

Fabrication of Meso/Macroporous Carbon Monolith and its Application as a Support for Adsorptive Separation of *D*-Amino Acid from Racemates

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(*S*)-Alanine Racemase Chiral Analogue ((*S*)-ARCA) was used as an efficient adsorbent for the selective separation of *D*-amino acids (*D*-AAs), which are industrially important as chiral building blocks for the synthesis of pharmaceutical intermediates. The organic phase, containing (*S*)-ARCA adsorbent and phase transfer reagents, such as ionic liquid type molecules (Tetraphenylphosphonium chloride (TPPC), Octyltriphenylphosphonium bromide (OTPPBr)), were coated on the surfaces of mesoporous carbon supports. For the immobilization of chiral adsorbents, meso/macroporous monolithic carbon (MMC), having bimodal pore structures with high surface areas and pore volumes, were fabricated. The separation of chiral AAs by adsorption onto the heterogeneous (*S*)-ARCA was performed using a continuous flow type packed bed reactor system. The effects of loading amount of ARCA on the support, the molar ratio of AA to ARCA, flow rates, and the type of phase transfer reagent (PTR) on the isolation yields and the optical purity of product *D*-AAs were investigated. *D*-AAs were selectively combined to (*S*)-ARCA through imine formation reaction in an aqueous basic solution of racemic *D/L*-AA. The (*S*)-ARCA coated MMC support showed a high selectivity, up to 95 ee%, for the separation of *D*-type phenylalanine, serine and tryptophan from racemic mixtures. The ionic liquids TPPC and OTPPBr exhibited superior properties to those of the ionic surfactant Cetyltrimethyl ammonium bromide (CTAB), as a PTR, showing constant optical purities of 95 ee%, with high isolation yields for five repeated reuses. The unique separation properties in this heterogeneous adsorption system should provide for an expansion of the applications of porous materials for commercial processes.

Key Words : Mesoporous carbon, Monolith, Amino acid, Chiral separation, Adsorption

Introduction

The isolation of chiral compounds as pure isomers is an important issue within pharmacological, pharmacokinetic and toxicological fields.¹⁻⁴ Many research efforts are currently focused on the production of optically pure products, due to increasing demands for drugs which may be administered in optically pure forms.⁵⁻⁷ Among this category of drugs, chiral amino acids and alcohols are important and widely utilized intermediates for the synthesis of a variety of biologically active molecules. In the last few decades, numerous efforts have been devoted to the synthesis and isolation of chiral amino acids. *L*-amino acids (*L*-AAs) are dominant in nature compared to *D*-amino acids (*D*-AAs). *L*-form AAs are directly digested and synthesized in the living body, but *D*-AAs, having an opposite optical activity, are not. However, some *D*-AAs, such as *D*-serine and *D*-alanine, are known to be valuable building blocks for the production of neurotransmitters and cell walls, respectively, within biological chemistry.^{8,9} Therefore, a proper asymmetric synthetic method for their production would provide scientifically and economically valuable molecules with high optical purity. The selective recognition of chiral amino acids (AAs) and alcohols is generally based on non-covalent interactions through hydrogen bonding, metal coordination, and hydrophobic interactions.¹⁰⁻¹³ The development of new chiral receptors as hosts, showing enantioselective differentiation

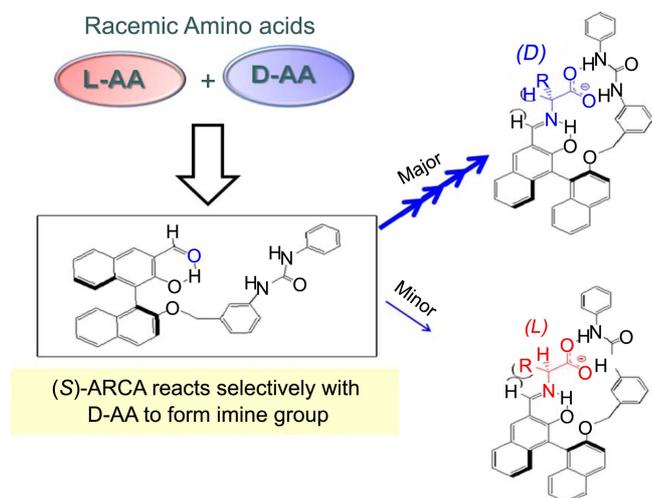
towards racemic guests, is a very important task, and is of specific interest within a number of pharmaceutical fields. Kim *et al.* have shown that an aldehyde can be a good stereoselective recognition center for 1,2-amino alcohols and amino acids, *via* reversible imine formation with resonance assisted hydrogen bonding.^{14,15} *D*-AA in the racemic *D/L*-AA mixture can be selectively attached to (*S*)-ARCA through imine formation.¹⁶ (*S*)-ARCA selectively adsorbs amino acids of *D*-AAs, and (*R*)-ARCA selectively adsorbs *L*-type amino acids, as shown in Scheme 1. (*S*)-ARCA is an imitated organic compound, providing chiral properties on alanine racemase enzymes which exist in the walls of bacteria cells.^{9,14} It is possible to convert a variety *L*-AAs into *D*-AAs, and to separate single optical forms of amino acid from the racemates, using ARCA as an efficient chiral catalyst or adsorbate. The direct conversion of naturally abundant *L*-AAs into *D*-AAs has great potential in large scale production processes. In nature, *L*-AAs are converted to *D*-AAs by pyridoxal phosphate dependent enzymes that racemize amino acids.¹⁷

