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Molecular Modeling of Biological Carbon Fixation

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Molecular Modeling of Biological Carbon Fixation

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Introduction

Ribulose-1, 5-biphosphate (Rubisco)-one of the most important proteins-is the predominant catalyst of carbon fixation. As ubiquitous RuBisCo's presence is in the natural world, it is a relatively inefficient enzyme due to its poor O_2/CO_2 specificity as well as its slow catalytic rate (Figure 1). A better understanding of RuBisCo using molecular dynamics could provide insight into RuBisCo's properties and provide possible ways to genetically engineer the enzyme in order to combat the rising levels of atmospheric CO_2 levels (Figure 2).

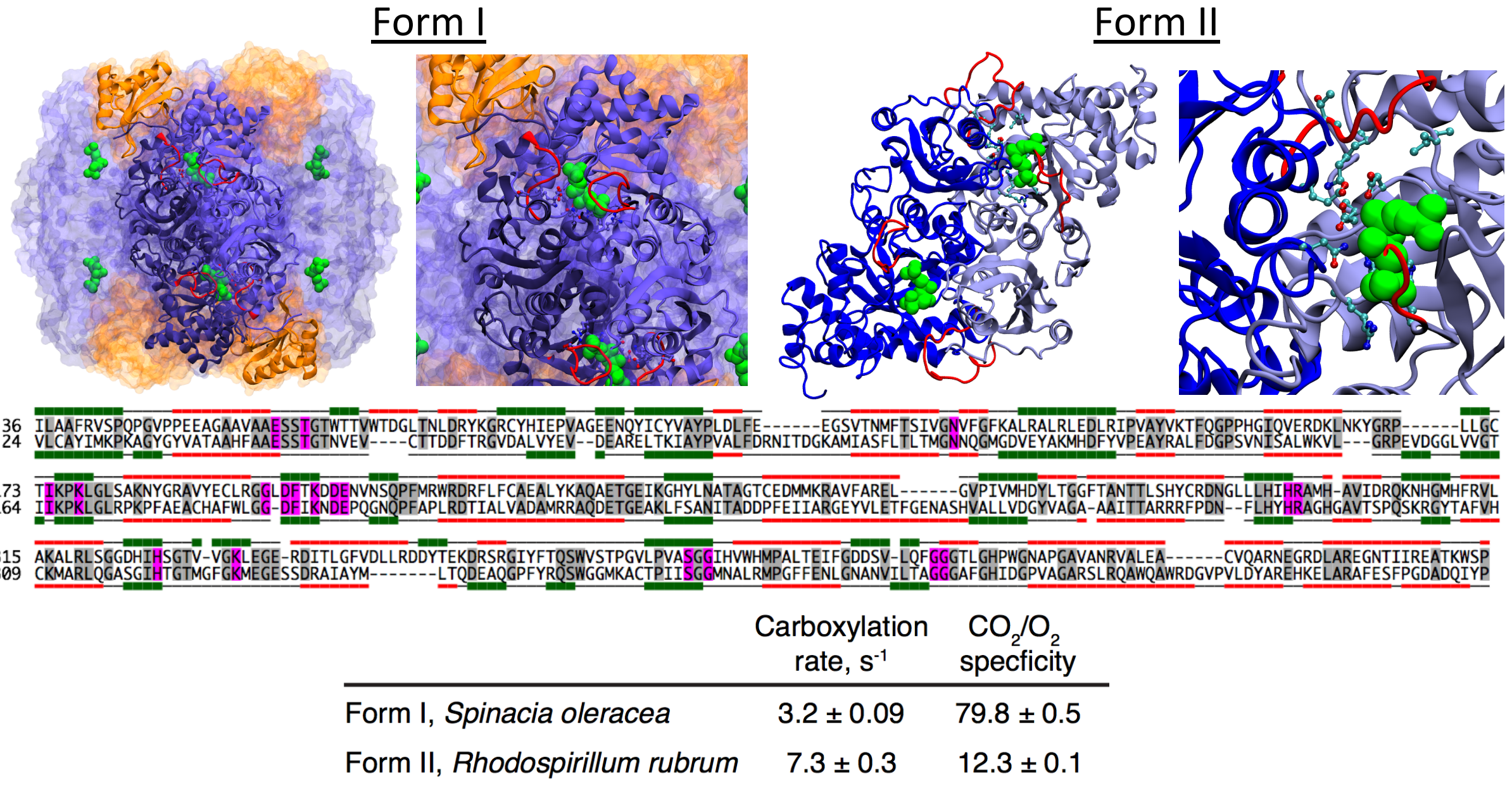


Figure 1. Depicts the two forms of RuBisCo and the active sites are represented by the green spheres. The table shows the respective rates and specificity of the two forms of RuBisCo. [1]

