

Article

Mechanistic Investigations of the Synthesis of Lactic Acid from Glycerol Catalyzed by an Iridium–NHC Complex

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Abstract: In the present work, the reaction pathways and the origin of catalytic activity for the production of lactic acid from glycerol catalyzed by an iridium–heterocyclic carbene (Iridium–NHC) complex at 383.15 K were investigated by DFT study at the M06-D3/6-311++G (d, p) // SDD level. Compared to the noncatalytic reaction pathway, the energy barrier sharply decreased from 75.2 kcal mol^{−1} to 16.8 kcal mol^{−1} with the introduction of the iridium–NHC complex. The catalytic reaction pathway catalyzed by the iridium–NHC complex with a coordinated hydroxide included two stages: the dehydrogenation of glycerol to 2,3-dihydroxypropanal, and the subsequent isomerization to lactic acid. Two reaction pathways, including dehydrogenation in terminal and that in C2–H, were studied. It was found that the formation of dihydroxyacetone from the H-removal in C2–H was more favorable, which might have been due to the lower energy of LUMO, whereas dihydroxyacetone could be easily transferred to 2,3-dihydroxypropanal. The analyses of electrostatic potential (ESP), hardness, and *f* Fukui function also confirmed that the iridium–NHC complex acted as a hydrogen anion receptor and nucleophilic reaction center to highly promote the conversion of glycerol to lactic acid.

Keywords: iridium–NHC complex; glycerol conversion; lactic acid; DFT study; reaction mechanism



Citation: Chen, S.; Xu, S.; Ge, C.; Hu, C. Mechanistic Investigations of the Synthesis of Lactic Acid from Glycerol Catalyzed by an Iridium–NHC Complex. *Processes* **2022**, *10*, 626. <https://doi.org/10.3390/pr10040626>

Academic Editor: Alok Kumar Patel

Received: 8 March 2022

Accepted: 21 March 2022

Published: 23 March 2022

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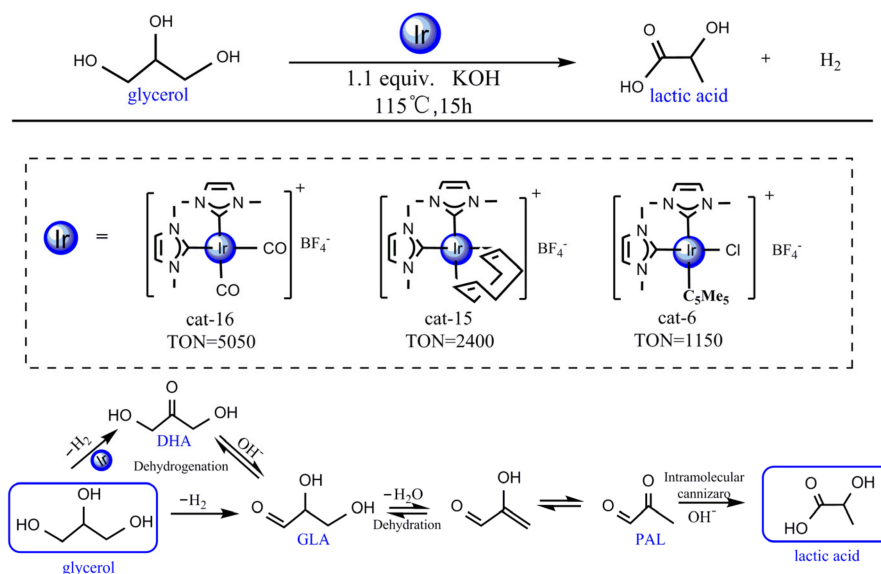


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1. Introduction

The multiutilization of biomass as a renewable resource has attracted much attention in green and sustainable chemistry [1–3]. With the increase in biodiesel production [4–7], glycerol, as the main byproduct with enormous quantities, has also received much attention [8,9]. The rational conversion of glycerol [10–12] provides new ideas for the development of the biodiesel industry. As one of the biomass-based resources, glycerol could be converted to several value-added chemicals [13], such as propanediols [14–16], acrolein [17–19], dihydroxyacetone (DHA) [20–22], glycerol carbonate [23–25], and lactic acid [26–30]. Among these, lactic acid, as a promising platform chemical [31,32], can be used to synthesize green solvents and a variety of poly lactic acid (PLA) [33,34]. Lactic acid is mainly produced by sugar fermentation [35], but this method has several drawbacks, such as a low yield and a complex purification process, as well as the generation of a large amount of waste. Chemoselective methods to produce lactic acid could offer advantages. Tao and coworkers employed M salts of PMo₁₂O₄₀^{3−} (M = K⁺, Zn²⁺, Cu²⁺, Al³⁺, Cr³⁺, and Fe³⁺) to catalyze the selective aerobic oxidation of glycerol to lactic acid, and a high yield of 88% was obtained [30]; they developed further a polyoxometalate-based microfluidic device to promote the process, and a very high TOF of 20,000 h^{−1} was achieved [36]. An iridium–NHC complex performed well in dehydrogenation [37]. An iridium–NHC [38–40] complex with high activity was synthesized by Liam S. Sharninghausen et al., and was successfully used to catalyze the direct dehydrogenation of glycerol to lactic acid with high conversion (>95%) and selectivity (≥95%) without a hydrogen acceptor [41]. The optimal reaction conditions were the following: 115 °C, 15 h, and 1.1 equivalents of KOH in the

