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Review

Recent Progress and Novel Applications in Enzymatic Conversion of Carbon Dioxide

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Academic Editor: Fernando Rubiera González
Received: 4 March 2017; Accepted: 27 March 2017; Published: 3 April 2017

Abstract: Turning carbon dioxide (CO_2) into fuels and chemicals using chemical, photochemical, electrochemical, and enzymatic methods could be used to recycle large quantities of carbon. The enzymatic method, which is inspired by cellular CO_2 metabolism, has attracted considerable attention for efficient CO_2 conversion due to improved selectivity and yields under mild reaction conditions. In this review, the research progress of green and potent enzymatic conversion of CO_2 into useful fuels and chemicals was discussed. Furthermore, applications of the enzymatic conversion of CO_2 to assist in CO_2 capture and sequestration were highlighted. A summary including the industrial applications, barriers, and some perspectives on the research and development of the enzymatic approach to convert CO_2 were introduced.

Keywords: carbon dioxide (CO_2); enzymatic conversion of CO_2; CO_2 utilization; CO_2 capture; CO_2 sequestration

1. Introduction

Global warming and climate change, referring to increased average global temperatures, have inspired a global effort to reduce the amount of atmospheric carbon dioxide (CO_2). Many approaches have been considered and adopted for reducing CO_2 emissions, including enhancing energy efficiency and promoting energy conservation; increasing the usage of low carbon fuels, including natural gas, hydrogen, or nuclear power; deploying renewable energy sources such as solar, wind, hydropower, and bioenergy; applying geoengineering approaches such as afforestation and reforestation; CO_2 capture and storage (CCS); and converting CO_2 into fuels and chemicals [1]. Among these approaches, turning CO_2 into fuels and chemicals offers a win–win strategy to both decrease atmospheric CO_2 and efficiently exploit carbon resources [2].

From fundamental research to industrial applications, the efficient transformation of CO_2 has attracted growing international interest. The concept behind the CO_2 conversion to chemicals and fuels is attractive: the direct energy supply via combustion of carbonaceous energy carriers produces CO_2, which could be converted back into the energy carrier, thereby resulting to an artificial carbon cycle that recycles CO_2 and balances anthropogenic emissions [3,4]. To catalyze CO_2 conversion, chemical, photochemical, electrochemical, and enzymatic methods have been employed. In the first three methods, high operating temperature and pressure or additional electric or luminous energy are

required, and some selectivity and yield issues accompany these methods [5]. Meanwhile, occurring under mild reaction conditions with high yields and selectivity and without any side effect on the environment, the enzymatic conversion of CO_2 has comparative benefits [5–7].

Interestingly, the enzymatic conversion of CO_2 can be applied not only for efficient CO_2 utilization [7], but also for assisting CO_2 capture [8], the process of capturing waste CO_2 from fossil fuel power plant flue gas using absorption or membrane technologies, and CO_2 sequestration [9], the capture and long-term storage of atmospheric CO_2. Although these promising concepts have been applied in industry, their application is still in the interim period between the research stage and the application stage, in addition to other barriers. Thus, in this paper, we review recent developments in the enzymatic conversion of CO_2 in vitro, which mimics cellular CO_2 metabolic processes. Applications of the enzymatic conversion of CO_2 to assist CO_2 capture and sequestration are highlighted. Industrial applications, barriers, and some perspectives on the research and development of the enzymatic conversion of CO_2 are also discussed.

2. Natural Conversion of CO_2 in Cells

The fixation of inorganic carbon into organic material (chemoautotrophy) is a prerequisite for life and represents the starting point of biological evolution [10]. Biological fixation, an essential factor in controlling atmospheric CO_2 concentrations, can occur through six major pathways including the Calvin–Benson–Bassham cycle, the reductive citric acid cycle, the reductive acetyl-CoA pathway, the 3-hydroxypropionate/malyl-CoA cycle, the 3-hydroxypropionate/4-hydroxybutyrate cycle, and the dicarboxylate/4-hydroxybutyrate cycle [11]. They impact substantially to the global carbon cycle, in which enzymes play crucial roles in catalyzing the CO_2 fixation [12]. Beside, a large number of enzymes, such as decarboxylase enzymes in carboxylation reactions derived from catabolic pathways, utilize CO_2 or HCO_3^- as a reaction substrate and do not belong to chemoautotrophic pathways [2,12,13].

Generally, such CO_2 transformation processes are coupled with oxidation processes that generate reducing equivalents, sometimes conjunctive with the hydrolysis of phosphoanhydride bonds [12,14–16]. Adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide hydride (NADH) or their equivalents are required in all known natural CO_2 conversion pathways [12,15]. Various pathways for the conversion of CO_2 associated to the dependence of chemoautotrophic organisms on CO_2 have been developed (Figure 1) [10,12]. These enzymatic conversions of CO_2 and carboxylation reactions derived from catabolic pathways are considered fundamental to science and have inspired in vitro studies and industrial applications.

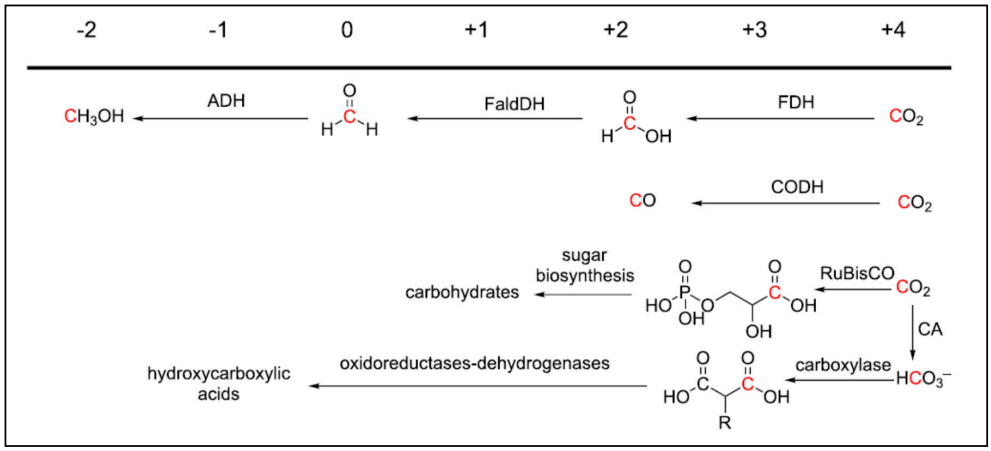


Figure 1. Biocatalytic routes for the conversion of CO_2 into compounds with carbon in the reduced oxidation states indicated at the top. FDH: formate dehydrogenase, FaldDH: formaldehyde dehydrogenase, ADH: alcohol dehydrogenase, CODH: carbon monoxide dehydrogenase, RuBisCO: ribulose-1,5-bisphosphate carboxylase oxygenase, CA: carbonic anhydrase, R: H, CH_3 [12].