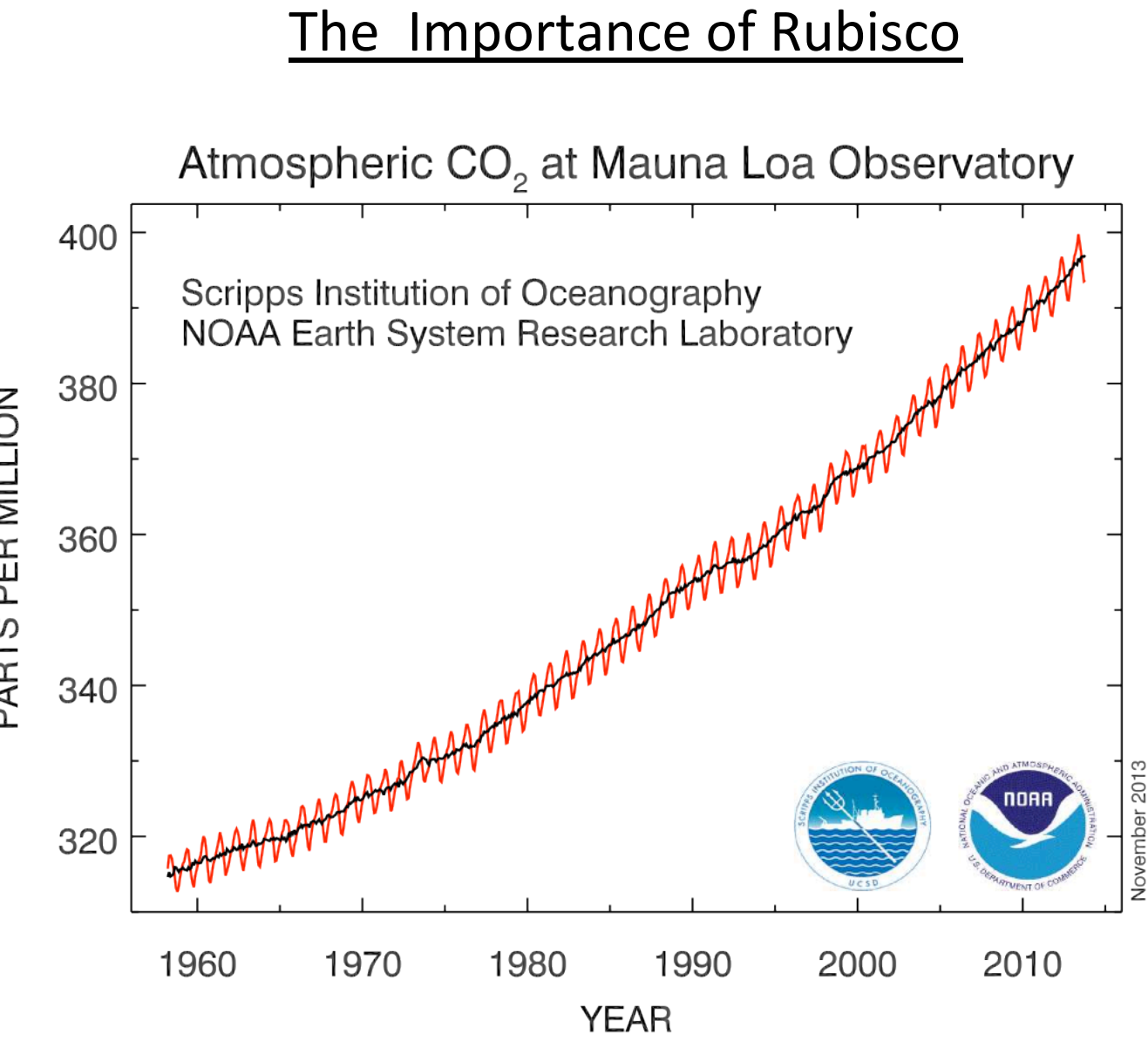


Figure 2. Depicts the rising level of CO_2 in the atmosphere from 1960 to 2010. [2]