In the enantioselective adsorption of *D*-AA on (*S*)-ARCA from racemates, the reactive extraction process can be adopted, because ARCA is soluble only in organic solvents, while AA is only soluble in aqueous solution.^{18,19} One adsorptive resolution cycle is composed of three liquid-liquid extraction steps: a stereoselective reversible imine formation, a stereoselective irreversible imine hydrolysis,

and the recovery of ARCA and optically pure AAs. The resolution of enantiomers by solvent extraction appears to be a time-saving and cost-effective process. However, industrial scale applications of most extractors which have been developed thus far are limited, due to low enantioselectivity as well as the narrow range of applicable substrates.

In this work, the organic phases containing (*S*)-ARCA adsorbent were coated onto the surfaces of mesoporous carbon supports, and these heterogeneous adsorbents were packed into a circulating flow type bed for the separation of *D*-AA. The continuous adsorption/desorption treatment was performed in the same reactor. This heterogeneous system has overcome the disadvantage of homogeneous liquid-liquid extraction process for the separation of *D*-AA using ARCA. To increase the contact rate between two compounds under such immiscible conditions, phase transfer reagents (PTRs) were added to the system.

Ordered Mesoporous Carbon can provide unique properties as a support, and is widely used in many applications because of its large pore volume and well-defined mesoporosity.^{20,21} Mesoporous materials with pore diameters in the range of 2–10 nm are suitable for a wide range of associated applications.^{22,23} The formation of porosity on a number of different length scales with hierarchical structure may provide for a greater ease of diffusion of reactants to the active sites for catalysis, aiding the adsorption process. Mesoporous silica, alumina and carbons are good candidates for use as supports for the immobilization of (*S*)-ARCA. Among these materials, porous carbon was chosen as a support in this work, as organic ARCA has a hydrophobic nature. We have designed and prepared meso/macroporous monolithic carbons (MMC) to immobilize *S*-ARCA for the direct separation of *D*-AA from racemic *D/L*-AAs. The chiral (*S*)-ARCA supported on porous carbon showed high selectivity to *D*-AAs in fixed bed systems where the aqueous AA solution was circulated by pump. (*S*)-ARCA coated on an MMC support has a unique property for the selective adsorption of *D*-AA (up to 95% selectivity) from racemic mixtures.



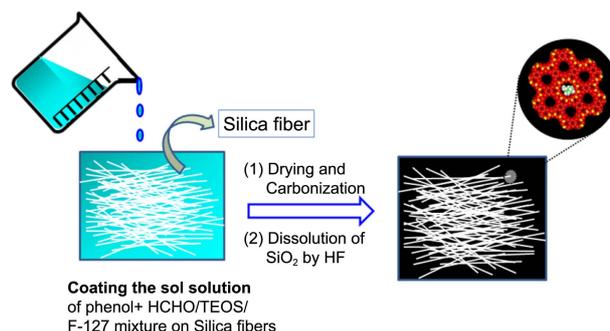
Scheme 1. Selective adsorption of *D*-AA on (*R*)-ARCA.

Experimental

Synthesis of MMC. The low-molecular-weight phenolic resin (Resol solution) and silica sol precursors were prepared according to previously reported methods.^{24,25} As a typical procedure, 0.65 g of phenol (Junsei; > 98%) was melted in a flask and was mixed with 0.15 g of 20 wt % NaOH (Daejung, > 98%) solution. After stirring for 30 min, 1.1 g of formalin (Duksan Pure Chem.; 36 wt % aqueous solution) was added dropwise, at a temperature below 50 °C. The mixture was reacted at 70 °C for 1 h, after which the pH was adjusted to 7.0 through the addition of HCl at room temperature. The final Resol solution was dissolved in ethanol after the removal of water. The mass ratio of TEOS/EtOH/H₂O/HCl in the silica sol was 2.1/12/1.0/70/7 × 10⁻³. The final mass ratio of the composite was fixed at F127/Resol/TEOS/EtOH/H₂O/HCl = 2.5/2/2.1/12/1.0/70/7 × 10⁻³. This carbon/silica composite sol was concentrated by evaporating the solvent until the volume of the sol mixture was reduced to 1/3 of the initial volume. The carbon precursor sol was mixed with silica fibers, and this composite was dried at 120 °C overnight. After carbonization at 900 °C in an N₂ stream, the silica component was dissolved in HF solution (Duksan Pure Chem.; 50%). The typical procedure to fabricate the macro/mesoporous carbon is shown in Scheme 2.

