Enzymatic reaction – computational approach

Antonija Tomić & Borislav Kovačević

DPP III Minisymposium

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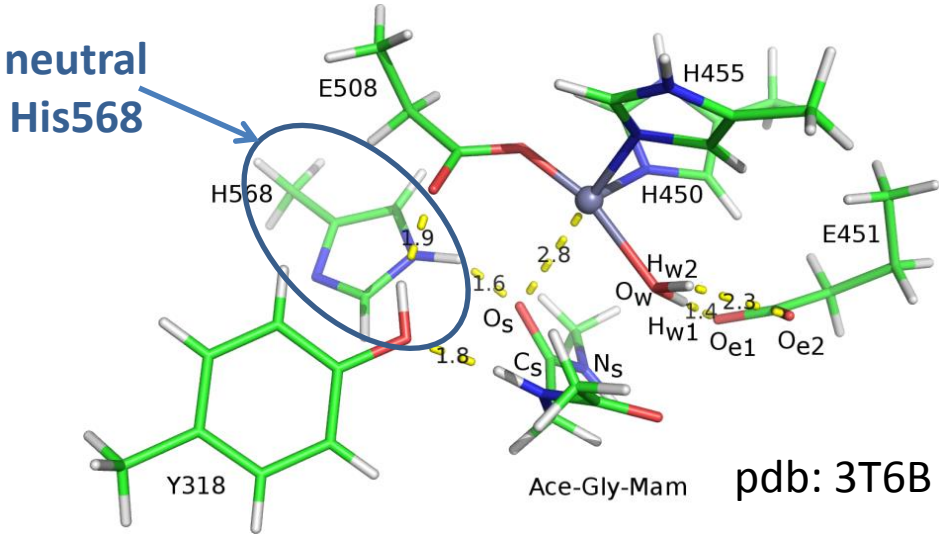
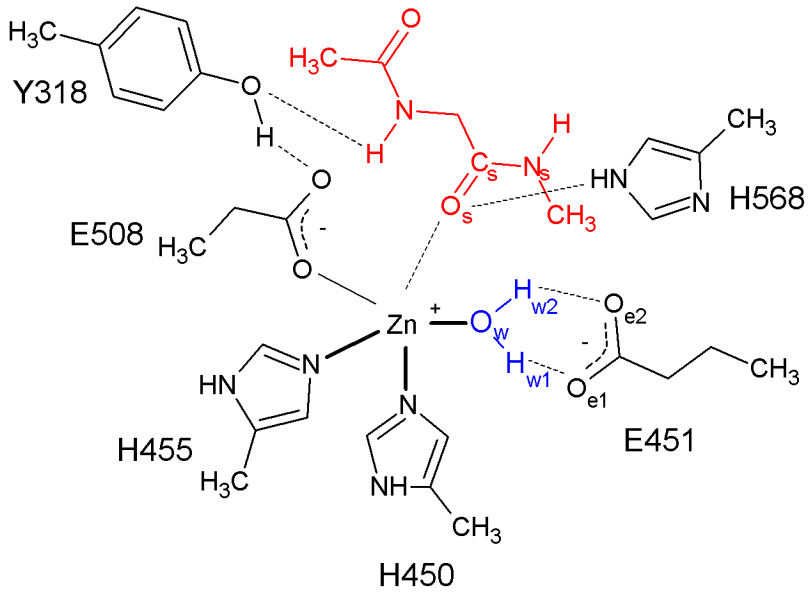
QM calculations

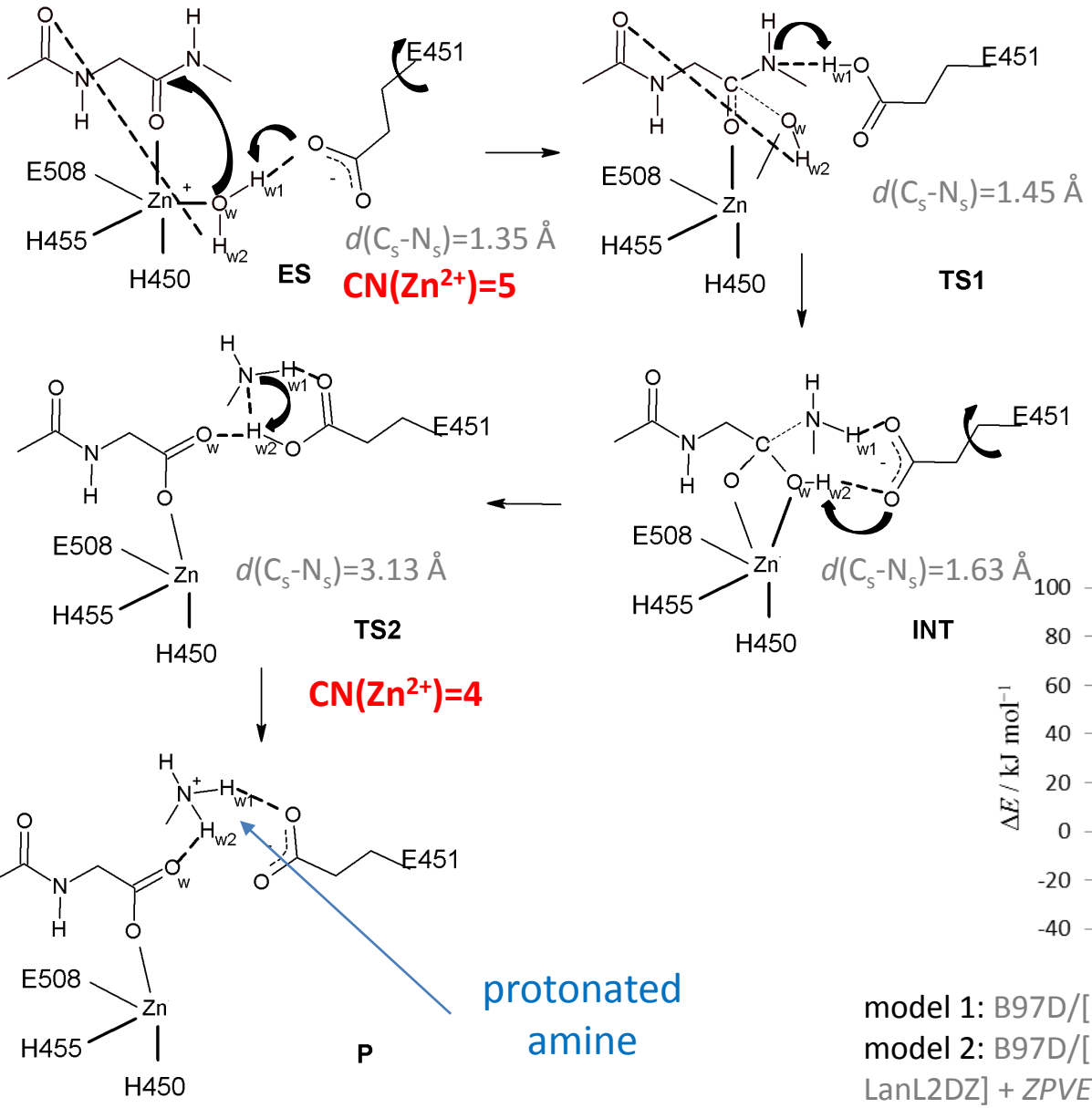




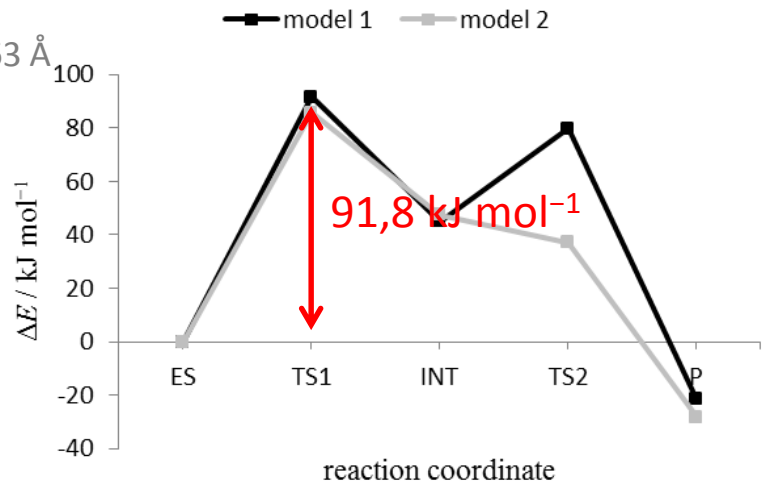
- Minima (ES, INT, P)→ *scan* method
- Maxima (TS) → *Quadratic Synchronous Transit* method (QST)
- Vibrational analysis
- Intrinsic reaction coordinate, IRC
- Levels of theory:
  - **1. opt.**: B97D/[6-31G + LanL2DZ]
  - **2. opt:** B97D/[6-31G(d) + LanL2DZ]
  - **SP:** B97D/[6-311++G(d,p) + LanL2DZ]

➢ CPCM (ε=4)

B97D/[6-31G + LanL2DZ]



	ΔE / kJ mol^{-1}	
system	model 1	model 2
ES	0.0	0.0
TS1	91.8	85.7
INT	45.2	47.4
TS2	79.7	37.3
P	−21.5	−28.3



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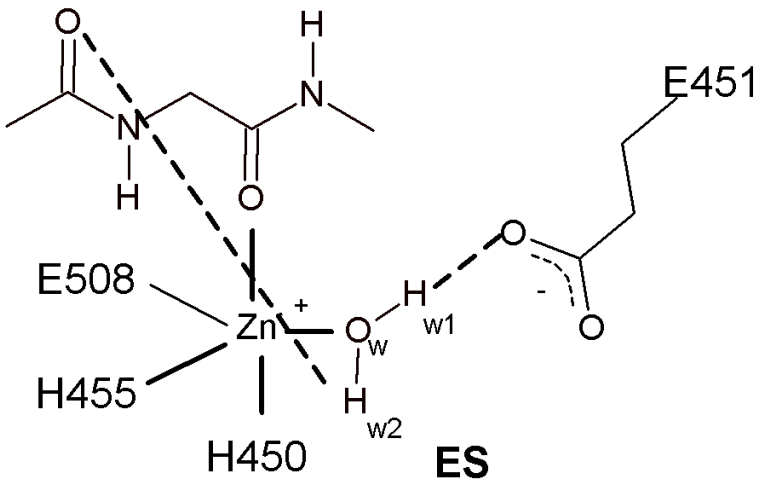

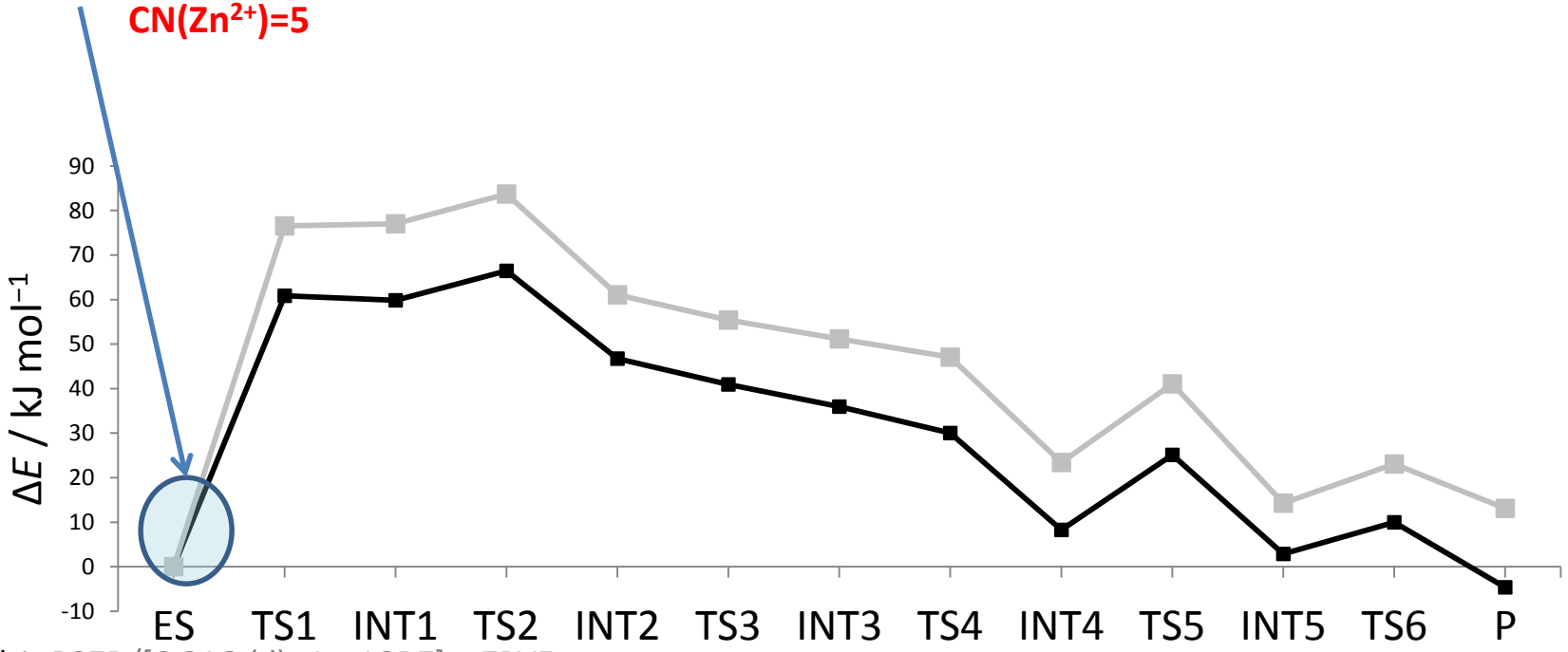

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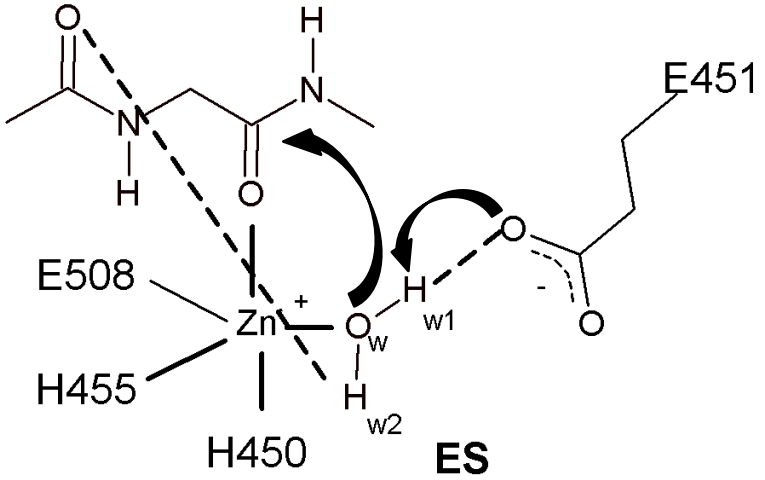

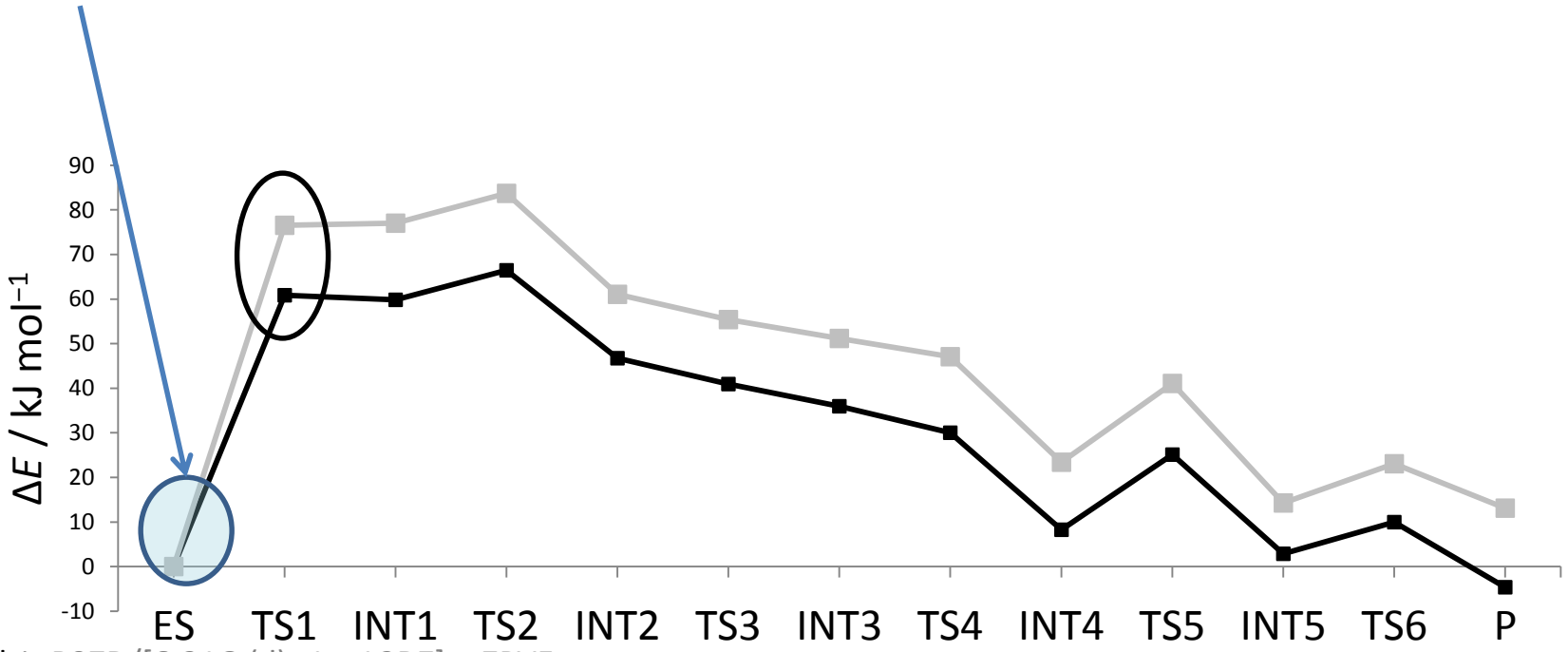

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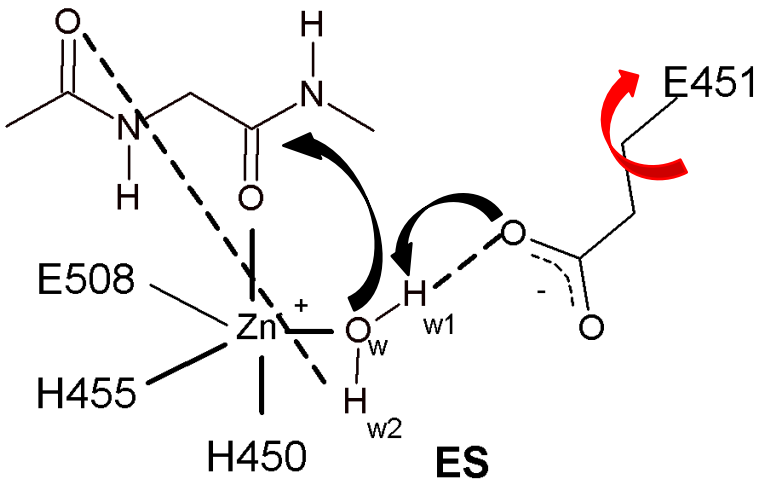

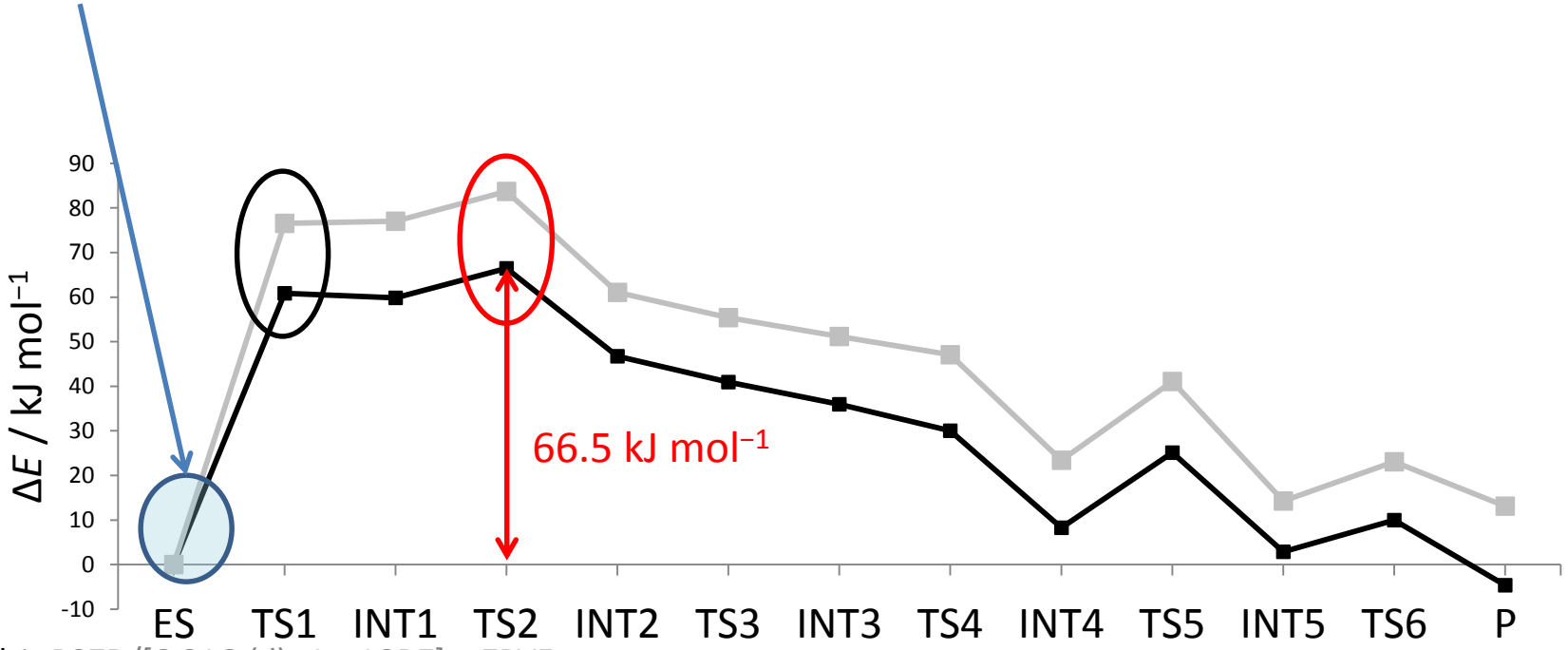

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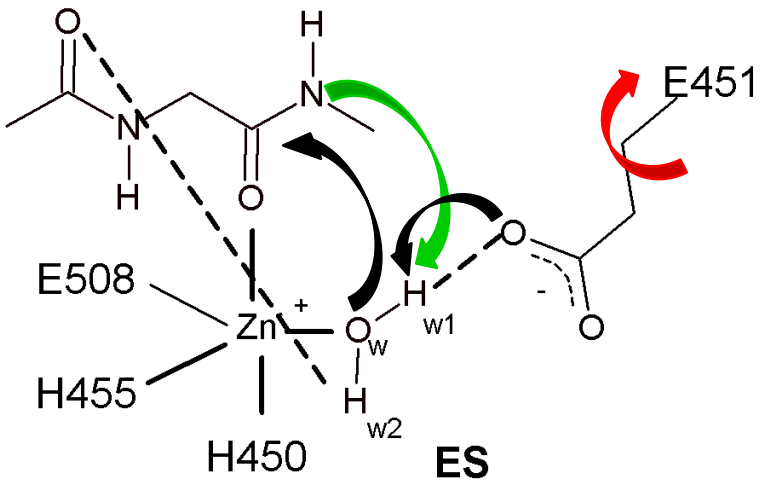

