectivity than salicyl-based one. The $^1$H NMR studies show that the imine formation ratio of (S)-2 is near to completion in the ELLE of phenylalanine. The computational data quite reasonably explain the orientation of chiral carbon center to amino group of the orthoaminophenyl aldehyde is a good approach to obtain a simple and efficient chiral extractor for underivatized amino acids.

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Supporting Information. Additional supporting information may be found online in the Supporting Information section at the end of the article.

References
