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# Efficient Conversion of Pyruvic Aldehyde into Lactic Acid by Lewis Acid Catalyst in Water

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Homogeneous and heterogeneous catalysts with water-tolerant Lewis acids, such as $Sc(OTf)_3$ and $Nb_2O_5 \cdot nH_2O$, effectively promote the hydride transfer of pyruvic aldehyde into lactic acid in water at 383 K, whereas Brønsted acid catalysts cannot function as effective catalysts under mild conditions. NMR measurement in the presence of $D_2O$ suggests that the reaction on a Lewis acid catalyst proceeds via the Meerwein–Ponndorf–Verley (MPV) reduction.

Lactic acid has received much attention as a starting material for the production of industrially important chemicals, such as biodegradable polymers[1] and solvents,[2] and for traditional food, pharmaceutical, and cosmetic chemistry applications.[3] The anaerobic fermentation of dextrose with bacteria, as shown by lactic acid bacilli, is a conventional industrial method for the synthesis of lactic acid;[1,4] however, this process has some serious drawbacks, such as a long reaction time of a few days and careful control of the reaction broth pH by the continuous addition of $Ca(OH)_2$ is required to maintain bacterial activity.[5] An energy-inefficient work-up process for acidification of the evolved calcium lactate with sulfuric acid is also necessary in the process, which results in the production of large amounts of gypsum as a by-product. Therefore, large-scale lactic acid production requires a more environmentally benign chemical synthesis route that reduces hazardous work-up processes and worthless by-products.

Lactic acid can be synthesized from glyceraldehyde (GLA) or 1,3-dihydroxyacetone (DHA) over an acid catalyst.[6] These molecules are readily produced by the oxidation of glycerol, a main by-product in biodiesel production. Therefore, an efficient catalytic system that converts GLA and DHA into lactic acid without drawbacks in the biochemical process would be a promising candidate for lactic acid production. The reaction pathway for lactic acid synthesis from GLA and DHA in the presence of an acid catalyst is often proposed (Scheme S1).[7] Pyruvic aldehyde is first evolved from DHA and GLA by dehydration. The pyruvic aldehyde is a highly reactive dicarbonyl compound and is present in water in the original aldehyde, monohydrate, and dihydrate forms with typical distributions of trace levels, 57% and 43%, respectively, which was confirmed by $^1$H NMR analysis (monohydrate pyruvic aldehyde: $\delta$ 2.20 ppm (3H), 5.18 ppm (1H), dihydrate pyruvic aldehyde: $\delta$ 1.27 ppm (3H), 4.73 ppm (1H)).[8] Monohydrate pyruvic aldehyde is subsequently converted into lactic acid through hydride transfer. As the reaction proceeds, most of the dihydrate pyruvic aldehyde is continuously converted into the monohydrate form to keep equilibrium distribution, and the monohydrate pyruvic aldehyde finally turns into lactic acid. While Brønsted acids such as HCl and $H_2SO_4$ can, in principle, enhance these reactions,[9] they are not effective catalysts for lactic acid production. However, some Lewis acids, such as metal chlorides[7] and metallosilicates (Sn-$\beta$ zeolite[10,11] and Al-, Ga-, and Sn-containing MCM-41[12]), have been reported to be active catalysts for the production of lactic acid and alkyl lactates from DHA. Brønsted acids can function as more efficient catalysts for dehydration than Lewis acids can; however, previous reports on Lewis acids suggest that the hydride transfer of pyruvic aldehyde into lactic acid is a key step for efficient lactic acid production and that Lewis acids that are workable in water are much more effective catalysts for hydride transfer than Brønsted acids are. In this study, the hydride transfer of pyruvic aldehyde into lactic acid in water was investigated using various Brønsted and Lewis acid catalysts.