Substrate Specificity in RuBisCo

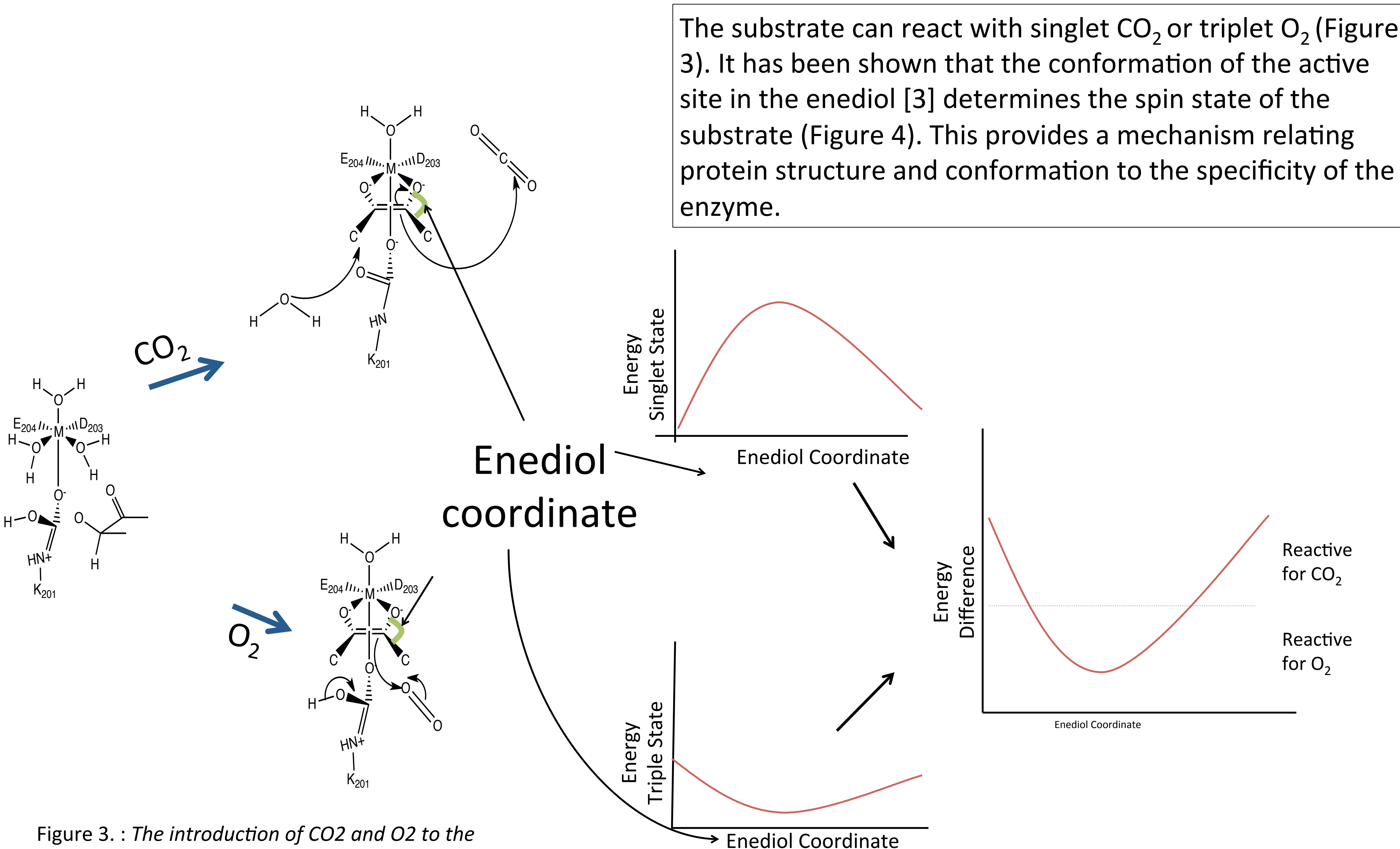


Figure 3. : The introduction of CO_2 and O_2 to the substrate catalyzes two different reactions, based on the conformation of the active site. Following [3].

The substrate can react with singlet CO_2 or triplet O_2 (Figure 3). It has been shown that the conformation of the active site in the enediol [3] determines the spin state of the substrate (Figure 4). This provides a mechanism relating protein structure and conformation to the specificity of the enzyme.