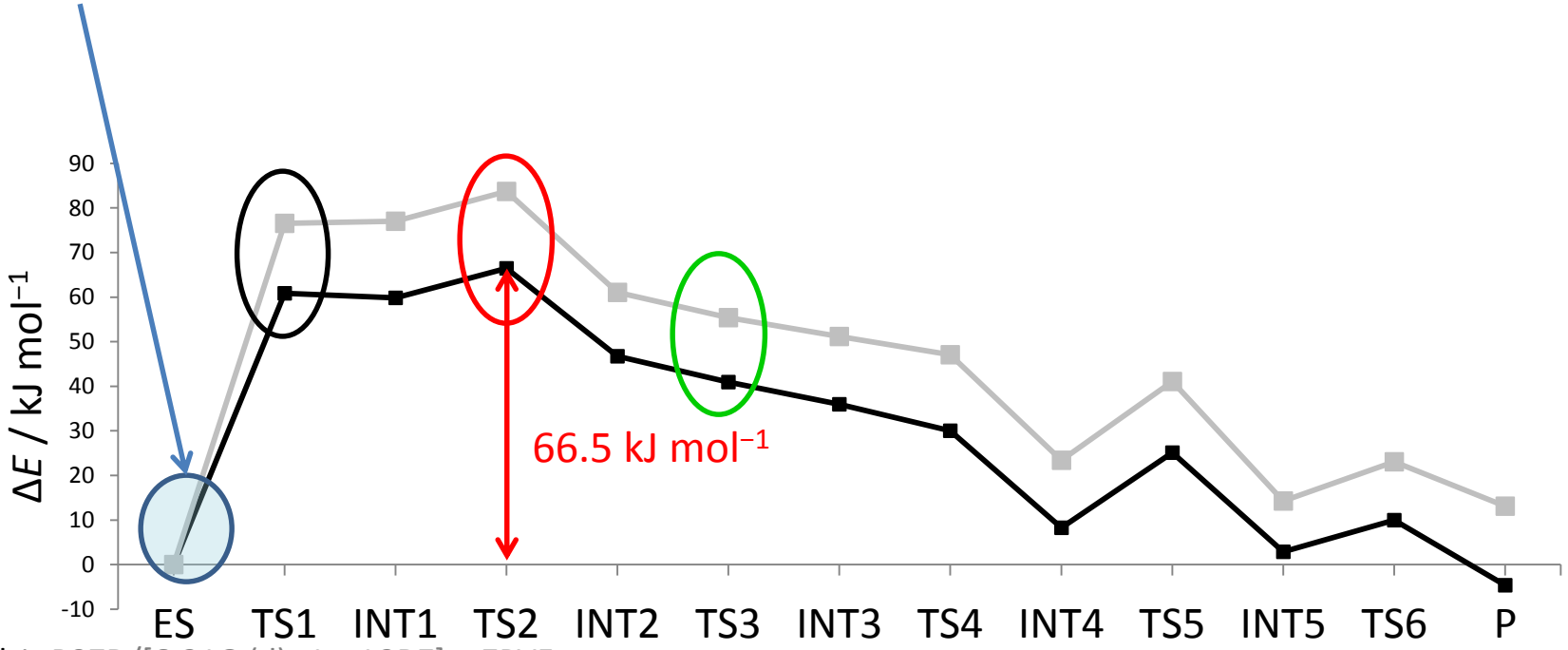

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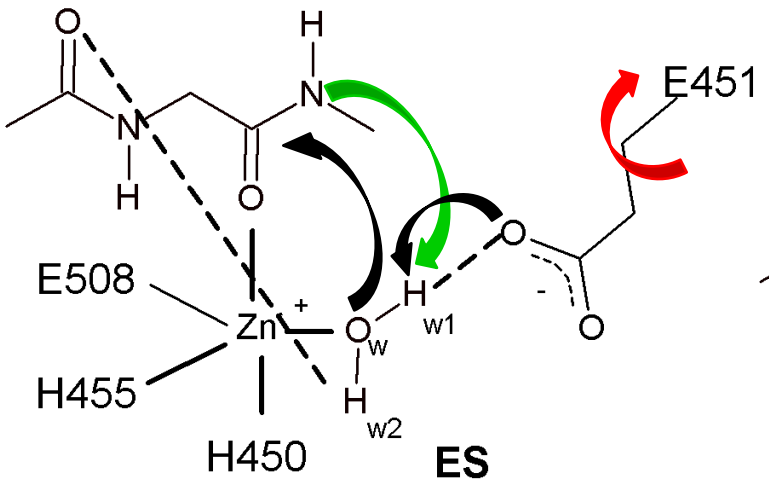
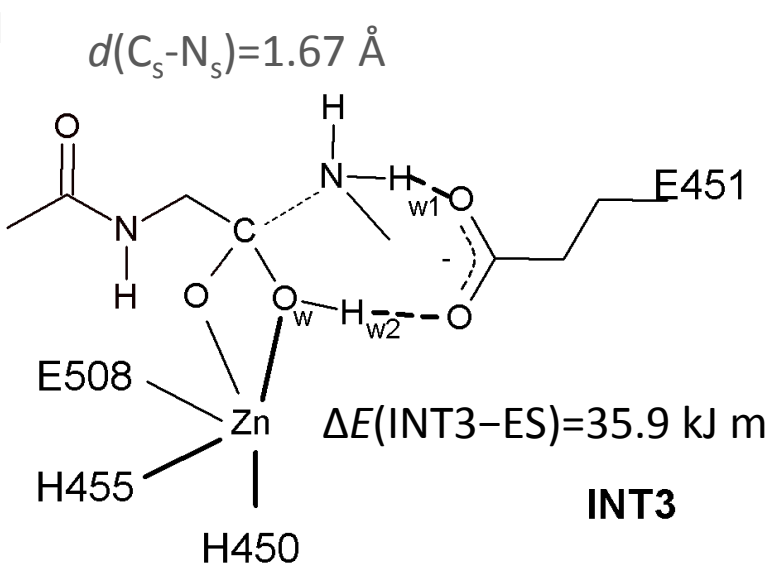
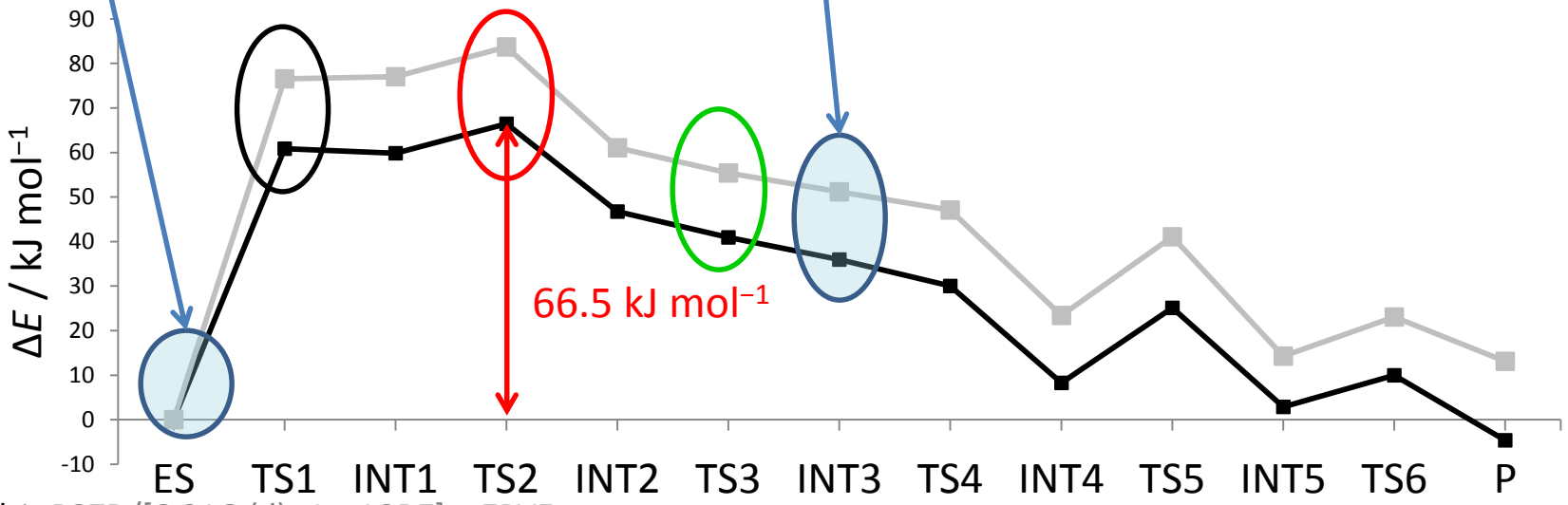




ΔE(INT3−ES)=35.9 kJ mol^{-1}



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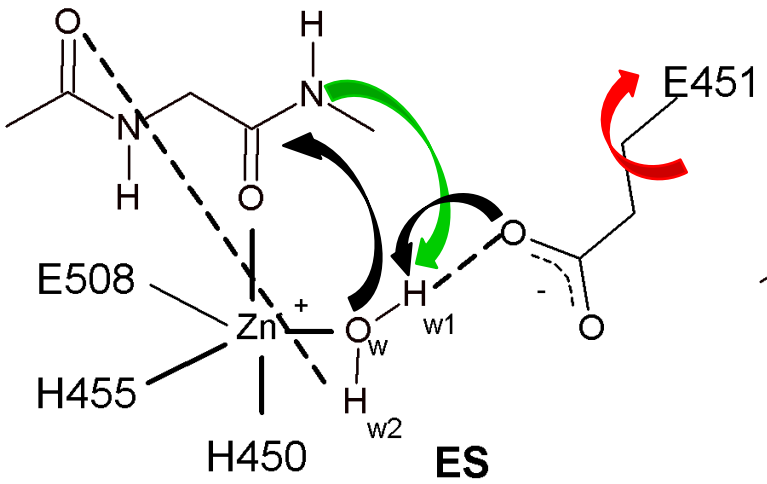

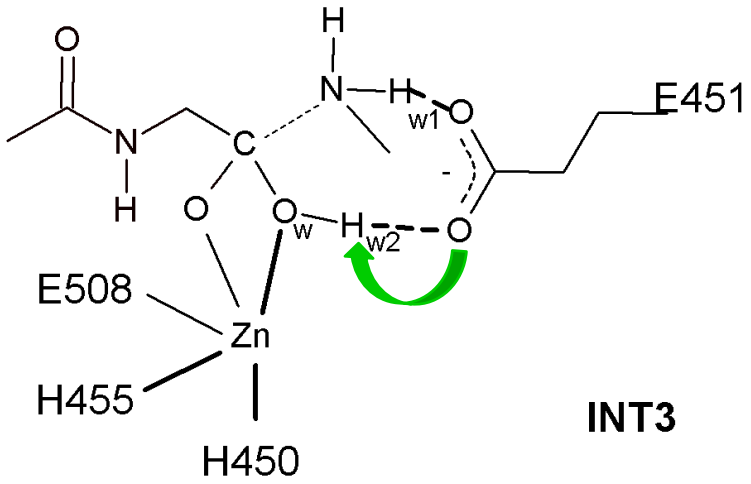

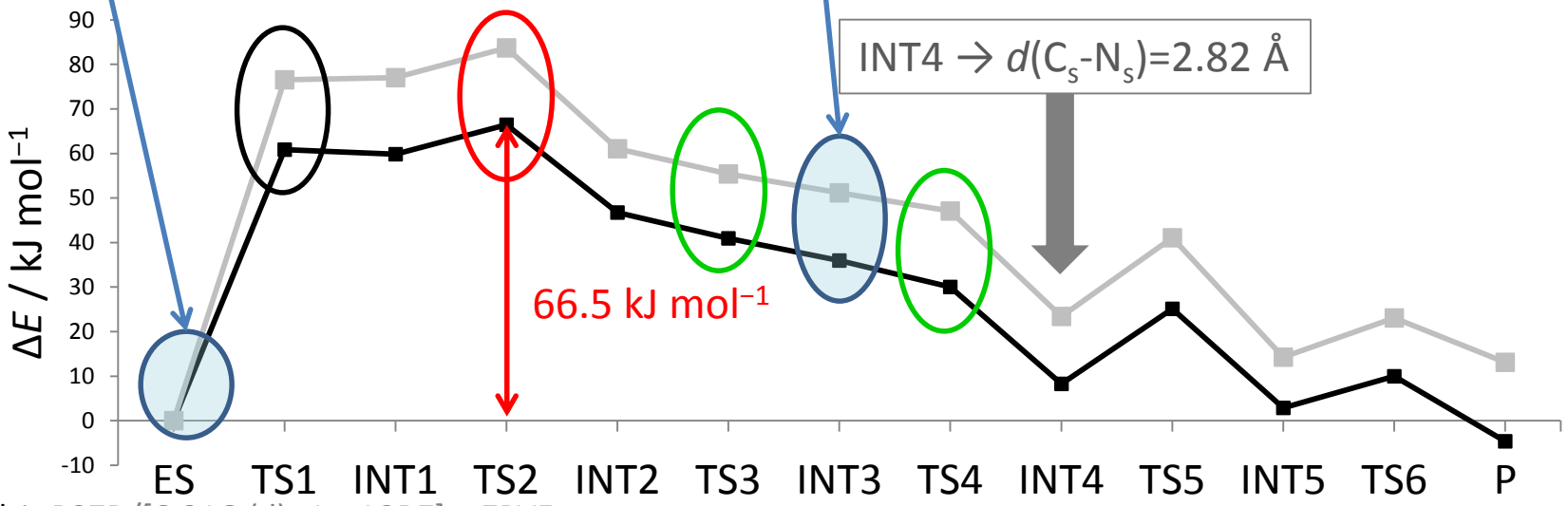

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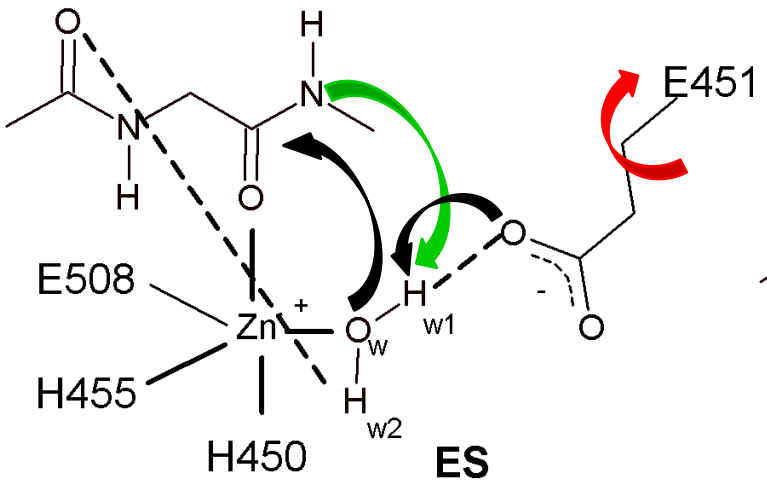

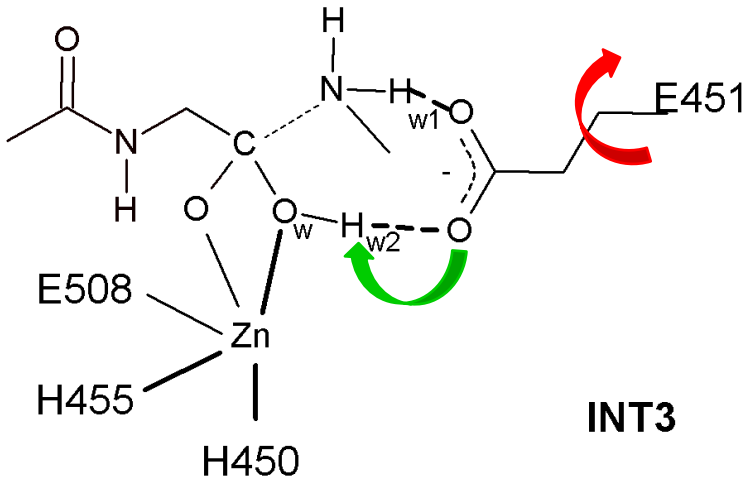

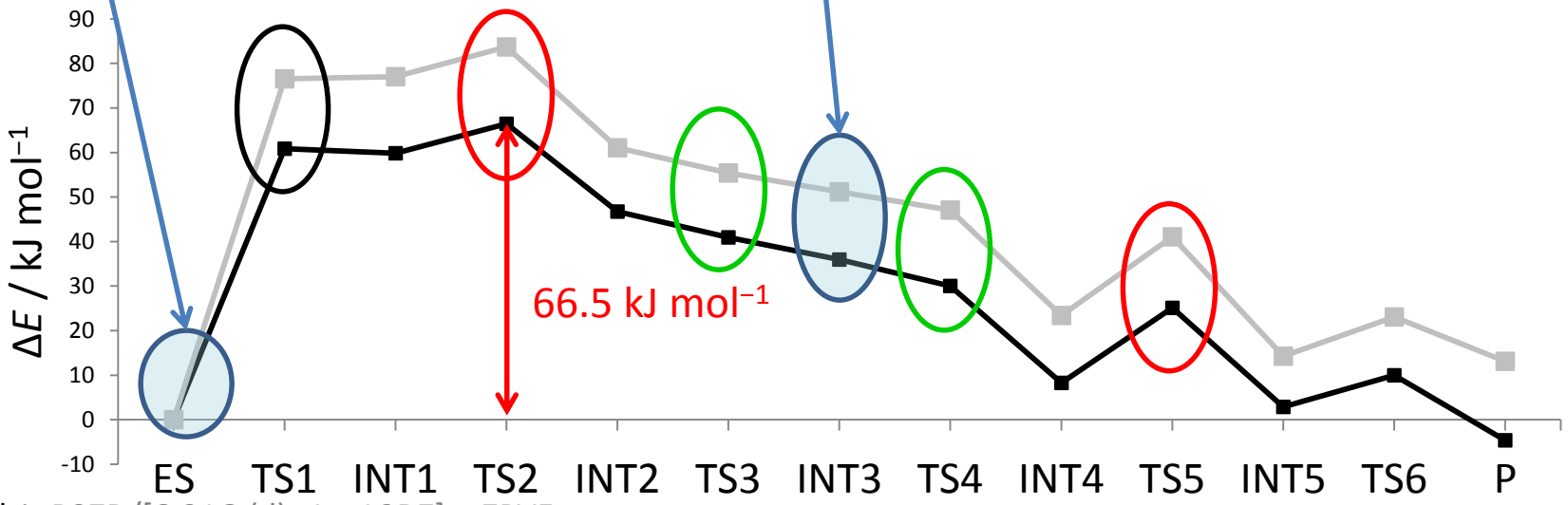

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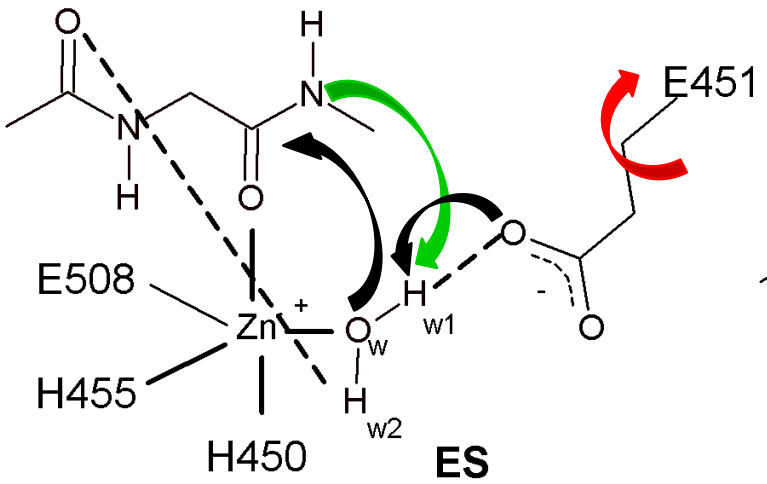