presence of a certain amount of bis-carbonyl iridium complex $[(\text{NHC})_2\text{Ir}(\text{CO})_2]^+\text{BF}_4^-$. Accordingly, a possible reaction mechanism for the title reaction was proposed (see Scheme 1), in which the results of ^1H NMR and in situ NMR confirmed the coordination of the NHC ligands with iridium (+1) [41]. Generally, the conversion of glycerol to lactic acid was considered to pass through the following process: dehydrogenation, dehydration, and hydration. Although the experimental results have provided valuable information for the mechanistic analysis, the specific catalytic performance of the metal iridium–NHC complex is still unclear. Herein, the mechanism and selectivity of the title catalytic reaction were investigated in detail by DFT calculations (see Scheme 1) [42,43].



Scheme 1. Title reaction and the catalytic reaction mechanism proposed in the experiment [41].

2. Computational Details and Models

All computations were performed using the Gaussian 09 program [44]. The structures of all the stationary points involved in this study were optimized using the M06 [45] density functional with the SDD basis set [46] for iridium atoms and the 6-311++G** (d, p) basis set [47,48] for all other atoms. Dispersion corrections using the Grimme's D3 [49,50] method was carried out in geometry optimization. Accordingly, the theoretical level was denoted as M06-D3/6-311++G**// (d, p) // SDD. Frequency calculations were performed at the same level with the temperature set at 383.15 K, identical to the experimental temperature [41]. Analyzing the vibrational frequency helped to ensure that each transition state had only one imaginary frequency, while others had none. The intrinsic reaction coordinate calculations at the same level were performed to make sure that each transition state connected to the expected reactants and products on the potential energy surface. Energy surface potential (ESP) [51] analyses were carried out using GaussView (version 6.0). Nucleophilicity [52] and hardness [53] were calculated by using Multiwfn [54] (version 3.6) software. The graphs of Fukui function (f^-) [55] and LUMO orbitals [56] were plotted with Multiwfn and rendered by VMD [57]. According to the experimental results [41], we assumed that the hydroxide acted as a proton acceptor and metal iridium center acted as a hydrogen anion acceptor. We studied the reaction mechanism with or without a catalyst in detail, and attempted to find explanations for the selectivity of the experiment at the molecular level. The computational conditions were consistent with the experimental conditions, which were the following: 115 °C, 15 h, and 1.1 equivalents of KOH in the presence of a certain amount of bis-carbonyl iridium complex $[(\text{NHC})_2\text{Ir}(\text{CO})_2]^+\text{BF}_4^-$ [41]. In order to describe the reaction mechanisms clearly, all structures were plotted without the anion of BF_4^- .

3. Results and Discussion

3.1. Reaction Mechanism

3.1.1. The Background Reaction of Glycerol to 2,3-Dihydroxypropanal

The background reaction of the glycerol conversion to 2,3-dihydroxypropanal was firstly studied, which included two possible pathways (see Figure 1). The first was the dehydrogenation of terminal carbon in glycerol to form 2,3-dihydroxypropanal, the energy barrier of which was $79.9 \text{ kcal mol}^{-1}$. The other was the dehydrogenation of C2-H to form dihydroxyacetone, and then subsequently isomerizing to 2,3-dihydroxypropanal. The energy barrier was $75.2 \text{ kcal mol}^{-1}$ and $8.2 \text{ kcal mol}^{-1}$, respectively. The results showed that the energy barriers in the two cases were too high without obvious selectivity.

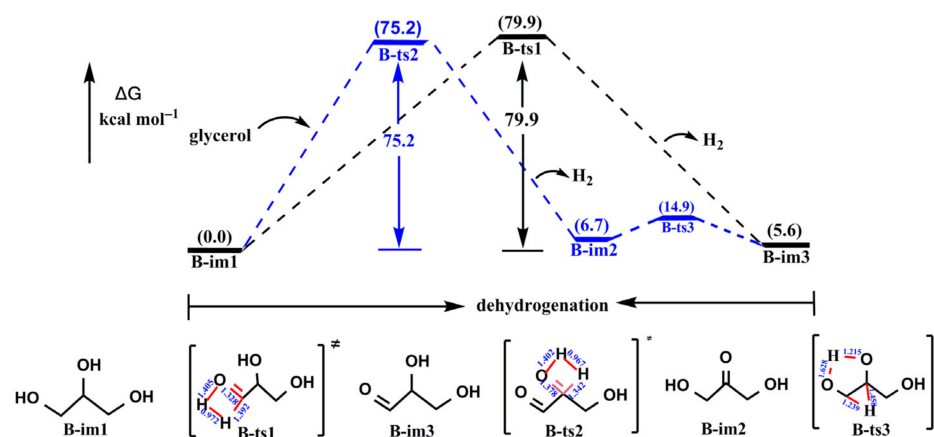


Figure 1. Energy profile for the background reaction of glycerol to 2,3-dihydroxypropanal.

