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# Selective Glucose-to-Fructose Isomerization in Ethanol Catalyzed by Hydrotalcites

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#### ABSTRACT

A combination of ethanol solvent and hydrotalcite (HT) with a Mg:Al ratio of 3:1 was effective for the isomerization of glucose to fructose in up to 56% yield with a high selectivity of 80%. The ethanol solvent shifts the isomerization equilibrium between glucose and fructose, which allows the fructose yield to exceed the upper limit of enzymatic isomerization conducted in water at modest temperatures (i.e., 50%). The HT catalyst maintained such high catalytic performance in repeated use at least three times via calcination and subsequent reconstruction of the original layered structure by the memory effect, which was operated in an aqueous solution containing ammonium carbonate. The results of catalyst screening, characterization, and isotope tracer analysis have revealed that the base sites of HT mainly contribute to its high catalytic activity for glucose-to-fructose isomerization.

### **1. INTRODUCTION**

Fructose is a well-known sweetener used as an alternative to conventional table sugar (sucrose) because it is 1.8–2-fold sweeter than the latter,<sup>1–3</sup> and it has also emerged as a key starting compound in biorefineries for the synthesis of value-added chemicals such as 5-hydroxymethylfurfural, 2,5-furandicarboxylic acid, levulinic acid, and lactic acid.<sup>4–7</sup> The industrial production of fructose has thus far relied on the enzymatic isomerization of glucose, which is an abundant and inexpensive sugar that can be obtained via the hydrolysis of starch and cellulose,<sup>8,9</sup> to produce an aqueous mixture of glucose and fructose with their ratio of 1:1; this sugar aqueous mixture has already been commercialized as so-called high-fructose corn syrup

(HFCS).<sup>1–3</sup> However, enzymatic systems involve inevitable issues such as short lifetime of enzymes and the requirement of strictly-controlled conditions including solvent and temperature.<sup>2,10</sup> In this context, the development of a fast and selective process for glucose-to-fructose isomerization with an easily-separable and reusable heterogeneous catalyst is required.



**Scheme 1.** Isomerization of glucose to fructose, along with side reactions typically observed in the presence of base catalysts.

Glucose-to-fructose isomerization proceeds via the Lobry de Bruyn–Alberda van Ekenstein (LdB–AvE) transformation initiated from  $\alpha$ -hydrogen abstraction by a base.<sup>11</sup> Homogeneous bases such as alkali hydroxides have been reported to be effective for this reaction,<sup>11–13</sup> while the desire to achieve ease of catalyst separation and consecutive reuse has led to the development of heterogeneous base catalysts such as alkaline-modified zeolites, Mg–Al mixed oxides, metallosilicates, and silica-supported *N*-containing compounds.<sup>13,14</sup> Although these reported heterogeneous bases exhibit good fructose selectivity at glucose conversion below 40%, none of them are comparable to enzymatic isomerization that selectively synthesizes fructose with an

almost quantitative yield (ca. 50%).<sup>2,15</sup> The decrease in fructose selectivity with an increase in glucose conversion is probably due to undesired side reactions, including retro-aldol reactions triggered by bases (see Scheme 1).<sup>9,16,17</sup>

In this study, we demonstrate a combination of ethanol solvent and hydrotalcite (HT), which is a layered double hydroxide consisting of Mg and Al, to selectively accelerate glucose-tofructose isomerization, even at high glucose conversion. The motivation to use ethanol as a reaction solvent originated from a previous report where the addition of ethanol into water was demonstrated to shift the isomerization equilibrium between glucose and fructose to the latter.<sup>18</sup> This change in equilibrium can be rationalized by solvation effect: given the fact that solubility—which reflects solvation enthalpy—of fructose in ethanol at 293 K is ca. 2.8-fold higher than that of glucose,<sup>19</sup> fructose more readily undergoes the solvation by ethanol molecules to be stabilized, compared to glucose. Such a shift in equilibrium could increase the maximum fructose yield to over 50%, which is the upper limit under aqueous conditions at modest temperatures.<sup>2,20</sup> We also address methods to reuse HT by the memory effect for the reconstruction of active HT for glucose-to-fructose isomerization.<sup>21</sup> A mechanistic study was also conducted using isotope tracer analysis to elucidate whether base sites in the HT catalysts are responsible for the isomerization of glucose in ethanol.

#### 2. EXPERIMENTAL SECTION

**2.1. Synthesis of HTs.** HTs consisting of Mg and Al with various molar ratios (i.e., 12:1, 7:1, 5:1, 4:1, 3:1, and 1:1) were synthesized by following the reported co-precipitation method.<sup>22</sup>

50 mL of aqueous solution **A** containing both *x* mol of Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (Kanto Chemical) and *y* mol of Al(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O (Kanto Chemical), where x + y = 0.075, and 50 mL of aqueous solution **B** containing 0.2 mol of (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> (Wako Pure Chemical Industries) were prepared and charged into separate syringes. Both the aqueous mixtures **A** and **B** were simultaneously added from each syringe in a dropwise manner at a rate of 0.83 mL min<sup>-1</sup> to 25 mL of distilled water heated at 338 K under vigorous stirring. 28.0–30.0 wt% of NH<sub>3</sub> aqueous solution (Wako Pure Chemical Industries) was added to the resulting white suspension until the pH became 7.6–8.0 (monitored with a pH meter), and the suspension was further stirred vigorously at 338 K for 3 h. The resulting mixture was filtered using a Büchner funnel with filter paper 4A. The white solid was washed with at least 500 mL of distilled water and was subsequently dried in an oven at 373 K for 18 h. The HTs thus synthesized were denoted as HT(*x*:*y*), where *x*:*y* represents the initial molar ratio of Mg(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O to Al(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O.