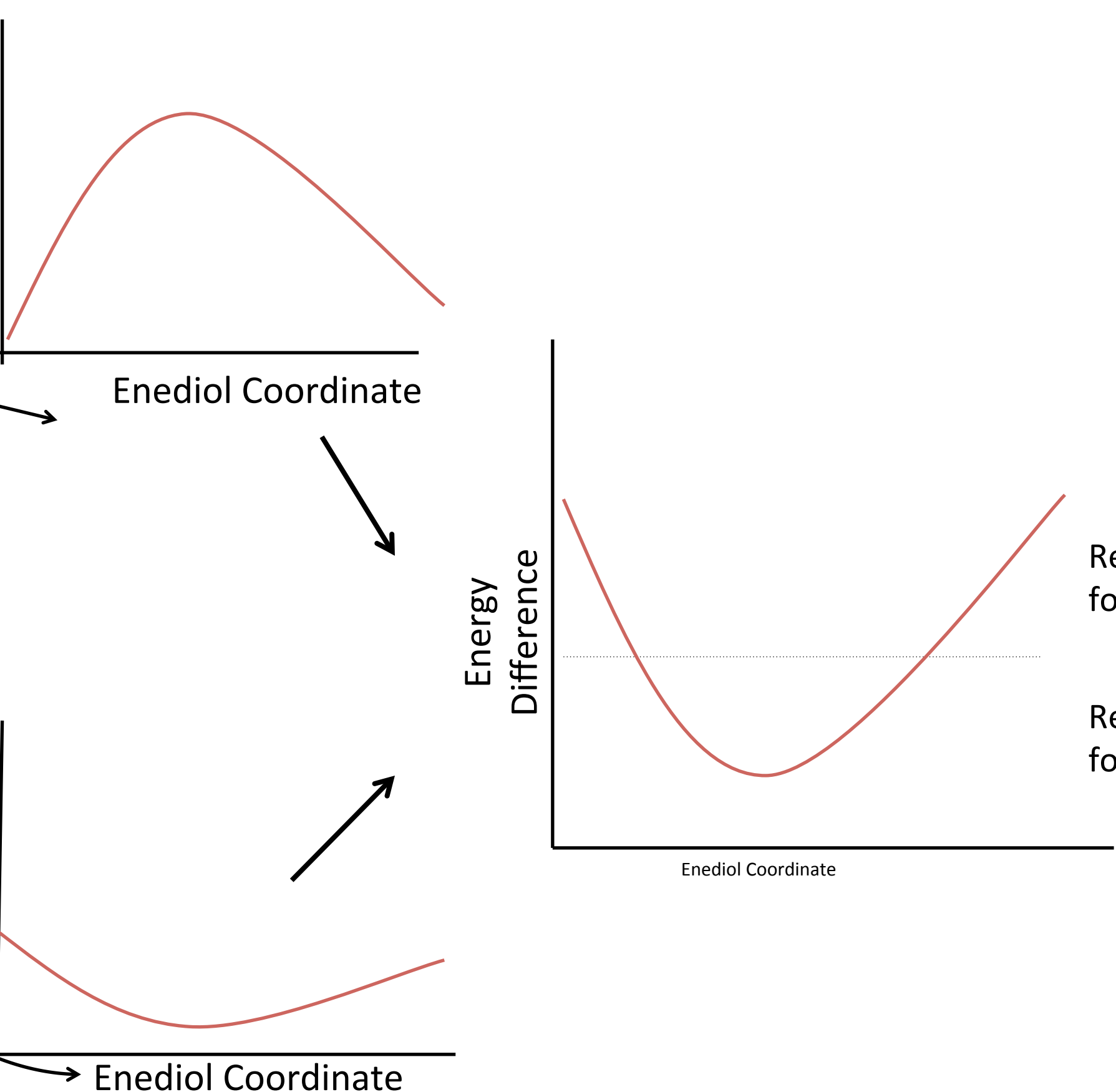


Figure 4. Comparison of energy levels of active site. In both the singlet and triplet state of Ribulose-1,5-biphosphate.