3. Enzymatic Conversion of CO_2 In Vitro

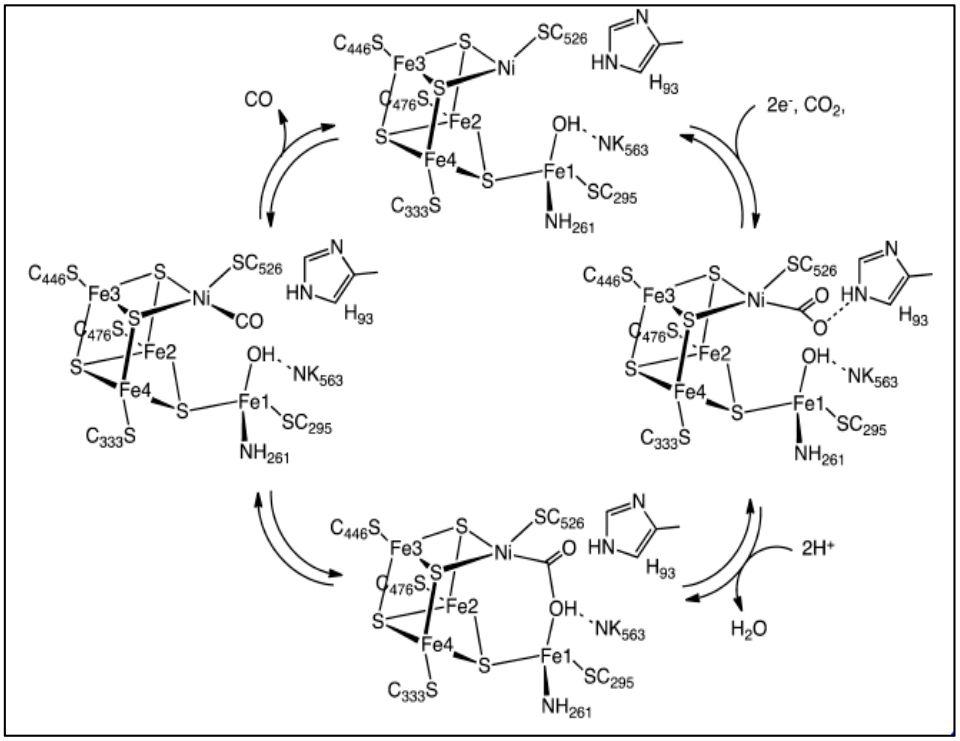
A tremendous amount of effort has been dedicated to constructing CO_2 conversion systems in vitro inspired by cellular CO_2 metabolic processes. These processes can consist of a single enzyme, using oxidoreductases or lyases, or of multiple enzymes such as multiple dehydrogenases in methanol production.

3.1. Reduction Reactions

3.1.1. Conversion of CO_2 to Carbon Monoxide

Converting CO_2 to carbon monoxide (CO), the feedstock for various synthetic processes, through the production of hydrocarbons (Fischer-Tropsch process), acetic acid (Monsanto and Cativa processes), and methanol catalyzed by carbon monoxide dehydrogenases (CODHs) has received much attention [17–19]. There are two types of CODHs including the O_2-sensitive enzymes from obligate anaerobes containing [Fe_4S_4Ni] and air-stable enzymes with [MoSCu] active sites [20]. The [NiFe] CODHs result turnover frequencies for CO oxidation as high as 40,000 s^{-1} and 45 s^{-1} for CO_2 reduction, while the [MoCu] CODHs do not catalyze the reduction of CO_2 to CO [19,20]. The conversion of CO_2 to CO is accomplished using [NiFe] CO dehydrogenases with the proposed mechanism presented in Scheme 1 [20].

Shin et al. (2003) [21] first found that CODH is a suitable catalyst for electrochemical CO2 reduction, exhibiting almost no overpotential. Woolerton et al. [17,22] discovered an innovative efficient technique that combines photocatalysis efficiently and cleanly in the enzymatic conversion of CO_2 to CO. Figure 2 shows the hybrid system comprising metal oxide nanoparticles functionalized with the enzyme CODH, and sensitized to visible light using a ruthenium bipyridyl photosensitizer [22]. Of the semiconductor materials that they investigated, photocatalysts prepared with Evonik Degussa P25 TiO_2 (a commercially available 3:1 mixture of anatase/rutile) and ordinary anatase TiO_2 nanoparticles were found to be the most effective, in terms of overall turnover rate.



Scheme 1. Proposed mechanism for the reduction of CO_2 to CO by [NiFe] CODH [20].