2.2. Characterization of HTs. The synthesized HT materials were characterized using powder X-ray diffraction (PXRD; Rigaku, Ultima IV, Cu K $\alpha$  radiation). Acid-base titration was also conducted to quantify base sites of the HTs that can function in ethanol. Briefly, 50 mg of HT was dispersed in 1 mL of ethanol containing a small amount of phenolphthalein color indicator and the suspension was stirred at room temperature for 1 h. The mixture was then titrated with 3.5 mM of *p*-toluenesulfonic acid in ethanol until the color of suspension changed from pink to white, the latter of which is the original color of the HTs.

**2.3. Glucose Isomerization.** Glucose isomerization was conducted in a pressure-resistant glass vessel (Aceglass, 15 mL inner volume), into which 50 mg of glucose (Kanto Chemical), 50 mg of catalyst (descriptions of each catalyst tested in this study are summarized in Table S1 in

the Supporting Information), 7.0 mL of ethanol (Wako Pure Chemical Industries), and a stirring bar were charged. For isotope tracer studies, the reactant used was glucose-2-d<sub>1</sub> (Sigma-Aldrich). After purging with Ar, the reactor was immersed in an oil bath equipped with a magnetic stirrer under prescribed conditions, after which the reactor was cooled to room temperature in a cold water bath. The supernatant was obtained via centrifugation and decantation. The solid residue was washed with 2 mL of distilled water three times to extract any water-soluble compounds. The washing solvent was separated from the solid via centrifugation and decantation and was then mixed with the reaction mixture. The amounts of residual glucose and products in the reaction mixture were quantified using high-performance liquid chromatography (HPLC; Shimadzu, Prominence HPLC System, refractive index detector) with a SUGAR SH1011 column (Shodex,  $ø8.0 \times 300$  mm, mobile phase of distilled water at a flow rate of 0.5 mL min<sup>-1</sup>, column temperature of 323 K), where an absolute calibration method was employed.

For isotope tracer studies using glucose-2-d<sub>1</sub> as a reactant, after the reaction, the solvent was removed by rotary evaporation and the products were dissolved into 1 mL of distilled water, and sodium acetate-d<sub>3</sub> (Toronto Research Chemicals) was then added to the mixture as an internal standard. In addition to HPLC analysis, the products with sodium acetate-d<sub>3</sub> in water were analyzed using <sup>2</sup>H nuclear magnetic resonance spectroscopy (NMR; JEOL, JNM-ECX600, <sup>2</sup>H 92.1 MHz). The reaction mixture dissolved in deuterium oxide (Acros Organics) was also analyzed using proton-decoupled <sup>13</sup>C NMR spectroscopy (<sup>13</sup>C 100 MHz) and distortionless enhancement by the polarization transfer technique (DEPT).

**2.4. Catalyst Regeneration via Memory Effect of HT and Reuse.** After washing of the solid residue after the reaction, the solid was calcined at 723 K for 7 h in air to remove organic

compounds deposited on the surface. The calcined material was treated at room temperature for 8 h in 1 mL of an aqueous solution containing 5 mM of ammonium salt ((NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, (NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>, (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub>, NH<sub>4</sub>NO<sub>3</sub>, or NH<sub>4</sub>Cl). When synthesizing HT that involves hydroxide ions in the interlayer spaces, the calcined material was treated in 1 mL of water without ammonium salt. The sample was then completely dried on a hot plate at 383 K. The dried powder was employed for subsequent runs of glucose isomerization by the same procedure described previously. Each regenerated catalyst was characterized by PXRD, high-precision field-emission scanning electron microscopy (SEM; JEOL, JSM-7400F), and N<sub>2</sub> sorption measurement at 77 K (BEL Japan, BELSORP-mini, the range of relative pressure is from 0.05 to 0.995)

## **3. RESULTS AND DISCUSSION**

**3.1. Textural Properties of HTs.** The crystalline structures of the HTs with different Mg:Al ratios were characterized by PXRD measurement. The PXRD pattern of HT(3:1) in Figure 1 presents prominent diffraction peaks at  $2\theta$  of 11.3°, 22.8°, 34.9°, 39.5°, 46.7°, 60.8°, and 62.0°, which are identical to those of typical HT materials previously reported.<sup>22–24</sup> The interlayer distance of HT(3:1) can be calculated from the diffraction at 11.3°, which originates from the (003) plane of HT,<sup>22,23</sup> to be 7.8 Å based on Bragg's law. In the cases of higher Mg:Al ratio, (i.e., 12:1, 7:1, 5:1, and 4:1), new peaks (e.g., 13.7°, 15.2°, 21.1°, and 30.7°) belonging to Mg<sub>5</sub>(CO<sub>3</sub>)<sub>4</sub>(OH)<sub>2</sub>·4H<sub>2</sub>O (hydromagnesite)<sup>22,25</sup> appeared along with the same peaks observed for HT(3:1), which indicates that these HTs involve both HT and Mg<sub>5</sub>(CO<sub>3</sub>)<sub>4</sub>(OH)<sub>2</sub>·4H<sub>2</sub>O phases. HT(1:1) has diffraction peaks at  $2\theta$  of 18.4° and 20.2° that originate from the MgAl<sub>2</sub>(OH)<sub>8</sub>