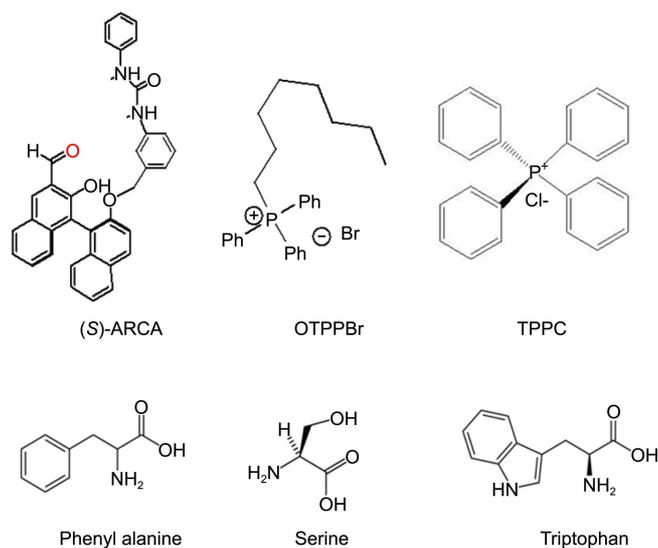
Characterization. The morphology and microstructures of the prepared MMC samples were characterized by field emission transmission electron microscopy (FE-TEM, S-4200), and field emission scanning electron microscopy (FE-SEM, JEM-2100F). The phase structure was determined by X-ray powder diffraction analysis (Phillips PW22XX and Rigaku DMAX 2500 diffractometer with CuK α radiation). Nitrogen adsorption/desorption analysis was performed at -196 °C using a surface area and porosity analyzer (Micromeritics, ASAP 2010). The concentration of amino acid was analyzed using an Alliance HPLC (Waters 2695 system), using a chiral column (CH SCA(-)-51002546; 250 × 6 mm), in the eluent of MeOH 60%, water 40%, HClO₄ 5 mmol at a flow rate of 1.0 mL/min.

Separation of *D*-AA from Racemic *D/L*-AA by Adsorption. Organic compounds containing 1.0 eq. (*S*)-ARCA (Aminologics Co., > 98%, 3 g), 1.4 eq. of TPPC (Aldrich, > 98%) (or OTPPBr (synthesized in our lab.), CTAB (Aldrich, > 98%)) in 10 mL ethylene dichloride (EDC; Duksan Pure



Scheme 2. Procedure for the fabrication of MMC.

Chem., > 98%) were mixed and stirred until the ARCA was fully dissolved. TPPC, OTPPBr and CTAB were used as PTR for the rapid diffusion of AA into an organic layer, allowing contact with ARCA. The organic solution mixture was coated on MMC, and EDC solvent was then partially evaporated. After packing the final product into a tube-type reactor, pure water was circulated by pump until the solution became clear. For the adsorptive separation reaction, the aqueous basic solution of racemic *D/L*-AAs (Aldrich, > 98%) was prepared by dissolving *D/L*-AAs and a base in distilled water. Typically, 2.0 eq. of NaOH (DaeJung, > 98%), trimethylamine (TEA; DaeJung, > 98%) or diisopropylamine (DIPA; DaeJung, 99%) were used to investigate the effect of base type. The total volume of aqueous solution was fixed at 300 ml. The basic solution of *D/L*-AAs was injected at various speeds, and was circulated through the reactor, which was packed with (*S*)-ARCA/carbon support for the adsorption of *D*-AA. After adsorption was carried out for 1 h, the packed bed was washed with pure distilled water, after which the circulating solution was changed to 3 M HCl solution for the hydrolysis of adsorbed AAs for an additional 1 h. The AAs, which were adsorbed on ARCA through imine formation reaction between aldehydes of ARCA and NH_2 in AAs, were hydrolyzed in the acidic solution. The hydrolyzed AA was diffused into acidified water during the circulation by pump *via*. back-extraction. The concentration of amino acid which remained in the aqueous solution was determined using HPLC with a prolonged adsorption time. For the repeated use of ARCA/support in the separation of chiral AA from racemic *D/L*-AAs, a fresh basic solution of *D/L*-AA was prepared, after which the same procedure for adsorption/desorption treatment was performed as described above. *D*-AA in acidic solution was isolated as a crystallized powder in methanol solvent with 3 h stirring. The structures of AAs, ionic liquids and ARCA are listed in Scheme 3. In addition, the diagram of the fixed bed type reactor adopted in this work is shown in Figure 1.