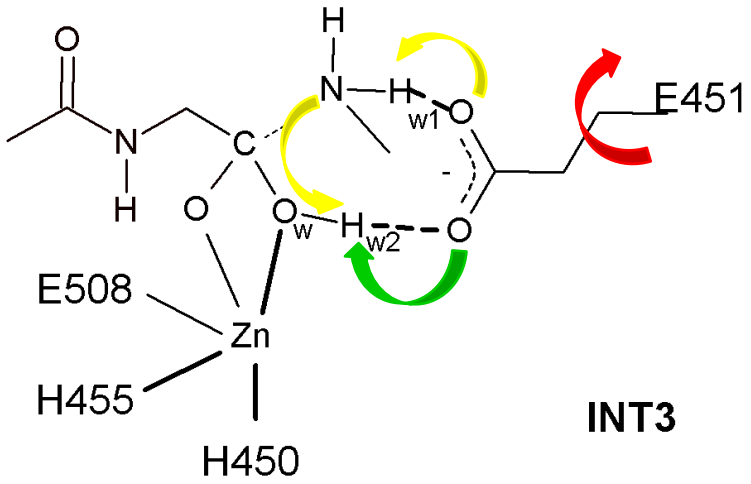

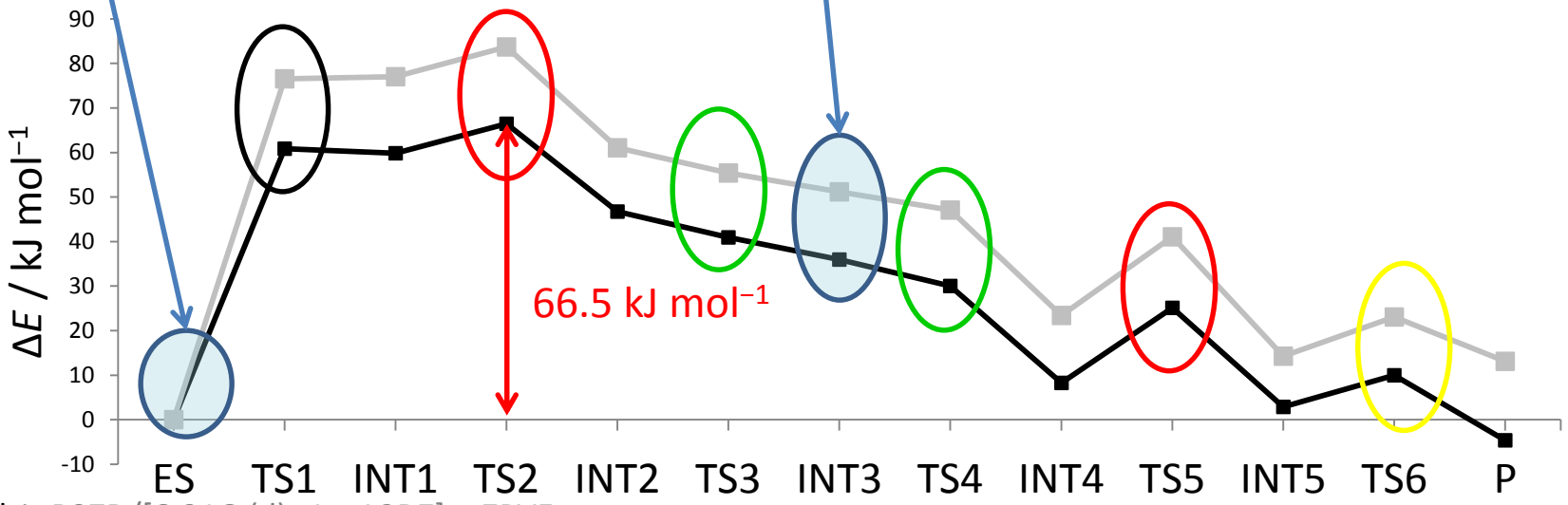

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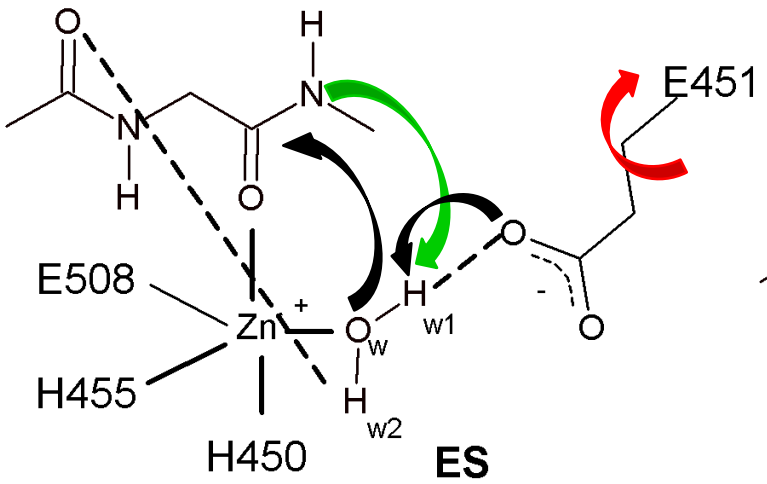
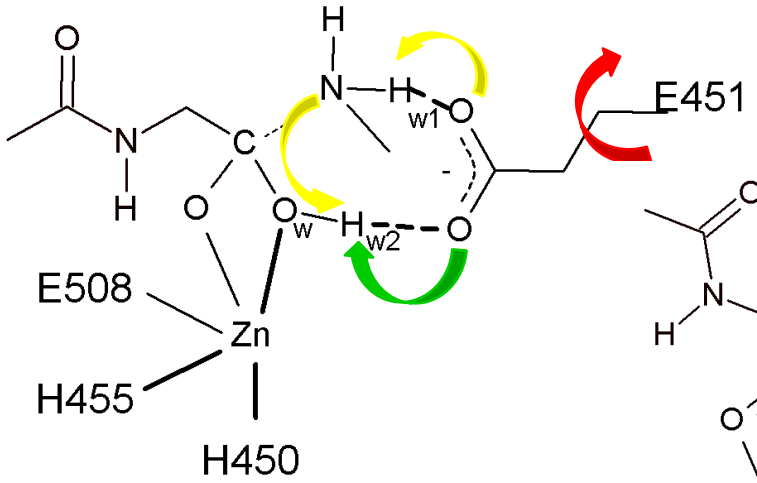
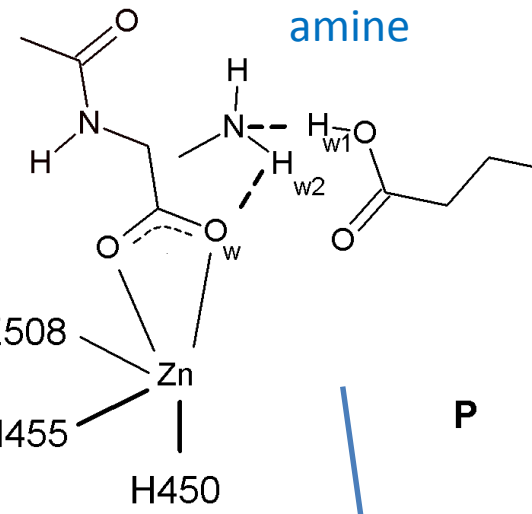
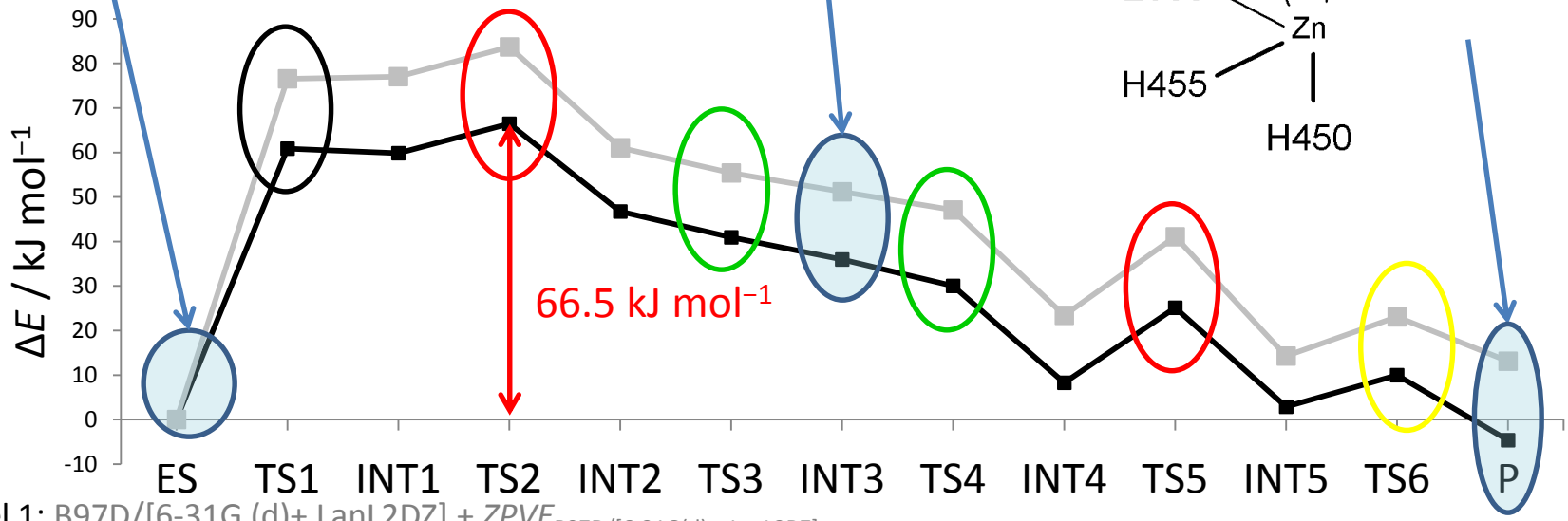




neutral amine





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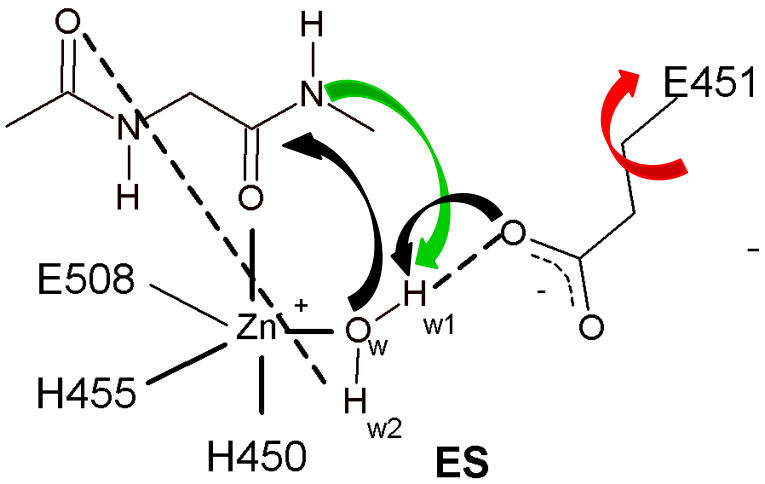
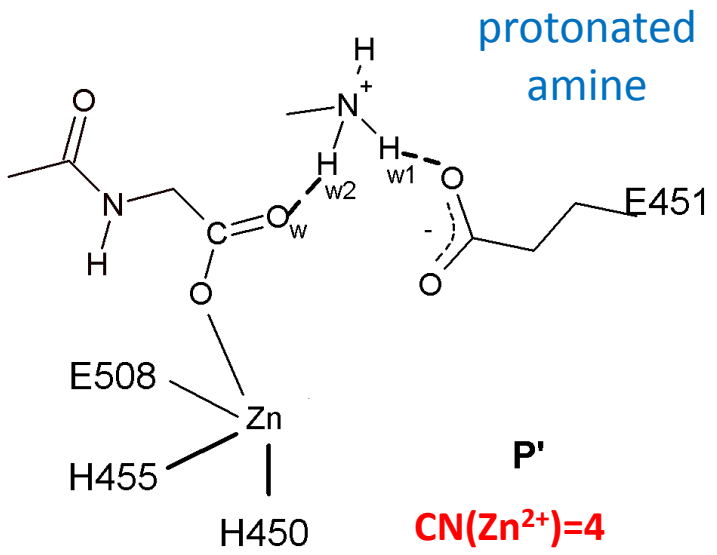
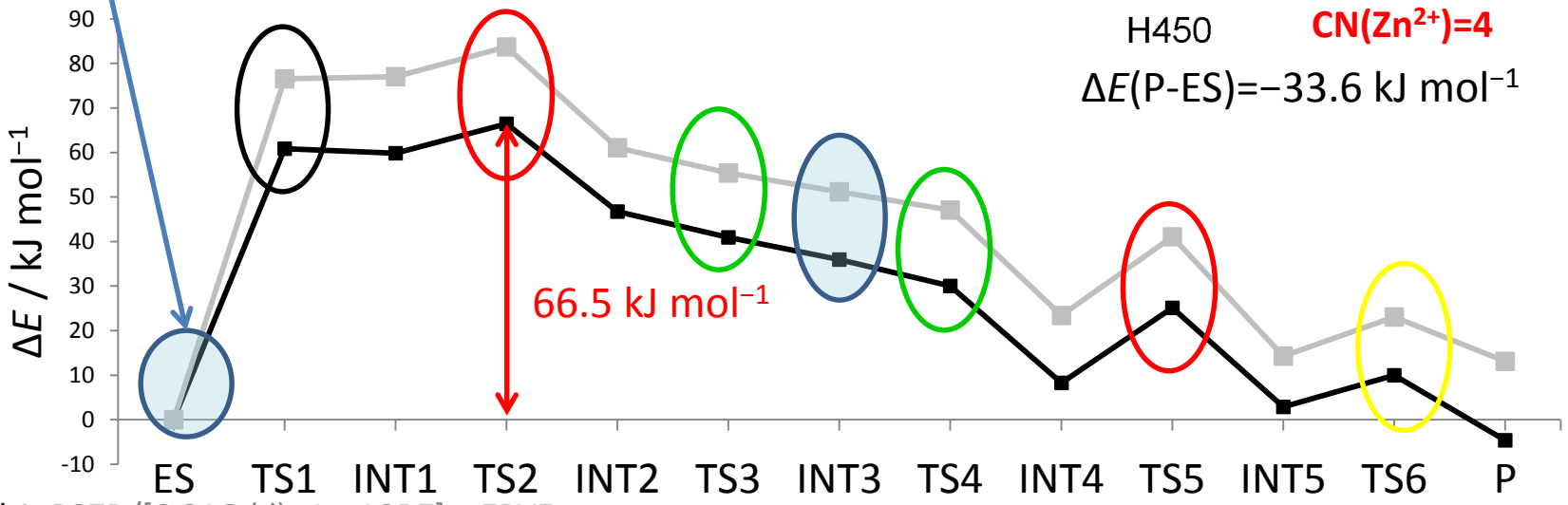




ΔE(P-ES)=−33.6 kJ mol^{-1}



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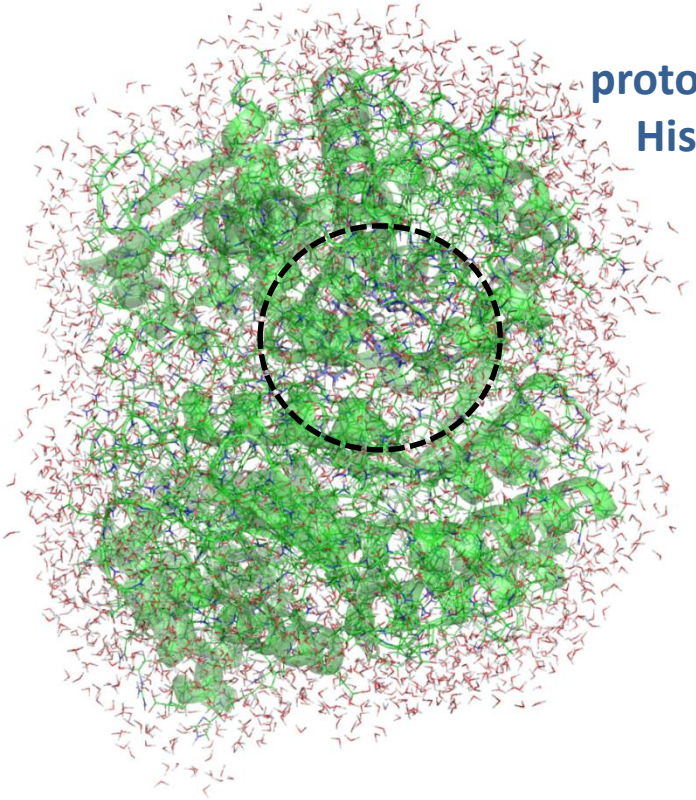
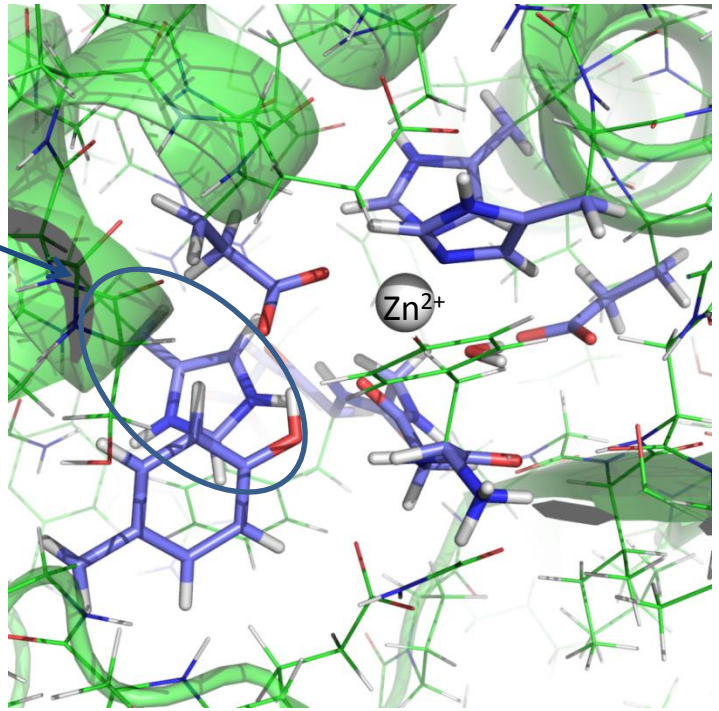
QMMM calculations



protonated
His568

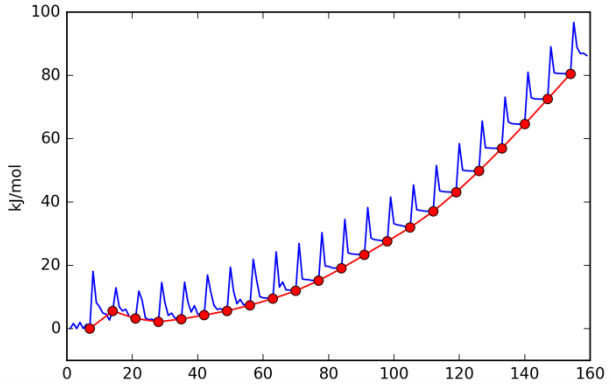


- SYSTEM = enzyme + Leu-enkephalin + water
- 105/6 QM atoms
- ONIOM calculations:

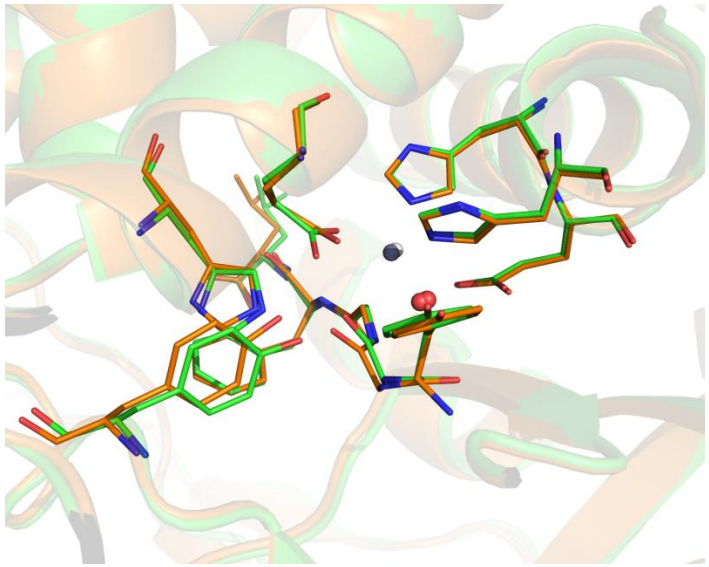
$$E^{\mathrm{ONIOM}}=E_{\mathrm{MM}}(\mathrm{S})+E_{\mathrm{QM}}(\mathrm{SM})-E_{\mathrm{MM}}(\mathrm{SM})$$

- B97D/[6-31G(d) + LanL2DZ]

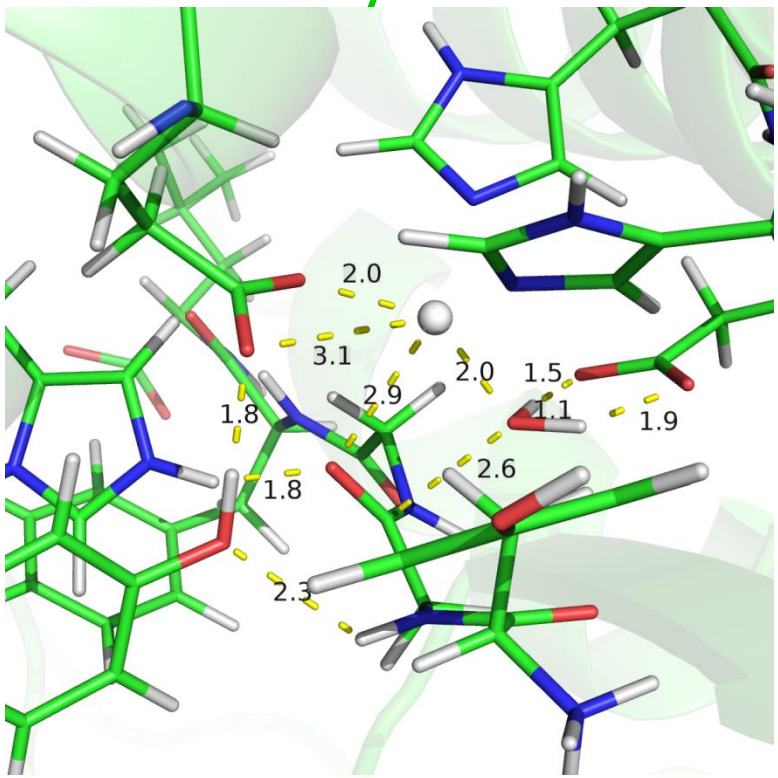
Reaction profile with neutral His568?