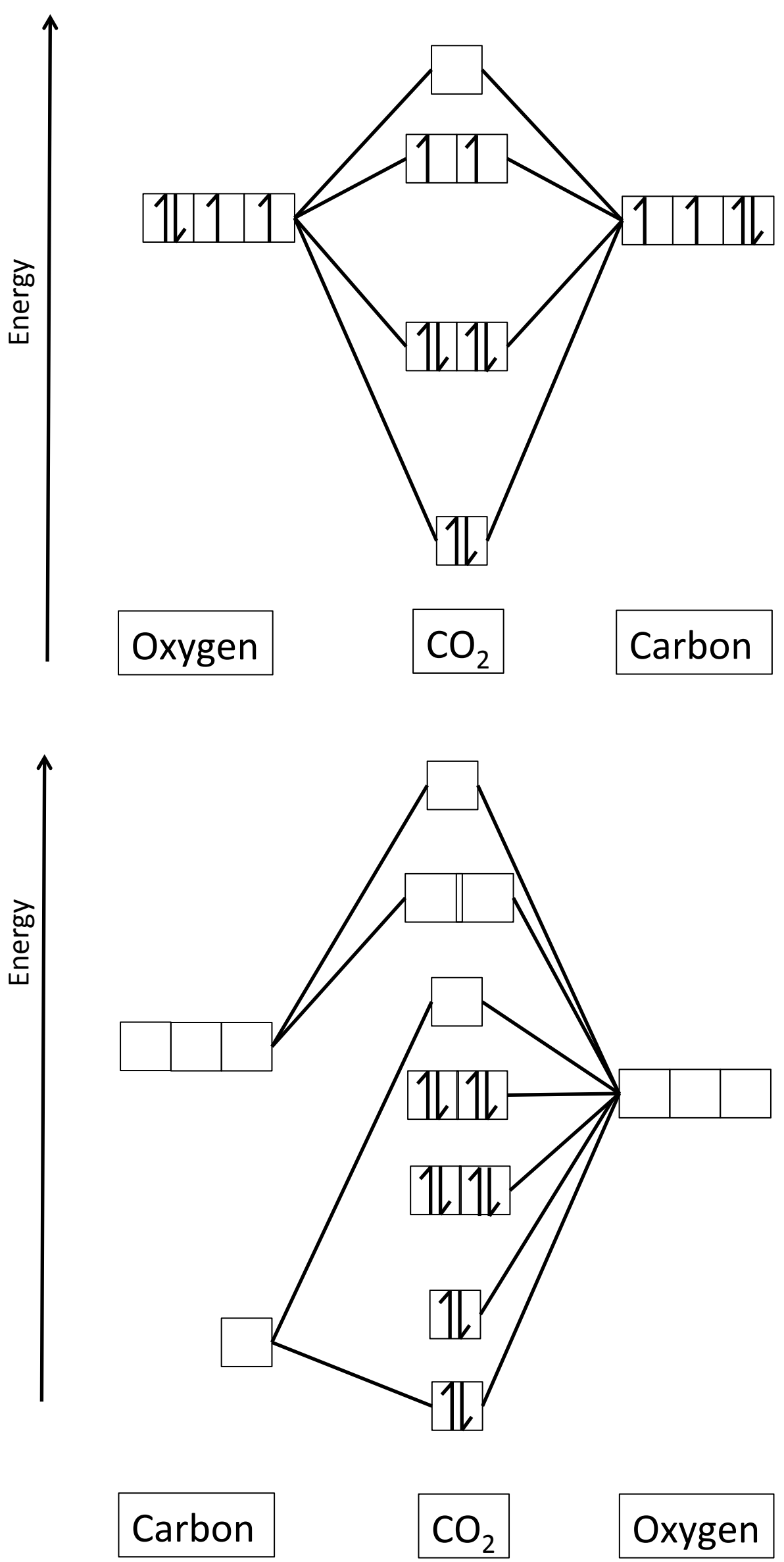


Figure 5. Molecular orbital diagrams of singlet state CO_2 and triplet state O_2

Catalytic Rate

RuBisCo has a problem discriminating between CO_2 and O_2 as substrates and thus the carboxylation to oxygenation reaction ratio is roughly 4:1. There is an observable trade-off between substrate specificity and catalytic turnover (Figure 6). This is seen through a negative correlation between transition state analogs and the rate of catalysis. Thus, specificity and the rate-determining step are identical. These notions support the argument that RuBisCo cannot be further optimized (Figure 7).

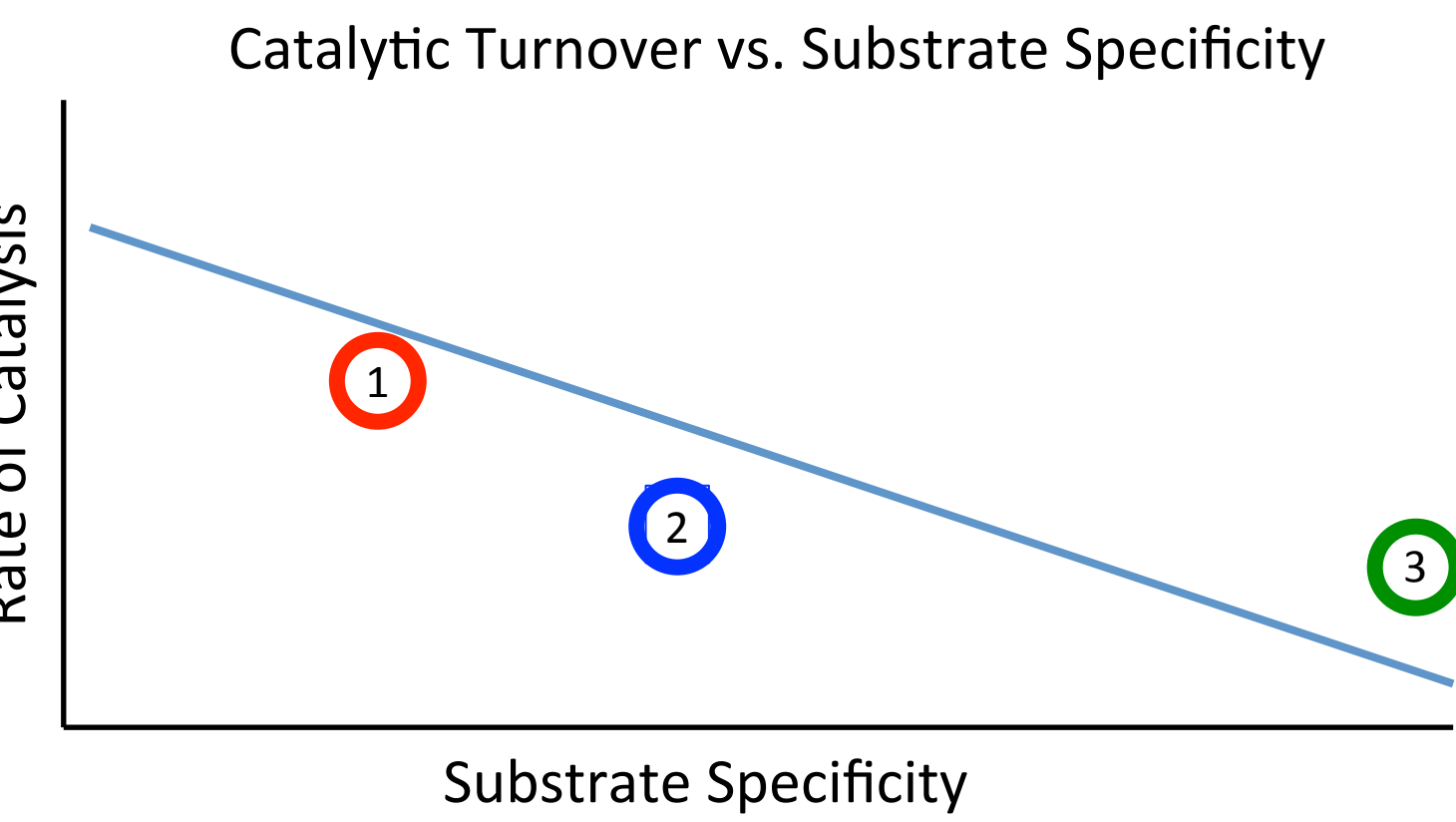


Figure 6 (left). Shows the negative correlation between the rate of catalysis and substrate specificity. The encircled numbers show in which organisms the RuBisCos were isolated from: 1, green algae; 2, spinach; and 3, red algae. Following [4].