Scheme 3. The structure of (*S*)-ARCA, TPPC, OTTPBr, and AAs used in this work.

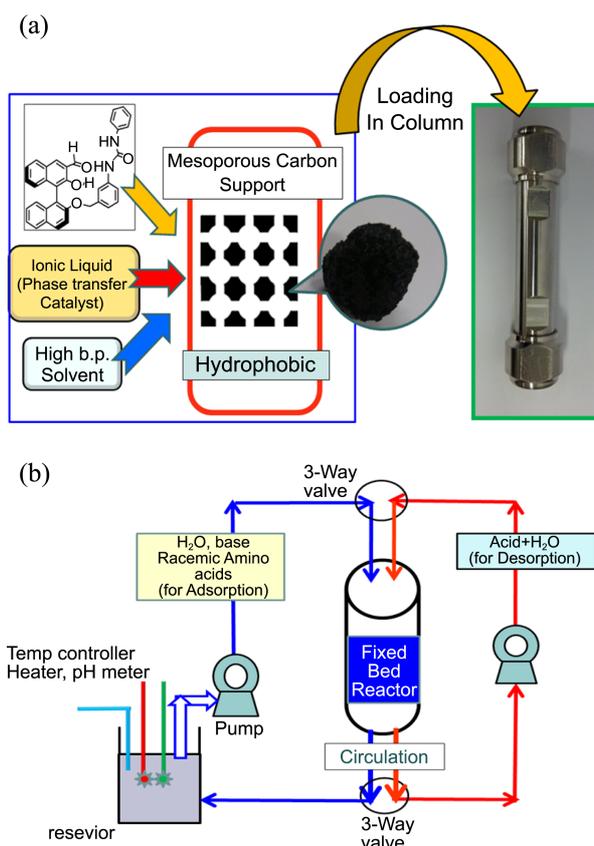


Figure 1. The internal structure of the adsorption bed (a) and a typical diagram of a circulating fixed bed adsorption system for *D*-AA separation (b).

Results and Discussion

Large-sized MMCs were easily fabricated from the mixture of triblock copolymers, phenolic resin/silica sol precursors and silica fibers. After carbonization of carbon/silica composite at 900 °C and dissolution of silica by HF, a high degree of macroporosity in three dimensions was developed within the monolith carbon body, and the remaining carbon walls exhibited uniform mesoporosity. The optical and SEM, TEM images of MMCs are shown in Figure 2. The size, density and bulk shape of MMC could be controlled according to the container which was used for preparation and the amount of added sol. A block of carbon was crushed into granules (3–5 mm size) for use as a support in the packed bed. Figure 2 shows the shape of the carbonized MMC foam which was constructed by replicating the shape of the container. Large fractions of macroporosity in three dimensions were observed on cross-sectional SEM images of MMC after dissolution of silica fibers by HF. The formation of mesopores in the walls of MMC were confirmed by TEM (Fig. 2(d)) and BET analysis (Fig. 2(f)). The analytical results revealed that the carbon material had well-developed mesopores, showing high surface areas (935 m²/g) and pore volumes (0.69 cm³/g) with a mean pore size of 57 °C. The MMC samples exhibited well-resolved peaks at 2θ angles below 5° in XRD patterns, showing hexagonally connected

