

Theoretical study of Al(III)-catalyzed conversion of glyoxal to glycolic acid: dual activated 1,2-hydride shift mechanism by protonated Al(OH)₃ species†

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Received (in Cambridge, UK) 10th February 2009, Accepted 3rd March 2009

First published as an Advance Article on the web 26th March 2009

DOI: 10.1039/b902729g

Density functional theory calculations demonstrate that Al(III)-catalyzed conversion of glyoxal to glycolic acid proceeds via a 7-membered dual Lewis acid-hydrogen bonding activation transition state of the 1,2-hydride shift, rather than the previously proposed 5-membered metal-alkoxide chelate activation transition state.

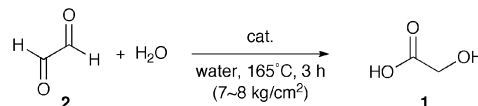
Glycolic acid (**1**) is one of the smallest molecules with both carboxylic acid and alcohol functionalities. Due to the hydroxyl group at the α -position of the carboxylic acid, **1** has higher acidity (pK_a 3.83) and stronger chelating properties toward metal ions than an unfunctionalized carboxylic acid ($pK_a \approx 4.8$). Thus, **1** is used industrially for rust removal, degreasing, etc. Although **1** occurs naturally in sugarcane, sugar beets, and in several fruits as a trace component, a highly efficient manufacturing process is required to provide a constant supply of this mass product. The acid-catalyzed reaction of formaldehyde with water under carbon monoxide produces an aqueous solution of **1** on an industrial scale,¹ but this process requires high temperature (200 °C), high pressure (> 300 kg cm⁻²), and removal of the remaining formaldehyde from the product mixture. On a laboratory scale, **1** can be synthesized by (i) hydrolysis of monochloroacetic acid with aqueous sodium hydroxide (> 2 equiv.)² or (ii) a Cannizzaro-type reaction of glyoxal (**2**) with aqueous sodium hydroxide (> 1 equiv.)³ The use of more than stoichiometric amounts of alkali metal hydroxide followed by acid treatment for neutralization is not suitable, however, for large-scale production.

We developed a direct conversion of **2** to **1** that resulted in high yield and high purity.^{4,5} We first found that **1** was produced by simply heating a 15% aqueous solution of **2** in a stainless autoclave (Table 1, entry 1). The yield of **1**, however, remained only moderate (up to 65%), even after various attempts, leading to screening for acid catalysts. Although some Brønsted acids, such as **1**, showed a positive effect, the yield was still unsatisfactory (entry 2). Based on the

excellent precedent of the Lewis acid (as opposed to Brønsted base)-assisted Cannizzaro reaction of aryl glyoxal,⁶ we examined various Lewis acids as a catalyst. Al, Si, Ga, and Sn complexes were good catalysts for this reaction, whereas B, Mn, and Fe complexes gave only moderate yields. Among them, AlX₃ complexes had higher catalyst activity than the other complexes. Because glycolic acid (**1**) is highly soluble in water and cannot be distilled even under high vacuum, it is difficult to remove counter anions (X⁻), such as chloride, nitrate, and sulfate, from the aqueous solution of product **1**. Thus, Al(OH)₃ was selected as the best catalyst for this process. In the presence of 0.2 mol% of Al(OH)₃, the reaction completed within 3 h at 165 °C to afford **1** in 92% yield (entry 3).⁵ This catalysis has several advantages: simple procedures, mild conditions, and inexpensive and harmless reagents. In addition, large-scale reaction (10 mol scale) proceeded with the same efficiency.

Under strongly basic conditions, an internal Cannizzaro reaction of **2** produces metal glycolate.³ The reaction conditions of the current acid catalysis, however, are quite different from the Cannizzaro conditions. Although a 1,2-hydride shift mechanism was proposed in previous reports of the Lewis acid-catalyzed Cannizzaro reaction,^{6a-c} such a mechanism was only speculative and has not been confirmed. To gain more detailed information about the reaction mechanism of this acid catalysis and to elucidate the effects of Brønsted and Lewis acids, we performed theoretical studies using the B3LYP⁷ hybrid density functional theory (DFT). Here we provide an evaluation of two possible mechanisms, the dehydration mechanism and the 1,2-hydride shift mechanism, of this transformation. On the basis of the DFT calculations, we propose that (i) the direct conversion of glyoxal (**2**) to

Table 1 Representative results of direct catalytic conversion of **2** to **1**^a



| Entry | Catalyst | Yield ^b (%) |
|-------|---|------------------------|
| 1 | — | 65 |
| 2 | HOOCCH ₂ OH (1) (10 mol%) | 68 |
| 3 | Al(OH) ₃ (0.2 mol%) | 92 |

^a 15% Aqueous solution of glyoxal (**2**, 646 mmol) in 500 mL stainless autoclave was heated at 165 °C. ^b Determined by HPLC analysis.

