

Subtleties in Nature inspire catalyst design for carbon dioxide reduction

Abstract Nature has perfected the design of enzymes to activate and catalyze the transformation of molecules such as carbon dioxide (CO₂) at minimum energetic consumption, while maintaining high efficiency and selectivity. Unlocking these tricks can inspire design of artificial technologies to alleviate the urgent concern of global warming and develop carbon-neutral production of fuels. Systematic modification of iron porphyrin catalysts with various “bio-inspired” strategies have led to significant control of the efficiencies and energetic costs of the electrochemical reduction of CO₂ to carbon monoxide. The latter being an energy carrier and important feedstock in the production of fuels. The structure-activity correlations revealed herein set up important considerations in designing CO₂ reduction catalysts.

Keywords Carbon dioxide, iron porphyrin, electrocatalyst, second coordination sphere, hydrogen bonding, electrostatic, artificial photosynthesis.

Résumé Les subtilités de la nature inspirent la conception de catalyseurs pour la réduction du dioxyde de carbone. La Nature a perfectionné la conception des enzymes pour activer et catalyser la transformation de molécules comme le dioxyde de carbone (CO₂) avec une consommation énergétique minimale, tout en maintenant une efficacité et une sélectivité élevées. Déverrouiller ces secrets peut inspirer des technologies artificielles pour résoudre le problème urgent du réchauffement climatique et développer une production de carburants neutres en carbone. La modification systématique des catalyseurs à base de porphyrine de fer avec différentes stratégies « bio-inspirées » a permis de contrôler l'efficacité et les coûts énergétiques de la réduction électrochimique du CO₂ en monoxyde de carbone. Ce dernier est un vecteur énergétique et une matière première dans la production de carburants. Les corrélations structure-activité révélées ici mettent en place des considérations importantes pour la conception de catalyseurs de réduction du CO₂.

Mots-clés Dioxyde de carbone, porphyrine de fer, électrocatalyseurs, deuxième sphère de coordination, liaison hydrogène, électrostatique, photosynthèse artificielle.

Mimicking Nature

It has long been strategized that learning how various mechanisms in Nature work can unlock opportunities in solving humankind's curiosities and problems. This so-called “biomimicry” or “bio-inspiration” has led to discovery of Velcro (after being inspired from the tiny hooks in burrs), adhesives (after toe pads of geckos), self-cleaning materials (after hydrophobic lotus leaves), airplane design (from aerodynamics observed in birds), spider webbing patterns in windshields to control crack propagation, and many more biomimetic multifunctional materials [1]. Faced with the urgent need to solve the global crisis on carbon dioxide (CO₂) emissions and increasing energy demands, Nature can teach us a trick or two [2]. The process of photosynthesis, where plants utilize sustainable sources of sunlight, CO₂ and water to produce energy-carriers in the form of carbohydrates (which constitute fossil fuels in the long-term), are already showing alleviation of atmospheric CO₂ levels during spring time, but remains insufficient with the critical CO₂ emissions from mankind. A new field of research, called “artificial photosynthesis”, is emerging with the goal of getting inspiration from the natural photosynthetic process to efficiently store and utilize solar energy, and from sophisticated design of enzymes, Nature's form of catalyst, to develop efficient and robust systems to transform CO₂ into an energy vector [3]. As such, artificial technologies can be designed to produce renewable solar fuels and synthetic building blocks from CO₂ as a feedstock, closing the carbon

cycle and simultaneously addressing the intermittency and storage concerns of solar energy harnessing.

At the heart of this field is the development of catalysts that can activate the highly stable CO₂ molecule and efficiently transform it at lower energetic penalties (called overpotential). One enzyme called carbon monoxide dehydrogenase (CODH) have been shown to efficiently and reversibly reduce CO₂ to carbon monoxide (CO), a two-electron energy carrier and an important chemical feedstock in Fischer-Tropsch reaction to produce liquid fuels. The active site of this enzyme [4] (*figure 1*, left) shows hints of important features that may be considered in designing efficient CO₂ reduction catalysts (*figure 1*, right). First, they consist of robust ligand structures that can store and supply electrons (in this case, an iron-sulfur cluster). Second, they have metal centers (nickel and iron) that are able to bind CO₂ in meticulously pre-arranged active sites with minimal changes in the geometry. Third, they employ a CO₂-activating environment, where the CO₂ molecule becomes “bent” from hydrogen bonding with nearby amino acid residues (lysine and histidine).