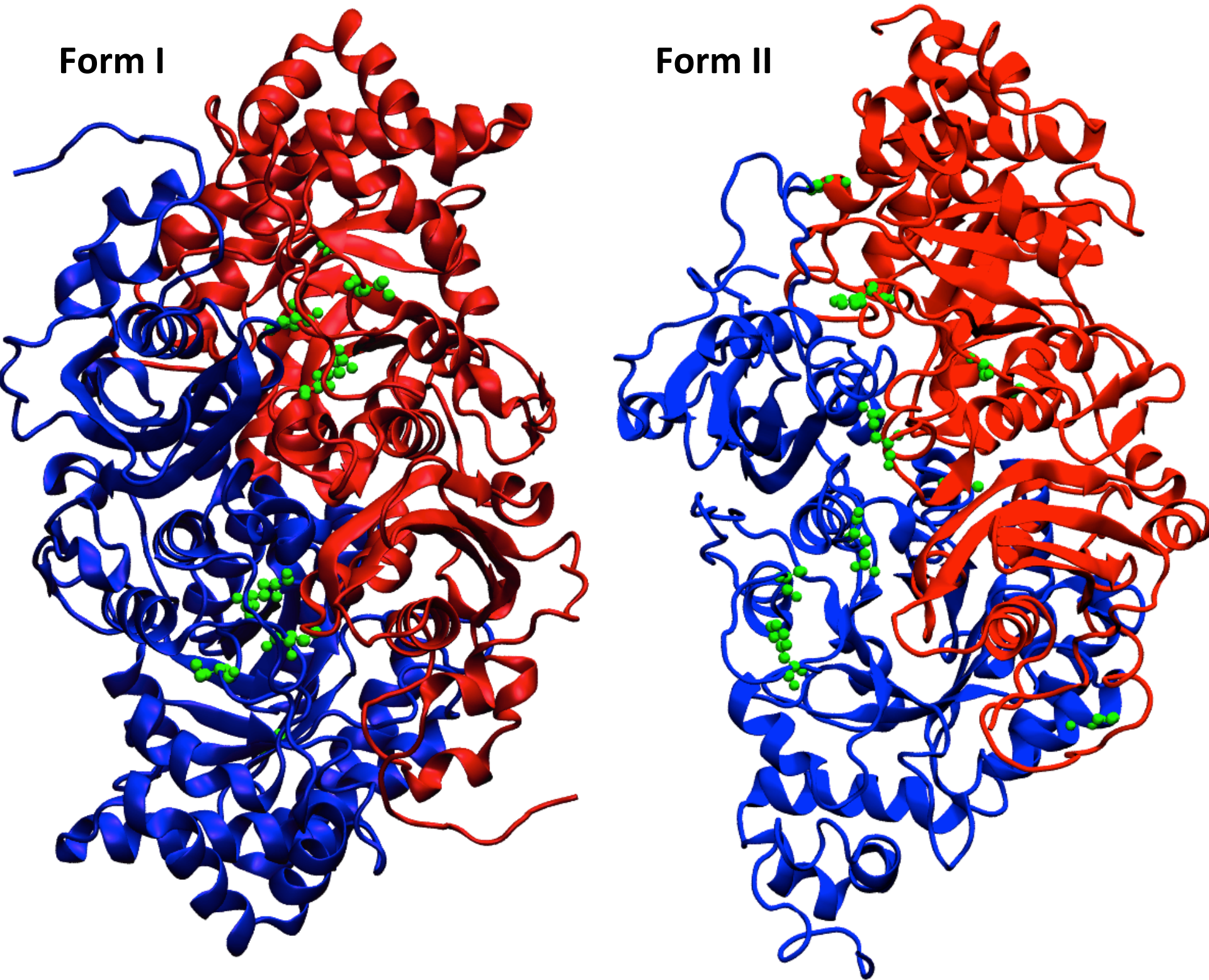


Figure 7 (left). Shows the structures of two different forms of Rubisco. Form I shows only 1 of the four dimers. Form II consists of only one dimer. The green spheres show different mutations done on amino acids in their respective large subunit. The effects they had on enzyme activity were either decreased or no activity at all. Following [5].