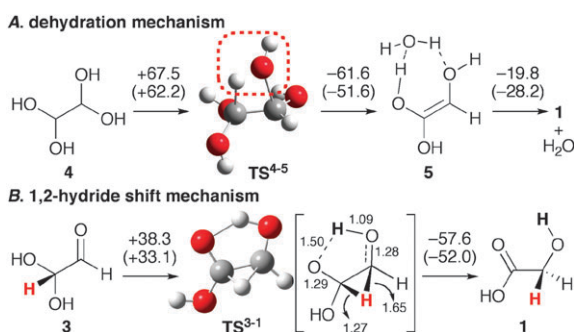
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† Electronic supplementary information (ESI) available: Experimental and computational data. See DOI: 10.1039/b902729g

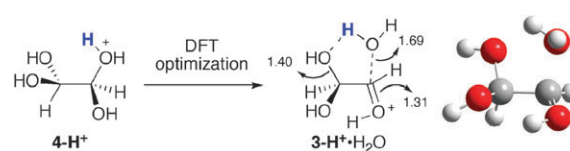


Scheme 1 (Top) Path *A*: possible reaction pathway of the dehydration mechanism. (Bottom) Path *B*: possible reaction pathway of the 1,2-hydride shift mechanism. Energy changes are shown in kcal mol⁻¹ on the arrows and bond lengths are shown in Å. Values in parentheses include solvation energies in water using the CPCM-UFF model.

glycolic acid (**1**) proceeds through an intramolecular 1,2-hydride shift reaction of monohydrate (HO)₂CH-CHO (**3**), (ii) dual activation⁸ by Lewis acid and hydrogen bonding is more favorable than a previously proposed metal-alkoxide chelate activation, (iii) protonation of the Al(III) complex decreases the activation energy (ΔE^\ddagger)⁹ more effectively than single activation by either Al(III) or a Brønsted acid, and (iv) other group 13 metal complexes Ga(III) and B(III) are slightly and much less effective catalysts, respectively. These calculated results are consistent with the experimental results.

In aqueous solution, **2** exists predominantly as dihydrate (HO)₂CH-CH(OH)₂ (**4**). Indeed, no peaks ascribed to aldehydes were detected in ¹H and ¹³C NMR spectra. Thus, we first considered the dehydration mechanisms of **4** to **1** (Scheme 1, path *A*). All the geometries were fully optimized at the B3LYP/6-31G(d,p) level of theory followed by single point energy calculation using the larger basis set 6-311+G(d,p). Frequency calculations were also performed at the B3LYP/6-31G(d,p) level to determine the nature of the stationary points. The reported energies include zero-point energy corrections.⁵ Results are also given for energies of solvation using the CPCM¹⁰-UFF¹¹ model. We located the transition structure **TS**⁴⁻⁵ with a large ΔE^\ddagger of 67.5 kcal mol⁻¹ for the *syn*- β -H elimination (dehydration) of dihydrate **4** to afford enol **5**, which is then easily isomerized to more stable glycolic acid **1**. The transition structure for either *anti*- β -H elimination or the 1,2-hydride shift reaction of **4** to **1** could not be located, and hence all our attempts resulted in the formation of monohydrate **3**. On the other hand, the ΔE^\ddagger of the transition structure **TS**³⁻¹ for the 1,2-hydride shift reaction of **3** to **1** (path *B*, $\Delta E^\ddagger = 38.3$ kcal mol⁻¹) is 29.2 kcal mol⁻¹ lower than that for the reaction of **4** (path *A*). Because the ΔE^\ddagger for the dehydrative conversion of **4** to **3** via 6-membered cyclic transition state **TS**⁴⁻³ is only 21.9 kcal mol⁻¹ (20.6 kcal mol⁻¹ in water),⁵ the 1,2-hydride shift reaction of **3** to **1** via **TS**³⁻¹ would be more energetically demanding than the dehydration reactions of **4** to **1** via **TS**⁴⁻⁵.