phase,<sup>22,26</sup> in addition to those from the HT phase; HT(1:1) is thus composed of HT and MgAl<sub>2</sub>(OH)<sub>8</sub>. This comparison indicates that a ratio of 3:1 is suitable for the synthesis of a wellordered HT material without impurity phases. Calcination of HT(3:1) at 803 K for 5 h (this calcined material is denoted as HT(3:1)<sub>cal</sub> hereafter) resulted in the loss of the peaks derived from HT(3:1), and instead afforded new and broad diffraction peaks centered at 35.4°, 43.2°, and 62.8°, which are attributed to a phase transition of the original HT phase to the MgO (periclase, 43.0° and 62.4°)<sup>27</sup> and/or monoclinic MgAl<sub>2</sub>O<sub>4</sub> spinel (36.6°, 44.5°, and 64.8°)<sup>28</sup> phases. This phenomenon is always observed for HT; calcination of HT above 673 K destroys its layered structure and produces a mixture of MgO, Al<sub>2</sub>O<sub>3</sub>, and/or a Mg–Al mixed oxide, whereas the original crystalline structure can be recovered with the resulting oxide in water, which is known as the memory effect, as discussed later.<sup>29</sup> Here, HT(3:1)<sub>cal</sub> was used as a reference catalyst for glucose-to-fructose isomerization (vide infra).



**Figure 1.** PXRD patterns of various HT materials. Legends: black diamonds = HT; red stars =  $Mg_5(CO_3)_4(OH)_2 \cdot 4H_2O$  (hydromagnesite); blue triangles = MgO (periclase) and/or monoclinic  $MgAl_2O_4$  spinel; purple circles =  $MgAl_2(OH)_8$ .

To elucidate the base sites of each synthesized HT that possibly function as active sites for glucose isomerization, acid-base titration in ethanol was conducted with several color indicators. None of the HTs changed the color of 2,4-dinitroaniline from yellow to violet, but all of them including HT(3:1)<sub>cal</sub> changed the color of phenolphthalein from colorless to pink. These results demonstrate that the  $pK_a$  value of the base sites present in all the HTs is in the range of 9.3 to 15.0.<sup>30</sup> The base site density was then quantified via titration using phenolphthalein (see Table 1), whereby most of the base sites that phenolphthalein and *p*-toluenesulfonic acid molecules can

access in ethanol are estimated. The density increases with the Mg:Al ratio from 1:1 (68  $\mu$ mol g<sup>-1</sup>) to 3:1 (178  $\mu$ mol g<sup>-1</sup>), but in turn decreases to 102  $\mu$ mol g<sup>-1</sup> upon further increase of the ratio to 12:1. This observed decrease in the density of base sites with the Mg:Al ratio can be rationalized by the co-presence of the Mg<sub>5</sub>(CO<sub>3</sub>)<sub>4</sub>(OH)<sub>2</sub>·4H<sub>2</sub>O phase in HT(12:1), HT(7:1), HT(5:1), and HT(4:1), because the control acid-base titration indicated that Mg<sub>5</sub>(CO<sub>3</sub>)<sub>4</sub>(OH)<sub>2</sub>·4H<sub>2</sub>O does not contain base sites that can be detected by phenolphthalein in ethanol. Despite a high density of HT(3:1)<sub>cal</sub> (207  $\mu$ mol g<sup>-1</sup>), these base sites formed on MgO and MgAl<sub>2</sub>O<sub>4</sub> are distinct from those formed on the original HT(3:1) phase.

<b>Fable 1. Textural Propertie</b>	s of Various	<b>HT Materials</b>
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Mg:Al ratio	Involved phase(s) <sup><math>a</math></sup>	Base site <sup><i>b</i></sup> / $\mu$ mol g <sup>-1</sup>
12:1	HT and Mg <sub>5</sub> (CO <sub>3</sub> ) <sub>4</sub> (OH) <sub>2</sub> ·4H <sub>2</sub> O (hydromagnesite)	102
7:1	HT and Mg5(CO3)4(OH)2·4H2O (hydromagnesite)	156
5:1	HT and Mg <sub>5</sub> (CO <sub>3</sub> ) <sub>4</sub> (OH) <sub>2</sub> ·4H <sub>2</sub> O (hydromagnesite)	122
4:1	HT and Mg5(CO3)4(OH)2·4H2O (hydromagnesite)	109
3:1	HT	178
3:1 <sup>c</sup>	MgO (periclase) and/or monoclinic MgAl <sub>2</sub> O <sub>4</sub> spinel	207
1:1	HT and MgAl <sub>2</sub> (OH) <sub>8</sub>	68

<sup>*a*</sup>Determined from PXRD patterns in Figure 1. <sup>*b*</sup>Quantified via acid-base titration using phenolphthalein as a color indicator. <sup>*c*</sup>HT(3:1) calcined at 803 K for 5 h (i.e., HT(3:1)<sub>cal</sub>).

**3.2. Glucose Isomerization over HTs.** We initially investigated catalytic activity of HT(3:1), which consists of only the HT phase as indicated by PXRD measurement (see Figure 1