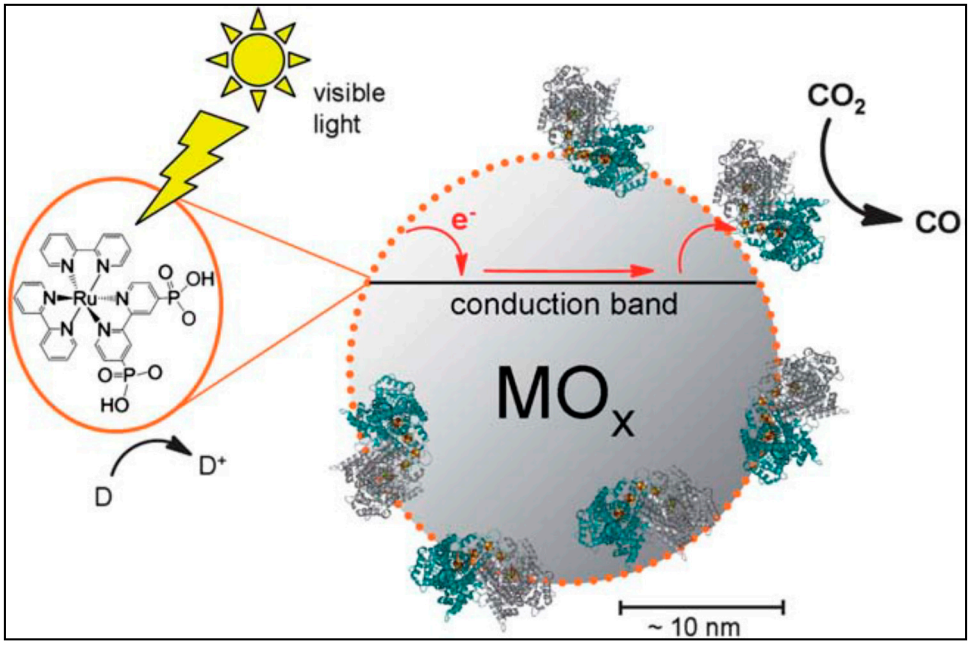


Figure 2. Cartoon representation of CO_2 reduction at an enzyme-modified metal oxide nanoparticle, sensitized with a ruthenium dye. D represents a sacrificial electron donor, used to regenerate the dye following photoinjection into MO_x. Dimensions of each species are approximately to scale for when MO_x is a Degussa P25 anatase TiO_2 nanoparticle [22].

More recently, Bachmeier et al. [23] demonstrated that semiconducting electrodes can be used to impose directionality on reversible catalysts operating in the region of the flatband potential. Although these enzymes are unsuited for long-term, large-scale systems, their results provide valuable insight for developing integrated artificial systems (based ultimately on abundant chemical catalysts) [23].

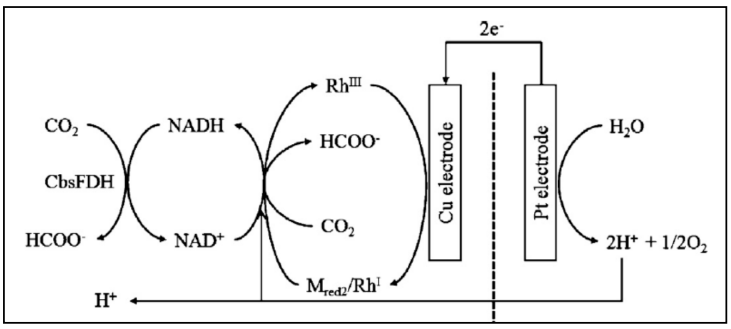
3.1.2. Conversion of CO_2 to Formic Acid/Formate

Formic acid/formate, which can be used for silage preservation, animal feed additives, textile finishing, and chemical intermediates [24], as one of the most promising candidate fuels for low-temperature fuel cells [25], and in paper and pulp production, is one of main products from the enzymatic conversion of CO_2 [26]. The formate oxidation to CO_2 occurs with the concomitant NAD^+ reduction to NADH catalyzed by formate dehydrogenase (FDH or $F_{ate}DH$) [27]. Interestingly, the reverse reaction, the reduction of CO_2 to formate, can be catalyzed by the same enzyme [28,29]. FDH from *Pseudomonas oxalaticus* has been used to reduce CO_2 into formate using oxidized methyl viologen as an electron relay [30]. The tungsten-containing FDH from *Syntrophobacter fumaroxidans*, known to be the most active catalyst for the reaction so far, has also been used to reduce CO_2 to formate [31].

To generate NADH, novel graphene-based visible light active photocatalyst which covalently bonded the chromophore, such as multianthraquinone substituted porphyrin with the chemically converted graphene as a photocatalyst of the artificial photosynthesis system was reported [32]. The rhodium complex shuttles as an electron mediator between the graphene photocatalyst and NAD^+, proving to be an efficient factor for regeneration of the NADH cofactor. Recently, a photocatalyst–biocatalyst coupled system developed using graphene-based visible light active photocatalyst in a highly efficient manner, leading to high NADH regeneration (54.02% $\pm$ 0.61%), followed by its consumption in exclusive formic acid production (144.2 $\pm$ 1.8 μmol) from CO_2 [33].

Because the NADH-independent FDH enzymes are highly unstable and inactive in the presence of O_2, Kim et al. [34] focused on the NADH-dependent FDH from *Candida boidinii* (CbsFDH), which was sufficiently stable for commercial use, and found that almost 100% selectivity can be achieved for

formate formation from CO_2 in recent study (as shown in Scheme 2). The reaction rate can be increased only within the optimized reaction conditions of electrochemical NADH regeneration. Therefore, a robust new FDH that operates in high NADH and enzyme concentrations should be identified or developed for an electroenzymatic method to convert CO_2 into formate on a preparative scale.



Scheme 2. Schematic diagram of electroenzymatic CO_2 reduction using CbsFDH [34].

3.1.3. Conversion of CO_2 to Methanol

Methanol, a fuel and key starting material for many important industrial applications, can be produced from CO_2 reduction. Obert and Dave [7] reported an enzymatically coupled sequential reduction of carbon dioxide to methanol using three different dehydrogenases including FDH, formaldehyde dehydrogenase ($F_{ald}DH$), and alcohol dehydrogenase (ADH). The overall reaction process, in which terminal electron donor in each dehydrogenase-catalyzed reduction is reduced NADH, is shown in Figure 3 [35].

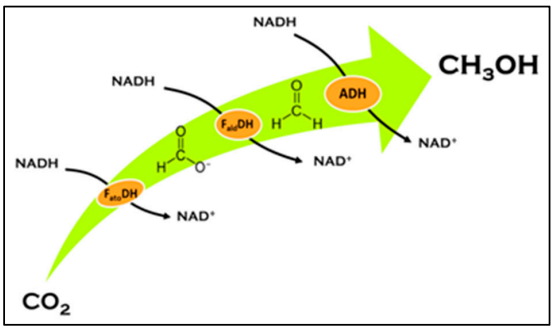
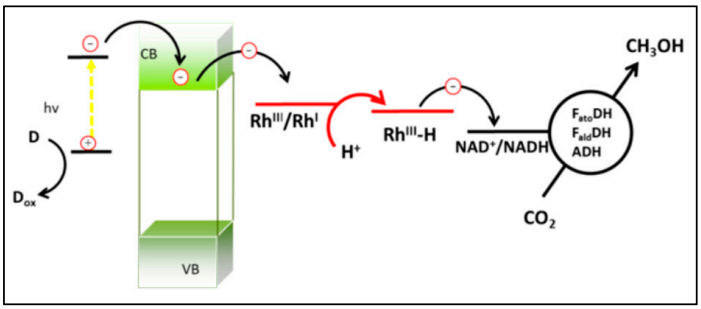


Figure 3. CO_2 reduction to methanol in water promoted by $F_{ate}DH$, $F_{ald}DH$, and ADH where three consecutive $2e^-$ steps are involved [35].

