

Theoretical Studies of Acetyl-CoA Synthase Catalytic Mechanism

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Abstract: DFT calculations were performed for the A-cluster from the enzyme Acetyl-CoA synthase (ACS). The acid constants (pK_a), reduction potentials, and pH-dependent reduction potential for the A-cluster with different oxidation states and ligands were calculated. Good agreement of the reduction potentials, dependent on pH in the experiment, was obtained. On the basis of the calculations, a mechanism for the methylation reaction involving two-electron reduction and protonation on the proximal nickel atom of the reduced A-cluster is proposed.

Keywords: acetyl coenzyme A synthase; ACS; nickel; protonation; methylation; pK_a ; reduction potential; DFT

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Table S1. pK_a values calculated for different protonation sites in one and two-electron reduced A-cluster (Model M1, dielectric constant $\epsilon=20$). Atom numbering from Figure 3.

	A _{red1} -S7	A _{red1} -S2	A _{red1} -S1	A _{red1} -S6	A _{red1} -NiH
pK _a	-14.3	-7.4	-5.8	-6.3	-1.2
	A _{red2} -S7	A _{red2} -S2	A _{red2} -S1	A _{red2} -S6	A _{red2} -NiH
pK _a	-6.5	-1.9	3.9	3.4	15.6

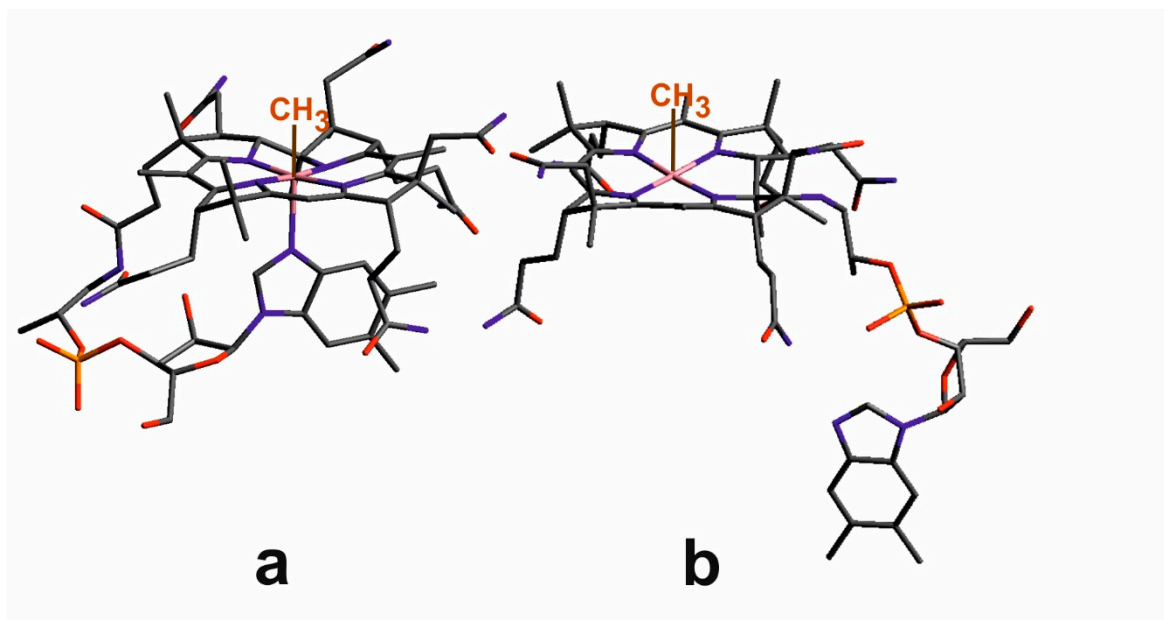


Figure S1. (a) *Base-on* methylcobalamin, (b) *Base-off* methylcobalamin.