3.1.2. The Dehydrogenation of Glycerol with the Iridium–NHC Complex

The dehydrogenation of glycerol was divided into two steps: hydrogen transfer and hydrogen release (see Figure 2). In the hydrogen-transfer step, both 2,3-dihydroxypropanal and dihydroxyacetone could be formed via two different pathways. For Path a, in the formation of 2,3-dihydroxypropanal, CO of the iridium–NHC complex was firstly substituted by glycerol and hydroxide to form A-im1. A-im1 was converted to A-im2 via the H transfer from C1-H to the metal iridium center and from C1-OH to the coordinated hydroxyl, respectively. It was a synergistic process, the energy barrier of which was $26.6 \text{ kcal mol}^{-1}$. For Path b, in the formation of dihydroxyacetone, H of C1 was transferred to the metal iridium center and H of C1-OH to the coordinated hydroxyl, respectively. The energy barrier of this process (A-ts2) was $16.4 \text{ kcal mol}^{-1}$. The energy barrier for the dihydroxyacetone formation was much lower than that for the 2,3-dihydroxypropanal formation. Therefore, glycerol tended to be dehydrogenated to dihydroxyacetone with a catalyst. Then, dihydroxyacetone was easily converted to 2,3-dihydroxypropanal by isomerization, and the energy barrier was $8.2 \text{ kcal mol}^{-1}$ (see Figure 1).

There were three possible pathways for hydrogen release: glycerol-assisted dehydrogenation, water-assisted dehydrogenation, and direct dehydrogenation. The energy barriers of hydrogen release in the three processes were calculated to be $14.6 \text{ kcal mol}^{-1}$, $9.5 \text{ kcal mol}^{-1}$, and $26.3 \text{ kcal mol}^{-1}$, respectively. Obviously, the energy barrier of water-assisted hydrogen release was lower. Therefore, the hydrogen releasing with water bridge should be the dominant reaction path. Finally, a molecule of hydrogen was released.

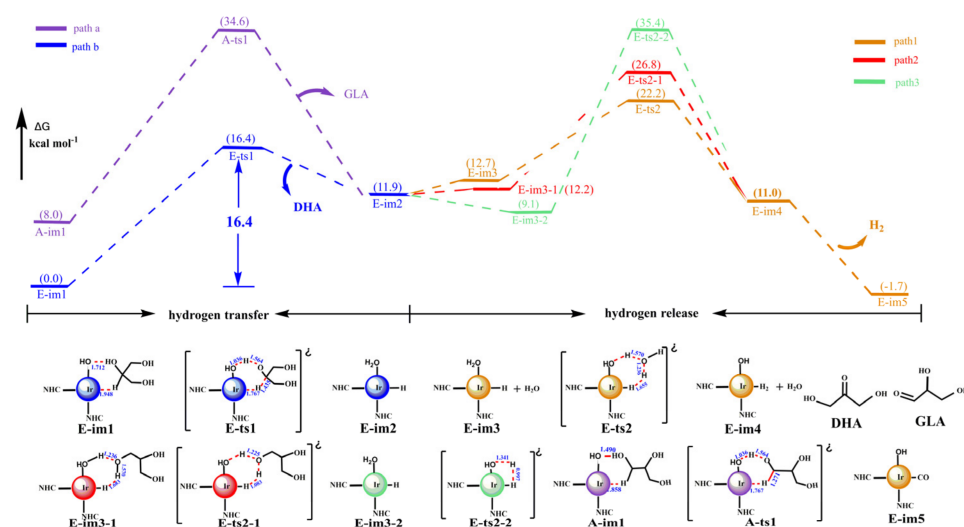


Figure 2. Energy profile for the dehydrogenation reaction of glycerol catalyzed by the iridium–NHC complex (path a: glycerol dehydrogenated to 2,3-dihydroxypropanal; path b: glycerol dehydrogenated to dihydroxyacetone; path 1: water-assisted dehydrogenation; path 2: glycerol-assisted dehydrogenation; path 3: direct dehydrogenation).

3.1.3. The Background Reactions of 2,3-Dihydroxypropanal to Lactic Acid

Firstly, we studied the mechanism of dehydration and hydration reactions without hydroxide and a catalyst (see Figure 3). The dehydration of 2,3-dihydroxypropanal to form C-im2 was a one-step reaction. C-im2 was converted to C-im3 (acetone aldehyde) by water-assisted isomerization. Then, the water attacked the terminal carbonyl group of C-im3 to form C-im4, and through a hydrogen migration process, C-im4 was converted to lactic acid. The energy barrier of the background reaction without hydroxide and a catalyst was 55.0 kcal mol^{−1}. Secondly, we studied the mechanism of dehydration and hydration background reactions with hydroxide but without a catalyst (see Figure 3). Dehydration occurred first, where the hydroxide removed the proton of 2,3-dihydroxypropanal (D-im2) to form D-im3, releasing a molecule of water to form D-im4. D-im4 lost the hydroxide to form D-im5, and with the addition of water, formed D-im6.1. A hydration reaction occurred next, where D-im6.1 was converted to D-im7.1 (acetone aldehyde) by water-assisted isomerization, and with the addition of hydroxyl, formed D-im8. Subsequently, the hydroxide attacked the end carbonyl group of pyruvic aldehyde (D-im8) to form D-im9, and then through a hydrogen migration process, lactic acid (D-im10) was formed. The rate-determining step of the dehydration and hydration reaction was the water-assisted isomerization, and the corresponding energy barrier was 33.5 kcal mol^{−1}. Obviously, the energy barrier of the uncatalyzed reaction with hydroxide was lower than that without hydroxide. This showed the importance of hydroxide in the dehydration and hydration reaction of 2,3-dihydroxypropanal.

