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# Adsorption-induced asymmetric transformation of planar-chiral pyridinophanes

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**Abstract**—Stereocontrol of cyclophane-type planar chirality was investigated via adsorption-induced asymmetric transformation (AIAT) on a series of inorganic porous adsorbents. The rope-skipping equilibria between bridged nicotinamides (*S*,3′*S*)-**1** and (*R*,3′*S*)-**2** shifted preferentially to (*R*,3′*S*)-**2** to accumulate (*R*)-configuration of planar chirality with up to 61% de (ca. 4/1 ratio) on alumina. The results are in good contrast to accumulation of the corresponding (*S*)-configuration via conventional crystallization-induced asymmetric transformation (CIAT) to the solid (*S*,3′*S*)-**1a**–**d**. © 2003 Elsevier Science Ltd. All rights reserved.

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Novel adsorption-induced asymmetric transformation (AIAT) shifted the rope-skipping equilibria preferentially to (*R*,3′*S*)-**2** on a series of inorganic porous adsorbents to accumulate (*R*)-configuration of planar chirality. The diastereomeric excess reached up to 61% de (ca. 4/1 ratio) on alumina.

Photochemical asymmetric transformation on zeolite[1,2] or chirally modified zeolite[1,3] is currently actively studied for the stereocontrol of chiral molecules. However, ground-state asymmetric transformation on such inorganic porous adsorbents has not been studied for synthetic purposes yet, although some analytical applications to dynamic HPLC has been reported as enantiodifferentiating isomerization (deracemization) on chiral stationary phases.[4] We have previously reported crystallization-induced asymmetric transformation (CIAT) of planar-chiral [10](2,5)pyridinophanes,[5] which are the key precursors of chiral bridged NADH analogs[6] effecting biomimetic reduction with high enantioselectivity. The CIAT of the solid and the liquid diastereomers, (*S*,3′*S*)-**1a**–**d** and (*R*,3′*S*)-**2a**–**d**, achieved stereocontrol of their planar chirality with efficient disequilibriation via rope-skipping isomerization to the solid isomer (*S*,3′*S*)-**1a**–**d** with up to 99% de. Reversing the selectivity toward the liquid isomers, on the other hand, requires some sort of supramolecular assistance stabilizing the liquid isomer preferentially, and such diastereodifferentiating method could be an alternative transformation to CIAT[5,7,8] and also lead to unrestricted stereocontrol of planar chirality. To realize such asymmetric transformation, we focused on several inorganic porous adsorbents interacting with diastereomeric pyridinophanes as adsorbates. We report here the first synthetic application of thermodynamic adsorption-induced asymmetric transformation (AIAT): preferential formation of planar-chiral pyridinophanes, (*R*,3′*S*)-**2**, over the corresponding diastereoisomer, (*S*,3′*S*)-**1**, on inorganic porous adsorbents.

We initially investigated their AIAT on silica gels, since most TLC and HPLC analyses of (*S*,3′*S*)-**1** and (*R*,3′*S*)-**2** exhibit that the latter is a longer-retaining isomer and is, therefore, better adsorbates on such adsorbents. Since reaction rate of the rope-skipping isomerization shows temperature dependency and CIAT to (*S*,3′*S*)-**1** is best accomplished at 110°C,[5] AIAT between (*S*,3′*S*)-**1a**,**b** and (*R*,3′*S*)-**2a**,**b** adsorbed on silica gels was carried out upon heating at 110°C (Table 1). The equilibria shifted to the liquid side and the extracts from ethanol recovered (*R*,3′*S*)-**2a**,**b** enriched mixtures with 23% de (66–70% recovery) to accumulate (*R*)-configuration of planar chirality in contrast to the results of CIAT affording (*S*,3′*S*)-**1a**,**b**. (entries 1 and 2). It is interesting to note that the extracts after treating with hydrofluoric acid recovered a mixture of (*S*,3′*S*)-**1a**,**b** and (*R*,3′*S*)-**2a**,**b** almost quantitatively, but their diastereomeric excesses decreased to 12–15% de (entries 3 and 4). These results indicate that ca. 1/3 of pyridinophane adsorbates penetrated onto some strong adsorption spots during the asymmetric transformation,[9] where the equilibrium shifted to a less diastereoselective direction. Indeed, only 7–12% de of