We next examined Brønsted acid-catalyzed reactions. DFT optimization of protonated dihydrate **4-H**⁺ resulted in the elimination of water to yield protonated monohydrate **3-H**⁺,⁵ suggesting that dihydrate **4** is unstable under acidic conditions (Scheme 2). We thus focused on the 1,2-hydride shift reaction

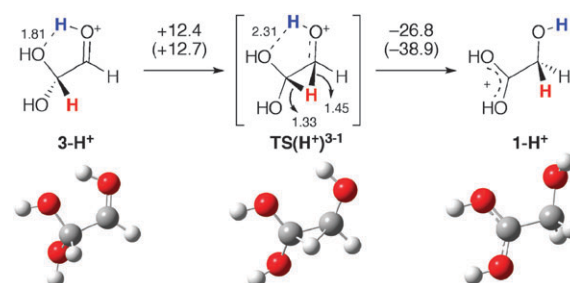


Scheme 2 Geometry optimization of protonated dihydrate **4-H**⁺.

of **3-H**⁺ and found that protonation of the carbonyl oxygen of **3** has a significant positive effect and the ΔE^\ddagger for **TS**(H⁺)³⁻¹ ($\Delta E^\ddagger = 12.4$ kcal mol⁻¹) is 25.9 kcal mol⁻¹ lower than that for **TS**³⁻¹ (Scheme 3). The moderate effects of the Brønsted acid catalyst (Table 1, entry 2) is attributed to the fact that the product **1** (p*K*_a 3.83) can act as a Brønsted acid catalyst and the addition of an external Brønsted acid would affect the reaction rate only in the initial stage.

In the case of the Al(OH)₃-catalyzed reaction (Table 1, entry 3), we located transition structures for the 1,2-hydride shift reaction of different activation modes including Al-glycolate complexes **Al-1** because product **1** is a strong chelating ligand for the Lewis acid (Fig. 1, left side). It is noteworthy that 7-membered dual Lewis acid-hydrogen bonding activation, **TS**(Al(OH)₃-cyclic)³⁻¹ and **TS**(Al-1-OH)³⁻¹, is more favorable than the previously proposed^{6a-c} 5-membered metal-alkoxide chelate activation, **TS**(Al(OH)₂)³⁻¹ and **TS**(Al-1)³⁻¹, respectively. Activation of the carbonyl electrophile by the Lewis acidic Al(III) ion, together with activation of the 1,1-diol unit by a Brønsted basic Al-OH moiety through a hydrogen bond constitutes the basis of the catalytic activity of Al(OH)₃ and **Al-1-OH**. In water, however, those Al-catalyzed pathways are energetically less favorable than the Brønsted acid-catalyzed pathway via **TS**(H⁺)³⁻¹.

Because the aqueous reaction mixture gradually changes from neutral to acidic, based on the formation of acidic product **1**, the effect of a Brønsted acid on the Al-catalyzed reactions was examined. For each transition structure of the Al-catalyzed reaction, we evaluated different protonation patterns and each of the energetically lowest-lying transition states are shown on the right side of Fig. 1. In all cases, protonation greatly decreased the relative energies of the **3-Al-H**⁺ complexes, transition states **TS**(Al-H⁺)³⁻¹, and **1-Al-H**⁺ complexes. The cyclic transition state, **TS**(Al(OH)₃-H⁺-cyclic)³⁻¹, activated by Al(OH)₃ and H⁺, is the most stable transition structure in the gas phase ($\Delta E^\ddagger = 11.1$ kcal mol⁻¹) and in water ($\Delta E^\ddagger = 10.4$ kcal mol⁻¹), which is 2.3 kcal mol⁻¹ lower than ΔE^\ddagger of **TS**(H⁺)³⁻¹ in water. Compared with the neutral transition state **TS**(Al(OH)₃-cyclic)³⁻¹, protonation of Al(OH)₃ increases Lewis acid activation and decreases Brønsted base activation. According to the transition state energies in water,



Scheme 3 Possible reaction pathway of Brønsted acid catalysis.