Subsequently, we studied the mechanism of dehydration and hydration reactions with the iridium–NHC complex and hydroxide, in view of the fact that the hydroxide could exist in two states: one in coordination with the metal iridium center, and another in the free state. Therefore, we considered two possible catalysis paths.

3.1.4. The Catalytic Reactions of 2,3-Dihydroxypropanal to Lactic Acid

With the free hydroxide: CO of the iridium–NHC complex was substituted by 2,3-dihydroxypropanal to form F-im1 (see Figure 4), and with the hydroxide to form F-im2. The hydroxide removed the α-H of F-im2 to form F-im3, which lost one water molecule to form F-im4. Then, F-im4 lost the hydroxide to form F-im5, completing the dehydration process. The hydroxide ions left to form F-im6. Then, through a hydrogen migration process, F-im6 was converted to acetone aldehyde (F-im7).

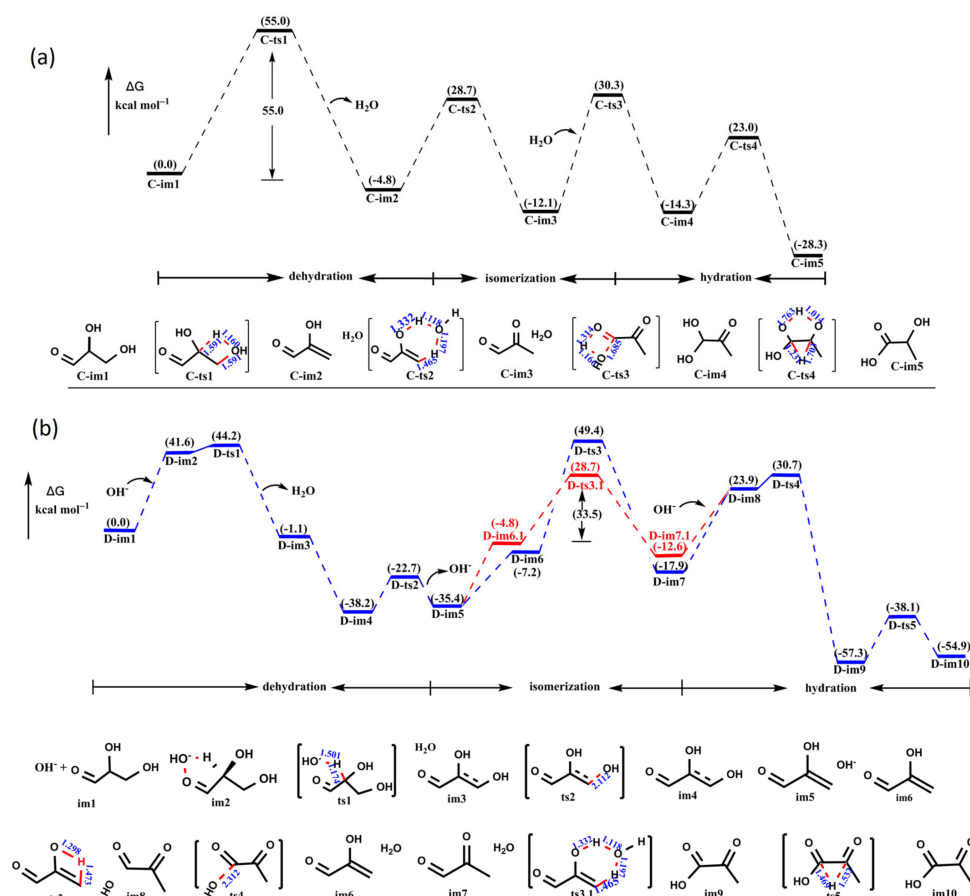


Figure 3. Energy profile for the dehydration and hydration background reaction of 2,3-dihydroxypropanal to lactic acid (path (a): with the addition of the hydroxyl; path (b): without the hydroxyl).