$H_2SO_4$, HCl, Amberlyst-15 (sulfonated polystyrene), and Nafion resin (perfluorosulfonated ionomers) were examined as homogeneous and heterogeneous Brønsted acid catalysts. The conversion of pyruvic aldehyde into lactic acid in the presence of rare earth metal triflates ($Sc(OTf)_3$, $Y(OTf)_3$, and $Yb(OTf)_3$) and $Nb_2O_5 \cdot nH_2O$, which are Lewis acid catalysts that are active even in water, was also examined. Rare earth metal triflates are stable and highly active homogeneous Lewis acid catalysts that function as versatile catalysts for a variety of acid-catalyzed reactions in water.[13] Recently, we reported that $NbO_4$ tetrahedra present on the surface of $Nb_2O_5 \cdot nH_2O$ act as Lewis acids, even in the presence of water.[14] $Nb_2O_5 \cdot nH_2O$ is an amorphous metal oxide composed mainly of distorted $NbO_6$ octahedra and $NbO_4$ tetrahedra. The Nb–O bonds in these distorted polyhedrons are highly polarized, so that a part of the surface OH groups function as Brønsted acid sites. In addition, some of the $NbO_4$ tetrahedra are found to work as Lewis acid sites in water.[14]

All chemicals were used as received. $Nb_2O_5 \cdot nH_2O$ (Companhia Brasileira de Metalurgia e Mineração; CBMM) was examined as a heterogeneous catalyst. The catalytic reaction involved the heating of a mixture of catalyst (0.1 or 0.02 g) and 2.0 mL of aqueous pyruvic aldehyde solution (0.1 M) in a sealed Pyrex tube at 383 or 413 K for 1 h. The solution was analyzed using high-performance liquid chromatography (HPLC; LC-2000 plus, Jasco) equipped with a refractive index (RI) detector. The lactic acid yield was estimated from the amount of introduced pyruvic aldehyde.

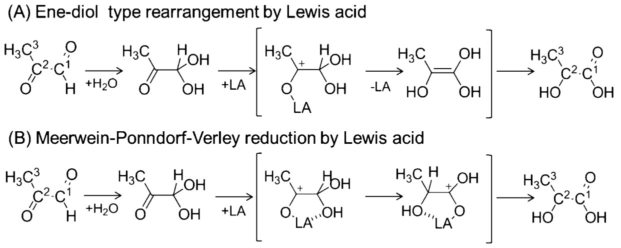
Table 1 shows the catalytic activities of the catalysts for the reaction. While the reaction proceeds effectively over $H_2SO_4$ and HCl at 413 K, these Brønsted acids cannot function as effective catalysts for the reaction at 383 K. In addition, the turnover numbers (TONs) of the tested Brønsted acids were much below 1 even at 413 K, under the present experimental conditions. In general, most Lewis acids cannot catalyze the

**Table 1.** Catalytic activity for the conversion of pyruvic aldehyde into lactic acid in water

| Catalyst | Temp. /K | Catalyst weight /g | Acid site density /mmol g$^{-1}$ BAS[a] | LAS[b] | Conv. /% | Yield /% | TON |
|---|---|---|---|---|---|---|---|
| Blank | 383 | — | — | — | 15.5 | 0.0 | — |
| concd $H_2SO_4$ | 383 | 0.1 | 19.6 | — | 15.7 | 14.8 | 0.02 |
| | 413 | 0.1 | | | 63.3 | 51.4 | 0.05 |
| concd HCl | 383 | 0.1 | 9.6 | — | 15.1 | 11.5 | 0.02 |
| | 413 | 0.1 | | | 89.0 | 73.7 | 0.2 |
| Amberlyst-15 | 383 | 0.1 | 4.8 | — | 9.4 | 5.9 | 0.02 |
| Nafion SAC13 | 383 | 0.1 | 0.13 | — | 11.1 | 0.0 | — |
| $Sc(OTf)_3$ | 383 | 0.1 | | 2.0 | >99 | 94.4 | 0.9 |
| | 383 | 0.02 | | | 86.8 | 77.2 | 3.8 |
| | 413 | 0.02 | | | >99 | 90.4 | 4.4 |
| $Y(OTf)_3$ | 383 | 0.1 | — | 1.9 | 72.3 | 40.2 | 0.4 |
| | 413 | 0.02 | | | >99 | 50.7 | 2.7 |
| $Yb(OTf)_3$ | 383 | 0.1 | — | 1.6 | 74.3 | 47.7 | 0.6 |
| | 413 | 0.02 | | | >99 | 60.3 | 3.7 |
| $Nb_2O_5 \cdot nH_2O$ | 383 | 0.1 | 0.14[c] | 0.03[c] | >99 | 78.3 | 52 |
| | 413 | 0.02 | | | >99 | 85.4 | 285 |