Herein, a closer biomimicry arising from inspirations of this active site was investigated to set up some important guidelines in designing highly efficient catalysts. All modifications are employed in an iron porphyrin catalyst (*figure 1*, right), a molecule closely resembling the macrocyclic heme structure in hemoglobin that is known to carry oxygen and carbon dioxide in red blood cells. This structure provides a robust framework for charge accumulation, flexibility for synthetic modification, and efficient reduction of CO₂ to CO but at

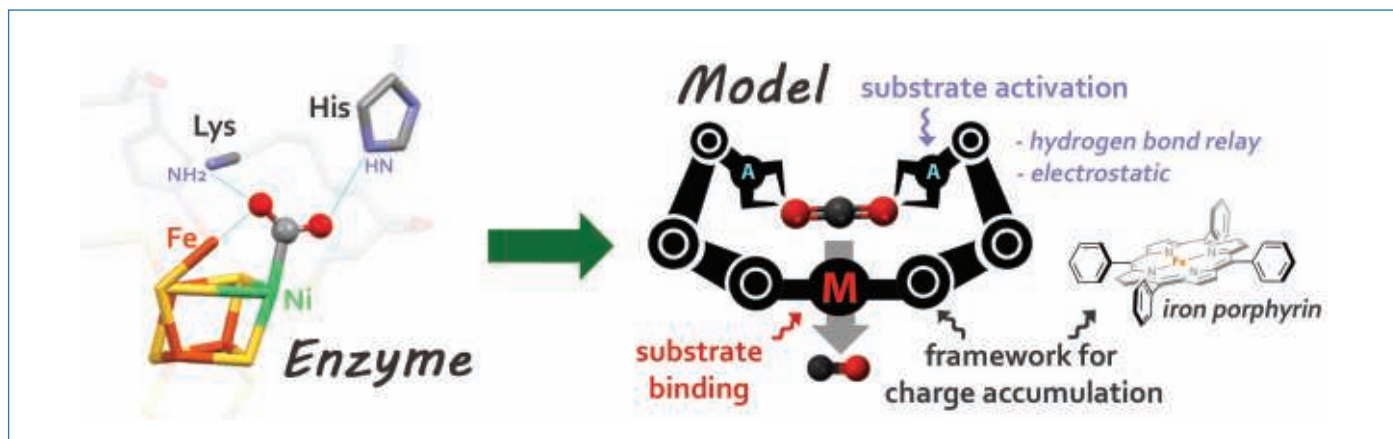


Figure 1 - (Left) Crystal structure of the active site of CO dehydrogenase (CODH) enzyme showing the binding of CO₂ substrate on a nickel metal (green) and the bending of the linear molecule due to activation from nearby amino acid residues (lysine (Lys) and histidine (His)). (Right) Mimicry of the structural subtleties in enzymes towards optimized design for artificial catalysts showing essential target features.