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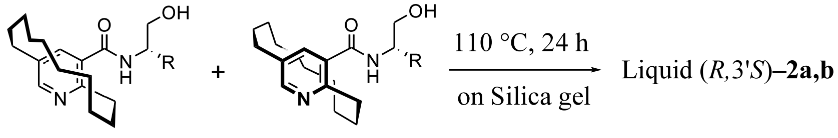
**Table 1.** Asymmetric transformation between (*S*,3′*S*)-**1a**,**b** and (*R*,3′*S*)-**2a**,**b** on silica gel[a]



Solid (*S*,3'*S*)–**1a,b** Liquid (*R*,3'*S*)–**2a,b**

| Entry | Adsorbent | 1,2 | R | | (*R*,3′*S*)-2a | |
|---|---|---|---|---|---|---|
| | | | | Work up[b] | De (%)[c] | Recovery (%) |
| 1[d] | Silica gel[e] | **a** | *i*-Pr | A | 23 | 66 |
| 2[f] | Silica gel[e] | **b** | *t*-Bu | A | 23 | 70 |
| 3 | Silica gel[e] | **a** | *i*-Pr | B | 15 | 98 |
| 4 | Silica gel[e] | **b** | *t*-Bu | B | 12 | 98 |
| 5 | PDMS[g] | **a** | *i*-Pr | A | 4 | 76 |
| 6 | PDMS[g] | **b** | *t*-Bu | A | 6[h] | 85 |

[a] The asymmetric transformation was carried out upon heating 20 mg of pyridinophanes adsorbed on 500 mg of adsorbents.

[b] Method A: Extracted with EtOH. Method B: Extracted with $CH_2Cl_2$ after treating with hydrofluoric acid.

[c] The ratio was determined by HPLC by using SenshuPak PEGASIL Silica 120-5T column.

[d] Averaged data of three runs.

[e] Silica gel FL60D (Fuji Silisia Co.).

[f] Averaged data of two runs.

[g] Chromatorex DMS DM1020 (Fuji Silisia Co.).

[h] (*S*,3′*S*)-**1b** as a major isomer.

(*R*,3′*S*)-**2a**,**b** was recovered from the residual silica gel after removing the initial ethanol extracts. Both acidic silanol residue and pore diameters play important roles in AIAT on silica gels: (1) less significant shifts of the equilibrium were observed on PDMS or polydimethylsiloxane capping most of the silanol residue with methyl groups (entries 5 and 6) and (2) their diastereomeric excesses are dependent on pore diameters of silica gels during a range of 25–1000 Å as shown in Figure 1. Incidentally, no significant transformation was observed simply by heating such diastereomeric mixture dispersed on a non-porous material such as magnesium sulfate.

Since a standard silica gel does not seem to be a good adsorbent for highly diastereoselective transformation, we then turned our attention to alumina, known as a more active adsorbent than silica gel, to pursue more efficient AIAT. Table 2 summarizes the results of AIAT of (*S*,3′*S*)-**1a**–**c** and (*R*,3′*S*)-**2a**–**c** on silica-alumina and alumina. Heating a mixture of (*S*,3′*S*)-**1b** and (*R*,3′*S*)-**2b** on silica-alumina, JRC-SAH-1 and JRC-SAL-2, gave (*R*,3′*S*)-**2b** enriched mixture with 32 and 24% de, respectively (entries 1 and 2). These results are in good accordance with our expectation that the material containing higher $Al_2O_3$ ratio gave higher diastereoselectivity. The isomerization on commercially available alumina was investigated for compounds **1a**–**c** and **2a**–**c**, and the sterically hindered *t*-Bu group afforded the best selectivity resulting in (*R*,3′*S*)-**2b** with 39% de (entries 3–5). Then we carried out the transformation between (*S*,3′*S*)-**1b** and (*R*,3′*S*)-**2b** by using reference catalyst of alumina to give better results in terms of both diastereomeric excess (42–59% de) and recovery (75–83%) (entries 6–10). Table 3 indicates the results by using alumina JRC-ALO-A1 for various pyridinophane diastereomers, (*S*,3′*S*)-**1a**–**f** and (*R*,3′*S*)-**2a**–**f**. In all cases, (*R*,3′*S*)-**2a**–**f** isomers were formed predominantly with 32–59% de (entries 1–6). It is noteworthy that a liquid–liquid pair of **1e** and **2e** and a solid–solid pair of **1f** and **2f** also underwent AIAT with 41 and 46% de (more than 1/3 ratio), respectively. These results are in good contrast to their thermodynamic behavior without an adsorbent, showing the former exhibited no significant disequilibriation between **1e** and **2e** and the latter follows CIAT giving (*S*,3′*S*)-**1f** having a higher melting point with 40% de. The dependence on steric factors R suggests that the pyridinophane's side arm plays a key role as adsorbate on alumina. Sterically more demanding substituents such as *i*-Pr and *t*-Bu groups afforded better diastereoselectivity reaching almost 1/4 ratio giving