#### **ACS Catalysis**

and Table 1), for glucose isomerization in ethanol under Ar at 363 K for 2 h (see Table 2). The HT(3:1) catalyst consumed 61% of glucose and fructose was synthesized in 50% yield (entry 2), the latter of which is 38-fold higher than that for the blank reaction (1.3%, entry 1). We simply postulate that the base sites in HT(3:1) function as active sites for glucose isomerization, so that the turnover number (TON) for fructose production can be estimated to be 16 on the basis of the base sites shown in Table 1. The calculated fructose selectivity of HT(3:1) was 83%. Such high fructose selectivity has been achieved probably due to mild reaction temperature (363 K) and a lack of strong base sites in the HT material (i.e., the  $pK_a$  value of base sites involved in HTs is 9.3-15.0, see Section 3.1), since undesired retro-aldol reaction of fructose is known to proceed either at reaction temperatures of typically over 423 K<sup>31-33</sup> or in the presence of strong base catalysts such as calcined MgO,<sup>34</sup> the p $K_a$  value of which is higher than 15.0.<sup>30</sup> It should be noted that, to the best of our knowledge, no chemical catalysts have been reported to show such a high fructose selectivity at a high glucose conversion to date; in contrast to the results in this work, high fructose selectivity can be achieved only when the glucose conversion is carefully controlled below 40% in previous reports.<sup>12,13,35</sup> The present results thus demonstrate that the combination of HT(3:1) and ethanol solvent realizes a very efficient catalytic system, where the choice of both catalyst and solvent is the key to simultaneous achievement of high fructose yield and selectivity (vide infra).

In control reactions using solely MgO and  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> as catalysts, in contrast to HT(3:1), neither MgO (entry 3) nor  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> (entry 4) produced a high yield of fructose ( $\leq$ 17%), and a physical mixture of both also lacked catalytic activity (7.4% of fructose yield, entry 5).  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> has exhibited catalytic activity identical to another form of aluminum oxide, boehmite ( $\gamma$ -AlO(OH)), as tested in the previous report, where the Lewis acid sites have been invoked as

active sites for the isomerization.<sup>36</sup> Another Mg-containing material, Mg<sub>5</sub>(CO<sub>3</sub>)<sub>4</sub>(OH)<sub>2</sub>·4H<sub>2</sub>O, which was detected in the HTs with the Mg:Al ratio of larger than 3:1 and did not have detectable base sites, was almost inactive (entry 6). HT(3:1)<sub>cal</sub> consisting of MgO and/or MgAl<sub>2</sub>O<sub>4</sub> (see Figure 1 and Table 1) gave 23% yield of fructose (entry 7), regardless of an almost 1.2-fold higher content of base sites compared to HT(3:1). These data indicate that HT(3:1) is superior to MgO, Al<sub>2</sub>O<sub>3</sub>, and Mg–Al mixed oxide with respect to glucose-to-fructose isomerization. Heterogeneous and homogeneous base catalysts were also examined for comparison. Typical metal oxides known to exhibit basic (CaO) and amphoteric (TiO<sub>2</sub>, ZrO<sub>2</sub>, and CeO<sub>2</sub>) properties were poor and non-selective catalysts (fructose yield and selectivity were at most 23% and 59%, respectively, see entries 8–11). The same reaction conditions in the presence of a homogeneous base consisting of either NaOH or NaOC<sub>2</sub>H<sub>5</sub> converted ≥66% of glucose; however, the fructose yield was less than 1%, possibly due to side reactions caused by their excessively strong basicity (entries 12 and 13).

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Entry Catalyst <sup>b</sup>		Conv. <sup>c</sup> Product yield <sup>d</sup> /%C					
		/%	Frc <sup>e</sup>	GLA <sup>f</sup>	DHA <sup>g</sup>	PVA <sup>h</sup>	EtGlc <sup>i</sup>
1	None	16	1.3 (8.0)	0.0	0.0	0.0	0.0
2	HT(3:1)	61	50 (83)	0.8	1.4	1.2	0.4
3	MgO	18	4.5 (25)	0.0	0.1	0.2	0.1
4	γ-Al <sub>2</sub> O <sub>3</sub>	29	17 (60)	0.7	0.3	0.4	0.1
5	MgO + $\gamma$ -Al <sub>2</sub> O <sub>3</sub> <sup>j</sup>	16	7.4 (46)	0.0	0.2	0.0	0.1
6	$Mg_5(CO_3)_4(OH)_2 \cdot 4H_2O$	14	7.3 (51)	0.2	0.4	0.4	0.1
7	$HT(3:1)_{cal}^k$	38	23 (61)	0.5	0.9	0.8	0.3
8	CaO	38	23 (59)	0.4	1.0	1.1	0.4
9	TiO <sub>2</sub>	35	9.8 (28)	0.9	0.0	0.8	4.8
10	ZrO <sub>2</sub>	19	5.5 (30)	0.5	0.1	0.2	0.0
11	CeO <sub>2</sub>	16	1.3 (8.0)	0.0	0.0	0.3	0.0
12	NaOH	66	0.7 (1.1)	0.0	0.0	0.0	0.0
13	NaOC <sub>2</sub> H <sub>5</sub>	98	0.0 (0.0)	0.0	0.0	0.0	0.0

 Table 2. Glucose Isomerization in Ethanol over Various Catalysts<sup>a</sup>

<sup>*a*</sup>Reaction conditions: glucose 50 mg; catalyst 50 mg; ethanol 7.0 mL; Ar 1 atm; 363 K; 2 h. <sup>*b*</sup>Descriptions of each catalyst are summarized in Table S1 in the Supporting Information. <sup>*c*</sup>Glucose conversion. <sup>*d*</sup>Carbon-based yield. <sup>*e*</sup>Fructose, where the values in parentheses represent selectivity. <sup>*f*</sup>Glyceraldehyde. <sup>*g*</sup>1,3-Dihydroxyacetone. <sup>*h*</sup>Pyruvaldehyde. <sup>*i*</sup>Ethyl  $\alpha$ -D-glucopyranoside. <sup>*j*</sup>Physical mixture of MgO and  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> (25 mg each). <sup>*k*</sup>HT(3:1) calcined at 803 K for 5 h.