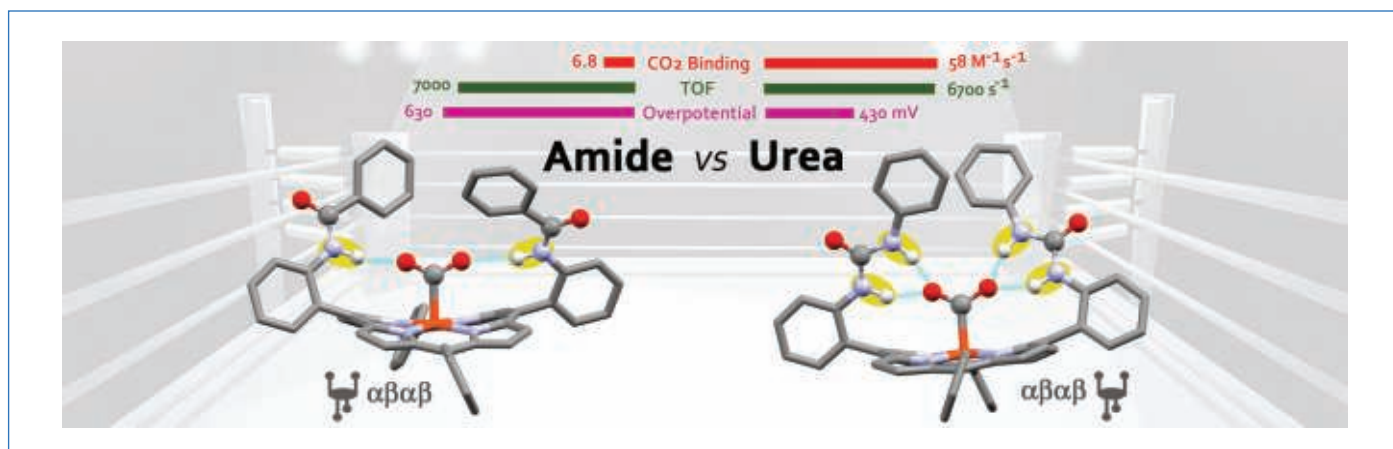


Figure 2 - Effect of the functional group (amide vs urea) acting as hydrogen bond relays on the electrocatalytic properties of the catalyst (CO₂ binding rate constant, turnover frequency TOF, and overpotential) towards CO₂-to-CO reduction.

higher energetic penalties [5-6]. By designing systematic and subtle changes in the local environment of iron porphyrins inspired from features observed in the active site of CODH, important structure-function correlations can be drawn to understand and optimize its catalytic activities [7-8].

Role of multi-point hydrogen bonding relays

The hydrogen bonding that nearby amino acid residues establish to activate the CO₂ substrate in the active site of the CODH enzyme has inspired the search and optimization of distal hydrogen bonding moieties in the catalytic site. To this end, iron porphyrin catalysts containing either amide (figure 2, left) or urea functional groups (figure 2, right) have been synthesized to mimic similar substrate activation scheme [9]. The choice of such functional groups was inspired by a urea scaffold that fixes atmospheric CO₂ as carbonate clusters through extensive hydrogen bonding between the N-H fragments of urea and the carboxyl groups (C-O) of carbonate [10]. The difference in these two functional groups arises from the number of N-H fragments that can establish hydrogen bonding on the oxygen atoms of CO₂: one in amide groups, and two in urea groups. Furthermore, the modified iron porphyrin complexes possess $\alpha\beta\alpha\beta$ configuration to provide two sets of hydrogen bonding network in a *face-to-face* fashion towards the metal bound CO₂ molecule and at the

same time to confer two identical chemical faces on each side of the porphyrin molecular platform.

Electrochemical characterization of the complexes showed promising results. First, the energy required to transfer two electrons and two protons to transform CO₂ into CO is significantly lowered compared to the non-functionalized iron porphyrin, which requires an overpotential of 730 mV. The amide derivative only needs an overpotential of 630 mV while the urea derivative needs an even lower overpotential of only 430 mV, almost half of that required for the non-functionalized catalyst. Second, the complexes were able to operate at these lower overpotentials while maintaining high efficiency of ~ 7000 catalytic cycles per second indicated as turnover frequency (TOF) and high selectivity towards the production of CO (91%). This is a noteworthy milestone as most chemical modifications to lower the overpotential of the catalysts usually lead to significant lowering of the efficiency (a classical penalty between thermodynamics and kinetics of the reaction) [5]. Third, the presence of such hydrogen bond relays has significantly improved the rate of CO₂ capture with higher CO₂ binding rate constant of $58 \text{ M}^{-1}\text{s}^{-1}$ observed for the urea derivative compared to $6.8 \text{ M}^{-1}\text{s}^{-1}$ of the amide derivative. The substantial enhancements of catalytic properties were primarily achieved because of the pre-organized positioning of the N-H hydrogen bonding fragments towards the iron carboxylate intermediate (Fe-CO₂), modifying the second