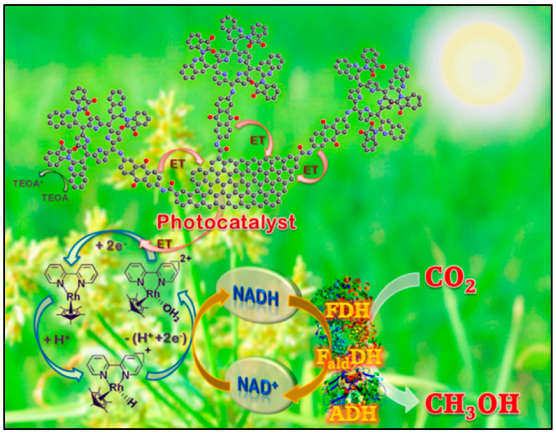
However, this process still has several problems such as cosolvents and catalysts are in the sol-gel process due to low water solubility and reactivity of the silica precursor, and the alcohol liberated from hydrolysis, cosolvents, and catalysts are deleterious to bioactivity [36]. To overcome these problems, several modifications to the sol-gel technique were proposed to improve the stability of the biological activity [36–40]. The dehydrogenases encapsulated in the alginate-silicate composite showed high initial enzyme activity retention, and significantly improved stability during storage and reuse [36]. These enzymes can be also immobilized in flat-sheet polymeric membranes simultaneously or separately by simple pressure-driven filtration (i.e., by directing membrane fouling formation), without any addition of organic solvent [41]. As a result, enzyme activity was fully retained by this non-covalent immobilization strategy.

Three moles of NADH is required to produce one mole of CH_3OH from CO_2 (Figure 3), therefore, NADH regeneration is necessary [35]. To provide the possibility for practical application, a hybrid enzymatic/photocatalytic approach for efficient converting CO_2 into methanol was recently

proposed [35]. The proposed approach includes two processes: the enzymatic transformation of CO_2 to methanol promoted by NADH, and the in situ photocatalytic reduction of NAD^+ to generate NADH using semiconductors with the expected mechanism shown in Scheme 3. As a result, 100 to 1000 mol of CH_3OH can be produced from 1 mol NADH, creating the possibility for practical application. More recently, a photocatalyst/biocatalyst integrated system for highly selective methanol production directly from CO_2 was reported [42]. The system was obtained by combining a newly developed graphene-based photocatalyst with sequentially coupled enzymes (FDH, $F_{ald}DH$, and ADH) as depicted in Scheme 4.



Scheme 3. Expected mechanism of NADH regeneration and further dioxide reduction to methanol [35].



Scheme 4. Schematic illustration of the photocatalyst/biocatalyst integrated system for producing methanol from CO_2 [42].

Very recently, direct injection of electrons into immobilized dehydrogenases without any sacrificial co-enzyme delivered for the electrochemical CO_2 reduction to methanol around 0.15 ppm was reported [43]. Faradaic efficiencies of around 10% were obtained. These results show for the first time that all three dehydrogenases can directly be addressed with electrochemistry without requiring any sacrificial mediator or electron donor such as NADH.

Nevertheless, the reported reaction rates and equilibrium yields are generally low and, therefore, are not suited for large-scale CO_2 utilization [44]. For kinetic considerations, there is a need to intensify biocatalysts for faster and more efficient CO_2 conversion. This requires the discovery of new enzymes and the engineering of reaction systems for improved catalytic efficiency.

3.1.4. Conversion of CO_2 to Methane

It was found that the nitrogenase MoFe protein is able to catalyze the CO_2 reduction to methane (CH_4) [45]. In total, 21 nmol of CH_4 can be formed using 1 nmol of this enzyme under optimized conditions within 20 min. The doubly substituted MoFe protein also has the capacity to catalyze the

unprecedented formation of propylene through the reductive coupling of CO_2 and acetylene. Recently, Rebelein et al. [46] observed that vanadium nitrogenase can reduce CO_2 to C_2 hydrocarbons involving C–C coupling.

3.1.5. Conversion of CO_2 to Glucose

A variety of energy-storing carbon compounds can be formed via the photosynthetic carbon reduction cycle using ATP resulting from the light-dependent reactions in conjunction with the carbon-fixing enzyme ribulose-1,5-bisphosphate carboxylase/oxygenase (RuBisCO) [47]. Inspired by this, an in vitro artificial photosynthesis system coupling the requisite enzymes of the Calvin cycle with a nanoscale photophosphorylation system was constructed for converting CO_2 to sugars [48]. In total, 116 nmol of glucose/(mL/h) can be produced with a chemical conversion efficiency approaching 96% using this photosynthetic foam.

3.2. Conversion of CO_2 to Bicarbonate

As another strategy of CO_2 conversion, an enzyme called carbonic anhydrase (CA) can directly convert CO_2 to bicarbonate (HCO_3^-) via catalysis at a high turnover rate, up to 10^6 per second [49,50]:

$$CO_2 + H_2O \rightarrow HCO_3^- + H^+, \quad (1)$$

CA has one of the fastest reaction rates among all enzymes [51]. The CA-mediated catalytic conversion of CO_2 has attracted much research interest and used to assist three techniques including absorption, membrane, and mineralization in CO_2 capture, sequestration, and utilization. CO_2 absorption is slower in solvents, but absorption can be accelerated with CA [52]. In addition, CA has been also shown to allow a lower heat of desorption, thus a far lower energy requirement is feasible for CO_2 capture and sequestration [53].

However, under the rough conditions of these processes such as from 50 to over 125 °C in operating temperature; high organic amine concentrations; and the presence of sulfur, nitrogen oxides and trace contaminants such as heavy metals, the stability and activity of naturally derived CA are poor, which have restricted their use [53]. To overcome these limitations, several approach have been proposed including sourcing CAs from thermophilic organisms, using protein engineering techniques to create thermotolerant enzymes, immobilizing the enzyme (for both stabilization and restriction to cooler process zones), or process modifications such as cooling the flue gas [54,55]. Recently, an innovative potassium carbonate-based absorption process, in which the CA enzyme is immobilized onto a new group of nonporous nanoparticles to improve thermal stability and chemical resistance, has been proposed to improve energy efficiency when capturing CO_2 from coal combustion flue gas (shown in Figure 4) [56]. After 60-day test period at 50 °C, the immobilized enzymes remained 56–88% of their original activity as compared to a 30% activity retention when using free CA enzyme.