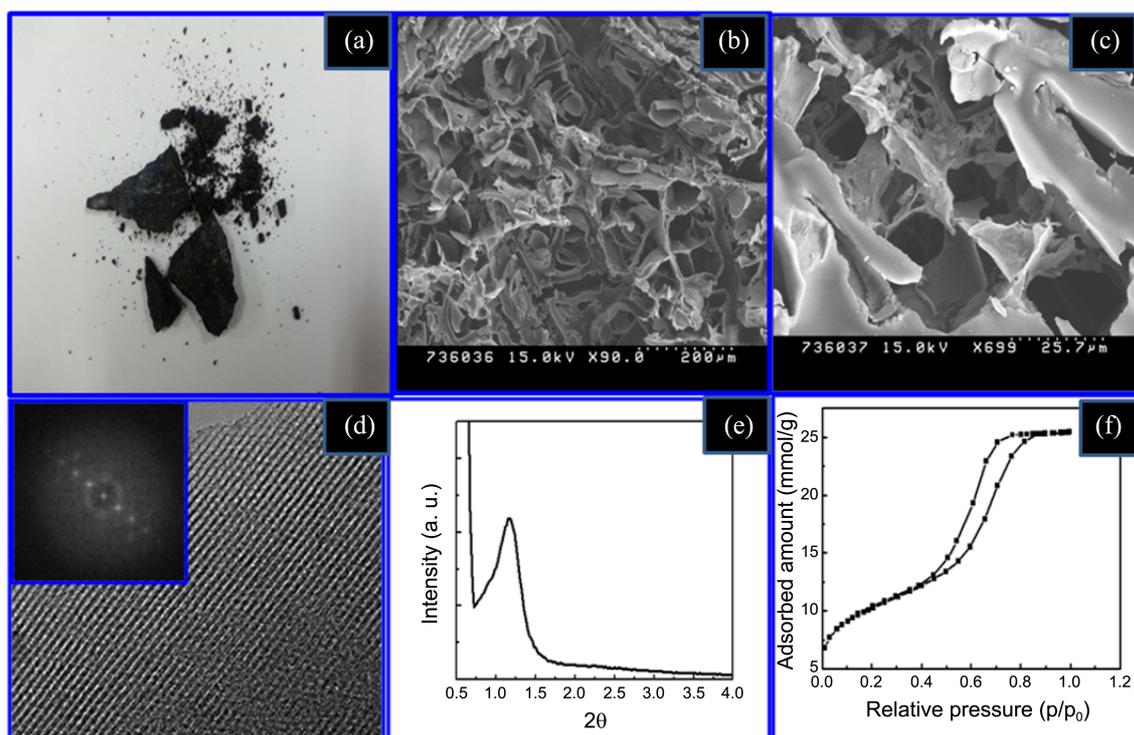


Figure 2. OM (a), SEM (b, c) and TEM (d), XRD image (e) and N_2 adsorption-desorption isotherm (f) of mesoporous carbon monolith.

mesopores.

Figure 3 depicts the processes of two extractions which were performed in this work by controlling the pH of solutions. The first one is a reversible stereoselective imine formation, and the second one is an irreversible stereoselective imine hydrolysis. The chiral AAs were recovered and isolated from acidic solution. Many inconvenient liquid-liquid extraction and decantation steps are involved in the conventional adsorptive separation of AA. After the initial adsorption of AA under basic pH conditions, the organic phase must be separated, and an acidic aqueous solution must then be added. In that liquid-liquid extraction process, the loss of expensive (*S*)-ARCA occurs during the solvent extraction, and repeated phase separation should be carried out in an independent batch system. In this work, by applying the heterogeneous adsorbent system in the packed bed, the continuous adsorption/desorption treatment was performed in the same reactor, and the phase separation of solutions into organic and aqueous layers was not necessary. This heterogeneous system has overcome many disadvantages of homogeneous liquid-liquid extraction processes, providing a simple process for the adsorption and desorption of chiral AAs. After saturated adsorption, HCl solution was injected into the bed for the hydrolysis of imine groups to isolate the adsorbed *D*-AA. The repeated separation of *D*-AA from racemic *D/L*-AA could be simply performed in the fixed bed.

Methylene chloride (MC) is commonly used as a solvent in liquid-liquid systems for the ease of separation of organic phases from aqueous solution. Because MC has a low boiling point, it should be resupplied during the repeated recycle

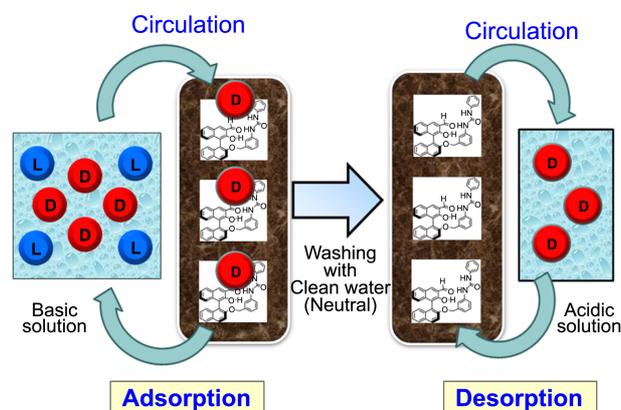


Figure 3. Selective adsorptive separation of chiral AA by ARCA.

because of severe losses in volume. However, in terms of solvent choice, EDC or toluene were determined to be more efficient than MC. Additionally, a small amount of EDC should be supplied to the reaction system to prevent ARCA from completely drying out on the carbon support. In addition, the effect of the base additive on the activity of ARCA in the adsorptive separation of AA was investigated. The use of organic bases such as DIPA and TEA was less effective than NaOH. The addition of one equivalent NaOH was determined to be optimal for the complete dissolution of AAs in water, and was sufficient to combine the AAs to ARCA by imine formation under such basic pH conditions.