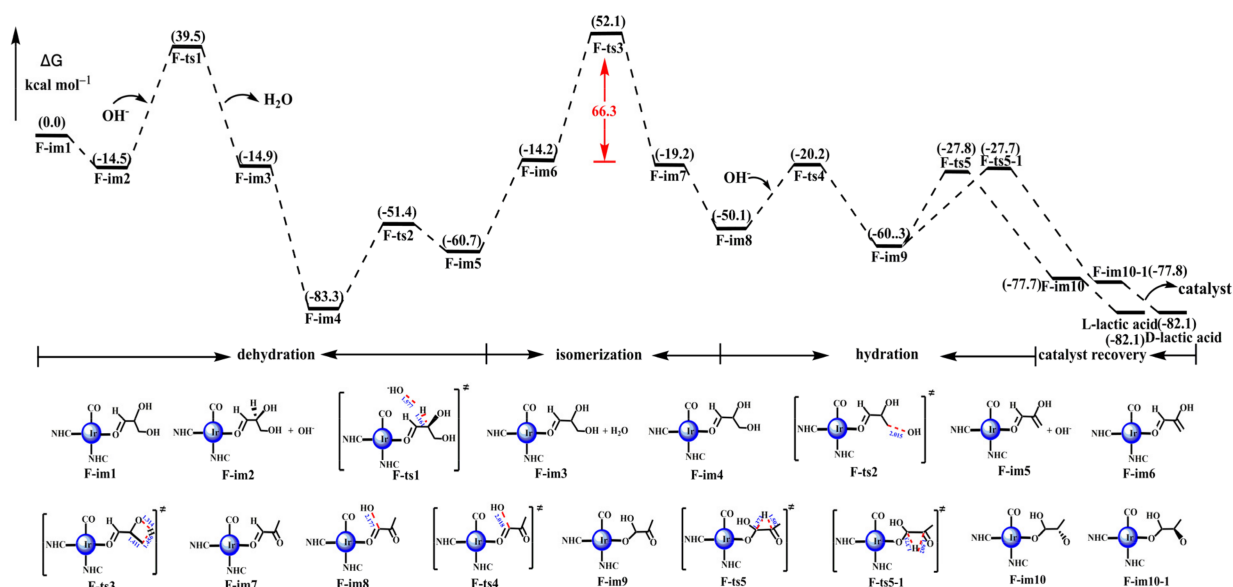


Figure 4. Energy profile for the dehydration and hydration reaction of 2,3-dihydroxypropanal to lactic acid catalyzed by the iridium-NHC with the free hydroxide.

Next, the hydroxide attacked the terminal carbonyl group of pyruvic aldehyde (F-im8) to form F-im9, and then it was converted to lactic acid through a proton-migration process. Finally, a molecule of lactic acid was released, and the iridium-NHC catalyst was reformed.

The rate-determining step of the dehydration and hydration reaction catalyzed by the iridium–NHC with the free state of hydroxide was the hydrogen-migration process of F-im6, the energy barrier of which was 66.3 kcal mol^{−1}. With the coordinated hydroxide: 2,3-dihydroxypropanal and hydroxide substituted the CO of the iridium–NHC complex to form G-im1 (see Figure 5). Next, coordinated hydroxide removed the α-H of 2,3-dihydroxypropanal using a six-membered ring to form G-im2. Using a seven-membered ring with the coordinated hydroxide, G-im2 lost the hydroxide to form G-im3, and it lost water to form G-im4. Then, we considered three possible paths: path1, in which the coordinated hydroxide removed the hydroxyl hydrogen of G-im4, and with water-assisted proton transfer, formed G-im7; path 2, in which the primary carbonyl groups coordinated with the metal, and with water-assisted proton transfer, G-im3-1 was converted directly to G-im7; path3, in which the secondary carbonyl groups coordinated with the metal, and G-im3-2 was converted directly to G-im7. The energy barriers of path1, path2, and path3 were 13.9 kcal mol^{−1}, 24.4 kcal mol^{−1}, 42.3 kcal mol^{−1}, respectively. Obviously, path1 was the dominant path.