Given the results that HT(3:1) exhibited the highest catalytic performance for glucose isomerization (Table 2), the impact of the Mg:Al ratio of HT on the activity was then examined. Under the same reaction conditions as those given in Table 2 (i.e., 363 K, 2 h), all HTs afforded similar conversion of glucose (54–64%, entries 14–19, Table 3) as well as yield and selectivity

of fructose (44–50% and 67–84%, respectively), because all cases should reach the equilibrium of isomerization between glucose and fructose. Therefore, the initial isomerization rates far away from the isomerization equilibrium were investigated to make a fair comparison of the catalytic activity of the HTs. As shown in Figure S1 in the Supporting Information, three HTs (i.e., HT(5:1), HT(4:1), and HT(3:1)) exhibited the steeper slopes, which correspond to initial isomerization rates of 239, 226, and 203 µmol g<sub>catalyst</sub><sup>-1</sup> min<sup>-1</sup> (Table 3), respectively, and the other three HTs gave similar reaction rates to each other (106–121 µmol g<sub>catalyst</sub><sup>-1</sup> min<sup>-1</sup>). While the calculated turnover frequency (TOF) values of HT(5:1) and HT(4:1) are superior to that of HT(3:1) as shown in Table 3, the weight-basis activity (= reaction rate) of HT(5:1) and HT(4:1)is almost the same with that of HT(3:1). We can therefore simply rationalize that the HT phase involved in HTs mainly contributes their catalytic performance. because to Mg<sub>5</sub>(CO<sub>3</sub>)<sub>4</sub>(OH)<sub>2</sub>·4H<sub>2</sub>O as the impurity phase of HT(5:1) and HT(4:1) has no detectable base sites and thus does not function as a catalyst or inhibitor for glucose isomerization (see entry 6 in Table 2). Hereafter, we chose HT(3:1) as one of the most active catalysts for further study, in order to simplify the catalytic system by using single-phase material.

Б (	Conv. <sup><i>b,c</i></sup> $\operatorname{Frc}^{b,d}$ Initial isomerization rate <sup><i>e</i></sup>		Initial isomerization rate <sup>e</sup>	TOF	
Entry	Catalyst	/%	/%C	$/\mu mol \ g_{catalyst}^{-1} \ min^{-1}$	$/h^{-1}$
14	HT(12:1)	54	46 (84)	121	71
15	HT(7:1)	64	50 (78)	113	43
16	HT(5:1)	61	48 (67)	239	118
17	HT(4:1)	66	44 (79)	226	124
18	HT(3:1)	61	50 (83)	203	68
19	HT(1:1)	60	46 (76)	106	94

Table 3. Glucose Isomerization in Ethanol over Various HT Materials<sup>a</sup>

<sup>*a*</sup>Reaction conditions: glucose 50 mg; catalyst 50 mg; ethanol 7.0 mL; Ar 1 atm; 363 K. <sup>*b*</sup>Reaction time was 2 h. <sup>*c*</sup>Glucose conversion. <sup>*d*</sup>Fructose yield, where the values in parentheses represent selectivity. <sup>*e*</sup>Determined from the linear slope of each time course for glucose isomerization, as shown in Figure S1 in the Supporting Information. <sup>*f*</sup>Turnover frequency calculated from initial isomerization rate divided by base site density shown in Table 1.

The solvent effects on glucose isomerization were next investigated for the lead catalyst, HT(3:1), and the results are summarized in Table 4. The reaction conducted in water gave a lower fructose yield of 16% and selectivity of 57% (entry 20), relative to ethanol (see entry 2 in Table 2). Other alcohols such as methanol (entry 21) and 1-propanol (entry 22) were also examined; both alcohols gave better results than water, but slightly lower fructose yields than ethanol. Conventional organic solvents used in the conversion of biomass-related compounds<sup>37</sup> such as dimethylsulfoxide (entry 23) and *N*,*N*-dimethylformamide (entry 24) were not as good as the alcohols investigated here. There could be multiple possibilities to rationalize the observed solvent effects: (i) as previously reported for ethanol,<sup>18</sup> alcohols shift the isomerization equilibrium between glucose and fructose to the latter sugar, and such a shift in equilibrium

allows the fructose yield to be easily increased, and (ii) alcohols stabilize a transition-state species, which leads to acceleration of the desired glucose-to-fructose isomerization with the suppression of undesired side reactions. With respect to the latter possibility, in related work investigating glucose isomerization via electronic structure calculations,<sup>38</sup> OH moieties involved in water molecules or at metal oxide surfaces have been reported to compensate and stabilize a negatively-charged species formed in the transition state (see Section 3.4), which synergistically promotes the reaction along with active sites.

Entry	Entry Solvent		Product yield <sup>c</sup> /%C				
Litty Solvent		/%	Fre <sup>d</sup>	GLA <sup>e</sup>	DHA <sup>f</sup>	PVA <sup>g</sup>	
20	Water	28	16 (57)	0.3	1.1	0.6	
21	Methanol	55	43 (78)	0.7	1.0	1.2	
22	1-Propanol	56	48 (86)	1.0	1.0	0.9	
23	Dimethylsulfoxide	24	16 (65)	0.1	0.2	0.2	
24	N,N-Dimethylformamide	48	35 (73)	0.0	1.1	0.0	

Table 4. Solvent Effect on Glucose Isomerization over HT(3:1)<sup>a</sup>

<sup>*a*</sup>Reaction conditions: glucose 50 mg; HT(3:1) 50 mg; solvent 7.0 mL; Ar 1 atm; 363 K; 2 h. <sup>*b*</sup>Glucose conversion. <sup>*c*</sup>Carbon-based yield. <sup>*d*</sup>Fructose, where the values in parentheses represent fructose selectivity. <sup>*e*</sup>Glyceraldehyde. <sup>*f*</sup>1,3-Dihydroxyacetone. <sup>*g*</sup>Pyruvaldehyde.