In order to increase the adsorption rates, (*S*)-ARCA and PTR were simultaneously coated on the carbon support as thin layers, maintaining the separated particles without any

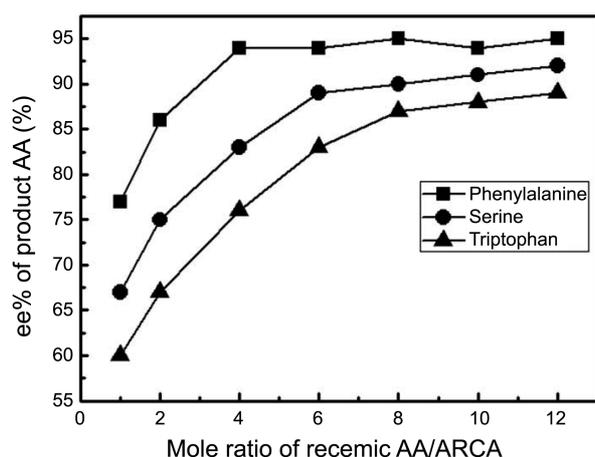


Figure 4. Effect of initial mole ratio of racemic AA/ARCA on the enantiomeric excess % of produced AAs (flow rate; 150 mL/min in the fixed type reactor, 2 h circulation, 20 wt % of ARCA loaded on support, TPPC used as a PTR).

substantial aggregation. Because AAs are soluble in aqueous solutions, but ARCA is only soluble in organic solvents, PTR should be added for the rapid diffusion of AA into the organic layer to contact with ARCA. When higher loadings of ionic liquids, such as PTR, are used, the completed dissolution and homogeneous coating of ARCA was achieved. However, the hydrophobic MMC supports have provided excellent properties for the loading of chiral ARCA on the surfaces as a thin layer. The racemic *D/L*-AA consists of 50% *D*-AA and 50% *L*-AA. In the adsorption of AA by ARCA, (*S*)-ARCA forms an imine group with *D*-AA, as shown in Scheme 1. Theoretically, only 1.0 eq. *D*-AA reacts with 1.0 eq. *D*-AA from 2.0 eq. *D/L*-AA, leaving 1.0 eq. of *L*-AA in the aqueous solution, and this excess AA in the solution may provide for a faster adsorptive reaction between AA and (*S*)-ARCA.

Figure 4 shows the effect of racemic AA/(*S*)-ARCA ratio on the ee% of AA isolated after HCl hydrolysis. For this experiment, an aqueous solution of 2.0 eq. *D/L*-phenylalanine (*D/L*-PA), 2.0 eq. NaOH dissolved in 300 mL of distilled water was prepared, and it was circulated through the fixed bed packed with (*S*)-ARCA/MMC adsorbent. The loading amount of ARCA over MMC was fixed as 20 wt % and the flow rate was 150 mL/min. However, with increasing concentration of *D/L*-PA in the reactant solution, the adsorbed amount of *D*-AA increased with increased pumping speed. When the molar ratio of (*D/L*-PA)/ARCA was increased to more than 8, the ee% of isolated *D*-PA which was adsorbed on the (*S*)-ARCA/MMC bed was around 95 ee% after 2 h circulation. The maximum ee% for serine and tryptophan were 92 and 88 ee%, respectively. At lower molar ratios of (*D/L*-PA)/ARCA (less than 8), the decreased ee% of the AA product was observed under the same adsorption conditions. To investigate the dependence of initial *D/L* ratio of PA on the separation efficiency, a *D*-AA rich reactant, instead of racemic AA (e.g. 7:3 *D*-AA/*L*-AA), was injected into the fixed bed system. In this case, a higher chiral selectivity was

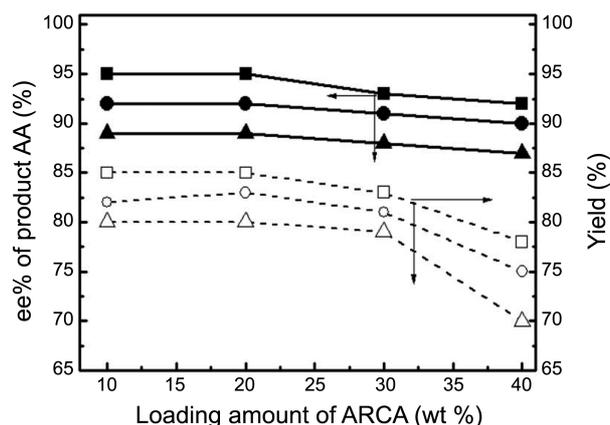


Figure 5. Effect of ARCA amount loaded over MMC support on the yields and enantiomeric excess % of product AAs (flow rate; 150 mL/min in the fixed type reactor, 2 h circulation, AA/ARCA ratio; 8, TPPC used as a PTR, AAs; Phenyl alanine (■□), Serine (●○), Tryptophan (▲△).

achieved, showing more than 97 ee% of *D*-AA adsorption on ARCA.