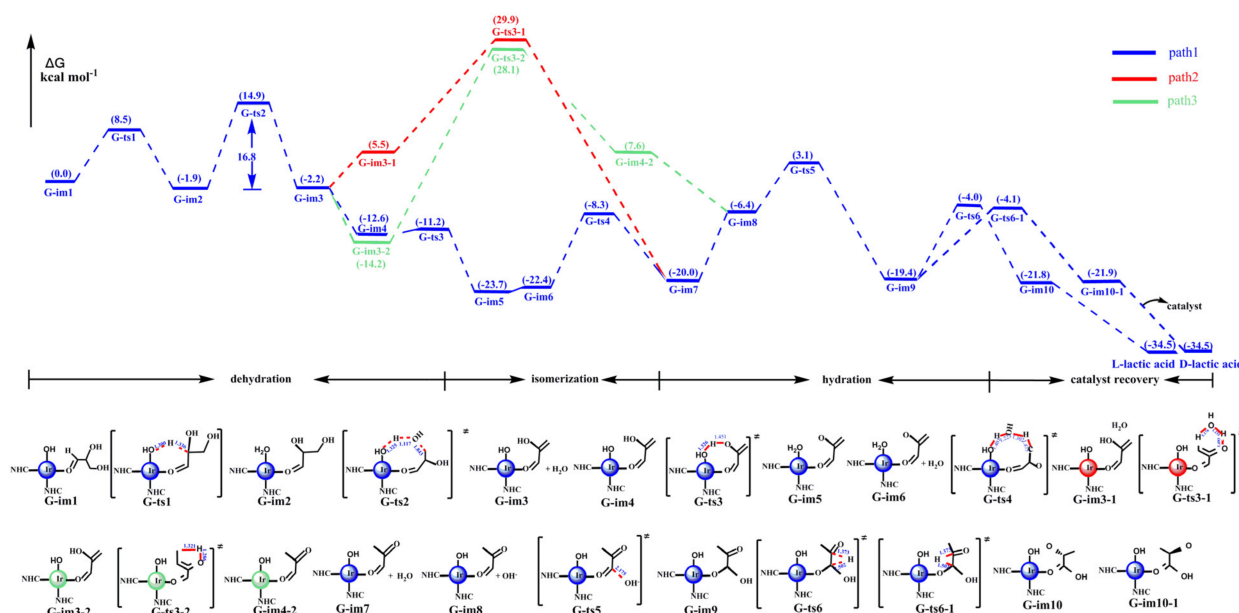


Figure 5. Energy profile for the dehydration and hydration reaction of 2,3-dihydroxypropanal to lactic acid catalyzed by the iridium–NHC with the coordinated hydroxide.

Then, the hydroxide attacked the end carbonyl group of pyruvic aldehyde (G-im8) to form G-im9. Subsequently, through a hydrogen migration process, G-im9 was converted to lactic acid. Finally, a molecule of lactic acid was released, and the catalyst was reformed. The rate-determining step of the dehydration and hydration reaction catalyzed by the iridium–NHC complex with a coordinated hydroxide was the loss of the hydroxyl group of G-im2, and the energy barrier was 16.8 kcal mol^{−1}.

As reported in the literature, lactic acid possessed two enantiomers, and the chiral controlling step was proved to be the 1,2-H-transfer shift in hydrated-PRA [56]. In the present work, we investigated the two competing pathways in the formation of D-/L-lactic acid. As shown in Figure 6, the energy barrier for the D-lactic acid formation was similar to that for L-lactic acid (15.3 kcal mol^{−1} vs. 15.4 kcal mol^{−1}), giving a racemic product in theory, since no chiral catalyst/ligand or chiral inducer existed or formed in the catalysis system. Therefore, we inferred that little enantioselectivity could be obtained in the catalysis of the iridium–NHC complex from glycerol.

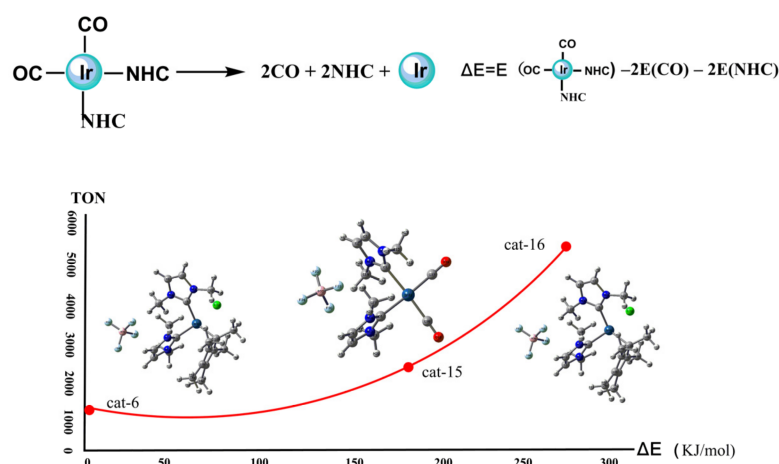


Figure 6. The relationship between binding energy and TONs.

3.2. Deep Insights on the Conversion of Glycerol to Lactic Acid

The title reaction mechanism can be described in detail as follows. With the iridium–NHC complex and coordinated hydroxide, the glycerol was dehydrogenated to dihydroxyacetone, and then it underwent an isomerization to form 2,3-dihydroxypropanal. Subsequently, with the coordinated hydroxide, the iridium–NHC complex catalyzed the dehydration and hydration of 2,3-dihydroxypropanal to form lactic acid. Finally, a molecule of lactic acid and the catalyst were released. We concluded that the loss of the hydroxyl group of G-im2 was the rate-determining step of the entire reaction. Therefore, we also concluded that the hydroxyl ions coordinated with the iridium–NHC complex to form a new catalytic species that played a catalytic role in the dehydrogenation, dehydration, and hydration reaction of the glycerol.