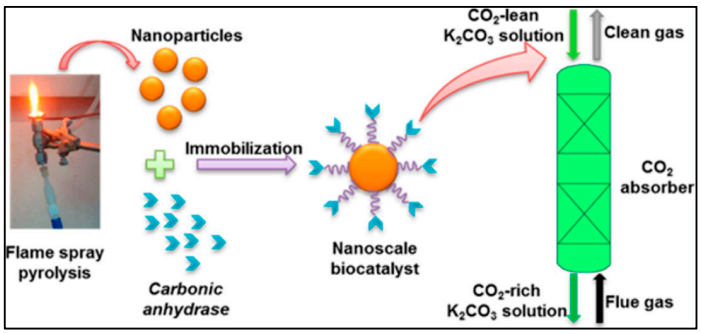


Figure 4. Schematic representation of the CA-catalytic CO_2 conversion process and potassium carbonate-based absorption process [56].

The catalytic conversion of CO_2 by CA has been applied to improve the performance of membranes including enhanced efficiency, speed, and increased specificity [57]. This invention is a process for gas separation wherein carbon dioxide in a mixed gas stream is converted to bicarbonate in the temperature range of 40–85 °C. The consequence is that many outlet gas streams such as flue gases can be used directly without the need for heat exchangers or other costly equipment or processes. The selective separation of CO_2 from mixed gas streams has been developed using a hollow fiber membrane reactor supported by immobilized CA (shown in Figure 5) [58]. This enzyme-based membrane reactor allows CO_2 at low concentrations to be separated from mixed gas streams. However, a variety of major problems including short lifetime, fouling and biofouling, separation of the enzyme from the immobilization surface, have limited the application of these enzymes in industrial settings [57].

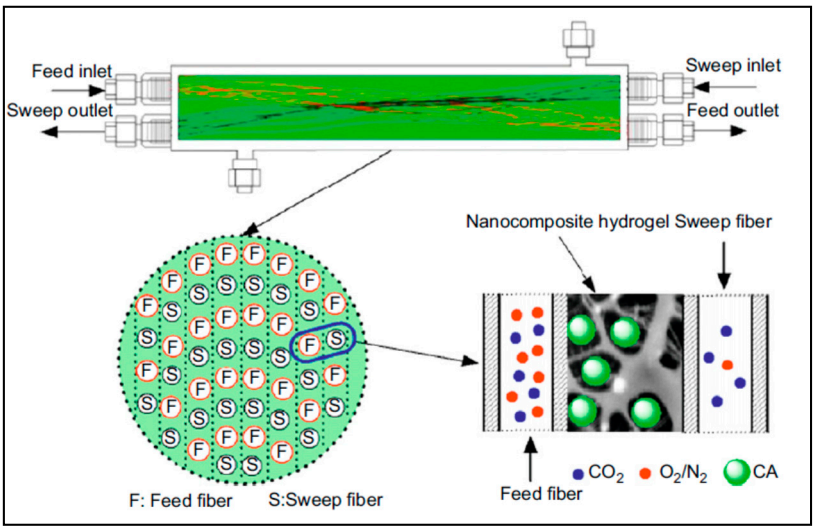


Figure 5. Schematic illustration of a hollow-fiber containing immobilized-enzyme membrane reactor [58].

Current carbon storage research has primarily focused on sequestering CO_2 in underground geologic formations such as saline aquifers, depleted oil and gas fields, and unmineable coal seams [59]. Although these methods have the advantage of being relatively low-cost, sequestration in geologic formations still has several potential issues including permanence, long-term monitoring, and verification, with many unknown effects and potential risks still to be determined [60]. Thus, carbon mineralization, where CO_2 is reacted with metal cations such as calcium to form calcium carbonate ($CaCO_3$), is considered an effective alternative to conventional geologic sequestration [61]. Note that bivalve shell composed of $CaCO_3$ is abundant and stable biomaterials in ocean [62]. This process can be seen in Equations (2)–(6) below:

$$CO_2\ (\text{gaseous}) \rightarrow CO_2\ (\text{aqueous}), \quad (2)$$

$$CO_2\ (\text{aqueous}) + H_2O \rightarrow H_2CO_3, \quad (3)$$

$$H_2CO_3 \rightarrow HCO_3^- + H^+, \quad (4)$$

$$HCO_3^- \rightarrow CO_3^{2-} + H^+, \quad (5)$$

$$Ca^{2+} + CO_3^{2-} \rightarrow CaCO_3, \quad (6)$$

Because these emerging mineralization methods are rapid, environmentally friendly, and cost-effective while offering permanent carbon dioxide disposal, they have rapidly grabbed a great deal of interest [61]. However, in the whole process, H_2CO_3 formation is the rate-limiting step [63]. Thus, CA has recently been utilized to enhance CO_2 sequestration through the conversion and mineralization

of CO_2 into $CaCO_3$ [62]. The converting CO_2 into carbonate compounds by using CA as a catalyst in a biomimetic approach is thermodynamically advantageous compared to other CO_2 storage methods and technologies. Furthermore, the biomimetic CO_2 storage approach does not need a monitoring system for potential leaks as CCS strategies do, and carbonate compounds can be used for building or industrial materials [62,64]. Recently, a new carbonic anhydrase isolated and characterized from the thermophilic bacterium *Sulfurihydrogenibium* sp. YO3AOP1 was reported [65].

Although CA can efficiently accelerate mineralization for CO_2 sequestration, CA recycling can be a barrier. Several efforts have attempted to address this challenge. A recent study reported the strategy of CA-assisted formation of biomineralized calcium carbonate crystalline composites (CCCCs) [66]. The CCCCs produced in this study preserved their catalytic activity even after ten repeated usages, and were stable for more than 50 days at room temperature.