The effects of both reaction time and temperature were explored further with the HT(3:1) catalyst in the best solvent, ethanol (see Tables 2 and 4). Figure 2 shows time courses for glucose isomerization conducted at 333, 363, and 393 K. The fructose yield at 363 K gradually increased

with the reaction time from 26% at 15 min to 50% at 2 h and then became constant (Figure 2B), which indicates that the glucose-to-fructose isomerization reached its equilibrium at 2 h. At a lower temperature of 333 K (Figure 2A), isomerization proceeded slowly and the fructose yield was still 39% even at a reaction time of 24 h. In stark contrast, the time course at 393 K (Figure 2C) shows that a fructose yield as high as 56% with 80% selectivity can be achieved within 30 min, which is higher than 50% of the fructose yield obtained at 363 K for 2 h (Figure 2B). Upon continuing the reaction longer than 30 min at 393 K, both the fructose yield and selectivity decreased to ca. 50% and 60%, respectively, probably due to degradation of the produced fructose. These data indicate that high-yielding, selective synthesis of fructose from glucose can be accomplished within a short reaction time of 30 min at high temperature.



**Figure 2.** Time courses for glucose isomerization over HT(3:1) in ethanol at (A) 333 K, (B) 363 K, and (C) 393 K. Glc, Frc, and EtGlc represent yields of glucose, fructose, and ethyl  $\alpha$ -glucopyranoside, respectively, and C3 represents the total yield of glyceraldehyde, 1,3-dihydroxyacetone, and pyruvaldehyde. Reaction conditions: glucose 50 mg; HT(3:1) 50 mg; ethanol 7.0 mL; Ar 1 atm.

At the very end of this section, we also investigated the effect of initial glucose concentration on the isomerization rate at 15 min, which is far from the time reaching equilibrium (see Figure 2B), at 363 K by using the HT(3:1) catalyst in ethanol (Table S2 in the Supporting Information). The rate of fructose production increased from 38  $\mu$ mol g<sub>catalyst</sub><sup>-1</sup> min<sup>-1</sup> to 291  $\mu$ mol g<sub>catalyst</sub><sup>-1</sup> min<sup>-1</sup> upon an increase of initial glucose concentration from 7.9 mM to 198 mM. These results indicate that mass transfer limitation is not the case of this glucose-to-fructose isomerization using HT(3:1) in ethanol.

**3.3. Repeated Use of HT(3:1) via Regeneration Using Memory Effect.** After any reactions using the lead catalyst HT(3:1), the color of the solid changed from white to yellowish or even brownish. This color change implies the formation and deposition of insoluble humin-like compounds over the HT(3:1) surface, which often behave as catalyst inhibitors.<sup>39–41</sup> Such deposited organic species can be removed by simple calcination in air; however, in the present case, the heat-treatment process is accompanied by phase transition of the highly active HT(3:1) catalyst to the less active HT(3:1)<sub>cal</sub> (see Figure 1 and Tables 1 and 2). Given the fact that calcined HT, which lacks a layered structure, returns to its original layered phase (i.e., HT) via treatment in water in the presence/absence of salts (so-called memory effect),<sup>29</sup> a two-step regeneration process was employed for the repeated use of spent HT(3:1) in the isomerization of glucose, which consisted of calcination and subsequent reconstruction via the memory effect.

Before the repeated use of HT(3:1) via regeneration, the effects of anion species employed for the reconstruction process were examined. Anion species derived from salts are taken into the Page 19 of 42

#### **ACS** Catalysis

interlayer spaces of the resultant HT to compensate the positive charges of double hydroxide layers consisting of Mg and Al,<sup>42</sup> and such dosed anions would affect the catalytic activity of the reconstructed HTs. To this end, the HT(3:1) material calcined at 723 K for 7 h was treated in aqueous solutions containing a variety of ammonium salts (i.e., (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, (NH<sub>4</sub>)<sub>2</sub>HPO<sub>4</sub>, (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub>, NH<sub>4</sub>NO<sub>3</sub>, or NH<sub>4</sub>Cl).<sup>28,43</sup> For the synthesis of HT containing hydroxide ions, the calcined material was simply treated in pure water without ammonium salts.<sup>43</sup> Although the dose of OH<sup>-</sup> species actually requires strictly-controlled experimental procedure that completely keeps away the material from air in order to avoid  $CO_3^{2-}$  contamination,<sup>44</sup> the data of both characterization and glucose isomerization indicate that even using our experimental procedure, we can still see the difference between the HT reconstructed in  $(NH_4)_2CO_3$  aqueous solution and that in pure water (vide infra). The PXRD patterns shown in Figure 3A indicate that all resultant materials, except for the case of  $(NH_4)_2$ HPO<sub>4</sub>, have layered structures that are similar to that of bare HT(3:1), while the interlayer distance of these materials depends on a class of anion dosed (see Table S3 in the Supporting Information). Besides, in the PXRD patterns of the materials reconstructed in  $(NH_4)_2SO_4$  and  $NH_4NO_3$ , the broad peak centered at ca. 20° was also observed possibly as a result of the formation of MgAl<sub>2</sub>(OH)<sub>8</sub> phase.<sup>22,26</sup> Figure 3B summarizes the isomerization results by using these reconstructed HTs and demonstrates their catalytic activity to be significantly dependent on the type of anion species; among the ammonium salts tested, the reconstruction of HT in an aqueous solution containing (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> generates the most active material that is comparable to bare HT(3:1).