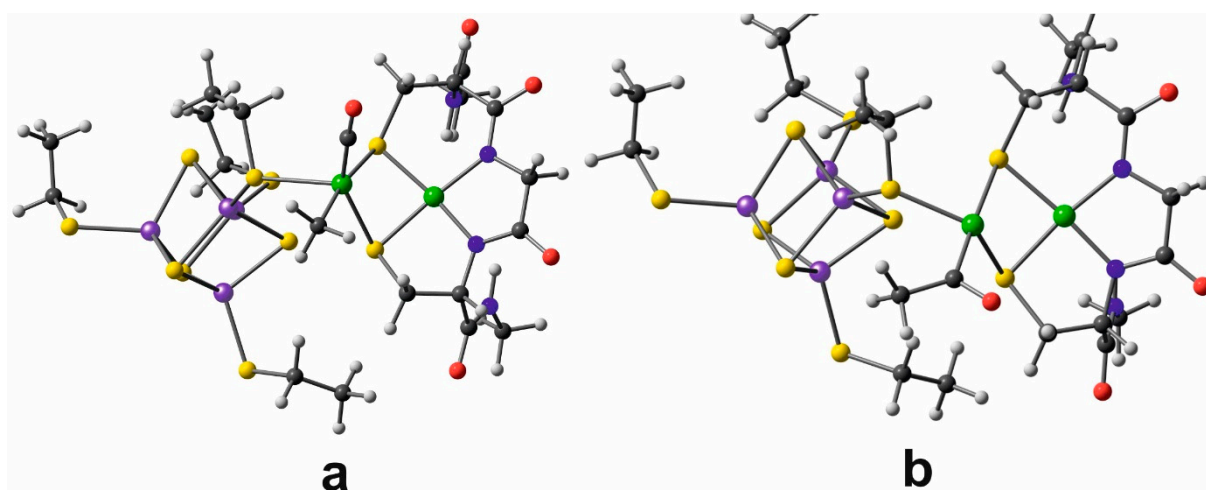


Figure S2. (a) Five-coordinate intermediate of the methylation and carbonylation reactions of the A-cluster, Fe₄S₄NiP(CH₃)(CO) (b) Acetyl derivative of the A-cluster, Fe₄S₄NiP-acetyl.

Table S2. pKa values calculated for M1 and M2 models.

ϵ	20	80	20	80
	M1 ^{a)}		M2 ^{a)}	
A_{red1-}	5.1	1.5	−1.2	−2.6
A_{red2-}	17.4	12	15.6	12.6
	M1-L ^{a)}		M2-L ^{a)}	
$A_{red1-HCOO(H_2O)}$			11.5	7.3
$A_{red1-HCOO(4H_2O)}$			6.1	3.0
$A_{red1-H_2O(4H_2O)}$			0.6	2.2
$A_{red2-HCOO}$	26.6	18.9	18.8	11.9
$A_{red2-HCOO(H_2O)}$			33.6	26.2
$A_{red2-HCOO(4H_2O)}$			29	23.3
$A_{red2-OH(4H_2O)}$			32.6	25.5
$A_{red2-H_2O(4H_2O)}$			16	16.8
	M1-OH/M1-H ₂ O ^{b)}		M2-OH/M2-H ₂ O ^{b)}	
A_{ox-OH}	12.8	9.2	9.1	7.2
$A_{ox-OH(4H_2O)}$	8.9	7.1		
$A_{ox-OH(4H_2O)}$	17.5	14		

a) Protonation on Nip; b) Protonation on hydroxyl ligand.

Table S3. Reduction potentials of the M1 And M2 models versus NHE (in V).

ϵ	20	80	20	80
E_0	(A_{ox}/A_{red1})		(A_{red1}/A_{red2})	
M1	−0.553	−0.353	−1.195	−0.859
M2	−0.324	−0.232	−1.052	−0.849
			L=HCOO [−]	
M1--L	−1.358	−1.021	−1.930	−1.467
M2--L	−1.065	−0.839	−1.384	−1.045
M2--L(H ₂ O)	−0.960	−0.755	−1.479	−1.152
M2--L(4H ₂ O)	−0.894	−0.701	−1.532	−1.231
			L=OH [−]	
M2--L(4H ₂ O)	−1.104	−0.892	−1.669	−1.351
			L=H ₂ O	
M2--L(4H ₂ O)	−0.591	−0.482	−1.279 ^{a)} (−0.879 ^{b)})	−1.060 ^{a)} (−0.766 ^{b)})
			L=CH ₃	
M1-CH ₃			−0.200	
M2-CH ₃			−0.071	

a) A_{red2-H_2O} product; b) $A_{red2H-OH}$ product.