The success of enzymatic CO_2 conversion requires the successful immobilization and stabilization of CA, which enables enzyme recycling and improves the economics of enzymatic conversion and the eventual CO_2 utilization. Various methods for immobilizing CA have been reported. CA immobilization on SBA-15 was explored [67]. Recently, CA has been immobilized on chitosan stabilized iron nanoparticles for the biomimetic carbonation reaction [68]. CA binding to carboxylic acid group-functionalized mesoporous silica (HOOC-FMS) was also investigated [51]. This resulted in a partial conformational change compared to the free enzyme in solution, but can allow increased protein loading density, resulting in higher enzymatic activity and immobilization efficiency. In addition, the use of bioinspired silica supporting CA for carbon capture has been presented [69]. The immobilization route was favorable compared to traditional methods due to its simplicity, mild conditions, low cost, one-step procedure, and short preparation time. More recently, a process for one-pot CO_2 utilization based on the simple conversion of CO_2 to bicarbonate at ambient temperature with no energy input, using the crosslinking-based composites of carboxylated polyaniline nanofibers and CA was developed [49]. The cell concentration with magnetically separable enzyme precipitate coatings was maintained as high as the first cycle after two repeated uses.

Keeping in mind the large-scale application of CA-driven CO_2 sequestration into mineral carbonates, the development of an adequate and economical means of pH control is presently a major research need since $CaCO_3$ is pH sensitive [70]. With the available research on CA-driven processes for CO_2 sequestration, smart efforts are needed with respect to choosing the right material and right CA immobilization technique so that enzyme leakage can be conquered and reusability can be enhanced, which eventually contributes to improved economic feasibility. Furthermore, more efforts are needed to build the fundamentals of mass transfer in CA mediated CO_2 sequestration [71].

3.3. Carboxylation Reactions

Carboxylation is a chemical reaction in which a carboxylic acid group is introduced in a substrate. Several decarboxylase enzymes, which catalyze the decarboxylation processes, exist in cells and also have potential for biocatalytic applications of carboxylation processes, including: (i) carboxylation of epoxides; (ii) carboxylation of aromatics; (iii) carboxylation of hetero-aromatic systems; and (iv) carboxylation of aliphatic substrates [72]. The main target of carboxylation reactions by decarboxylases is to make toxic raw compounds more hydrophilic. Overall, little (or no) energy is required by these reactions [72]. Recently, these decarboxylase enzymes have been utilized in CO_2 utilization as follows.

3.3.1. Carboxylation of Epoxides

A novel enzymatic reaction involving the metabolism of aliphatic epoxides by *Xanthobacter* strain Py2 has been investigated [73]. Cell extracts catalyzed the CO_2-dependent carboxylation of propylene oxide (epoxypropane) to form acetoacetate and beta-hydroxybutyrate, while propylene oxide and 1,2-epoxybutane were isomerized to form acetone and methyl ethyl ketone, respectively, as this process consumes CO_2. However, the potential for in vitro application and practical applicability of this process is low because the responsible enzymes could not be purified [72].

3.3.2. Carboxylation of Aromatics

There are several applications available for the enzymatic carboxylation of aromatics using decarboxylases. These processes can overcome the disadvantages of the Kolbe–Schmitt reaction because of occurring under conditions of high temperature and pressure, but cannot achieve completely mastered selectivity, which requires high energy in purification and produces waste [74,75]. The 4-OH benzoic acid synthesis from phenol and CO_2 at room temperature and sub-atmospheric pressure of CO_2 with 100% selectivity is the first application of a phenol carboxylase enzyme [6]. The use of the entire cell was excluded because the target product is further used by the bacteria as a carbon source. Thus, cells were lysed to obtain the crude extract, which was then purified using a membrane to eliminate most proteins and other cell components that are not involved in the carboxylation reaction. A turnover number of approximately 16,000 can be obtained in this clean process [75].

Recently, a new method was explored for the selective and ecological salicylic acid production by the enzymatic Kolbe–Schmitt reaction (as shown in Figure 6) [76]. In particular, salicylic acid decarboxylase (Sdc) is used for producing salicylic acid from phenol. The yeast *Trichosporon moniliforme* WU-0401 was enzymatically characterized with the Sdc gene heterologously expressed. More recently, Sdc enzyme has also been applied to convert m-aminophenol to p-aminosalicylic acid with a conversion yield of 70% (mol/mol) [77].

Similarly, 1,2-dihydroxybenzene (catechol) can be carboxylated to 3,4-dihydroxybenzoic acid using 3,4-dihydroxybenzoate decarboxylase in *Enterobacter cloacae* P241 with a conversion of 28% after 14 h at 30 °C [78]. Although the enzyme was completely regioselective for its "natural" substrate, it was also able to convert phenol, 1,2-dihydroxybenzene, and m-aminophenol at very low rates, while consuming considerable amount of CO_2 [74,79,80].

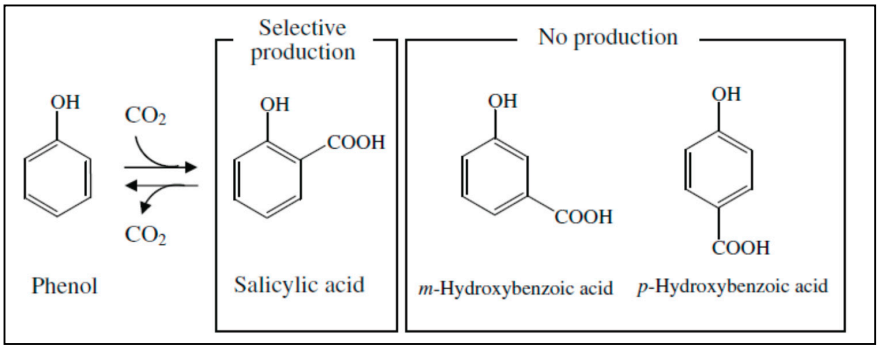


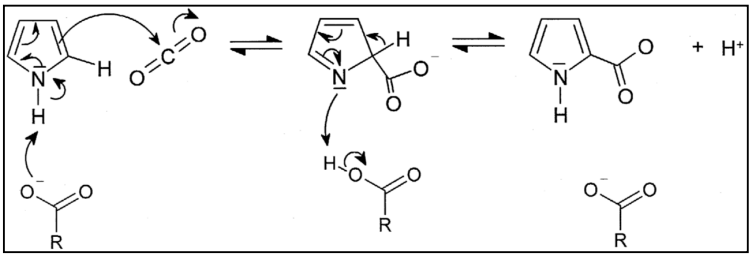
Figure 6. Reversible enzymatic conversion of salicylic acid and phenol [76].