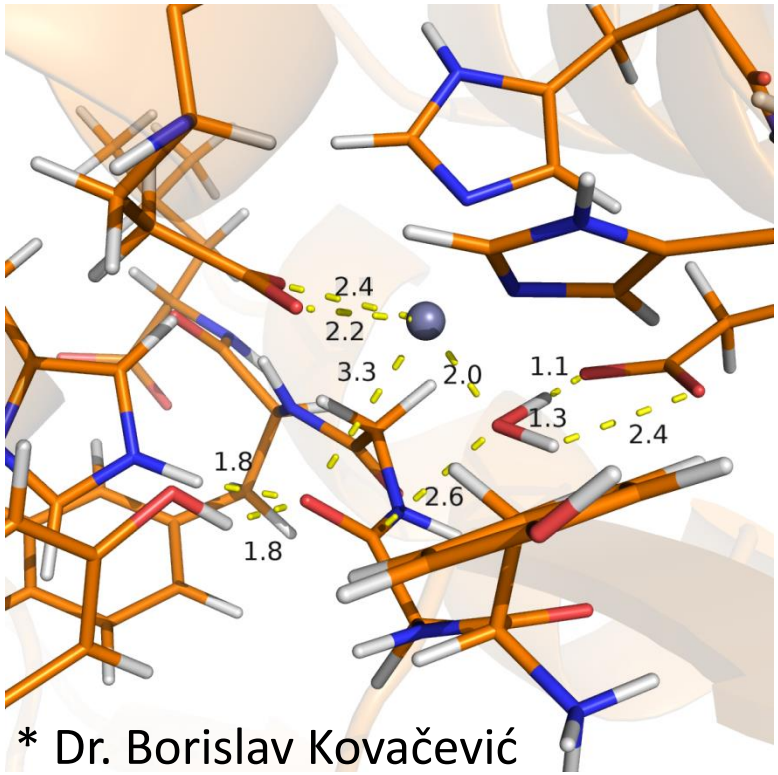
REACTION MECHANISM
with two ES structures:
MD
MD + X-ray