**Figure 3.** Effects of anion species used for the reconstruction process of calcined HT(3:1). (A) PXRD patterns of resultant materials treated in aqueous solutions containing each ammonium salt and (B) catalytic performance of the materials for glucose-to-fructose isomerization. Frc shows the yield of fructose and Others represents the total yield of by-products. Reaction conditions: glucose 50 mg; catalyst 50 mg; ethanol 7.0 mL; Ar 1 atm; 363 K; 2 h.

The effects of anion species on catalytic activity could be rationalized by the textural properties of each reconstructed HT material. Three poor catalysts (i.e.,  $SO_4^{2-}$ ,  $HPO_4^{2-}$ , and  $NO_3^{--}$ ) consist of HT and other phases, with no observable phases for the case of  $HPO_4^{2-}$  (Table S3 in the Supporting Information), which leads to a decrease of fructose selectivity ( $\leq$ 52%). In contrast, the other three selective catalysts (i.e.,  $CO_3^{2-}$ ,  $CI^-$ , and  $OH^-$ ) involve HT phase only. Although the order of base site density is  $OH^- > CO_3^{2-} > CI^-$  (see Table S3 in the Supporting Information), that of catalytic activity based on fructose yield is  $CO_3^{2-} > OH^- > CI^-$  (Figure 3B). This contradiction suggests that the catalytic activity of HTs is changed not only by base site density, but also is influenced directly by anion species themselves taken into the interlayer of HTs. We

hypothesize that anion species might show different degree of interaction with transition-state species as is the case for cellulose dissolution in ionic liquids, where the choice of anions impacts on cellulose solubility due to different degree of interaction between anion species and glucose unit involved in cellulose.<sup>45,46</sup> Such interaction would lead to stabilization of transition-state species, which results in promotion of glucose isomerization.

These results indicated the  $(NH_4)_2CO_3$ -treatment should be employed for repeated use of HT(3:1); therefore, two-step regeneration consisting of calcination and subsequent reconstruction in  $(NH_4)_2CO_3$  aqueous solution was conducted for spent HT(3:1). The PXRD measurement confirmed that reconstruction of the original layered structure of HT(3:1) was completed after the two-step regeneration process (Figure 4A), and the morphology looked similar before and after the regeneration process (SEM images are shown in Figure S2 in the Supporting Information), while the Brunauer-Emmett-Teller (BET) surface area determined from  $N_2$  adsorption-desorption measurement gradually decreased upon repeating reaction and regeneration (Table S4 in the Supporting Information). The reconstructed HT(3:1) maintained its catalytic performance as almost constant at least three times (Figure 4B), in which the total TON for fructose production was calculated to be as high as 46. HT(3:1) can be repeatedly used for glucose isomerization via the two-step regeneration process without a decrease in activity. These results also suggest that the isomerization mainly takes place between layers inside HT particles.



**Figure 4.** Repeated use of HT(3:1) for glucose isomerization after regeneration via calcination and subsequent treatment in (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> aqueous solution. (A) PXRD patterns of bare and reconstructed HT(3:1) recorded before each reaction, and (B) results of glucose isomerization. Frc shows the yield of fructose and Others represents the total yield of by-products. Reaction conditions: glucose 50 mg; catalyst 50 mg; ethanol 7.0 mL; Ar 1 atm; 363 K; 2 h.

3.4. Mechanistic Study and Contribution of Base Sites to Glucose Isomerization. Since HT(3:1) exhibits high catalytic performance in glucose isomerization (see Table 2), we examined whether the base sites of HT(3:1) function as active sites for the reaction and compared the reaction mechanism with those for control solid catalysts. Base-catalyzed glucose isomerization is known to proceed via the LdB–AvE mechanism involving  $\alpha$ -hydrogen abstraction from open-chain glucose, which is known to be present in various solvents due to anomerization equilibrium<sup>47,48</sup> and has been widely accepted as a starting form in previous reports,<sup>11</sup> as an initial step (Figure 5A). This mechanistic insight motivated us to conduct an isotope tracer study using glucose-2-d<sub>1</sub> as a reactant, to elucidate whether base sites of HT(3:1) abstract deuterium

#### **ACS** Catalysis

atom from the substrate. In the <sup>2</sup>H NMR spectrum of the reaction mixture obtained from glucose- $2-d_1$  with the HT(3:1) catalyst (Figure 5B), only peaks attributed to glucose- $2-d_1$  were observed, while the formation of fructose was confirmed by separate HPLC analysis for the same mixture (we observed 24% of fructose yield and 40% of glucose conversion (Table S5 in the Supporting Information), which indicates that C2–H bond cleavage is the rate-determining step in this reaction catalyzed by HT(3:1) in ethanol). Note that if fructose-1-d<sub>1</sub> was present in the reaction mixture as a product, its signal should be observed at 3.58–3.70 ppm.<sup>49</sup> The absence of this signal in the  ${}^{2}$ H NMR spectrum (Figure 5B) indicates that the produced fructose molecules lack deuterium as a result of its abstraction by HT(3:1) and subsequent diffusion of abstracted deuterium from the catalyst surface to the protic solvent (ethanol, in this study) via proton exchange. The <sup>13</sup>C NMR and DEPT spectra for the same reaction mixture dissolved in deuterium oxide also led to the same conclusion (see Figure S3 in the Supporting Information). These results clearly demonstrate that the HT(3:1) catalyst uses its base sites to promote glucose-tofructose isomerization. Note that another mechanism invoked for the glucose isomerizationintramolecular 1,2-hydride shift driven by Lewis acids (see Scheme S1 in the Supporting Information)<sup>15,50,51</sup>—can be ruled out; this mechanism transforms glucose-2-d<sub>1</sub> into a mixture of fructose-1-d<sub>1</sub>, glucose-1-d<sub>1</sub>, and unreacted glucose-2-d<sub>1</sub> (see Scheme S2 in the Supporting Information); however, such a mixture was not observed and only glucose-2-d<sub>1</sub> was detected by <sup>2</sup>H NMR spectroscopy (see Figure 5B).