[a]Brønsted acid site. [b]Lewis acid site. [c]Water-tolerant acid site.[14]

reaction because they do not function well or because they are decomposed in water. However, $Sc(OTf)_3$, $Y(OTf)_3$, and $Yb(OTf)_3$, which are water-tolerant homogeneous Lewis acids,[13] exhibit high catalytic performance for the reaction; the lactic acid yield with $Sc(OTf)_3$ reached 94.4% at 383 K. When the reaction was performed with 0.02 g of catalyst at 413 K, TONs of these triflates exceed 2, indicating that the tested Lewis acids can work catalytically. In particular, $Sc(OTf)_3$ and $Nb_2O_5 \cdot nH_2O$ have a significant advantage over Brønsted acids for the hydride transfer of pyruvic aldehyde in water. The efficient hydride transfer of pyruvic aldehyde was also observed on $Nb_2O_5 \cdot nH_2O$, which is a heterogeneous acid catalyst with both Brønsted and Lewis acid sites.[14,15] This suggests that the Lewis acid sites on $Nb_2O_5 \cdot nH_2O$ are quite effective for hydride transfer in water, despite the low density of Lewis acid sites. In addition, no significant decrease in activity was observed for three reuse of $Nb_2O_5 \cdot nH_2O$ (Figure S2), indicating that $Nb_2O_5 \cdot nH_2O$ works as a reusable catalyst for the reaction. However, mass balance is not satisfied for Lewis acid catalysts, including $Nb_2O_5 \cdot nH_2O$. This can be attributed to the formation of polymerized species by intermolecular reactions among molecules in the reaction system. Matrix-assisted laser desorption–ionization–time-of-flight (MALDI-TOF) mass spectrometric analysis revealed that the reaction solution for $Nb_2O_5 \cdot nH_2O$ contains numerous polymerized species with $m/e = 300$–900. Pyruvic aldehyde has reactive carbonyl (C=O) groups, and complex intermolecular reactions, such as aldol condensation, by Lewis acid catalysts would result in the formation of complex polymerized species. It should be noted that $Y(OTf)_3$ and $Yb(OTf)_3$ are not superior to $Sc(OTf)_3$ and $Nb_2O_5 \cdot nH_2O$ as shown in Table 1, meaning that the former are distinct from the latter in reactivity such as acid strength. The details for Lewis acidity are currently under investigation.