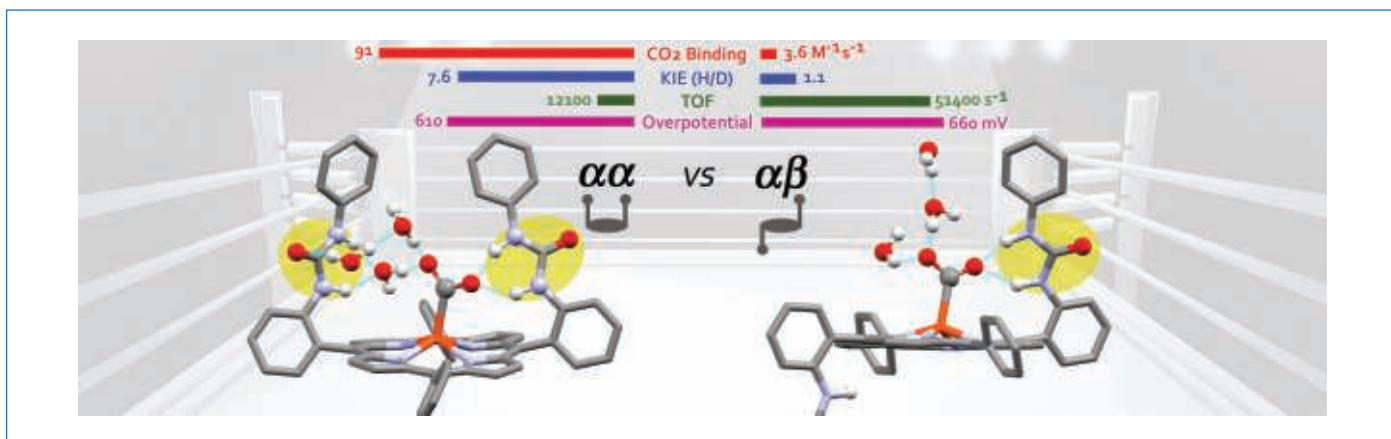


Figure 3 - Effect of the positioning ($\alpha\alpha$ vs $\alpha\beta$) of urea functions acting as hydrogen bond relays on the electrocatalytic properties of the catalyst (CO₂ binding rate constant, kinetic isotope effect KIE, turnover frequency TOF, and overpotential) towards CO₂-to-CO reduction.

coordination sphere of the catalyst. Since there are four N-H arms of the urea derivative to hold the oxygen atoms of CO₂ compared to the two N-H arms of the amide derivative, the urea-modified iron porphyrin showed a much stronger activation of the CO₂ substrate. Indeed, density functional theory (DFT) calculations showed stronger and shorter multi-point hydrogen bonds in urea functions (1.76-1.89 Å) compared to the weaker and longer single-point hydrogen bonds in the amide homologue (2.01-2.35 Å). More importantly, DFT calculations also show that the metal carboxylate intermediate remains in a quasi-unchanged topology while being put in contact with a water molecule, explaining the synergistic effect of water as a sufficient proton source for the catalytic reduction. This similarly mimics the way CODH enzyme manages its proton supply through a nearby water network, which was reported to be critical for the enzymatic activity [2].

Positional effects of hydrogen bonding relays

Simplistic look at the CO₂ activation scheme in the active site of CODH enzyme leads to an assumption of symmetric activation of the substrate by the nearby amino acids but the reaction otherwise involves a dissymmetric cleavage of only one of the C-O bonds to form the reduced CO product. Going beyond the optimized function of urea as multi-point hydrogen bonding relays, the topological positioning of these groups was then investigated by simplifying the catalyst design with only two urea groups and (while maintaining the same global chemical formulation) looking at two different atropisomers, $\alpha\alpha$ and $\alpha\beta$ [11]. The $\alpha\alpha$ atropisomer (figure 3, left) was synthesized to provide two urea groups positioned in a *face-to-face* fashion on one side of the porphyrin platform while the $\alpha\beta$ atropisomer (figure 3, right) positions the urea groups on opposite sides of the porphyrin platform, resulting to only one effective set of hydrogen bonding towards the Fe-CO₂ intermediate.

Electrochemical characterizations show that the modification of the second coordination sphere of these catalysts influences its functional properties. Indeed, the $\alpha\alpha$ atropisomer possesses a better affinity for CO₂ than the $\alpha\beta$ atropisomer, having almost 25 times higher binding rate constant for the former (91 M⁻¹s⁻¹) than the latter (3.6 M⁻¹s⁻¹). This is indicative that at least two urea arms are needed for the strong capture of the CO₂ molecule, while having just one arm significantly

lowered this affinity (even though it still stays much higher compared to the non-functionalized iron porphyrin having only 0.1 M⁻¹s⁻¹). Both atropisomers do not show significant difference in the overpotential (610 and 660 mV for $\alpha\alpha$ and $\alpha\beta$, respectively), but unexpectedly, higher efficiencies were observed for the $\alpha\beta$ isomer (51400 s⁻¹), which is four times higher than the $\alpha\alpha$ isomer (12100 s⁻¹).