Results

Molecular dynamics uses Newtonian equations of motion to simulate how the conformation of the enzyme changes over time. With a long enough timescale, the protein will have theoretically visited all possible conformations. Using the ergodic theorem, statistical mechanics can be applied to this motion to gain insight into its macroscopic properties, such as the mechanisms of conformational change, changes in free energy, and structural correlation. Thus, molecular dynamics offers a unique window into the properties of the enzyme that are not available through lab bench study.

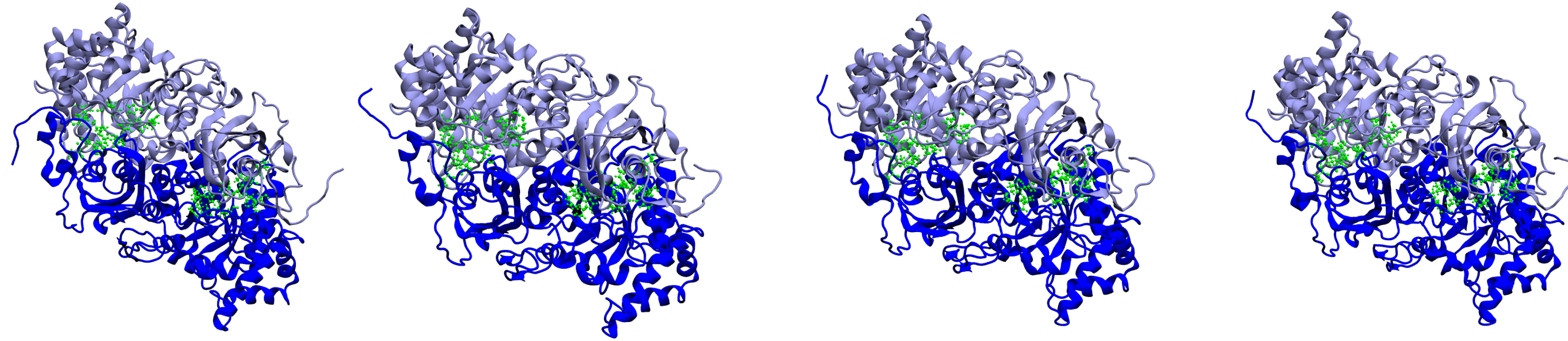


Figure 8. Snapshots of the conformations of the L-subunit dimer during the molecular dynamics run. The run lasted for more than 1 ns, fulfilling the ergodic theorem, and in an explicit solvent of water. The run included more than 97,483 atoms.