Recently, phenolic acid decarboxylases from bacterial sources catalyzed the β-carboxylation of para-hydroxystyrene derivatives with excellent regio- and (*E*/*Z*)-stereoselectivity by exclusively acting at the bcarbon atom of the C=C side chain to furnish the corresponding (*E*)-cinnamic acid derivatives in up to 40% conversion at the expense of bicarbonate as carbon dioxide source [81]. Enzyme kinetics together with the reaction thermodynamics in line with the verification of the catalytic mechanism of 2,6-dihydroxybenzoic acid decarboxylase from *Rhizobium* sp. with catechol as the phenolic substrate was investigated [82]. This study provides insights into the catalytic behavior of a nonoxidative aromatic decarboxylase and reveals key limitations (e.g., substrate oxidation, CO_2 pressure, enzyme deactivation, and low turnover frequency) in view of the employment of this system as a "green" alternative to the Kolbe–Schmitt processes.

3.3.3. Carboxylation of Hetero-Aromatics

Pyrrole-2-carboxylate, a potential herbicide employed in the synthesis of various pharmaceuticals, can be synthesized from pyrrole and CO_2 using pyrrole-2-carboxylate decarboxylase, which was

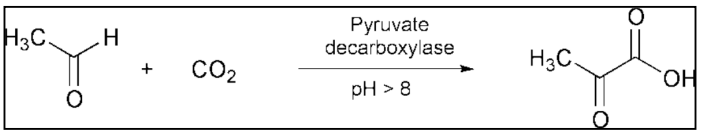
obtained from *Bacillus megaterium* PYR2910 (as shown in Scheme 5) [83–85]. The bioconversion yield was limited to 77–81% by the reaction equilibrium [84].



Scheme 5. Possible carboxylation mechanism [85].

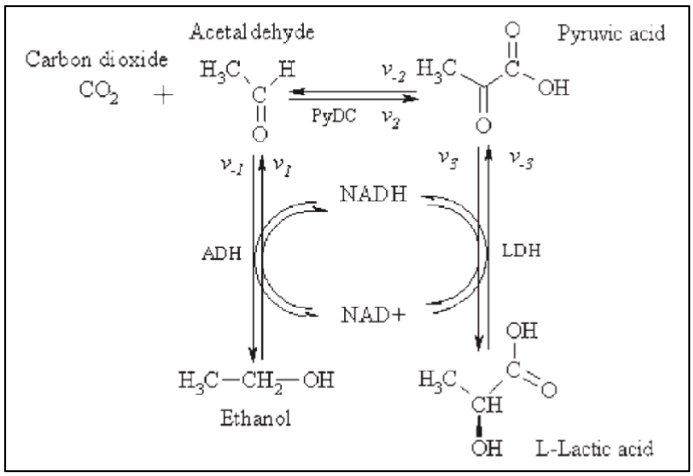
3.3.4. Carboxylation of Aliphatic Substrates

The enzymatic synthesis of pyruvic acid from acetaldehyde and CO_2 using the reverse reaction of Brewer's yeast pyruvate decarboxylase was explored as presented in Scheme 6 [5,86]. The maximum yield of 81% was achieved in 500 mM $NaHCO_3$-Na_2CO_3 buffer and pH 11. Especially, enzymatic reaction by lactate dehydrogenase can employed for the hydrogenation of pyruvic acid into lactic acid [86]. Thus, design a completely environmentally safe two-step enzymatic process for CO_2 immobilization is possible.



Scheme 6. Enzymatic reaction route for synthesis of pyruvic acid from CO_2 and acetaldehyde [86].

Recently, a new multienzyme reaction system was investigated for *L*-lactic acid production, which is used in food, cosmetic, pharmaceutical, and chemical industries, from carbon dioxide and ethanol (shown in Scheme 7) [87]. The unique internal cofactor regeneration cycle in this synthetic route can eliminate the need for additional reagents or energy for cofactor regeneration. Up to 41% in terms of ethanol conversion can be achieved in a batch reaction, while a turnover number of 2.2 day^{-1} was reached for cofactor regeneration with continuous ethanol feeding [87].



Scheme 7. Enzymatic reaction route for synthesis of L-lactic acid from CO_2 and ethanol [87].

For more detailed information regarding carboxylation reactions, as well as the enzyme purification methods applied for those reactions, please refer to Table S1 in the Supplementary Information Section of Reference [72].

4. Industrial Applications

Only a limited number of examples of industrial chemical processes using CO_2 as feedstock such as the Bosch–Meiser process [88] are recognized [12] because it requires large energy input due to strong bonds. This has motivated not only fundamental studies but also industrial applications of CO_2 enzymatic conversion in recent years.

A successful industrial application of enzymatic CO_2 conversion is using CA for accelerating CO_2 capture [89]. The use of chemical amine solvents has been primarily employed in conventional technology for capturing pure CO_2. However, these solvents require significant amounts of valuable, high-grade process heat for solvent regeneration, resulting in an inefficient process with high operating costs that suffers from significant operational and environmental issues including degradation, toxic aerosol emissions, sensitivity to flue gas contaminants, and corrosivity [89]. To solve these challenges, CO_2 Solutions' technology employs the most powerful known catalyst, the enzyme CA (as shown in Figure 7), resulting in both fast CO_2 absorption kinetics and significantly reduced energy consumption for carbon management.

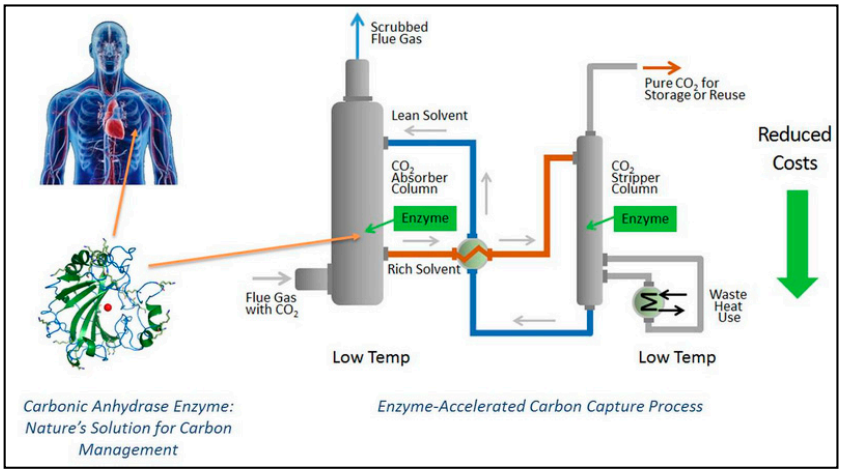


Figure 7. Schematic representation of CA-catalyzed CO_2 conversion and chemical absorption [89].