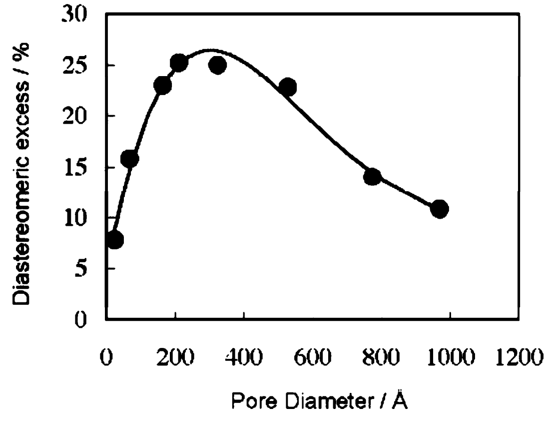


**Figure 1.** Diastereoselectivity of (*R*,3′*S*)-**2a** on MicroBead silica gel having various pore diameters.

**Table 2.** Asymmetric transformation between (*S*,3′*S*)-**1a**–**c** and (*R*,3′*S*)-**2a**–**c** on various silica-alumina and alumina[a]

$$(S,3'S)\text{–}\mathbf{1a\text{-}c} + (R,3'S)\text{–}\mathbf{2a\text{-}c} \xrightarrow[\text{on Silica-Alumina or Alumina}]{110\ °\text{C, 24 h}} (R,3'S)\text{–}\mathbf{2a\text{-}c}$$

**a**: R = *i*-Pr; **b**: R = *t*-Bu; **c**: R = Bn

| Entry | Adsorbent | 1,2 | (*R*,3′*S*)-2 | |
|---|---|---|---|---|
| | | | De (%)[b] | Recovery (%) |
| 1[c] | Silica-Alumina JRC-SAL-1[d] | **b** | 32 | 96 |
| 2[c] | Silica-Alumina JRC-SAL-2[d] | **b** | 24 | 95 |
| 3 | Alumina 90 Active Neutral[e] | **a** | 35 | 63 |
| 4 | Alumina 90 Active Neutral[e] | **b** | 39 | 64 |
| 5 | Alumina 90 Active Neutral[e] | **c** | 17 | 63 |
| 6 | Alumina JRC-ALO-1A[f] | **b** | 59 | 81 |
| 7 | Alumina JRC-ALO-2[f] | **b** | 52 | 81 |
| 8 | Alumina JRC-ALO-3[f] | **b** | 46 | 83 |
| 9 | Alumina JRC-ALO-4[f] | **b** | 45 | 81 |
| 10 | Alumina JRC-ALO-5[f] | **b** | 42 | 75 |

[a] The asymmetric transformation was carried out on the same experimental scale shown in Table 1. Method A was employed for work-up unless otherwise specified.

[b] The ratio was determined by HPLC by using SenshuPak PEGASIL Silica 120-5T column.

[c] Method B was employed for work-up.

[d] Silica-alumina JRC-SAH-1 ($Al_2O_3$ = 28.61%) and JRC-SAL-2 ($Al_2O_3$ = 13.75%) are reference catalysts available from Catalysis Society of Japan on member's request.

[e] Aluminum oxide 90 active neutral available from MERCK Co.