- MD – X-ray ES structure



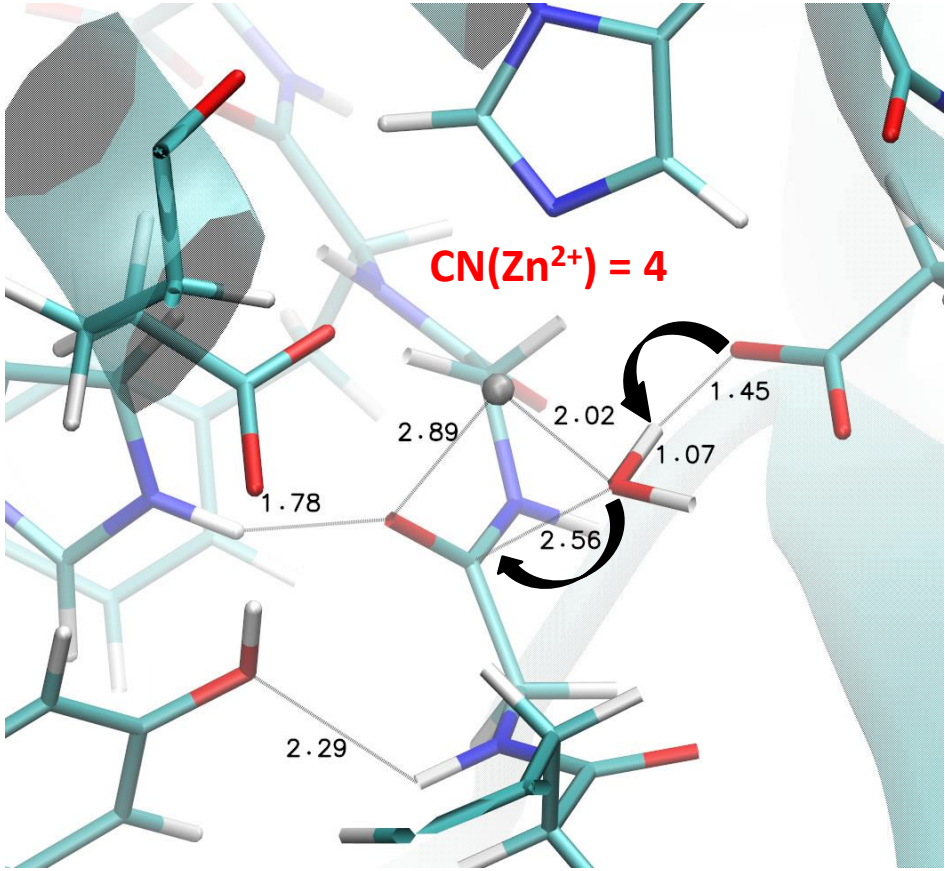
- MD ES structure*



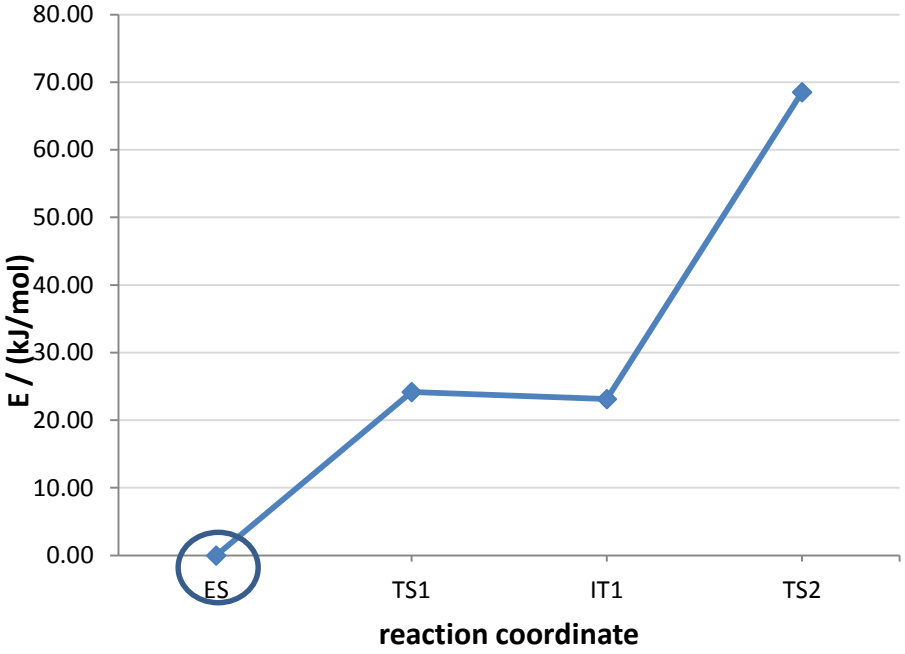
* Dr. Borislav Kovačević

MD – X-ray ES structure

ES

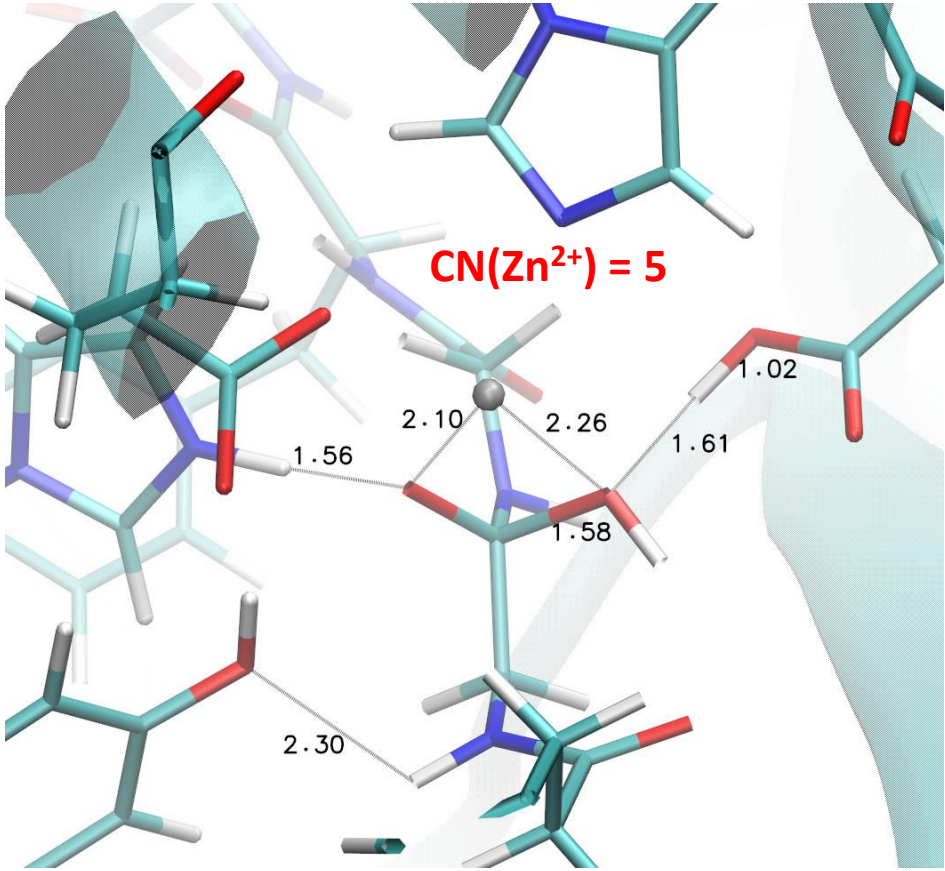


$d(C_s\text{-}N_s)$=1.36 Å

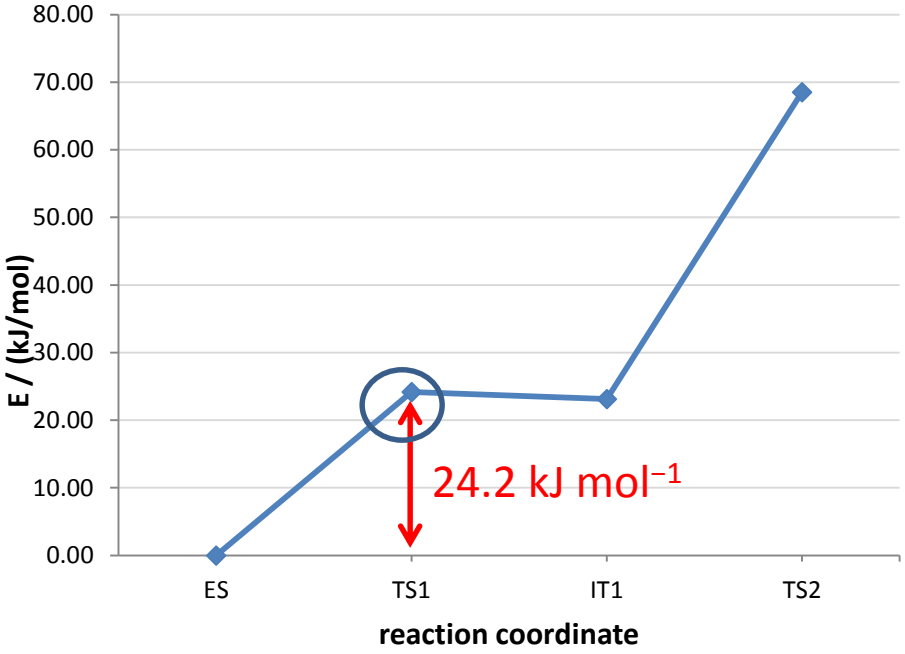


MD – X-ray ES structure

TS1

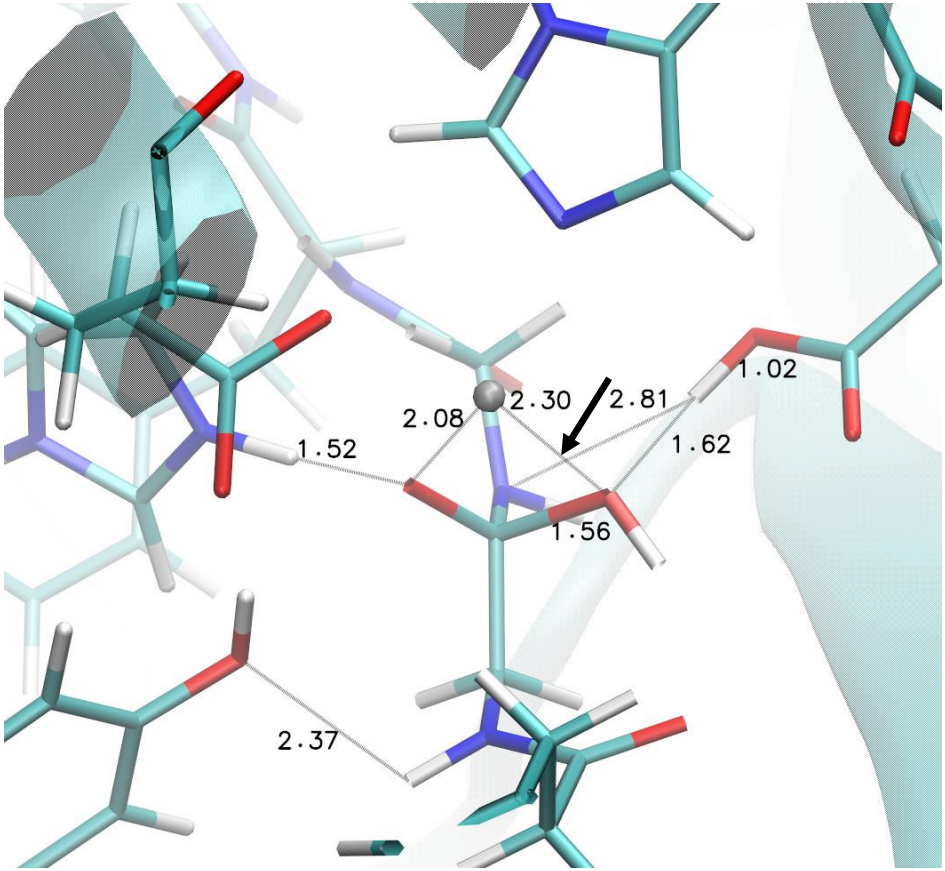


$d(C_s\text{-}N_s)$=1.42 Å

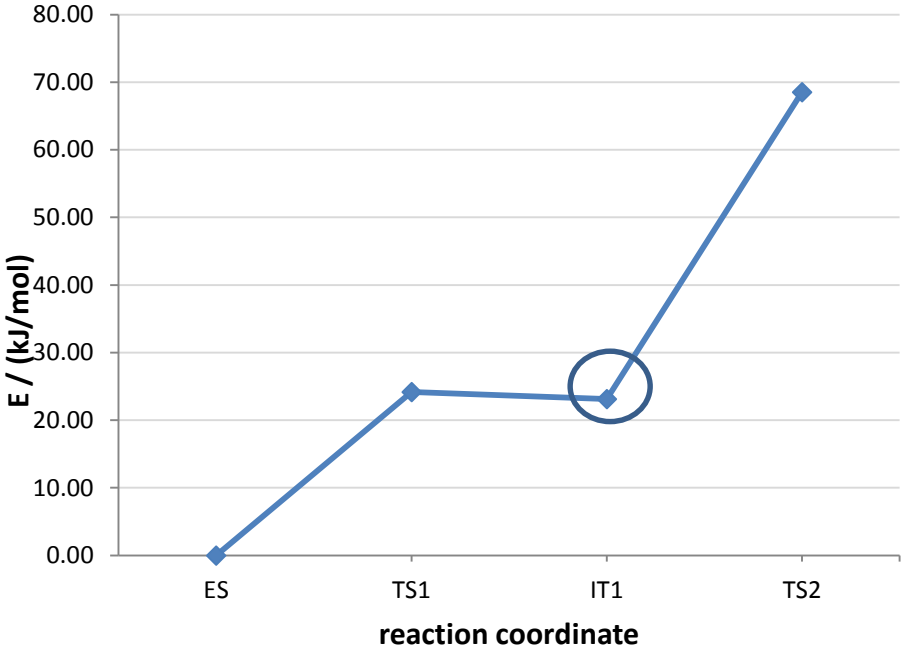


MD – X-ray ES structure

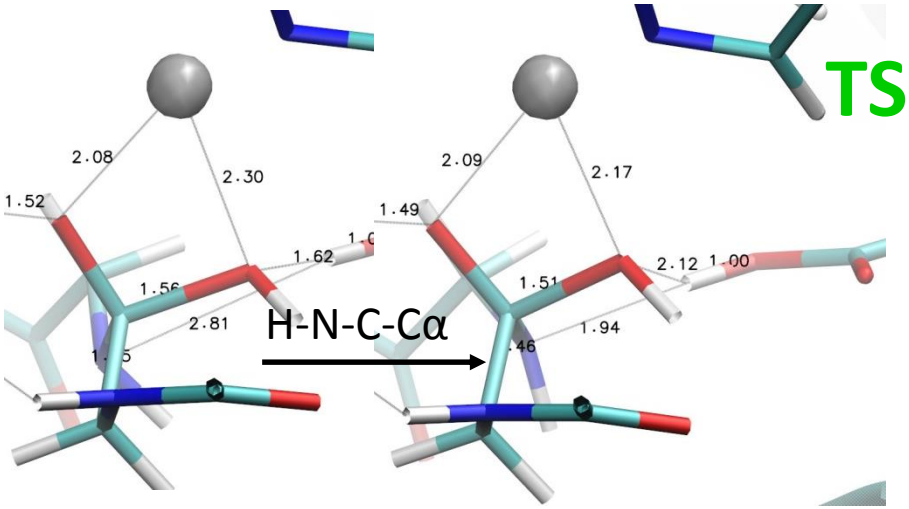
IT1



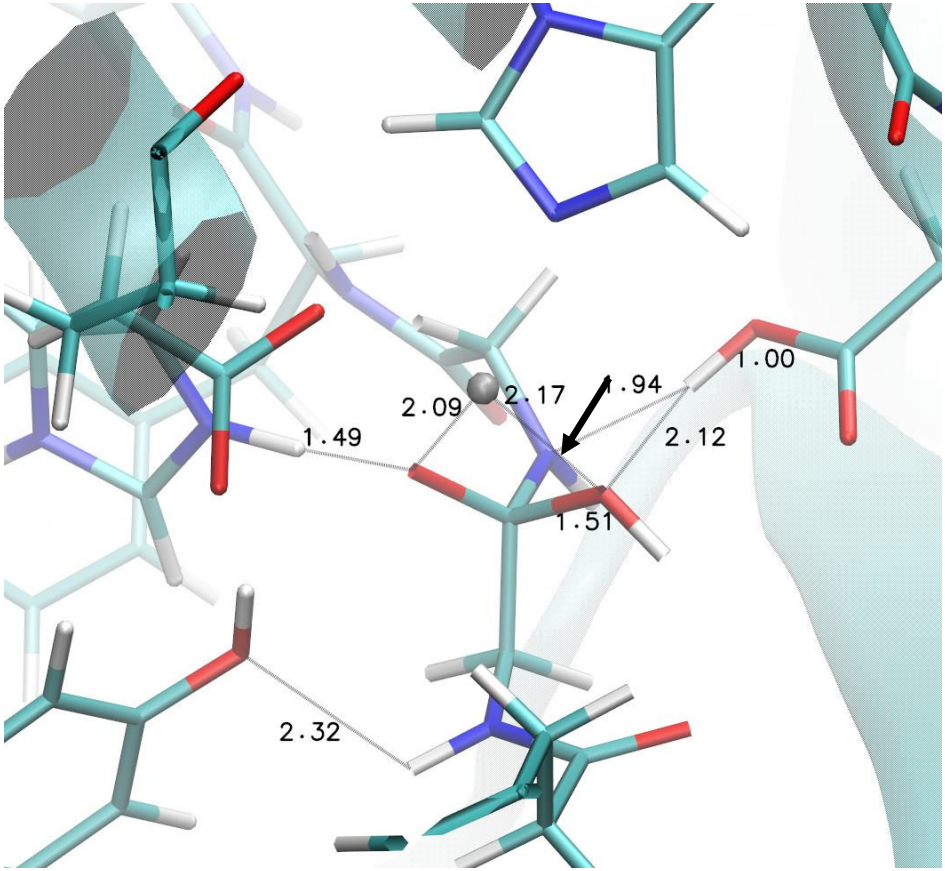
$d(C_s\text{-}N_s)$=1.44 Å

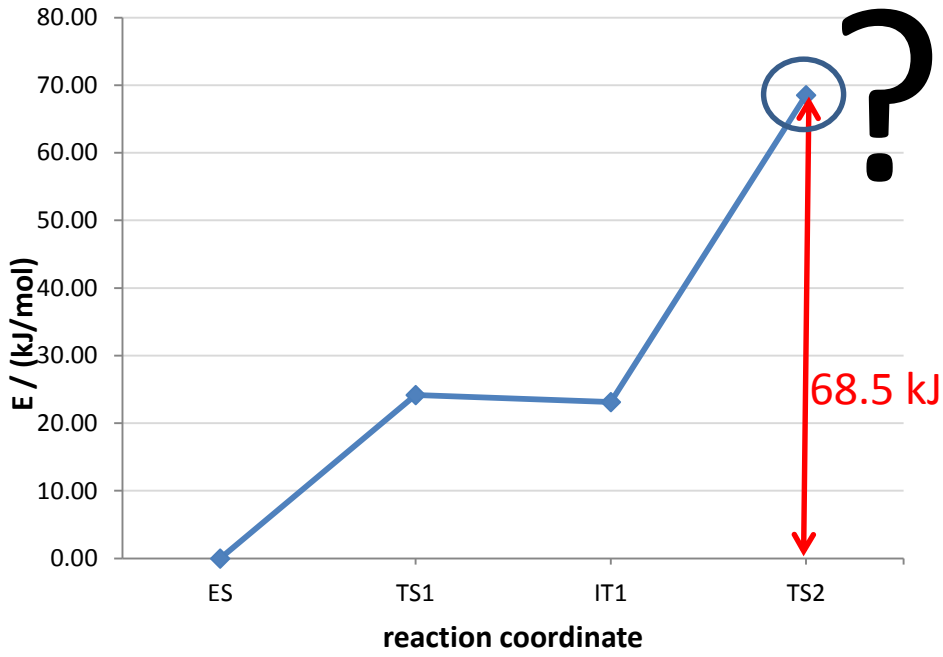


MD – X-ray ES structure



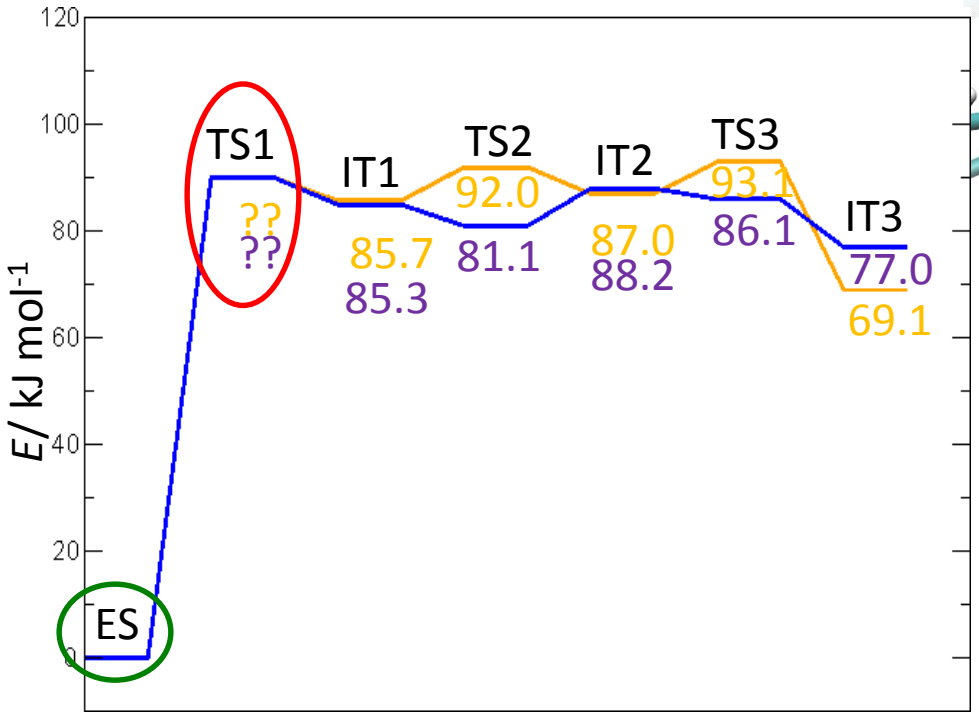
TS2



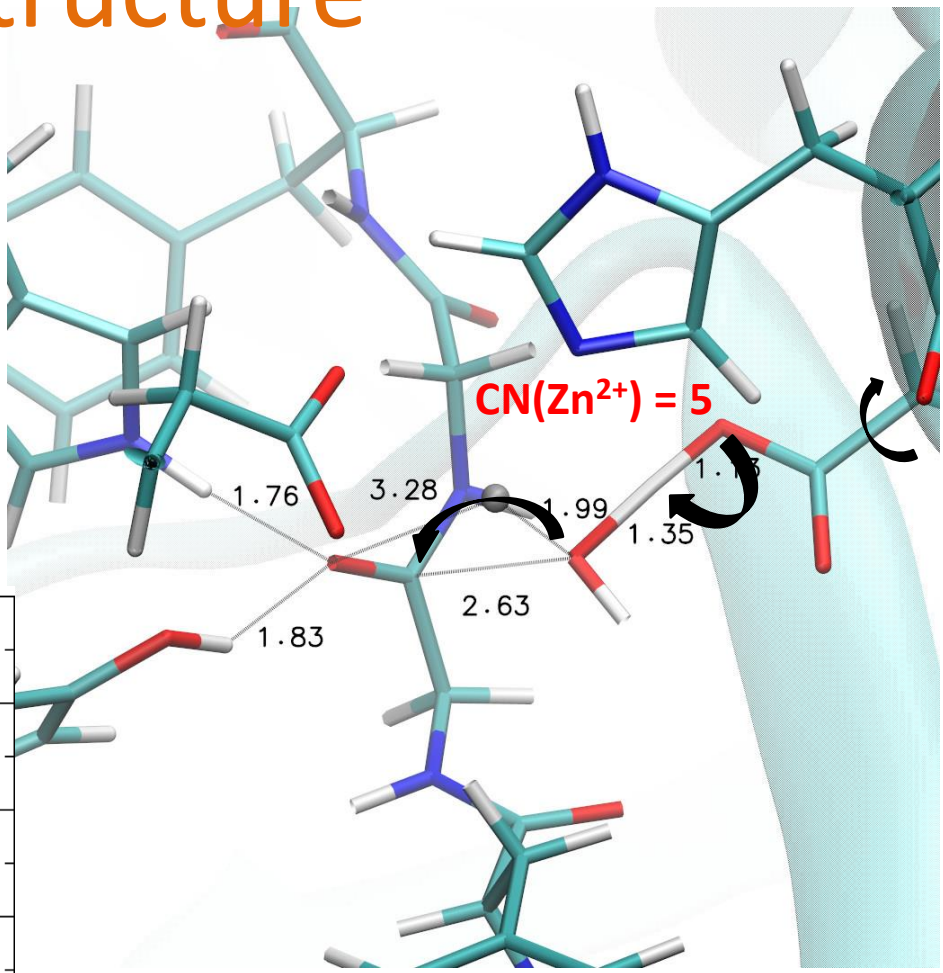


$d(C_s\text{-}N_s)$=1.46 Å

MD ES structure

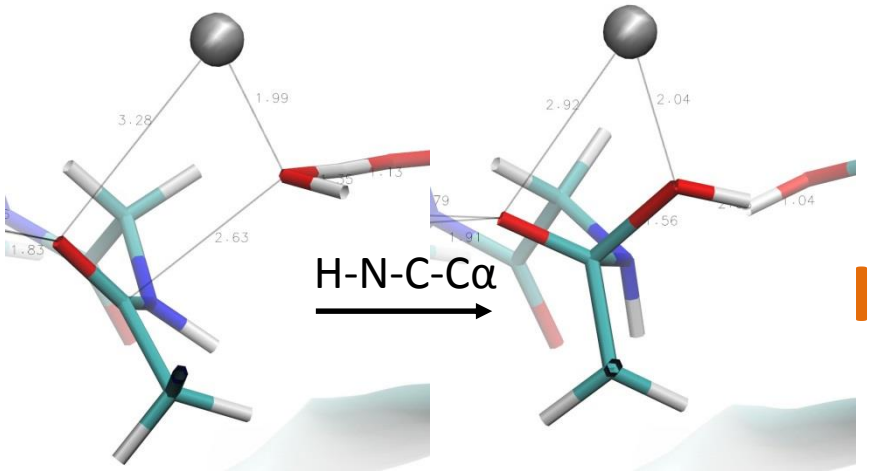


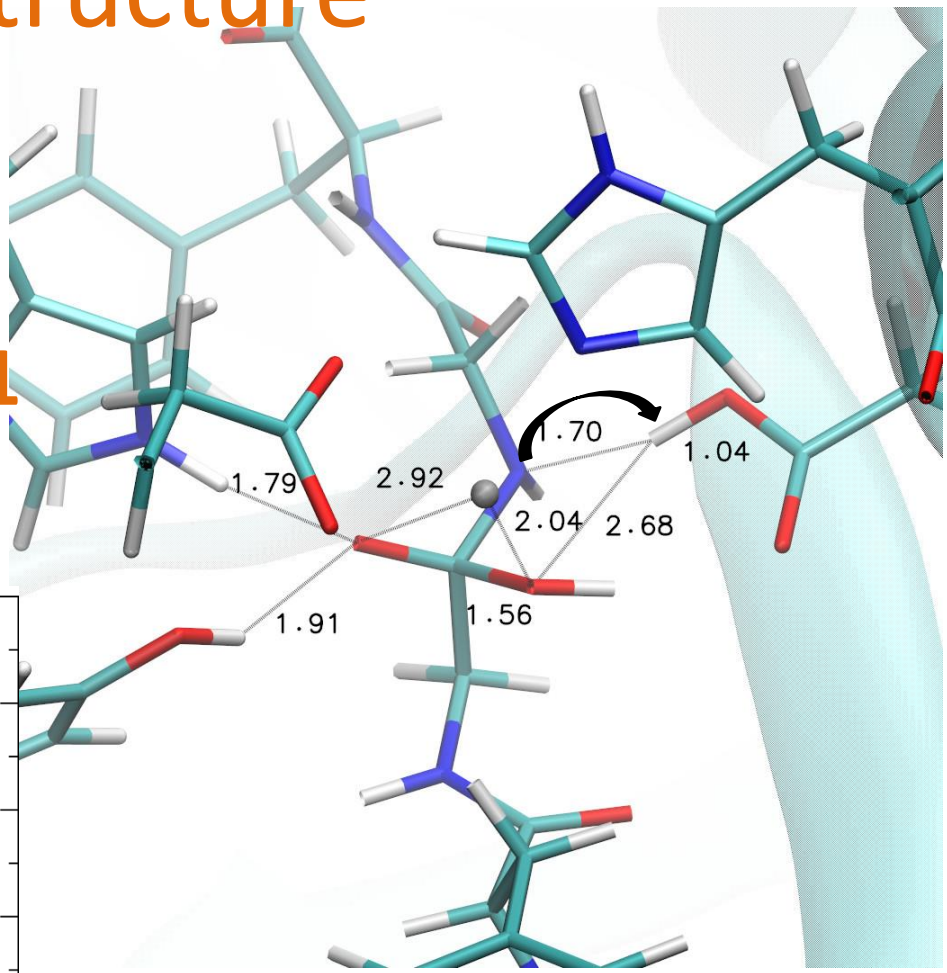
ES



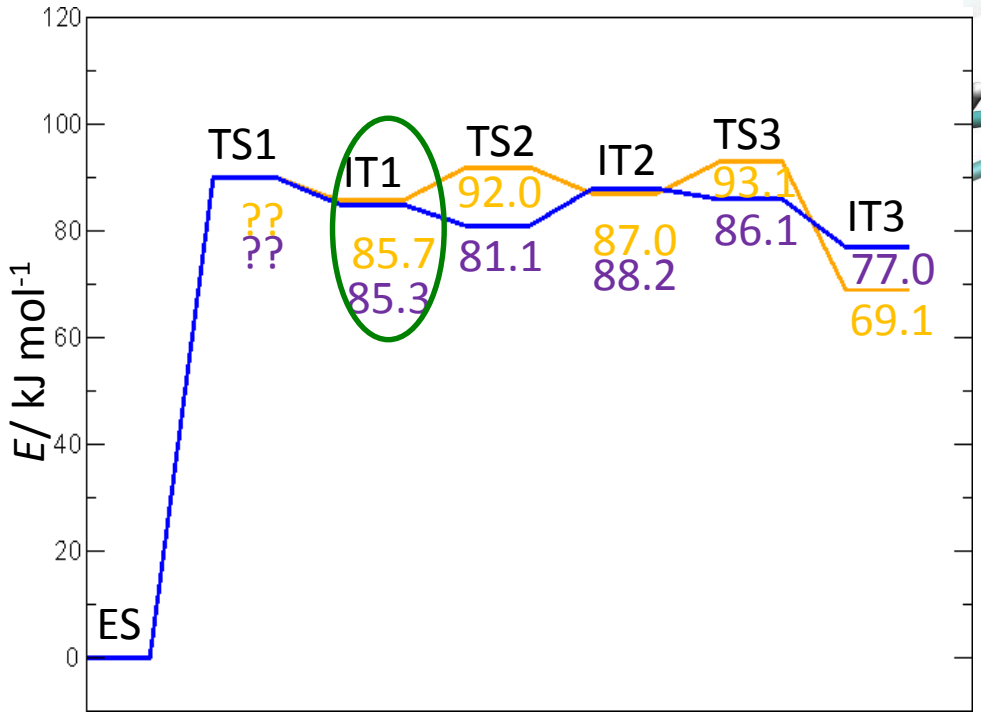