The counter-intuitive trends in the CO₂ binding affinity and the resulting catalytic efficiencies between the atropisomer point to another catalytic step (*i.e.* protonation) which is limiting the reaction. The effect of protonation was investigated by looking at the kinetic isotope effect (KIE) which shows how the kinetics of the reaction change when H₂O is replaced by a heavier isotope of D₂O. The KIE is significantly higher in the $\alpha\alpha$ atropisomer (7.6) than the $\alpha\beta$ atropisomer (1.1). This is indicative that protonation of the metal carboxylate intermediate is much more limiting the catalysis for the former than the latter. When the CO₂ molecule is trapped between the two urea groups in the case of the $\alpha\alpha$ atropisomer, the protonation step is very slowed down as water molecules need to disrupt the pre-established strong hydrogen bonding network within the Fe-CO₂ intermediate and urea arms. In the case of the $\alpha\beta$ atropisomer, however, the CO₂ molecule is held by only one set of hydrogen bonded urea arm thus allowing easy proton access to the other C-O arm of CO₂ for its eventual cleavage. These results point out that a better catalysis of CO₂ reduction requires a subtle control of its fixation at the catalytic site and of access to protons, an essential ingredient for the rupture of the C-O bond.

Role of electrostatic interactions

More than the role of hydrogen bond relays that the distal amino acid residues play in the active site of CODH, there are also hints that they play an electrostatic role as the amino acids become cationic (containing net positive charge) once they are protonated. This is in line with the works of the Nobel Prize laureate Arieh Warshel where he implicated that evolution has used electrostatic interactions for the unmatched catalytic activities of enzymes [12]. The idea is then to explore how nearby cationic groups can help stabilize and activate the anionic nature (containing net negative charge) of the Fe-CO₂ intermediate. The iron porphyrin molecular platform was modified by positioning cationic methylimidazolium pillars and interrogating the effect of the number of these units

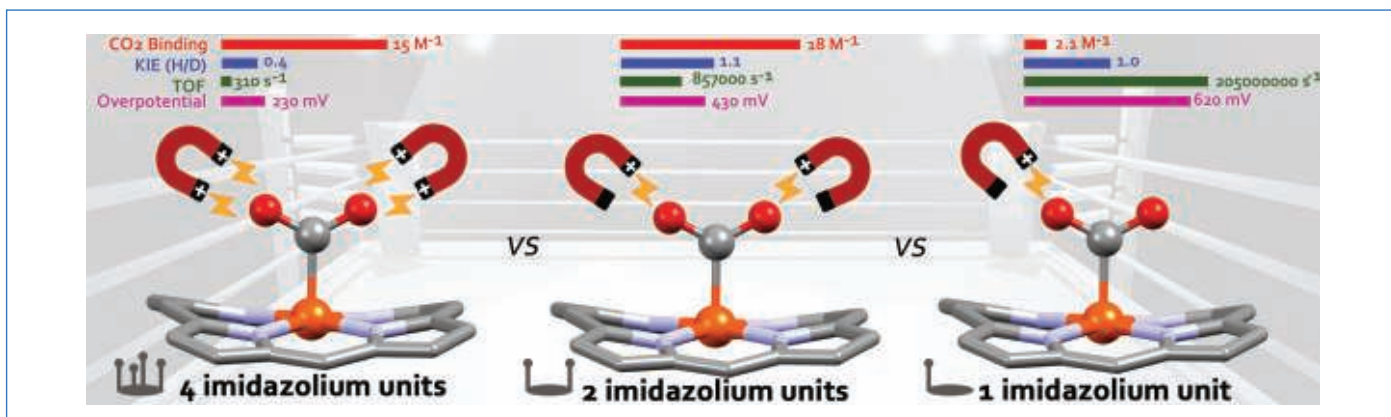


Figure 4 - Effect of the number of second coordination sphere cationic imidazolium units on the electrocatalytic properties of the catalyst (CO₂ binding rate constant, kinetic isotope effect KIE, turnover frequency TOF, and overpotential) towards CO₂-to-CO reduction.

(figure 4). Three modified complexes were synthesized having four, two or one cationic methylimidazolium groups while maintaining the same topology where all of the cationic pillars are located only on one side of the porphyrin platform [13-14]. The choice of methylimidazolium functional groups comes from recent reports where ionic liquids (containing similar cationic units) were found to improve the solubility and catalysis of CO₂ [15].