[f] Reference catalyst available from Catalysis Society of Japan.

(*R*,3′*S*)-**2a**,**b** predominantly. The thermodynamic asymmetric transformation afforded good results after heating **1b** and **2b** for 6 and 48 h; the former already reached 51% de in the highest recovery of 94% and the latter gave the highest selectivity with 61% de (entries 7 and 8). Finally, we investigated dependency of the diastereoselectivity on the amount of the adsorbent (entries 9 and 10). The less amount of alumina was used, the more amount of pyridinophane was recovered. However, the selectivity was not so good as the result shown in entry 2. Half and double amounts of alumina did not improve the results for AIAT of **1** and **2**.

Consequently, we have discovered novel AIAT, adsorption-induced asymmetric transformation, of planar-chiral pyridinophanes, (*S*,3′*S*)-**1a**–**f** and (*R*,3′*S*)-**2a**–**f**, which preferentially affords (*R*,3′*S*)-**2a**–**f** in contrast to the results obtained by CIAT. Our previous studies on X-ray analysis of (*S*,3′*S*)-**1a** indicate that the stereochemistry plays an important role in determining the physical states of **1a** and **2a** in terms of intermolecular hydrogen bonds (observed between N–$\underline{H}$ and C=$\underline{O}$ of the carbamoyl groups and between O–$\underline{H}$ and a pyridine nitrogen in crystal **1a**).[5,10] To alter diastereoisomerism from the (*S*,3′*S*)-form into the (*R*,3′*S*)-form apparently weakens their hydrogen bonds to have more attractive functional groups for supramolecular interactions with acidic sites of porous materials. These transformations are the first AIAT on silica gel, silica-alumina, and alumina to provide a possible alternative to CIAT and a new option for asymmetric synthesis of thermodynamically convertible molecules such as atropisomers.

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**Table 3.** Asymmetric transformation between (*S*,3′*S*)-**1a**–**f** and (*R*,3′*S*)-**2a**–**f** on alumina JRC-ALO-1A[a]

$$(S,3'S)\text{–}\mathbf{1a\text{-}f} + (R,3'S)\text{–}\mathbf{2a\text{-}f} \xrightarrow[\text{on JRC-ALO-1A}]{110\ °\text{C}} (R,3'S)\text{–}\mathbf{2a\text{-}f}$$

| Entry | 1,2 | | Mp (°C) | | | (*R*,3′*S*)-2 | |
|---|---|---|---|---|---|---|---|
| | | R | 1 | 2 | T (h) | De (%)[b] | Recovery (%) |
| 1 | **a** | *i*-Pr | 161 | Oil | 24 | 55 | 81 |
| 2 | **b** | *t*-Bu | 171 | Oil | 24 | 59 | 81 |
| 3 | **c** | Bn | 179 | Oil | 24 | 32 | 79 |
| 4 | **d** | *i*-Bu | 163 | Oil | 24 | 52 | 81 |
| 5 | **e** | Me | Oil | Oil | 24 | 41 | 80 |
| 6 | **f** | Ph | 171 | 140 | 24 | 46 | 81 |
| 7 | **b** | *t*-Bu | 171 | Oil | 6 | 51 | 94 |
| 8 | **b** | *t*-Bu | 171 | Oil | 48 | 61 | 77 |
| 9[c] | **b** | *t*-Bu | 171 | Oil | 24 | 46 | 95 |
| 10[d] | **b** | *t*-Bu | 171 | Oil | 24 | 54 | 76 |

[a] The asymmetric transformation was carried out on the same experimental scale shown in Table 1 otherwise specified. Method A was employed for work-up.

[b] The ratio was determined by HPLC by using SenshuPak PEGASIL Silica 120-5T column.

[c] Adsorbed on 250 mg of alumina.

[d] Adsorbed on 1000 mg of alumina.

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9. Pyridinophane derivatives were recovered in 98% yield by desorption with ethanol after being left on silica gel at room temperature for a month.
10. Crystal structure data for (*S*,3′*S*)-**1a** are available on request from the Director of Cambridge Crystallographic Data Center (CDCC), 12 Union Road, Cambridge CB2 1EZ, UK.