$d(C_s\text{-}N_s)$=1.35 Å

MD ES structure

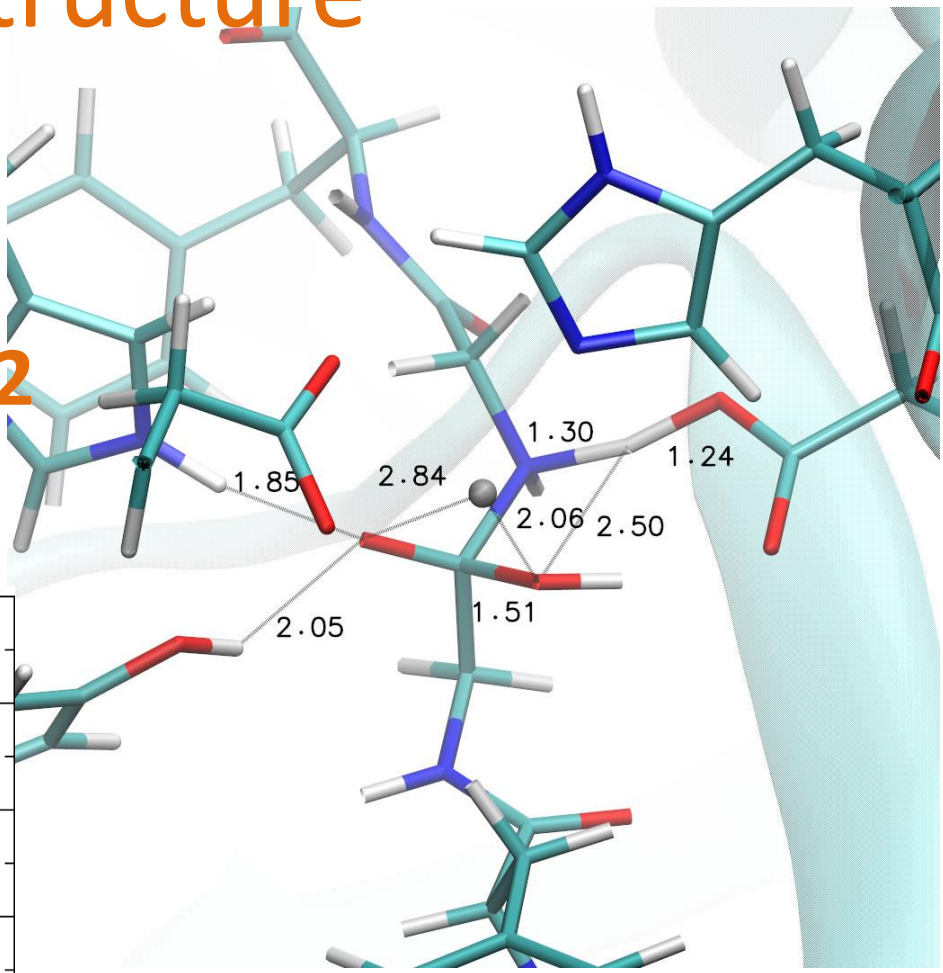




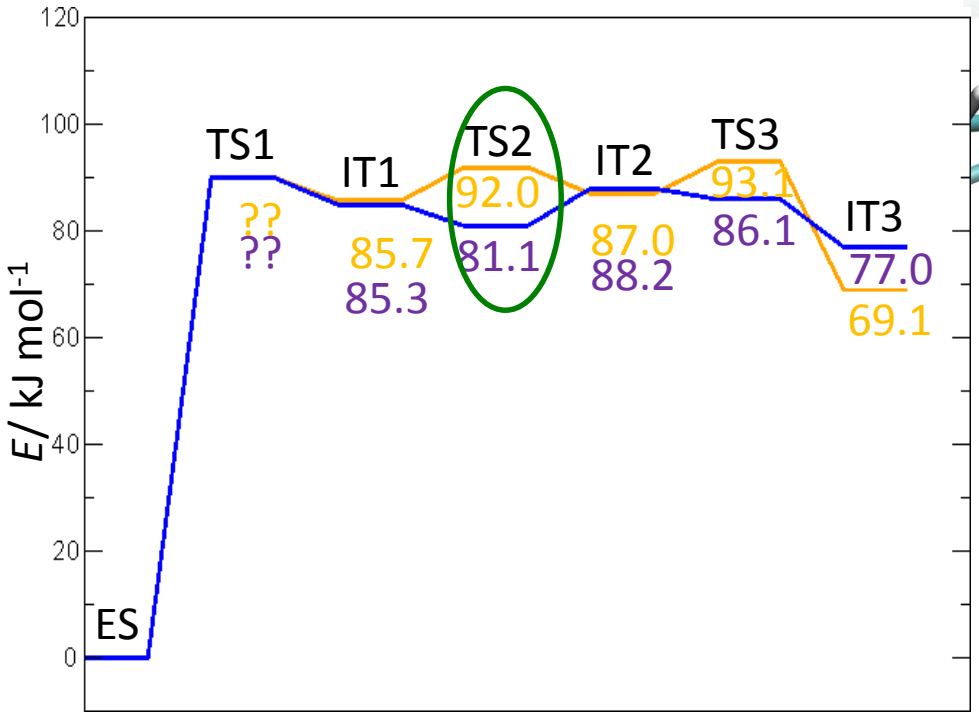
$d(C_s\text{-}N_s)$=1.51 Å



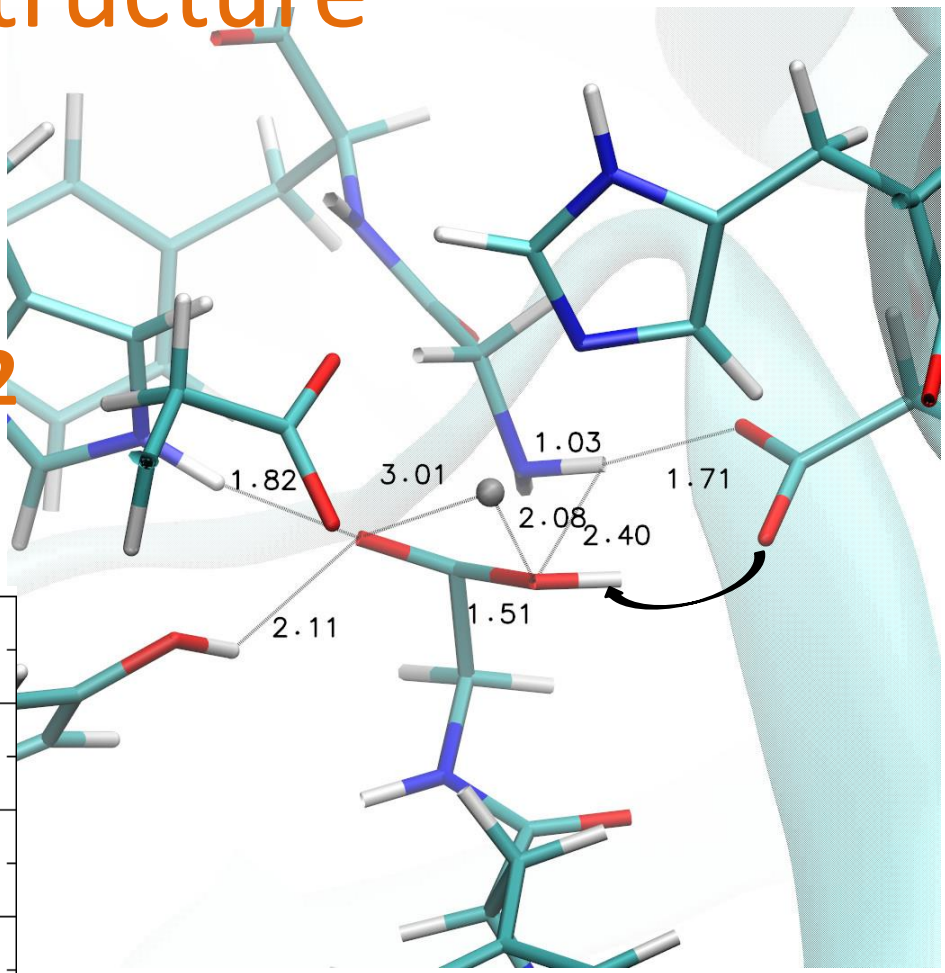
MD ES structure



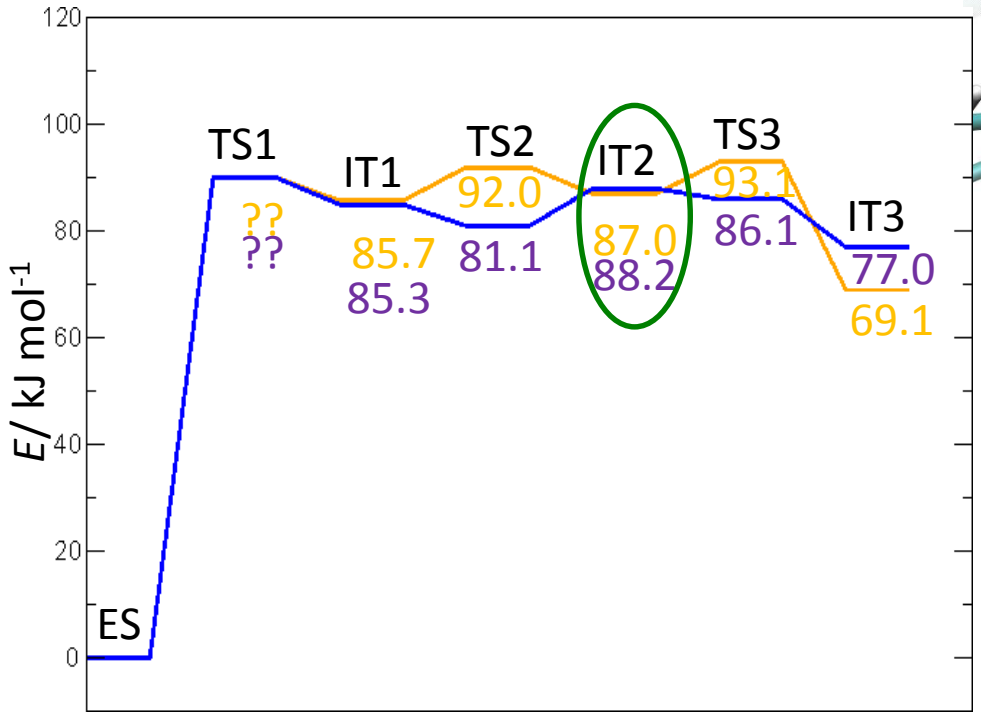
$d(C_s\text{-}N_s)$=1.59 Å



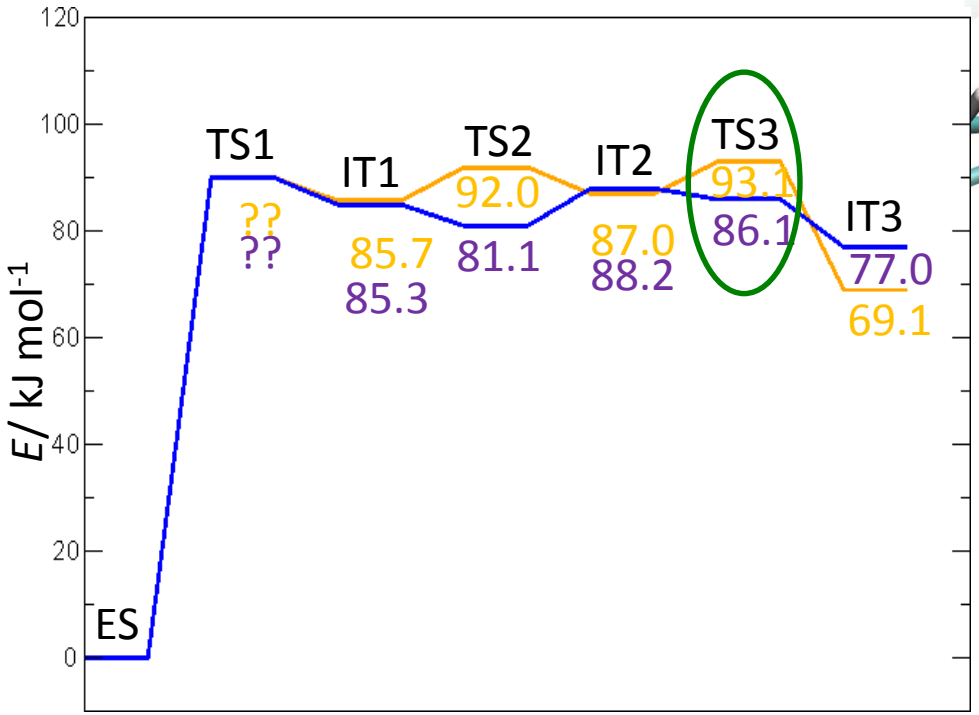
MD ES structure



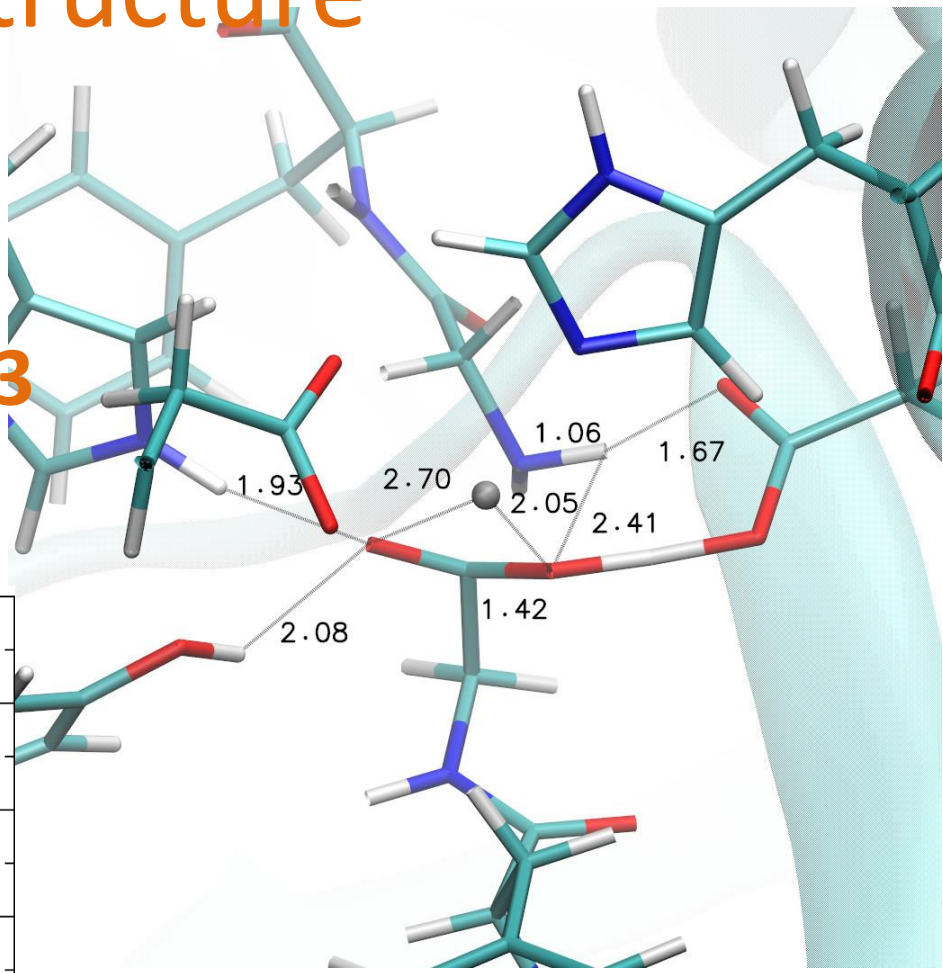
$d(C_s\text{-}N_s)$=1.67 Å



MD ES structure

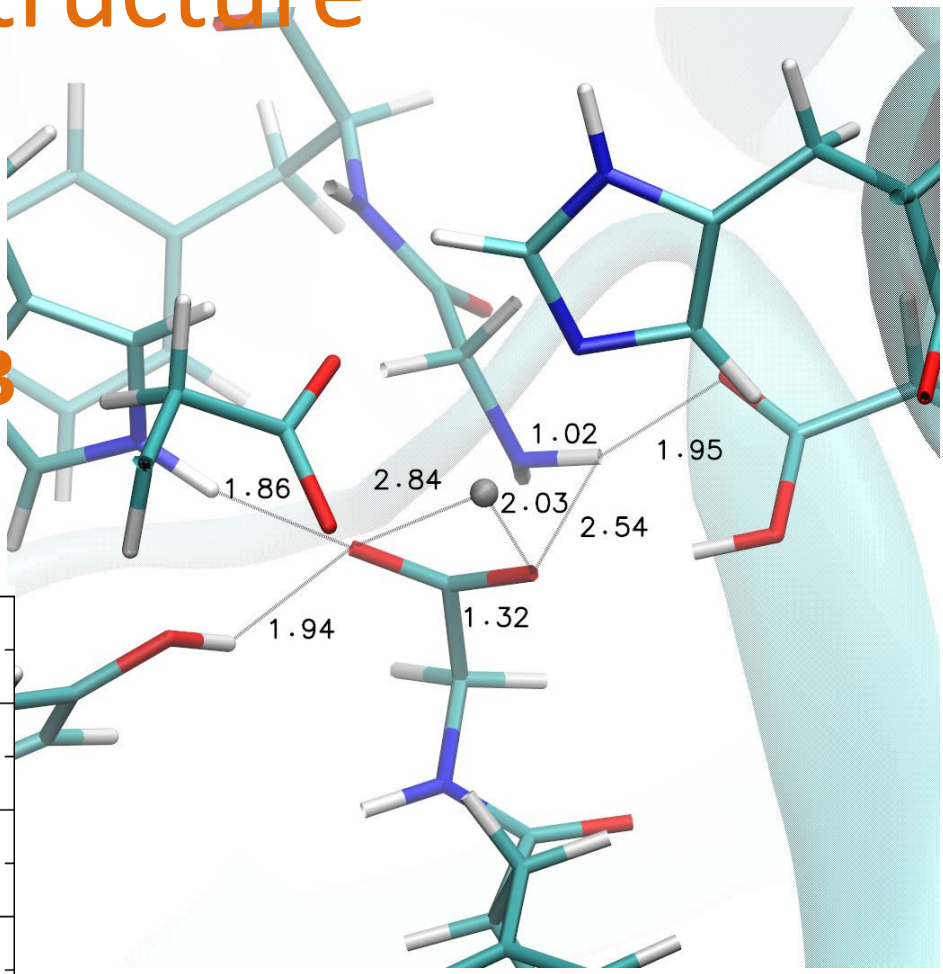


TS3

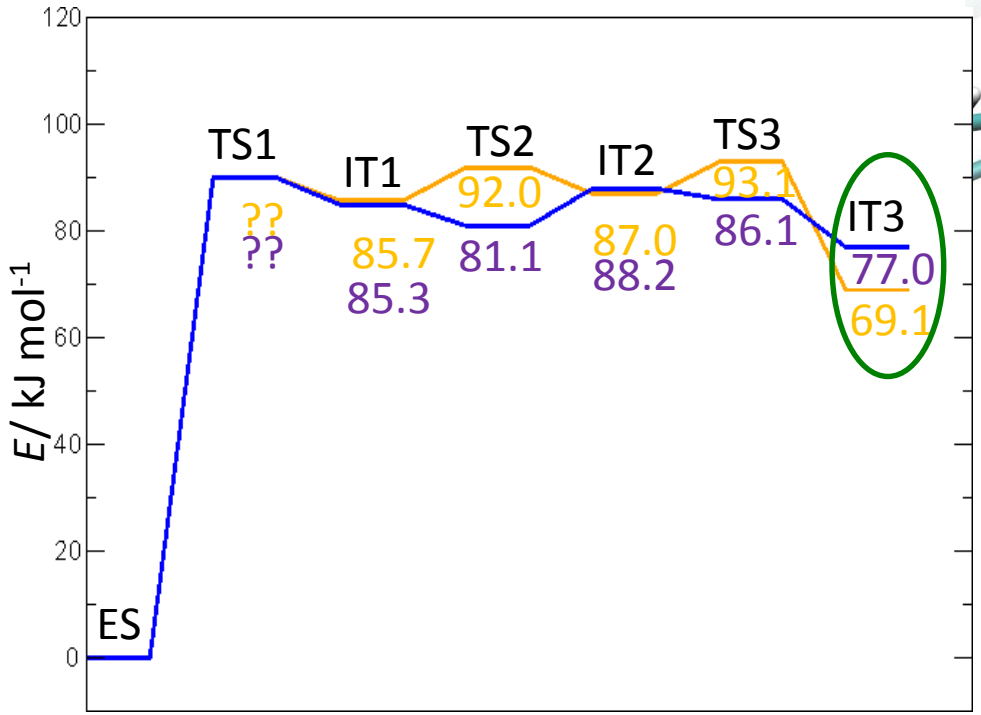


$d(C_s\text{-}N_s)$=1.76 Å

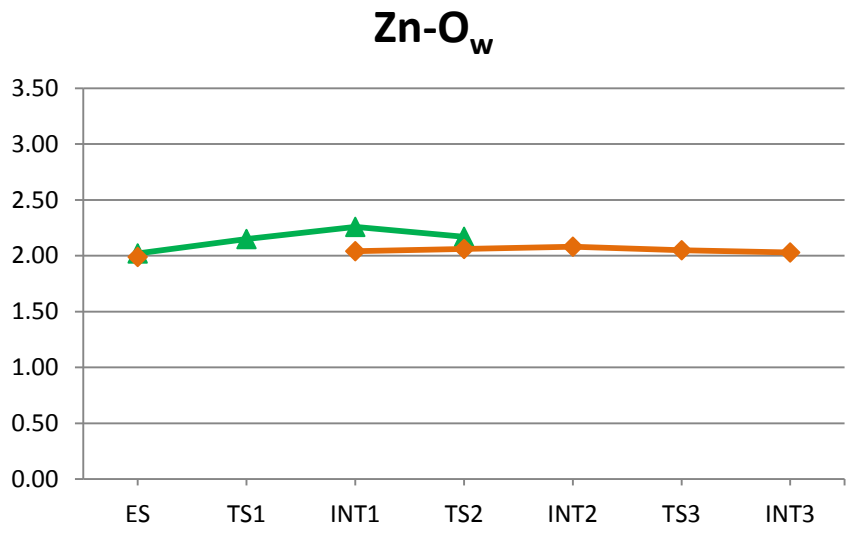
MD ES structure

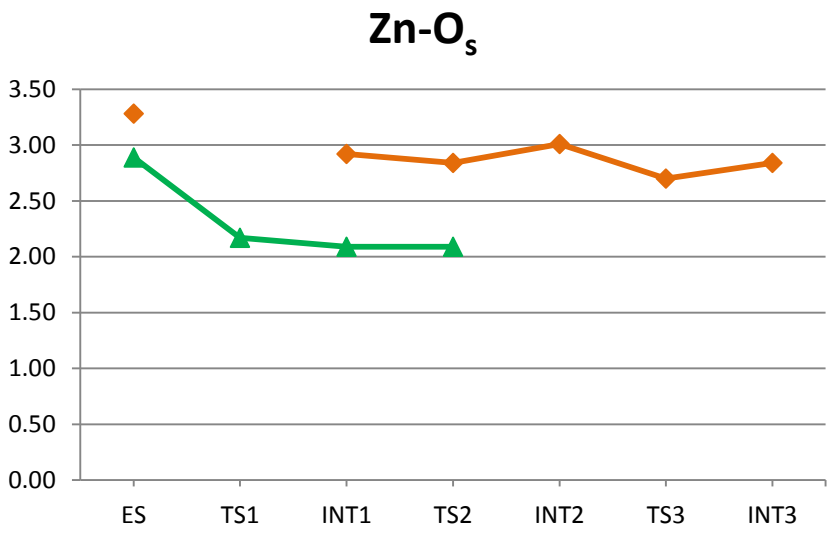


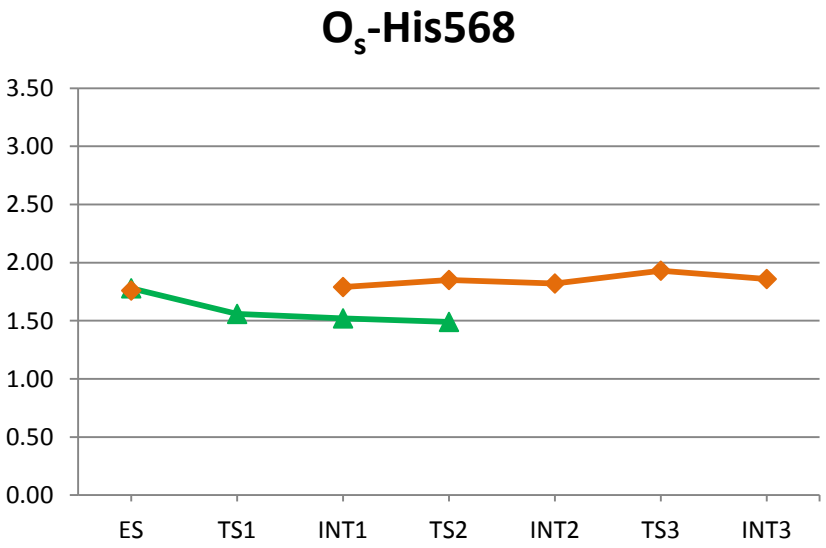
$d(C_s\text{-}N_s)$=2.24 Å

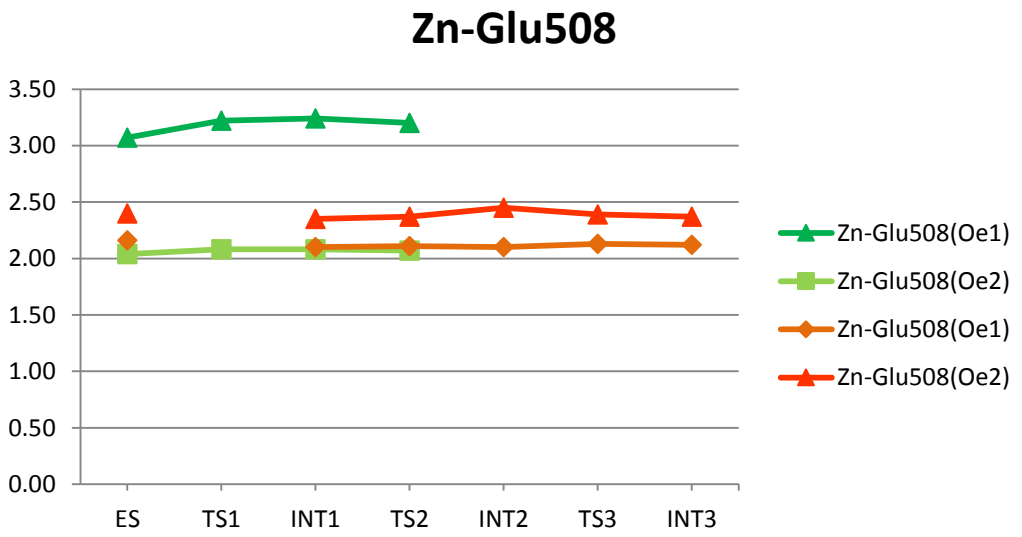


MD – X-ray ES str. vs. MD ES str.

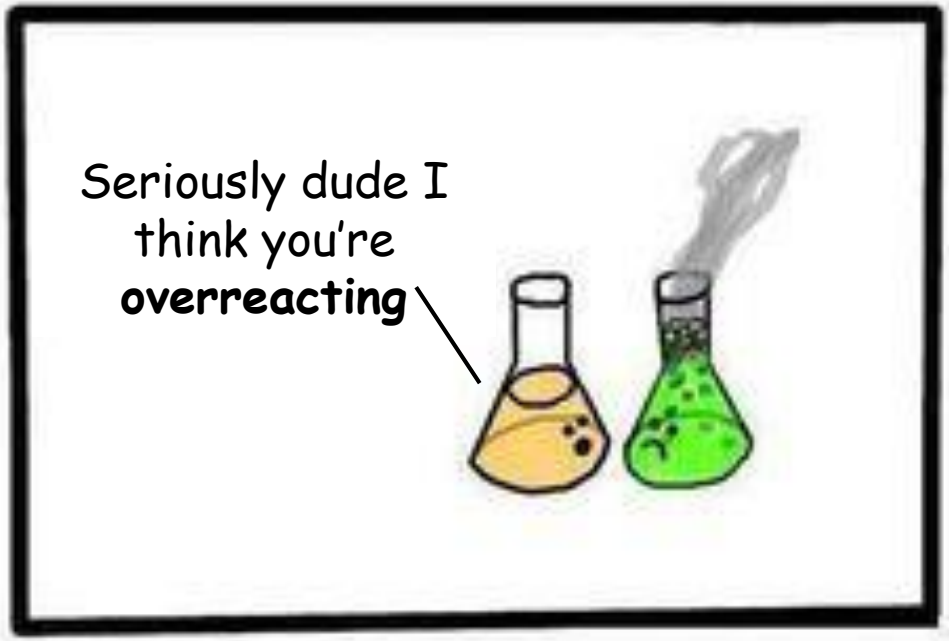




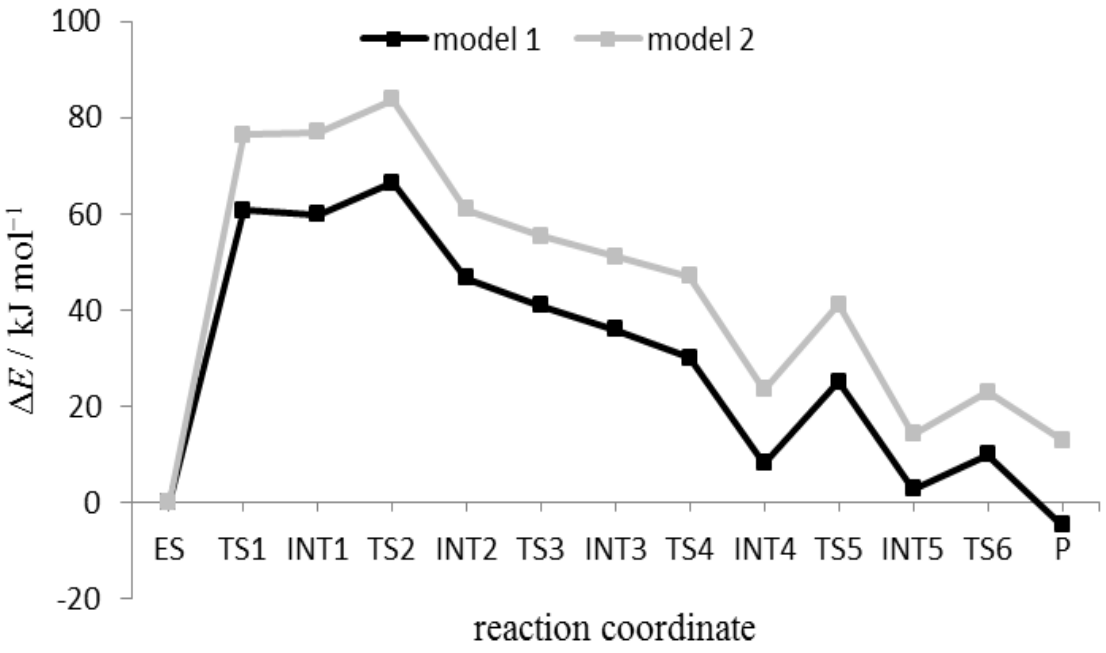




THANK YOU!