**Scheme 1.** Proposed reaction pathway for Lewis acid-catalyzed hydride-transfer reaction of pyruvic aldehyde in water.

The Lewis acid catalysts such as $Sc(OTf)_3$ and $Nb_2O_5 \cdot nH_2O$ are clearly superior to the Brønsted acid catalysts for the hydride-transfer reaction of pyruvic aldehyde into lactic acid in water. Two reaction pathways are possible (Scheme 1) for lactic acid formation from pyruvic aldehyde by Lewis acids: the classical ene–diol-type rearrangement and the Meerwein–Ponndorf–Verley (MPV) reduction. It has been reported that Lewis acids can effectively catalyze the hydride transfer of glucose into fructose in water through MPV reduction.[16] In the case of hydride transfer via MPV reduction, Lewis acid catalysts would be coordinated with the monohydrate form of pyruvic aldehyde in water to form a five-membered intermediate that is subsequently converted into lactic acid via a 1,2-hydride-transfer reaction (Scheme 1). In this study, NMR spectroscopy (Avance III 400, Bruker, $^1$H: 400.1 MHz, $^{13}$C: 100.6 MHz) was employed to clarify the reaction mechanism over a Lewis acid catalyst. The reaction was performed in pure $H_2O$ and $D_2O$ (>99 vol %) in the presence of $Sc(OTf)_3$ at 383 K. Figure 1 shows $^1$H and $^{13}$C NMR spectra of lactic acid synthesized with $Sc(OTf)_3$. The $^1$H NMR spectra have two signals at around 4.0 and 1.2 ppm that are assignable to CH and $CH_3$ atoms at the C2 carbon, respectively, and there is no significant difference between the $^1$H NMR spectra of lactic acid synthesized in $H_2O$ and $D_2O$ (Figures 1A(a) and 1A(b)). $^{13}$C NMR measurement also indicated no significant difference (Figure 1B). If the reaction proceeded via an ene–diol-type rearrangement in $D_2O$, then a deuterium atom would be incorporated at the C2 position of the resultant lactic acid. Therefore, the NMR spectra suggest that the reaction catalyzed by the Lewis acid does not proceed through an ene–diol rearrangement but via MPV reduction. Such a mechanism was also proposed for the formation of methyl lactate from pyruvic aldehyde over a solid Lewis acid catalyst.[17]

In this study, the reaction was also examined in the presence of a Brønsted acid in a similar manner. Although homogeneous and heterogeneous Brønsted acids cannot function as efficient catalysts for the reaction at 383 K, as shown in Table 1, an increase in the reaction temperature improved the lactic acid yield. For example, the pyruvic aldehyde conversion and lactic acid yield with conc. HCl for 1 h at 383 K are only 15 and 12%, respectively (Table 1). However, the reaction with conc. HCl at 413 K for 2 h gave a pyruvic aldehyde conversion of >99% and a lactic acid yield of 82%, which indicates that Brønsted acids can also function as effective catalysts for lactic acid production from pyruvic aldehyde at higher temperatures. Figure 2 shows $^1$H and $^{13}$C NMR spectra of lactic acid synthesized with HCl in pure $H_2O$ and $D_2O$ (413 K, 2 h). The signals at 4.0 and 1.2 ppm, attributable to CH and $CH_3$ atoms at the C2 carbon, respectively, are observed for the $^1$H NMR of lactic acid synthesized in $H_2O$

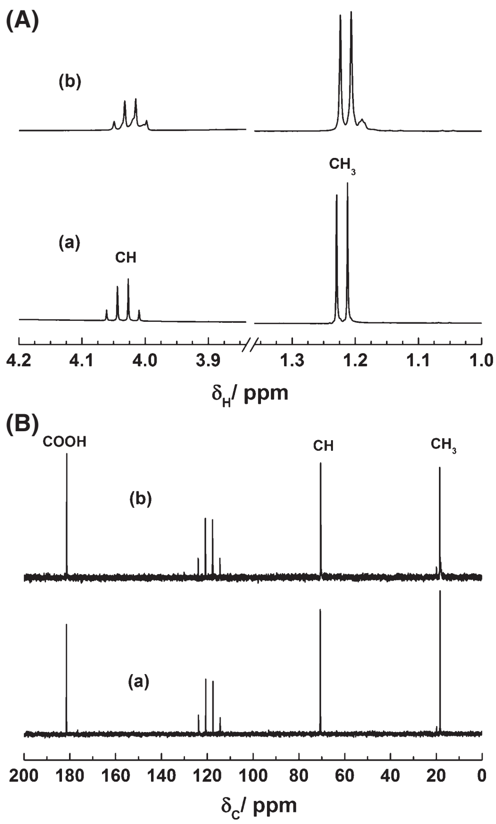


**Figure 1.** (A) $^1$H NMR and (B) $^{13}$C NMR spectra of lactic acid synthesized with Sc(OTf)$_3$ in (a) $H_2O$ and (b) $D_2O$. For NMR measurement, the products in $H_2O$ and $D_2O$ are dissolved in DMSO-$d_6$ and $D_2O$, respectively. The resonances at around 120 ppm are attributed to the $CF_3$ groups of Sc(OTf)$_3$.