When these cationic groups were placed in the local active site of the iron porphyrin catalyst, a significant lowering of the overpotential of the reaction was observed. With the overpotential of the non-functionalized iron porphyrin at 680 mV, increasing the number of cationic pillars, from one to two and to four, decreased the overpotential to 620, 430, and 230 mV, respectively. This is indicative that each cationic pillar establishes an electron-withdrawing effect on the porphyrin platform. The affinity for CO₂ was greater when having two or four cationic pillars (15-18 M⁻¹) compared to having just one cationic pillar (2.1 M⁻¹), indicating that at least two functional groups are needed to strongly capture the CO₂ molecule. It seems however, that the final catalytic efficiencies follow the trend where one > two > four cationic pillars, similar to what was observed to the overpotential of the reaction. These efficiencies are still way higher compared to iron porphyrins functionalized with the typical electron-withdrawing fluorine groups (e.g., for the same overpotential, having one cationic pillar improves the efficiency by four orders of magnitude, and having four cationic pillars improves it by one order of magnitude). This is indicative that the methylimidazolium cationic groups greatly improves the catalytic efficiencies of the reaction because of electrostatic charge stabilization of the Fe-CO₂ intermediate, but more than this, the results suggest a linear correlation between the number of cationic groups with catalytic efficiency and overpotential, providing synthetic flexibility on the required property of the catalyst. Because of the cationic nature of the catalysts, it was even possible to perform CO₂ reduction in water as a convenient and clean solvent and proton source, maintaining high efficiency (244000 s⁻¹) and selectivity (91% CO) at a much lower overpotential (418 mV) [13].

Lessons and opportunities

Learning from the perfected design that evolution has done on the active sites of enzyme, such as the carbon monoxide dehydrogenase, has given important points of inspiration for

designing carbon dioxide reduction catalysts. Subtleties on the functional features of nearby amino acid residues in the active site has been investigated by mimicking their roles as hydrogen bonding relays and electrostatic activators of the CO₂ molecule in the second coordination sphere of an iron porphyrin catalytic platform. Systematic studies showed the need for a stronger multi-point hydrogen bonding in urea functional groups (significantly lowering the energetic cost of the reaction while maintaining high efficiency) compared to weaker single-point hydrogen bonding of an amide homologue. The effect of positioning the N-H fragments was also investigated by exploring architectural modifications of the iron porphyrin atropisomer showing interesting aspects on CO₂ substrate binding rate (better with $\alpha\alpha$ atropisomer) and catalytic efficiency (higher with $\alpha\beta$ atropisomer), revealing the importance of access to proton supply during the catalytic reduction of CO₂. Stemming from the observation that protonated amino acid residues establish a cationic environment that can activate the anionic Fe-CO₂ intermediate, it was further shown that tethering cationic methylimidazolium units in the iron porphyrin structure resulted to substantial improvements in terms of both lowering the overpotential and improving the efficiency of the catalytic reaction. Furthermore, the number of such cationic units offer control on the desired property of the catalyst. As such, optimizing the properties of catalysts involves the quest for the *Goldilocks* combination of balanced activation and destabilization of substrates (both CO₂ and protons, in addition to proper timing and supply of electrons).

"Bio-inspired" catalyst design was applied here in homogenous molecular catalysts as it offers ease of structural tunability and applicability to common spectroscopic and electrochemical techniques in establishing structure-function correlations [8]. The advances made here in modifying the second coordination sphere of the active site of the catalysts have also been leveraged in heterogenized molecular electrocatalytic systems (by simple adsorption on carbon electrodes) to gain stability and performance in aqueous electrolytes [16], or coupling to sensitized photocatalytic systems where CO₂ reduction is driven from light-induced electron transfer steps [17]. Furthermore, the valorization of the reduced product (carbon monoxide) was even established in a *proof-of-concept* where starting from waste CO₂, one can produce (labeled) pharmaceutically relevant drugs through tandem CO₂ reduction and aminocarbonylation reaction [18], similar to the tandem biological scheme found between

CODH and acetyl CoA synthase enzymes. Herein a glimpse of opportunity for “bio-inspired” artificial design has been presented, but there are still a lot of tricks that Nature employs in its magnificent design, just waiting to be unraveled by the scientific community.

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