**Figure 5.** (A) Glucose-to-fructose isomerization via the LdB–AvE mechanism catalyzed by bases (**:B**) and (B) <sup>2</sup>H NMR spectrum of reaction mixture synthesized from glucose-2-d<sub>1</sub>, along with the spectrum for glucose-2-d<sub>1</sub> dissolved in water (i.e., standard). It should be noted that the proton (or deuterium) abstracted by base is diffused from the catalyst surface to protic solvent (in this study, ethanol) via proton exchange, and therefore, the return of such abstracted species to the substrate and/or product molecules hardly occurs. Reaction conditions: glucose-2-d<sub>1</sub> 50 mg; HT(3:1) 50 mg; ethanol 7.0 mL; Ar 1 atm; 363 K; 2 h. The two NMR peaks at 3.16 ppm and 3.45 ppm appeared due to the presence of glucose anomers (i.e.,  $\alpha$ -glucose-2-d<sub>1</sub> and  $\beta$ -glucose-2-d<sub>1</sub>).

The reaction mechanism was in turn investigated in the same manner using solely MgO and  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> as control catalysts, and the <sup>2</sup>H NMR spectra for each reaction mixture are shown in Figure S4 in the Supporting Information. Consistent with the case of HT(3:1) shown in Figure 5B, only peaks assigned to glucose-2-d<sub>1</sub> were observed when using either MgO or  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>. This indicates that both catalysts did not synthesize fructose-1-d<sub>1</sub> during the reaction, and furthermore, that the base sites of these oxides abstracted deuterium from glucose-2-d<sub>1</sub> to initiate

isomerization through the LdB–AvE mechanism, which is in contrast to the previous research where Lewis-acid sites involved in another class of aluminum oxide (boehmite) were reported as active sites for the isomerization.<sup>36</sup> The spectroscopic data thus demonstrate that base sites are solely responsible for glucose-to-fructose isomerization in all cases (i.e., HT(3:1), MgO, and  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>), while the performance is significantly dependent upon the nature of the base sites (see Table 2)—base sites formed in the HT phase are the most suitable for the synthesis of fructose from glucose.

#### **4. CONCLUSIONS**

We have successfully demonstrated the combination of ethanol solvent and HT to selectively catalyze glucose-to-fructose isomerization, which enables to simultaneously achieve high selectivity and yield of fructose. The use of ethanol as a reaction solvent allows the fructose yield to be increased beyond 50%, which is the upper limit with enzymatic isomerization conducted at modest temperatures in water.<sup>2,15</sup> In addition to environmentally preferable property of ethanol,<sup>52</sup> its use as a solvent is also possibly beneficial with respect to solvent removal after the reaction due to its lower boiling point than water, which has been used for the conventional HFCS production.<sup>1–3</sup> Such easier purification process of fructose in the case of ethanol solvent would enable simple reaction systems requiring single catalyst to further convert fructose to value-added chemicals from glucose has been investigated so far by using multiple catalysts at the same time,<sup>53</sup> such complicated catalytic systems sometimes conflict with each other and suffer from undesired side

reactions, to decrease both selectivity and yield of desired products. The HT(3:1) catalyst can be used repeatedly for the isomerization via a two-step regeneration process consisting of calcination to remove humin compounds deposited on the catalyst and successive treatment in an (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> aqueous solution to reconstruct the layered structure of HT(3:1). Our mechanistic study has revealed that base sites involved in all three materials (i.e., HT(3:1), MgO, and  $\gamma$ -Al<sub>2</sub>O<sub>3</sub>) function as active sites to accelerate glucose isomerization through the LdB–AvE mechanism, where HT(3:1) exhibits the highest catalytic performance due to its high density of base sites. Further precise control of the strength and density of base sites could lead to the development of an active and selective catalyst suitable for the large-scale production of fructose as a renewable feedstock in the future chemical industry.

#### ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.XXXXXXX.

Descriptions of catalysts tested for glucose isomerization, time courses of glucose isomerization over various HTs at 363 K, effect of initial glucose concentration on isomerization rate, textural properties of regenerated HT materials, SEM images of regenerated HT(3:1), BET surface area of reused HT(3:1), isotope effect on glucose isomerization by HT(3:1), <sup>13</sup>C NMR and DEPT spectra for the reaction mixtures synthesized with HT(3:1), isomerization mechanism via intramolecular 1,2-hydride shift catalyzed by Lewis acid, and <sup>2</sup>H NMR spectra for the reaction mixtures synthesized with MgO and  $\gamma$ -Al<sub>2</sub>O<sub>3</sub> (PDF)

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## Notes

The authors declare no competing financial interest.

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Fig.1 127x100mm (300 x 300 DPI)

◆ Glc ● Frc □ C3 △ EtGlc ◇ Others

Time /h

Fig.2

(C) 393 K

**Yield /%C** 09

◆ Glc ● Frc □ C3 △ EtGlc ◇ Others

Ð

Time /h





- 57 58
- 59
- 60





148x61mm (300 x 300 DPI)

3rd







148x53mm (300 x 300 DPI)







TOC 84x47mm (300 x 300 DPI)