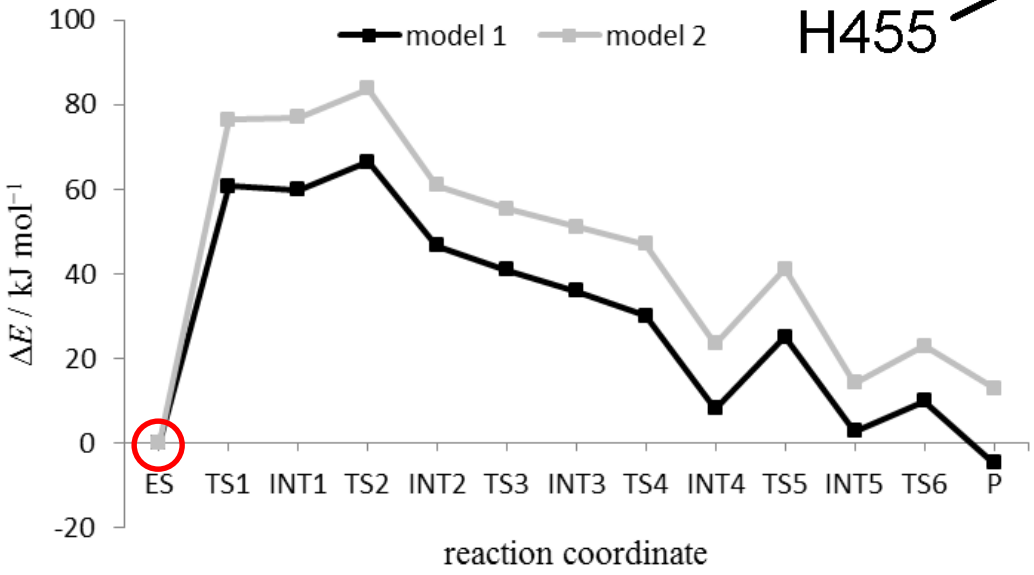
B97D/[6-31G(d) + LanL2DZ]

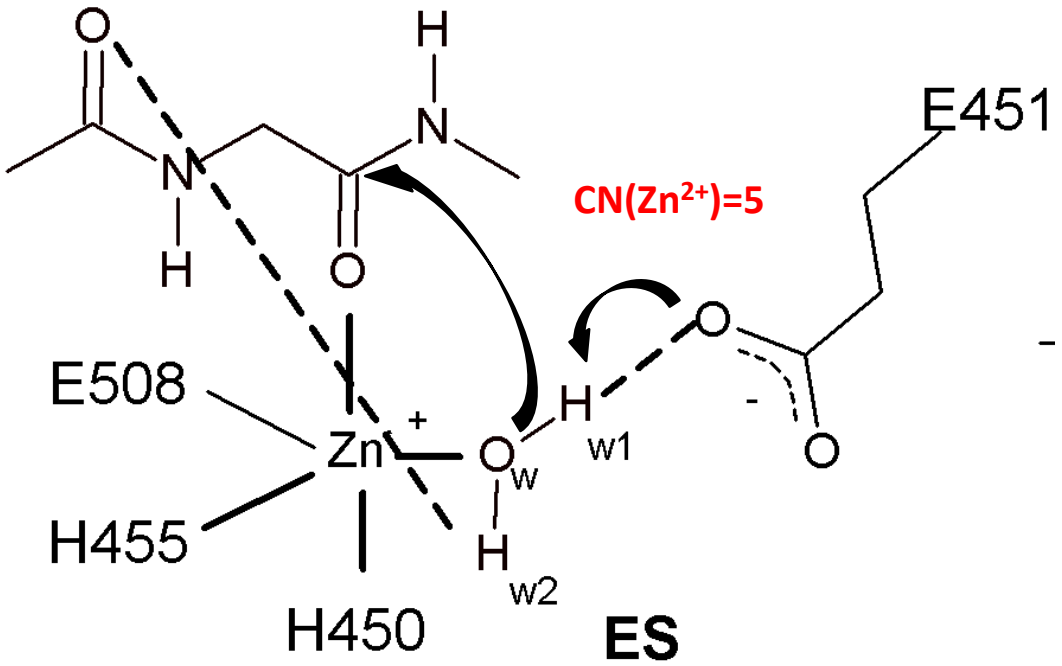


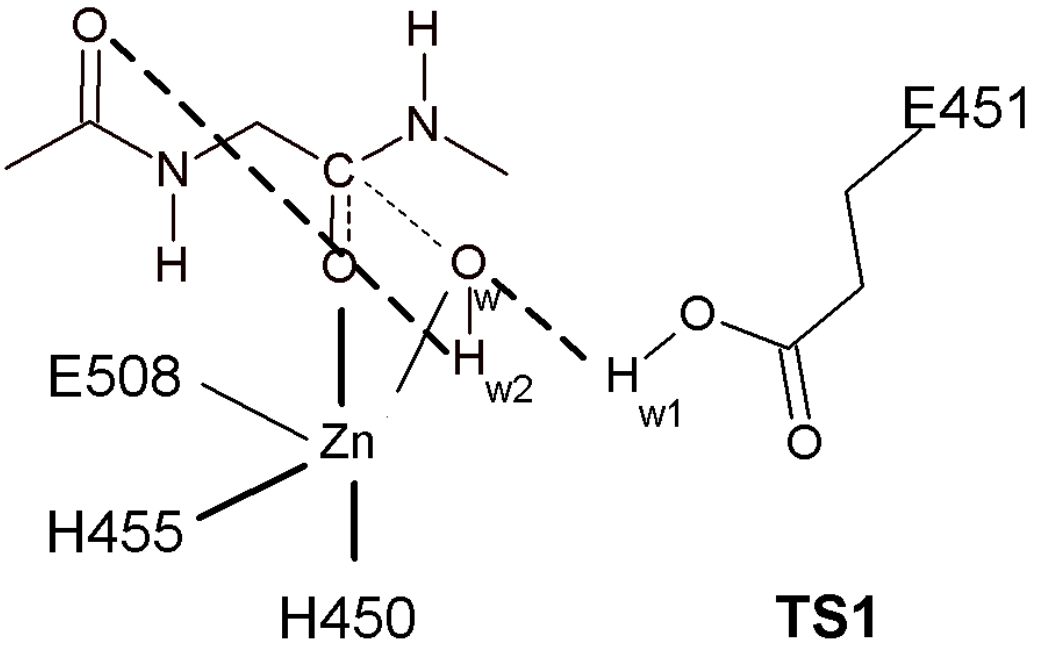
	ΔE / kJ mol⁻¹	
system	model 1	model 2
ES	0.0	0.0
TS1	60.8	76.5
INT1	59.9	77.1
TS2	66.5	83.7
INT2	46.8	61.0
TS3	40.9	55.4
INT3	35.9	51.1
TS4	30.0	47.1
INT4	8.3	23.5
TS5	25.2	41.1
INT5	2.9	14.3
TS6	10.0	23.1
P	−4.6	13.1
P’	−33.6	−30.2

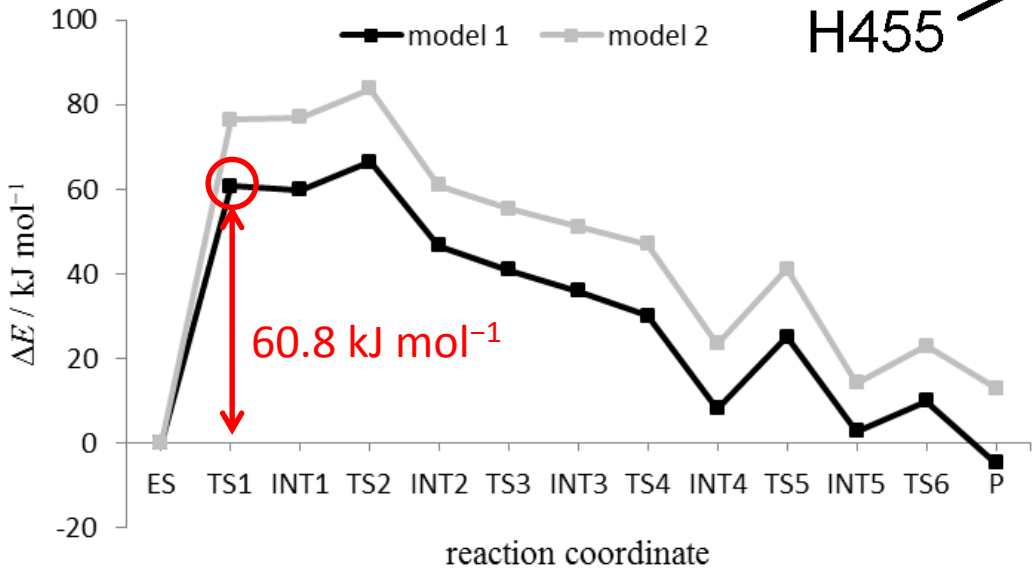
model 1: B97D/[6-31G (d)+ LanL2DZ] + $ZPVE_{\text{B97D/[6-31G(d) + LanL2DZ]}}$

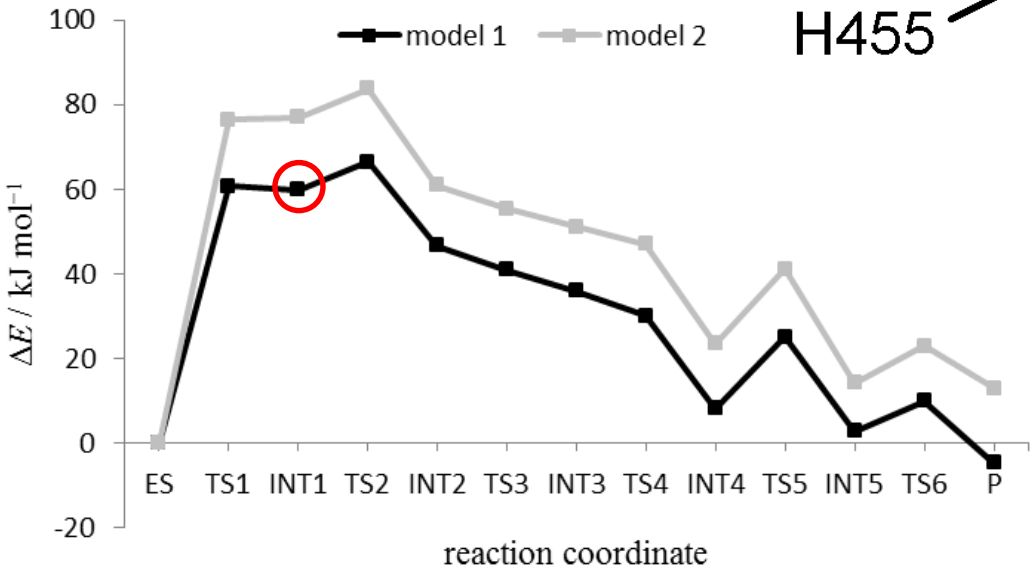
model 2: B97D/[6-311++G(d,p) + LanL2DZ]//B97D/[6-31G(d) + LanL2DZ] + $ZPVE_{\text{B97D/[6-31G(d) + LanL2DZ]}}$

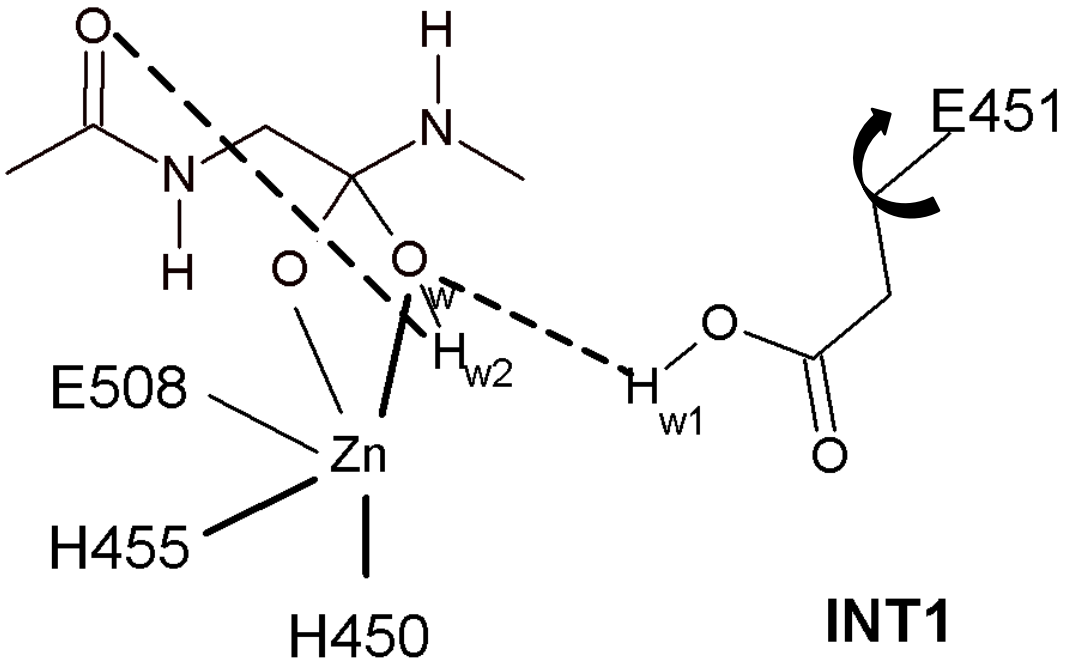

model 1
model 2
100
80
60
40
20
0
-20
ΔE / kJ mol⁻¹
ES
TS1
INT1
TS2
INT2
TS3
INT3
TS4
INT4
TS5
INT5
TS6
P
reaction coordinate


O
H
N
N
H
O
E451
CN(Zn2+)=5
E508
Zn
+
Ow
H
w1
O
-
O
H455
H
w2
H450
ES


O
H
N
N
C
H
O
O
w
H
w2
H
w1
O
O
E451
E508
Zn
H455
H450
TS1

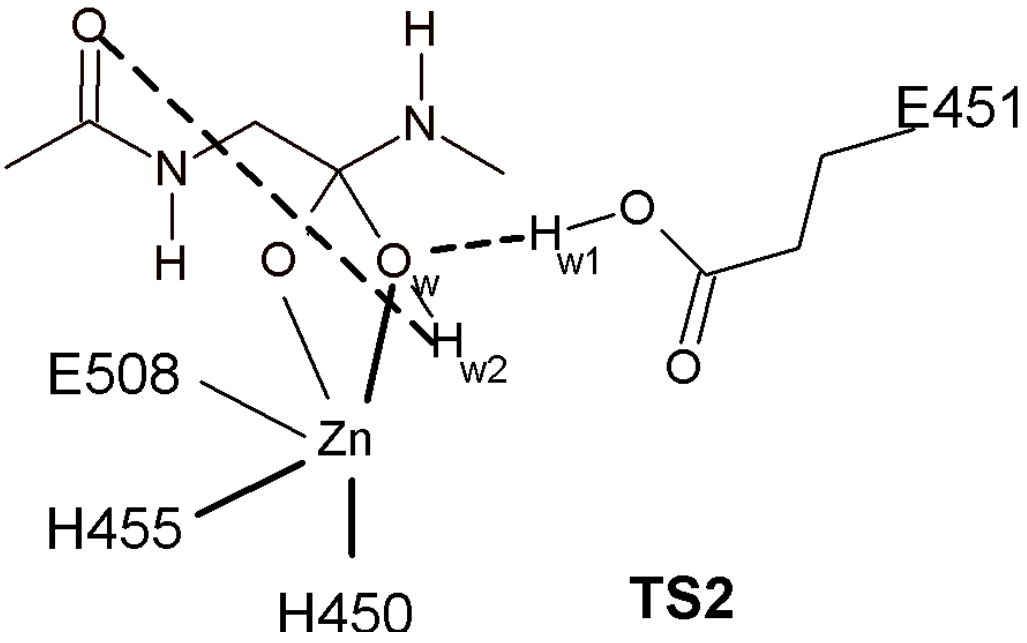

model 1
model 2
100
80
60
40
20
0
-20
ΔE / kJ mol⁻¹
60.8 kJ mol⁻¹
ES
TS1
INT1
TS2
INT2
TS3
INT3
TS4
INT4
TS5
INT5
TS6
P
reaction coordinate