Recently, the Quebec City-based company CO_2 Solutions verified the results of a carbon capture demonstration project at Salaberry-de-Valleyfield near Montreal, reporting that CO_2 Solutions' proprietary enzyme performed in a stable manner with negligible solvent consumption and without producing any toxic waste products (shown in Figure 8) [89,90]. Furthermore, a pilot-scale CO_2 capture process was constructed at the National Carbon Capture Center in Wilsonville, AL, USA by Codexis Inc., in which the rate of CO_2 absorption was enhanced 25-fold compared with the non-catalyzed reaction [91].

A process and a plant were invented for the recovery and recycling of the CO_2 emissions from the cement clinker production by Lalande and Tremblay of CO_2 Solution [92]. In this process, a gas/liquid CO_2 packed column absorption catalyzed by CA is used and subsequent with the production of limestone ($CaCO_3$). The sequence is accomplished when the $CaCO_3$ is used as first class raw material for the fabrication of Portland cement.

Climostat Ltd. (Cheshire, UK) has filed a patent application for an enzymatic process that converts CO_2 and methane to formic acid, a valuable commodity chemical [93]. One fifth of a ton of methane (about £50 worth) would be potentially converted into £720 worth of formic acid. Even after

conversion costs are taken into account, the process is expected to be of significant commercial value and especially so when any carbon levy is taken into account. Further value could be added by using the resulting formic acid as a feedstock for higher-value materials. In addition, Sweetwater Energy Inc. (New York, NY, USA) and Naturally Scientific Technologies Ltd. (Buckinghamshire, UK) announced a joint venture to produce sugar from carbon dioxide waste from facilities such as ethanol plants or natural-gas powered power plants [94].

Recently, within the "Biotechnology 2020+" strategy process, the funding measure "Basic technologies for a next generation of biotechnological processes" supports three selected projects with regards to enzymatic conversion of CO_2 with a total budget of 4.3 million Euros [95,96]. In addition, the US Department of Energy (DOE), through the National Energy Technology Labs (NETL) and academic partners, is funding a spectrum of research projects investigating closed-cycle catalysts to convert CO_2 to commodity products that are ideally energy and carbon neutral [97]. Even though these projects are still focused primarily on basic research, biotechnological approaches will play an important role in CO_2 utilization in the future [95]. With the current global dependency on fossil fuels for energy production, these approaches are expected provide a means to reduce human induced climate change [98].

Figure 8. Industrial application of CA-catalyzed CO_2 conversion and chemical absorption [89].

5. Barriers and Future Perspectives

Enzymes are generally expensive with poor stability, activity, and reusability, which restrict their industrial applications. Several enzymatic technologies such as enzyme modification and enzyme immobilization need further development for reducing cost, improving the activity/stability of the enzymes, and enhancing reusability, which eventually improves economic feasibility. Besides, low reaction rate is one of main barriers for the application of enzymatic CO_2 conversion in industry. For kinetic concerns, biocatalysts are needed for faster and more efficient CO_2 conversion. Thus, the discovery of novel enzymes as well as the reaction systems engineering are required to improve catalytic efficiency.

Especially, cofactor-dependent reactions widely occur in the enzymatic conversion of CO_2. However, some cofactors are expensive and have limited availability, which severely limits large-scale applications. Thus, considerable research effort should be applied toward the discovery of new low-cost and low-energy approaches for cofactor regeneration and reuse [2].

In addition, only a few multienzyme routes have been constructed in vitro due to reaction complexity. Therefore, designing and/or constructing of number of novel multienzyme routes are imperative to sustainably produce fuels and chemicals from CO_2 [2].

Furthermore, it is important to consider that the technologies for CO_2 conversion based on chemical, photochemical, and electrochemical methods also show great application potential [99]. Thus, combining these methodologies with enzymatic conversion is expected to be beneficial in terms of selectivity and productivity. These combination strategies should be further studied and evaluated.

For an industrial exploitation, the design of a suitable bioreactor is a key issue [40]. Furthermore, the unit operations for the separation of mixture including biological molecules differ from their counterparts in the chemical industry. Much effort in separation in downstream needs to investigate and evaluate. Especially, the use of enzymes within reactive separation to enhance both reaction and separation has increased its research interest. Because enzymes are sensitive to higher temperatures, many works are needed to develop. In addition, the development of thermodynamic data and models for description of systems containing enzyme as well as development of synthesis/design tools are crucial to support the quick implementation of those systems [100].

Although a considerable number of studies have been carried out, substantial scientific and technical advances are still needed for a link between fundamental research and industrial application of enzymatic CO_2 conversion.

6. Conclusions

Enzymatic CO_2 conversion represents a viable and promising new technology for both greenhouse gas recycling and efficient production of fuels and chemicals. In this review, we attempted to elucidate the major challenges for transitioning enzymatic conversion from promise to reality. Although there is much excitement about the potential of enzymatic CO_2 conversion as well as several real industrial applications, much work is still required in the field to discover facile and low-energy CO_2 conversion routes; improve catalytic efficiency; integrate with chemical, photochemical, and electrochemical technologies for higher efficiency; and assess downstream processes for large-scale utilization. There are several real industrial application examples that are working, thus, we are not so far from the extension of the technology in the industry.

Acknowledgments: This research was supported by C1 Gas Refinery Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2016M3D3A1A01913262). This study was also supported by Priority Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2014R1A6A1031189).

Author Contributions: Nguyen Van Duc Long designed the paper, conducted the literature review, and wrote the paper. Jintae Lee advised enzymatic conversion. Kee-Kahb Koo advised novel applications. Patricia Luis and Moonyong Lee equally conceived the core concepts for the research and provided academic advice. All authors collaborated in the preparation, revisions, and general editing of this manuscript.

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

Abbreviations

The following abbreviations are used in this manuscript:

ADH	Alcohol dehydrogenase
CO	Carbon monoxide
CO_2	Carbon dioxide
CCS	CO_2 capture and storage
CODH	Carbon monoxide dehydrogenases
CA	Carbonic anhydrase
FDH	Formate dehydrogenase
CCCCs	Calcium carbonate crystalline composites
$F_{ald}DH$	Formaldehyde dehydrogenase
CH_4	Methane
HCO_3^-	Bicarbonate
HOOC-FMS	Carboxylic acid group-functionalized mesoporous silica
RuBisCO	Ribulose-1,5-bisphosphate carboxylase/oxygenase

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