We believe that more detailed discussions about this mechanism could be quite valuable to help gain a deep understanding of the catalytic activity of the iridium–NHC complex. The binding energies of three iridium–NHC complexes (cat-6, cat-15 and cat-16) were firstly calculated. The experiments showed that their catalytic activity was more favorable, as their TONs were 1150, 2400, and 5050, respectively (see Scheme 1) [39]. Comparing the binding energy with TON indicated that the binding energy was positively correlated with TON to some extent (see Figure 6). We speculated that this might be related to the improvement in the stability of the catalyst by increasing the binding energy. Then, the nucleophilicity of the metal iridium center in the three catalysts was analyzed, and the interaction between the catalyst and the substrate increased. The hardness of cat-6, cat-15, and cat-16 was calculated to be 5.1, 6.8, and 7.6, respectively (see Table 1). Compared with the hardness of glycerol, cat-16 was more similar to glycerol, with a hardness of 12.2. Thus, to some degree, cat-16 more readily interacted with the substrate glycerol. As can be seen in the electrostatic potential (ESP) diagram in Figure 7, from cat-6 to cat-15 to cat-16, the positive electrical properties of the metal iridium center gradually increased. In other words, cat-16 was the best receptor of the hydrogen anion. To further verify that the hydrogen anion acceptor was metal iridium instead of the NHC ligand, we conducted a Fukui function analysis (see Figure 8). Figure 8 shows the iso-surface map of its f^- Fukui function and the numeric numerical value of f^- of all atoms, and it can be seen that the metal had the largest value of f^- instead of its NHC ligand. It was confirmed that the binding site of hydrogen anion and catalyst was on the metal center iridium. Therefore, this verified the hypothesis that the metal center was the hydrogen anion receptor. We considered that the dehydrogenation of glycerol was a reduction reaction, as cat-16 acted as an oxidizing agent firstly. In other words, the easier it was for the oxidant to gain electrons, the more oxidation capacity it had. The ability to obtain electrons depended on the character of the LUMO orbital. Therefore, in order to understand why the cat-16 catalyst led to a selective dehydrogenation in the second carbon of glycerol, we analyzed the LUMO orbitals of the intermediates before the dehydrogenation of glycerol. One intermediate (A-im1) was

formed when cat-16 acted on the first carbon of glycerol. Another intermediate (E-im1) was formed when cat-16 acted on the second carbon of glycerol (see Figure 9). Both the two intermediates had α and β LUMO orbitals, named gal- α -LUMO and gal- β -LUMO (glycerol directly to 2,3-dihydroxypropanal), and gly- α -LUMO and gly- β -LUMO (glycerol to dihydroxyacetone). The energies of the gal- α -LUMO, gal- β -LUMO, gly- α -LUMO, and gly- β -LUMO orbitals were -1.89 eV, -3.69 eV, -1.54 eV, and -3.47 eV, respectively. It was obvious that the energy of the orbitals generated by the reaction of glycerol with dihydroxyacetone was lower. This showed that the negatively charged particles more easily approached the metal iridium center.

Table 1. The hardness and nucleophilicity of cat-6, cat-15, and cat-16 (hardness refers to small, highly charged states with low polarizability).

Substance	Nucleophilicity	Hardness/eV
Cat-6 (Ir)	0.27	5.1
Cat-15 (Ir)	0.29	6.8
Cat-16 (Ir)	0.39	7.6
Glycerol		12.2

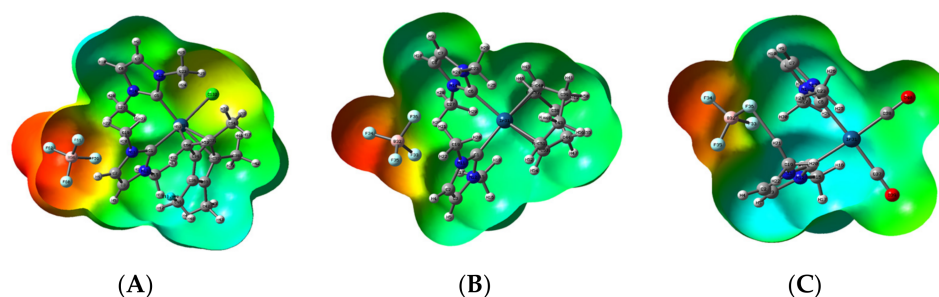


Figure 7. (A) The electrostatic potential (ESP) diagram of cat-6; (B) the ESP diagram of cat-15; (C) the ESP diagram of cat-16.

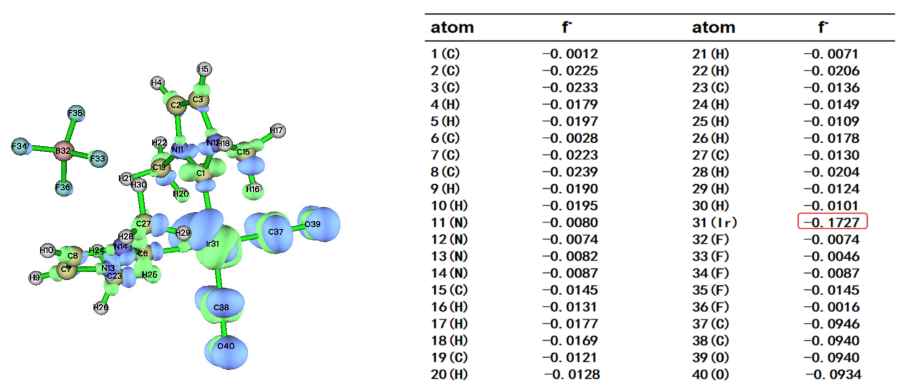


Figure 8. The iso-surface map of the f^- Fukui function is on the left, and the table of the numerical value of f^- of all atoms is on the right. The maximum value is within the red circle.