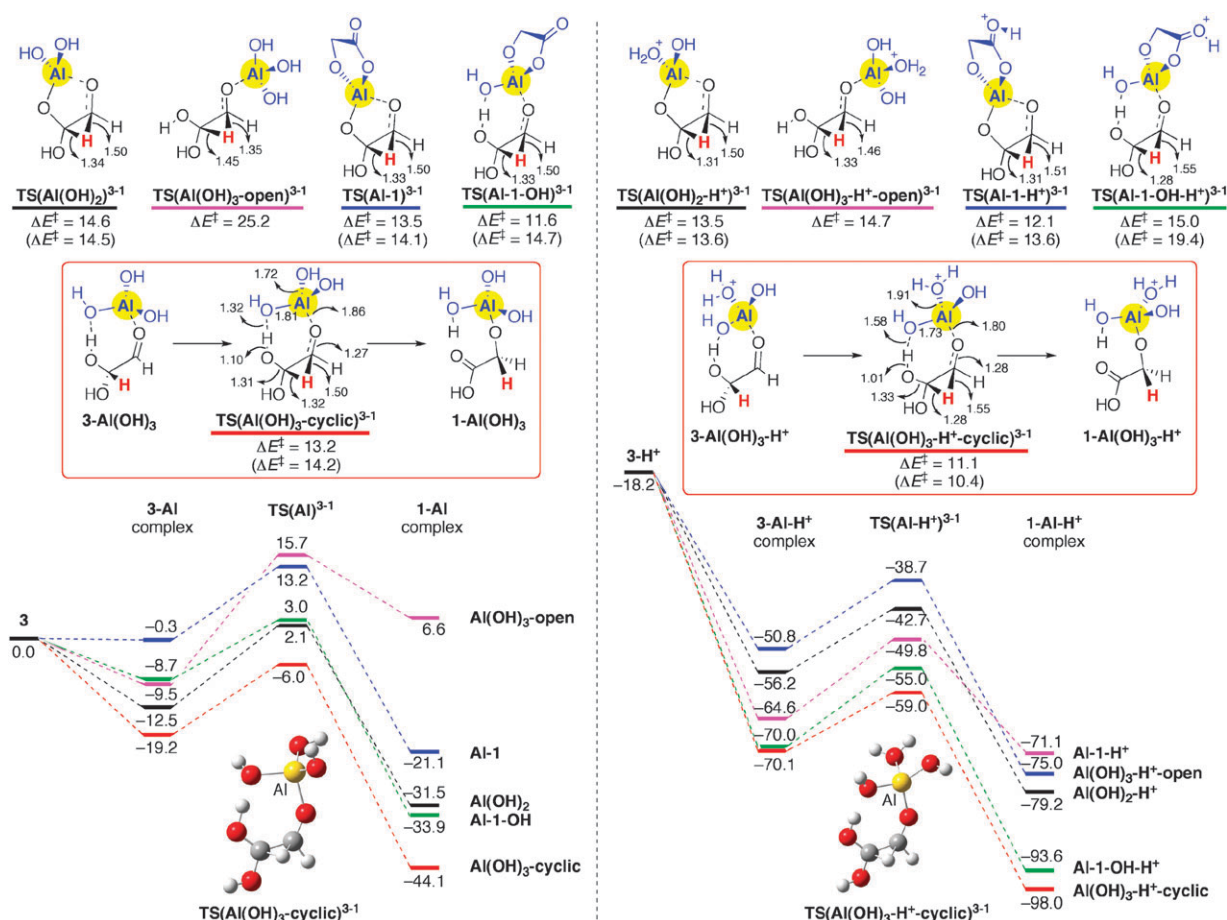


Fig. 1 Transition states, possible reaction pathway, and energy profile of Al(III) catalysis (left) and Al(III)-H⁺ catalysis (right).

experimental results, solubility of Al(OH)₃,¹² and acidic reaction conditions, the 1,2-hydride shift mechanism via TS(Al(OH)₃-H⁺-cyclic)³⁻¹ is likely to prevail.

Finally, we examined the metal effects on the 1,2-hydride shift mechanism by changing the Al(III) ion of TS(Al(OH)₃-H⁺-cyclic)³⁻¹ to other group 13 metal ions.⁵ On the basis of the B3LYP-calculated activation barriers, the Ga(III) ion is slightly less effective ($\Delta E^\ddagger = 13.5$ kcal mol⁻¹) and the B(III) ion is much less effective ($\Delta E^\ddagger = 24.8$ kcal mol⁻¹) than the Al(III) ion ($\Delta E^\ddagger = 11.1$ kcal mol⁻¹), consistent with the experimental observations.

In conclusion, we propose a new mechanism of Lewis acid-catalyzed direct conversion of glyoxal (2) to glycolic acid (1), namely, an intramolecular 1,2-hydride shift reaction of monohydrate 3 to 1 via dual activation by a protonated Al(OH)₃ species. The overall mechanistic study suggests that the reaction via TS(Al(OH)₃-H⁺-cyclic)³⁻¹ ($\Delta E^\ddagger = 10.4$ kcal mol⁻¹ in water) is the most favorable pathway. Moreover, the present mechanistic framework is useful for evaluating the reactions catalyzed by other group 13 metal complexes. These results provide a novel perspective towards finding a new efficient catalyst for various metal-catalyzed 1,2-hydride shift reactions, including enantioselective variants.

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