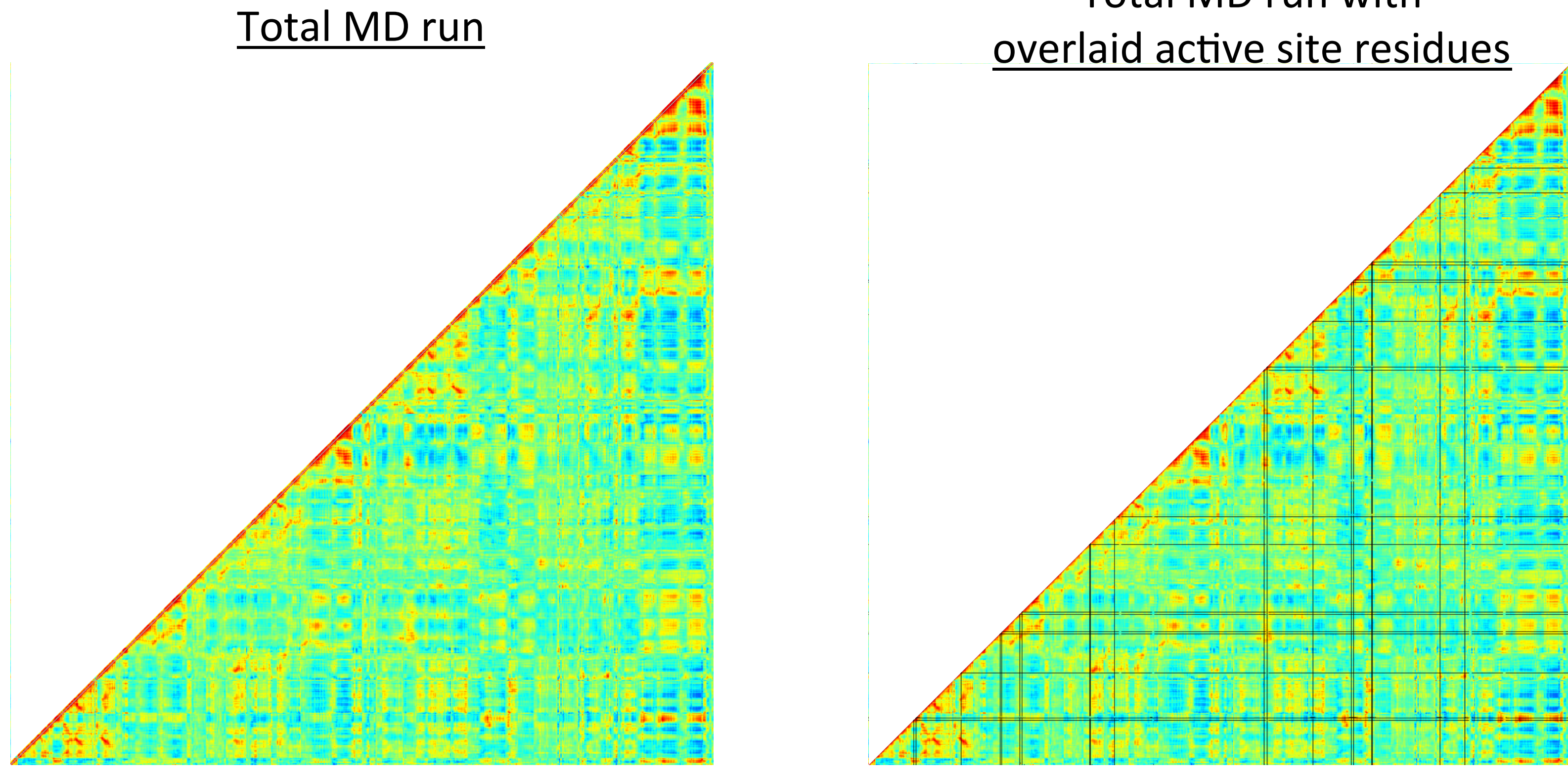


Figure 9. Correlation matrix generated from the full trajectory of molecular dynamics run. The correlation matrix highlights the relationship between the motion of a pair of alpha carbons in the dimer. Red highlights areas of high positive correlation, blue highlights areas of high negative correlation, and green means no correlation. Black lines indicate active site carbons.

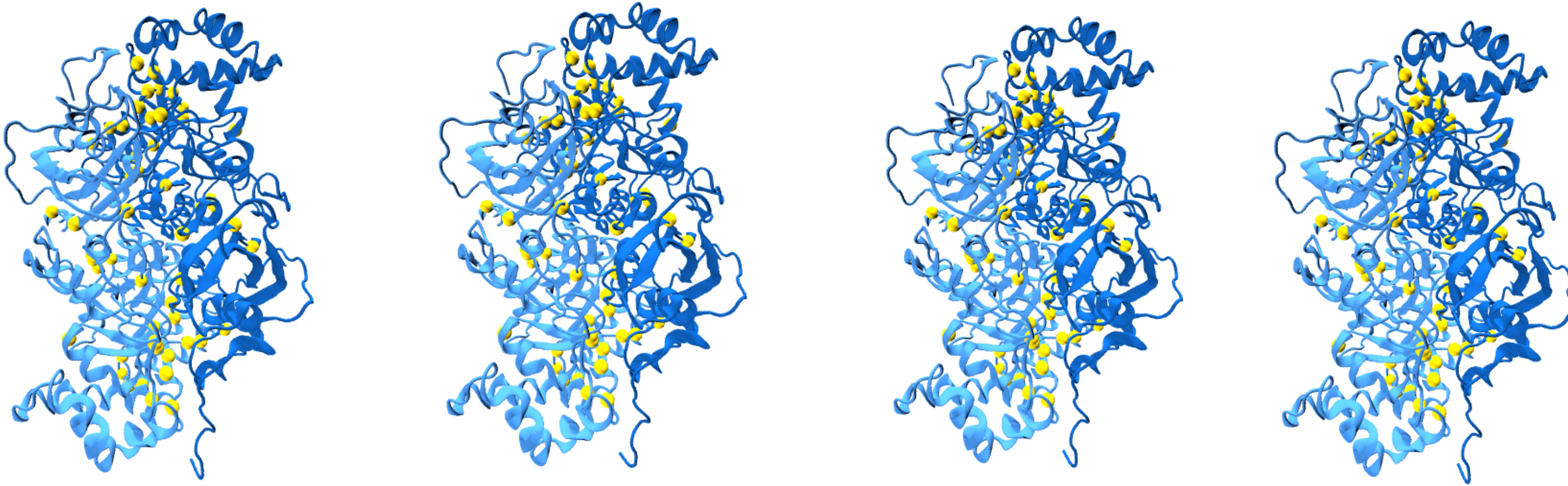


Figure 10. Snapshots of a principle component of the motion of the dimer generated through Normal Mode Analysis. Yellow spheres highlight the 50 residues in the dimer that are 90% or greater conserved among all forms of RuBisCo, and are therefore areas of high interest for further study.

Conclusions:

- MD simulations of RuBisCo can be run at Colby (Figures 8-10).
- Begun to characterize and analyze the motion of the L-subunit dimer. This motion can then be compared to Form II Rubisco.
- Clear correlation can be seen between active site motion and distant alpha carbon motion.

References

- [1] Structures and alignment from PDB structures 1RCX and 9RUB from L dimers. Kinetic parameters from Savier et al (2010) *PNAS* 107:3475 and Boeller et al (2011) *Geochim Cosmochi Acta* 75:7200.
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- [4] Tcherkez GGB et al (2006) *PNAS* 103:7246.
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