Therefore, we concluded that the selective dehydrogenation of glycerol with the catalysis of cat-16 was due to the lower LUMO orbital energy, causing the metal center to become more receptive to the hydrogen anions. In the dehydration and hydration reactions, hydroxyl coordinated with iridium-NHC acted as the real catalytic species. The energy barrier of isomerization via the transition states G-ts3 and G-ts4 was especially reduced compared with the background reaction. Therefore, compared with the uncatalyzed reaction, it led to a lower energy barrier.

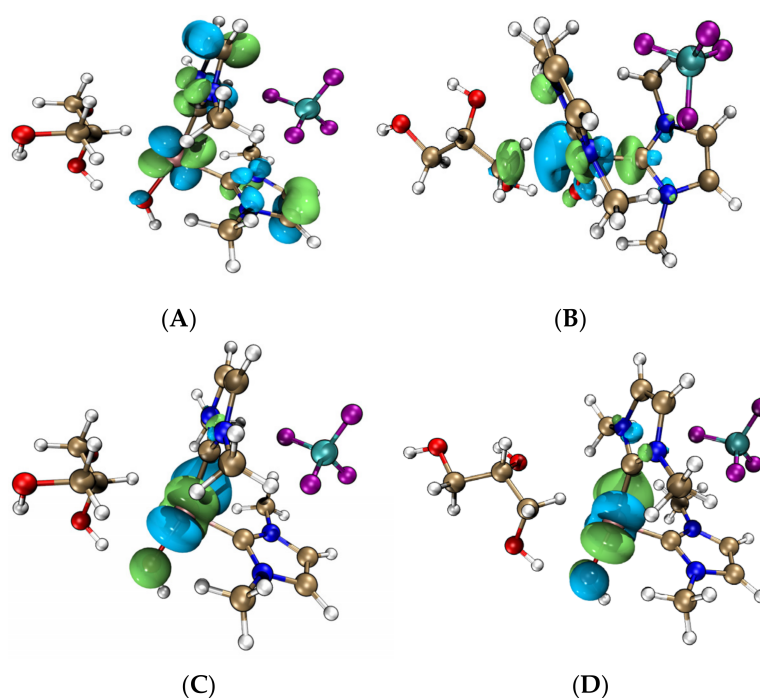


Figure 9. Diagrams of LUMO orbitals: (A) gal- α -LUMO (-1.89 eV); (B) gly- α -LUMO (-1.54 eV); (C) gal- β -LUMO (-3.69 eV); (D) gly- β -LUMO (-3.47 eV).

4. Conclusions

Mechanistic investigations on the preparation of lactic acid from glycerol catalyzed by an iridium–NHC complex were studied in detail using the DFT method. Accordingly, the following conclusions were reached.

- (1) The reaction from glycerol to lactic acid went through dehydrogenation, dehydration, and hydration. In the noncatalytic reaction, the rate-determining step (RDS) was the dehydrogenation of glycerol. In addition, there was no obvious selectivity in the dehydrogenation reaction of glycerol that occurred on the first carbon or second carbon. They both had a high energy barrier (79.9 kcal mol $^{-1}$ and 75.2 kcal mol $^{-1}$, respectively).
- (2) With the catalysis of the iridium–NHC complex, the catalytic effect of cat-16 was performed by the iridium–NHC complex with the coordinated hydroxide. Glycerol was dehydrogenated to produce dihydroxyacetone, which was isomerized to 2,3-dihydroxypropanal. Then, 2,3-dihydroxypropanal was dehydrated and hydrated to produce lactic acid. The rate-determining step (RDS) of the catalytic reaction was the loss of the hydroxyl group of G-im2, and the energy barrier was much lower: 16.8 kcal mol $^{-1}$ compared with 75.2 kcal mol $^{-1}$ (the noncatalytic reaction).
- (3) With the iridium–NHC complex, glycerol would selectively dehydrogenate to dihydroxyacetone with a lower energy barrier (16.8 kcal mol $^{-1}$), and the energy barrier of dehydrogenation to 2,3-dihydroxypropanal was 26.6 kcal mol $^{-1}$. LUMO orbital analysis showed that the orbital energy of dehydrogenation to dihydroxyacetone was lower than that of dehydrogenation to 2,3-dihydroxypropanal. Consequently, the hydrogen anion on the second carbon was more easily pulled out by metal iridium to form hydrogen.
- (4) The analyses of electrostatic potential (ESP), hardness, and f° Fukui function confirmed that the iridium–NHC complex acted as the hydrogen anion receptor and nucleophilic reaction center. The hydroxide performed catalytic effects compared to the noncatalyzed reaction, while the iridium–NHC complex with the coordinated hydroxide formed a new catalytic species that played a catalytic role in the dehydrogenation, dehydration, and hydration reactions of the glycerol.

Author Contributions: Investigation, S.C.; S.X.; C.G.; methodology, S.C.; S.X.; software, S.C.; S.X.; C.G.; computation, S.C.; funding acquisition, C.H.; writing—original draft, S.C.; writing—review & editing, S.C.; C.H.; supervision, S.C.; C.H.; All authors have read and agreed to the published version of the manuscript.

Funding: This work was financially supported by the National Natural Science Foundation of China (No. 21536007), the 111 project (B17030), and the Fundamental Research Funds for the Central Universities.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available within the article.

Conflicts of Interest: The authors declare no conflict of interest.

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