(Figure 2A(a)). For lactic acid synthesized in $D_2O$, the quartet peak at 4.0 ppm, attributable to CH at the C2 carbon, becomes a singlet, and the $CH_3$ signal at 1.2 ppm disappears completely (Figure 2A(b)). The $^{13}$C NMR spectrum of lactic acid synthesized in $D_2O$ is also different from that synthesized in $H_2O$. The $^{13}$C NMR spectra have some signals at around 20, 70, and 180 ppm that are assignable to $CH_3$, CH, and COOH, respectively. The weak signals marked with asterisks in Figure 2B(a) are attributed to lactic acid anhydride formed by intramolecular dehydration of the evolved lactic acid. The $CH_3$ signal at 20 ppm in Figure 2B(b) is much smaller than that in Figure 2B(a). These results are clearly due to the formation of a $CD_3$ moiety in lactic acid (Figure 2A, inset), which results in the disappearance of the $^1$H–$^1$H spin–spin coupling of CH with $CH_3$ and a reduction of the $^1$H–$^{13}$C spin–spin coupling of $CH_3$. H–D substitution of the $CH_3$ group would occur rapidly on a Brønsted acid through keto–enol tautomerization. Deuterium-substituted pyruvic aldehyde may be subsequently converted into lactic acid through methyl anion transfer, although it is generally more effectively catalyzed by a base catalyst through benzilic acid rearrangement. The details are currently under investigation.

In conclusion, water-tolerant Lewis acids such as Sc(OTf)$_3$ and $Nb_2O_5 \cdot nH_2O$ can effectively catalyze the hydride transfer of pyruvic aldehyde in water by MPV reduction under mild reaction conditions. NMR experiments revealed that the reaction mechanism for the hydride transfer of pyruvic aldehyde over these Lewis acids is distinct from that over Brønsted acids.

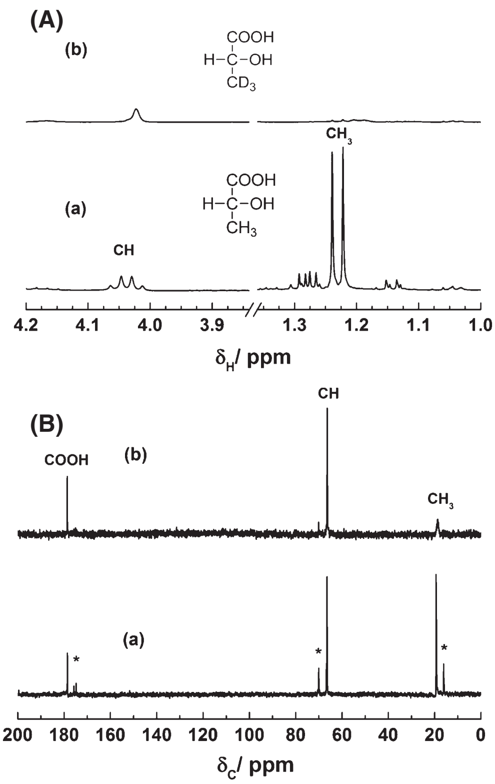


**Figure 2.** (A) $^1$H NMR and (B) $^{13}$C NMR spectra of lactic acid synthesized with conc. HCl in (a) $H_2O$ and (b) $D_2O$ dissolved in (A) DMSO-$d_6$ and (B) $D_2O$.

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