The effects of loading amount of (*S*)-ARCA over MMC on the yields of isolated *D*-AAs and product ee% were investigated, while the other conditions, such as flow rate and (*D/L*-PA)/ARCA ratio, were fixed. The obtained results are listed in Figure 5. The ee% of the AA product was almost identical, regardless of the amount of ARCA which was added. However, the isolated yield of product AAs was decreased with increasing load amount of ARCA on the support. As the impregnated amount of (*S*)-ARCA was higher, the coating layers of ARCA became thicker, whereupon only the (*S*)-ARCA present near the outer surfaces could adsorb the AAs effectively, resulting in the decrease of product yields. Adsorption saturation likely occurred rapidly at the surfaces, and the diffusion of AAs to the (*S*)-ARCA inside of coating layer was likely hindered.

The breakthrough of AA adsorption on the heterogeneous (*S*)-ARCA was investigated with different circulation speeds. The injection rates of the basic AA solution were controlled by piston pump in the ranges of 50–300 mL/min. The ee% of AA which was adsorbed on (*S*)-ARCA was determined over a prolonged adsorption time. Under the same concentration of racemic *D/L*-PA in solution and loading amount of (*S*)-ARCA over support, the adsorbed amount of *D*-PA increased with increasing circulation speed of PA solution. As the pumping speed increased from 70 mL/min to 300 mL/min, the adsorption rate of *D*-PA has increased, but the product ee% of PA was almost constant as 95 ee% after 2 h circulation. Typically the adsorbed amount of *D*-PA on to (*S*)-ARCA/MMC was 80 ee% for 1 h circulation, and 93 ee% for 1.3 h under the pumping rate of 150 mL/min. These ee% values represent product ee% of isolated PA after HCl hydrolysis.

The selective adsorption of *D*-PA was compared with that of ARCA/MMC carbon using different PTRs, such as TPPC, OTPPBr and CTAB, under the same reaction conditions.

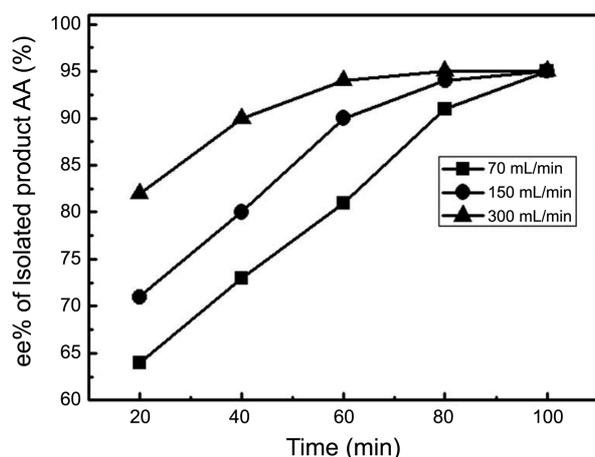


Figure 6. The performance comparison of *D*-AA adsorptive separation under different flow rates (AA; phenylalanine, AA/ARCA ratio; 8, 20 wt % of ARCA loaded on MMC, TPPC as a PTR).

The concentration of racemic *D/L*-PA in solution, the loading amount of (*S*)-ARCA over support, and the ratio of AA/ARCA were fixed, as indicated in Figure 7. Even though, only the break-through for PA adsorption on ARCA is shown in Figure 7, and a similar result was obtained in view of enantioselectivity for other AAs, such as serine and tryptophan. The fastest equilibrium for adsorption of *D*-PA was obtained when TPPC was used as a PTR. As the pumping speed increased from 60 mL/min to 150 mL/min, the adsorption rate of *D*-PA increased in the presence of the same PTR content, as shown in Figure 6, but the ee% of product PA became constant as 95 ee% after 2 h circulation.

Figure 8 shows that the heterogeneous ARCA maintains efficiency for more than 5 repeated uses, without any intermediate purification. The optical purity of isolated *D*-PA was maintained at 95% for every PTR at the first adsorption step. The ee% of adsorbed *D*-PA on (*S*)-ARCA was not substantially changed after five reuses, and no difference in

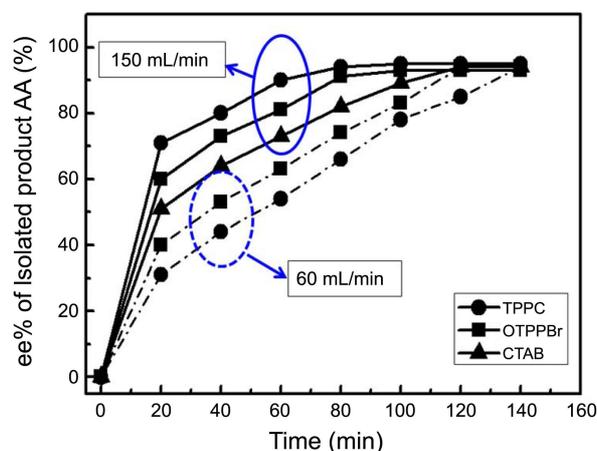


Figure 7. The effect of PTR type on the optical purity of *D*-AA adsorbed over heterogeneous ARCA under different flow rates (AA; phenylalanine, AA/ARCA ratio; 8, 20 wt % of ARCA loaded on MMC).

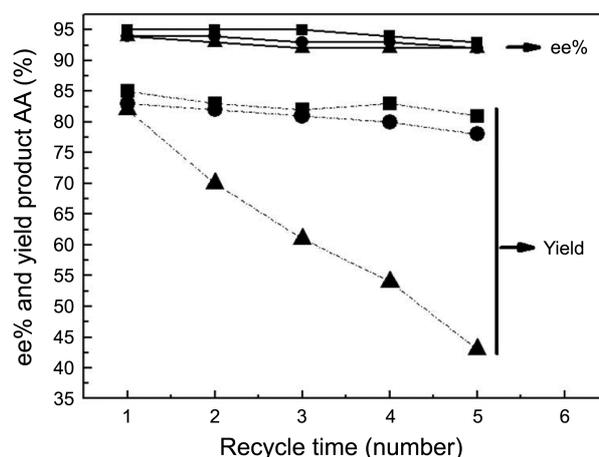


Figure 8. Effect of PTR type on the adsorptive separation of *D*-PA for the repeated use (flow rate; 150 mL/min, 2 h circulation, AA; phenylalanine, AA/ARCA ratio; 8, 20 wt % of ARCA loaded on MMC, PTR; TPPC (■), OTPPBr (●), CTAB (▲)).

the effect of the PTR type was determined. From the second reuse of the adsorption bed, the yields of isolated product *D*-PA were decreased drastically when CTAB was used as the PTR, but in the cases of TPPC and OTPPBr, isolation yields remained almost constant upon repeated uses. These phenomena were also observed in a batch type separation of *D*-PA from *D/L*-PA using an ARCA/MMC system. During the acid hydrolysis of *D*-PA for desorption from (*S*)-ARCA, small amounts of (*S*)-CTAB diffused into the acidic aqueous phase. The reduction of CTAB concentration ultimately contributed to the decreased yield. However OTPPBr and TPPC exhibited better results than CTAB, and acted as a good phase transfer reagents, showing no loss by extraction during the adsorption/desorption process. Ionic liquid type PTRs such as OTPPBr and TPPC were so stable that the unique property was maintained during repeated uses in the adsorptive separation of *D*-AAs. For repeated adsorption, a maximum adsorption of *D*-PA was achieved by using ionic liquids as PTR in the continuous circulation system.

Conclusion

Meso/macroporous carbon monoliths, having bimodal pore structures, were fabricated for the immobilization of chiral adsorbents. Such carbon materials with high surface areas and pore volumes could be used as an efficient supports for anchoring chiral (*S*)-ARCA to separate the chiral AA by enantioselective adsorption in continuous flow-type packed bed reactor systems. The mesoporous support provided good properties for the homogeneous loading of chiral ARCA on the surfaces over a thin layer. The effects of loading amount of (*S*)-ARCA on the support, the molar ratio of AA to (*S*)-ARCA, flow rates and the type of PTR were investigated on the isolation yields, and the optical purity of product *D*-AAs. *D*-AAs were selectively combined to (*S*)-ARCA through imine formation reaction in the aqueous basic solution of racemic *D/L*-amino acid. In the adsorptive separation of *D*/

L-AAs by using heterogeneous (*S*)-ARCA adsorbent, optically pure AAs up to maximum 95 ee% were isolated for the separation of *D*-type phenylalanine, serine and tryptophan in a continuous circulation system. The ionic liquids type TPPC and OTPPBr exhibited superior properties to those of the ionic surfactant CTAB as a PTR, showing constant optical purities of 95 ee%, with high isolation yields over 5 repeated uses. The unique separation properties of the heterogeneous adsorption system may expand the applications of porous materials for commercial processes in the future. The immobilization of (*S*)-ARCA through covalent bonding may provide for a unique methodology for the maximization of efficiency of (*S*)-ARCA molecules for the selective adsorption of *D*-AAs. The results of this study are currently being further investigated and expanded upon.

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