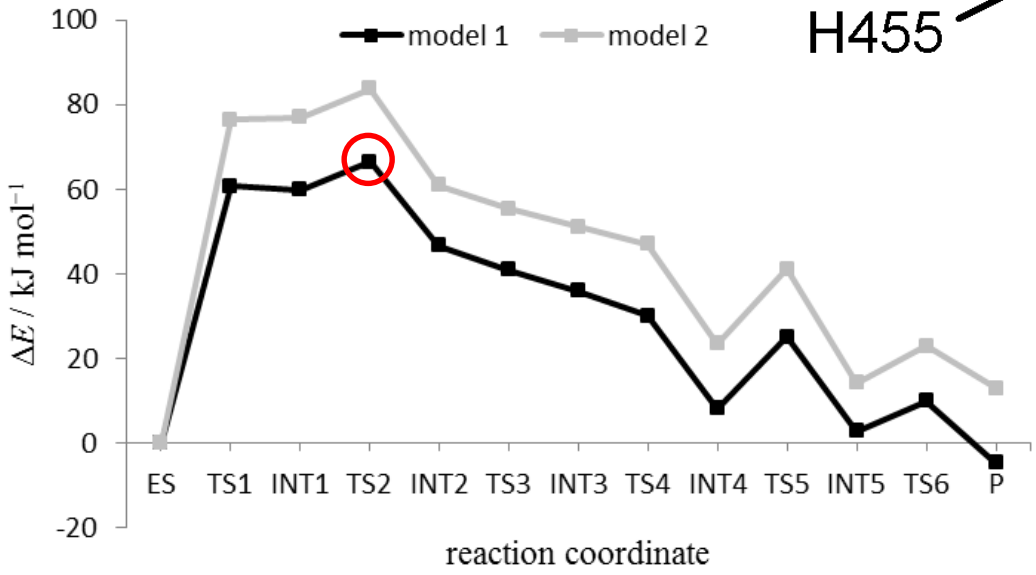


INT1

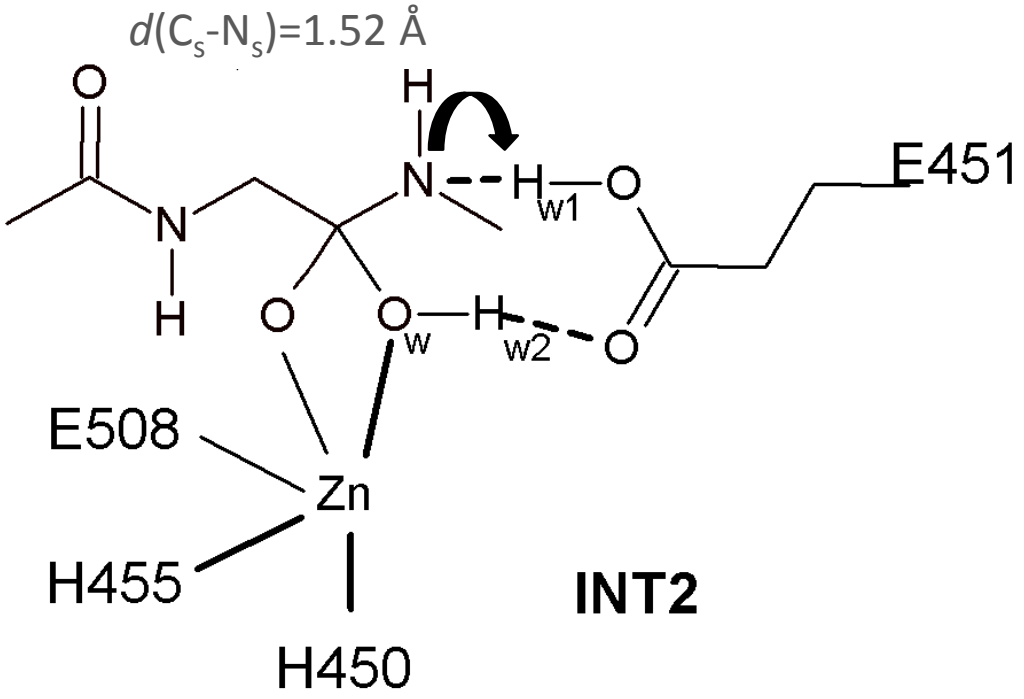
ΔE(INT1−ES)=59.9 kJ mol^{-1}

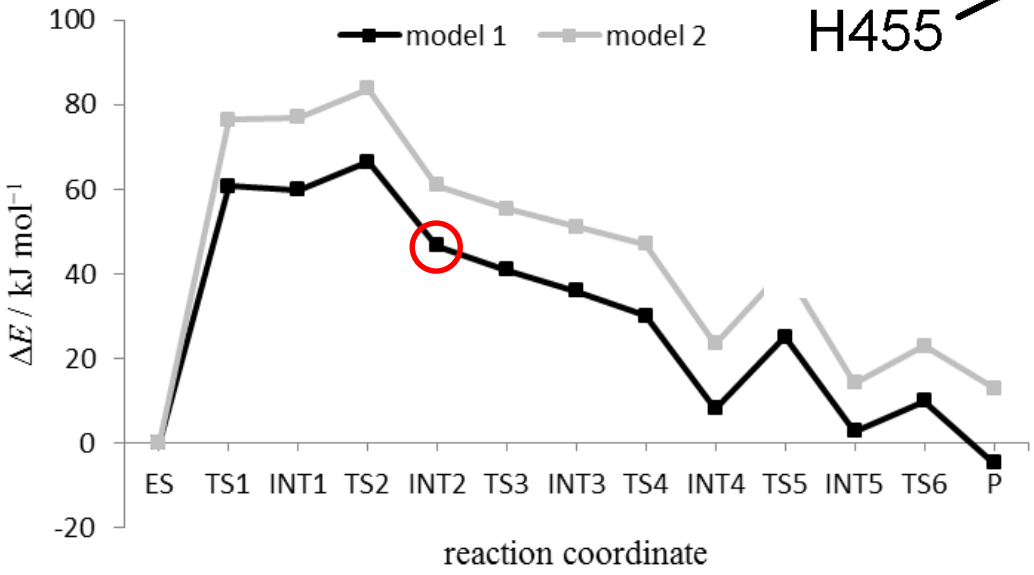


TS2

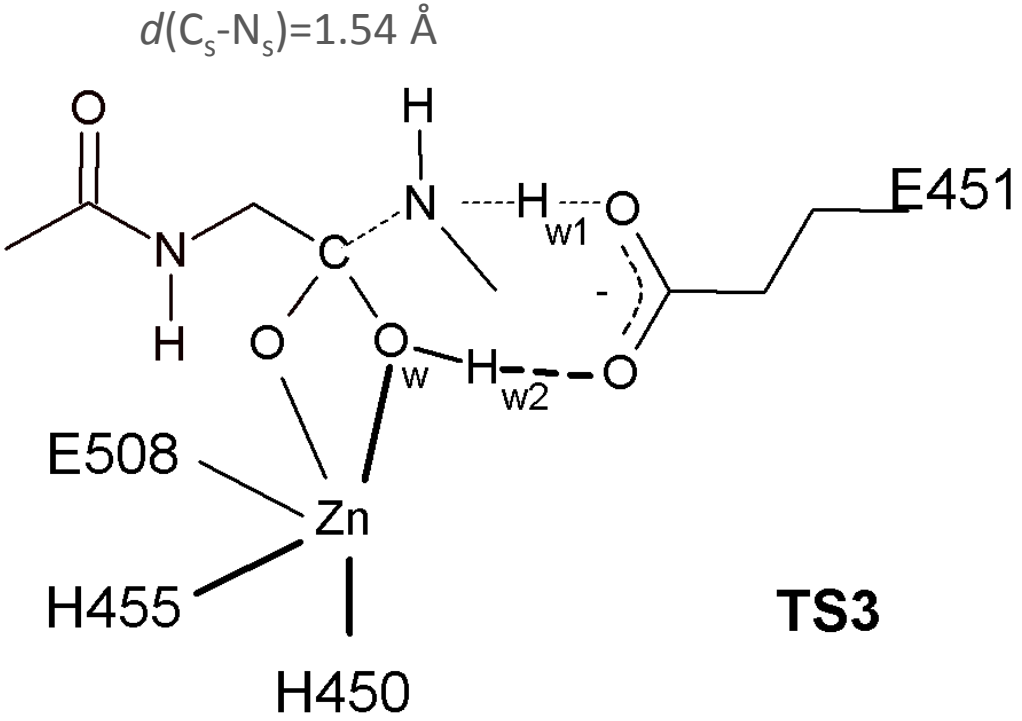


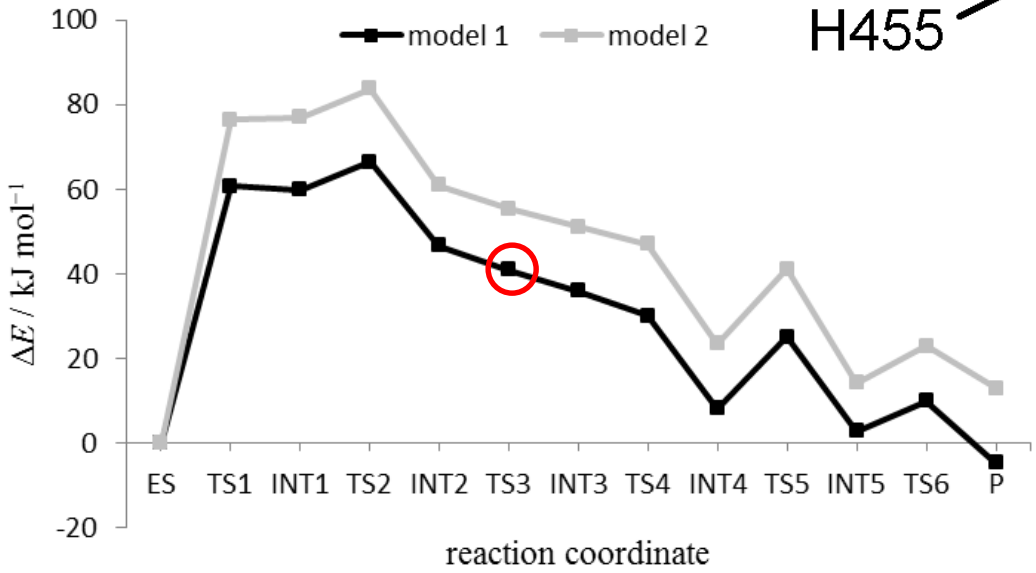
ΔE(TS2-INT1)=6.6 kJ mol^{-1}



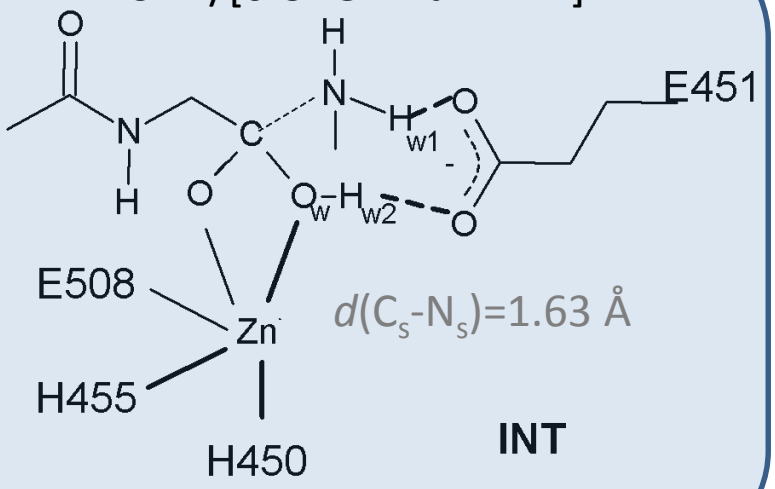


ΔE(INT1−ES)=46.8 kJ mol^{-1}


$d(C_s\text{-}N_s)$=1.54 Å
O
H
N
H
N
C
H
w1
O
E451
O
O
w
H
w2
O
E508
Zn
H455
H450
TS3

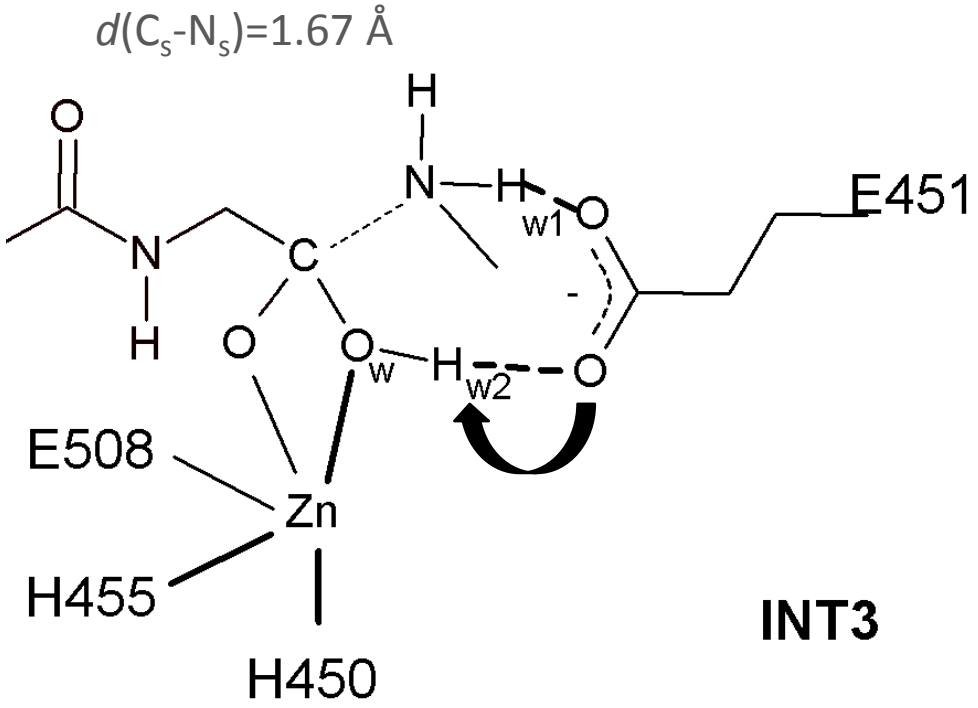

model 1
model 2
100
80
60
40
20
0
-20
ΔE / kJ mol⁻¹
ES
TS1
INT1
TS2
INT2
TS3
INT3
TS4
INT4
TS5
INT5
TS6
P
reaction coordinate

B97D/[6-31G + LanL2DZ]



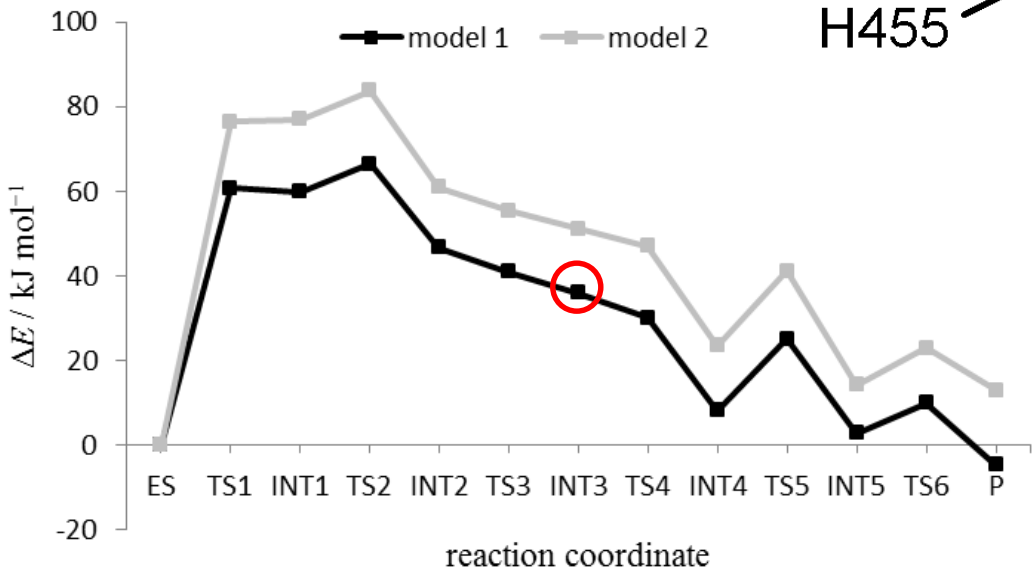
INT

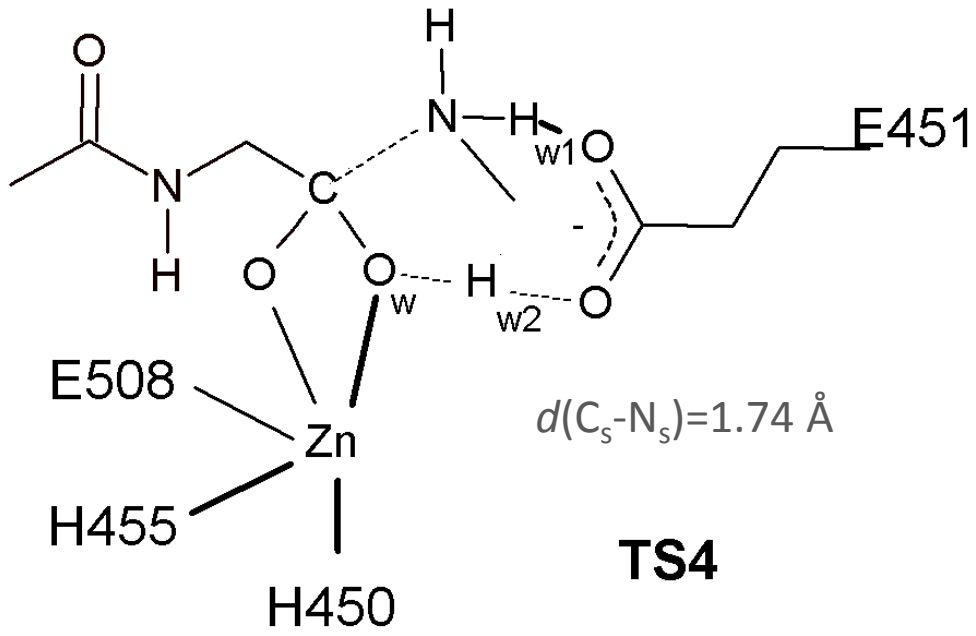
ΔE(INT−ES)=45.2 kJ mol^{-1}



INT3

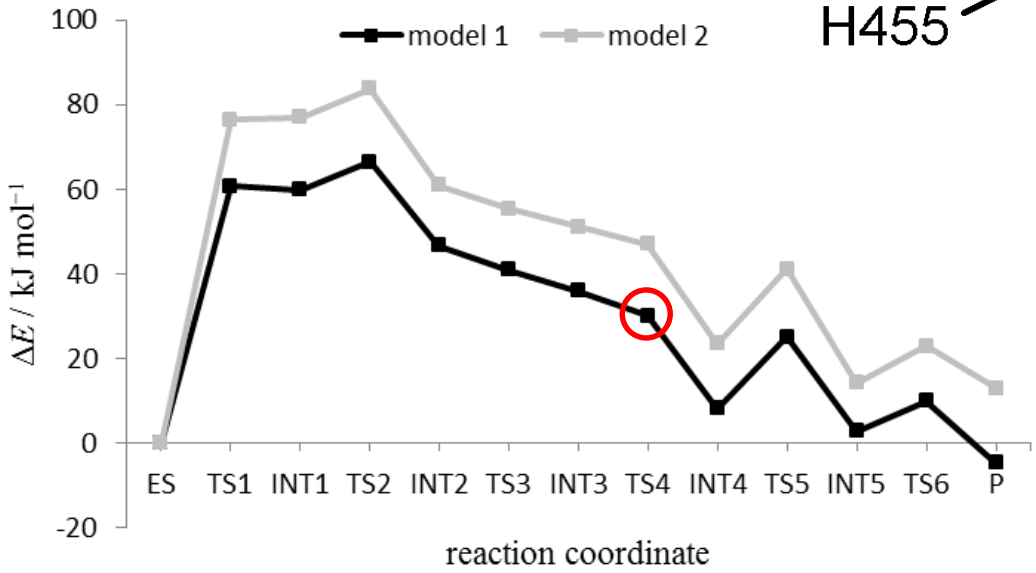
ΔE(INT3−ES)=35.9 kJ mol^{-1}

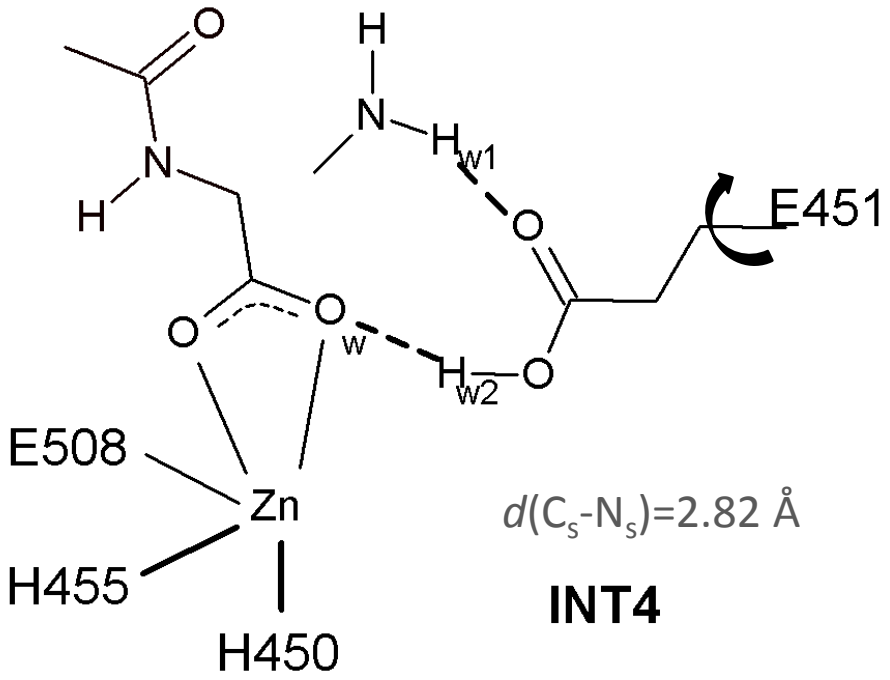




$d(C_s\text{-}N_s)$=1.74 Å

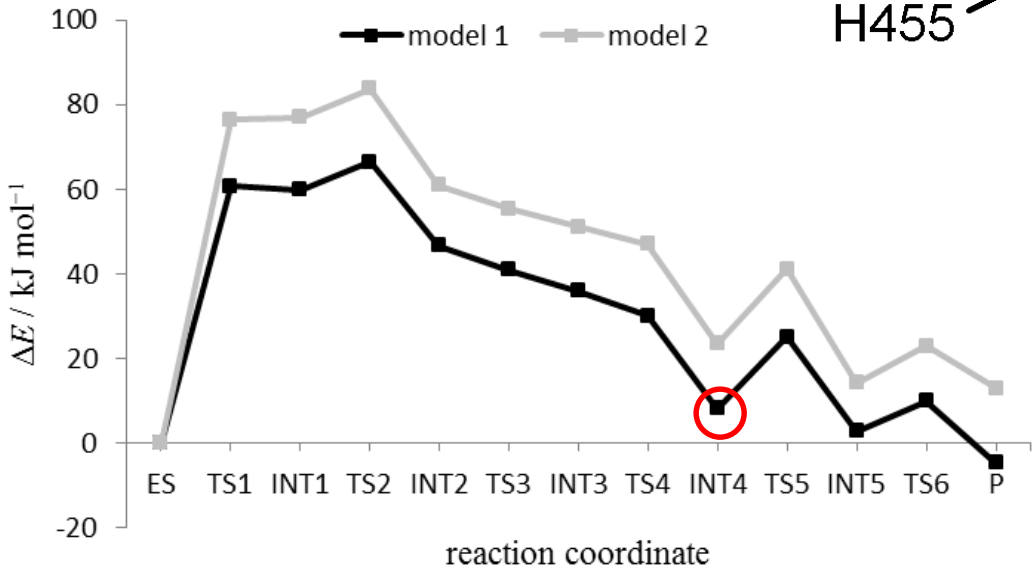
TS4



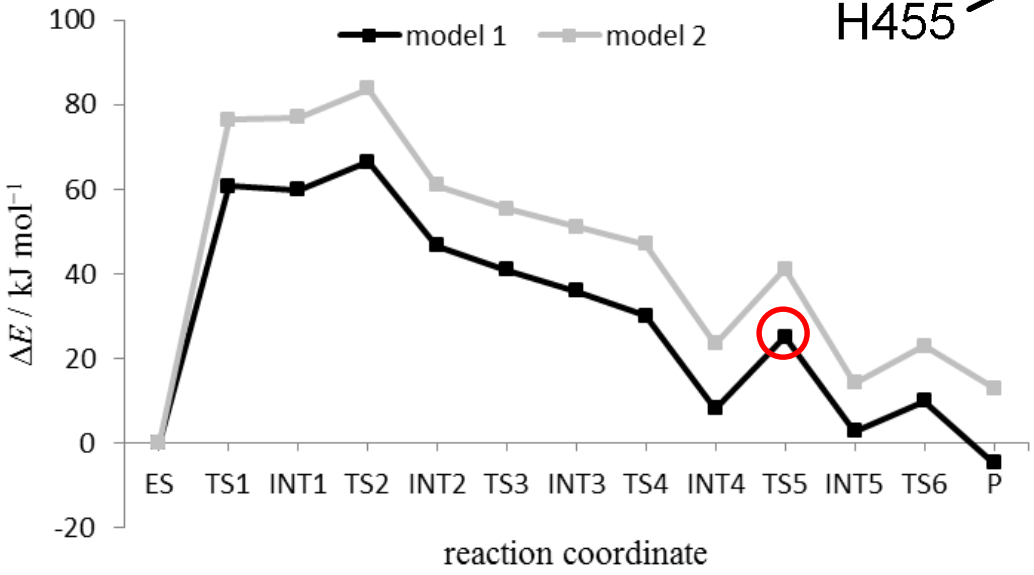


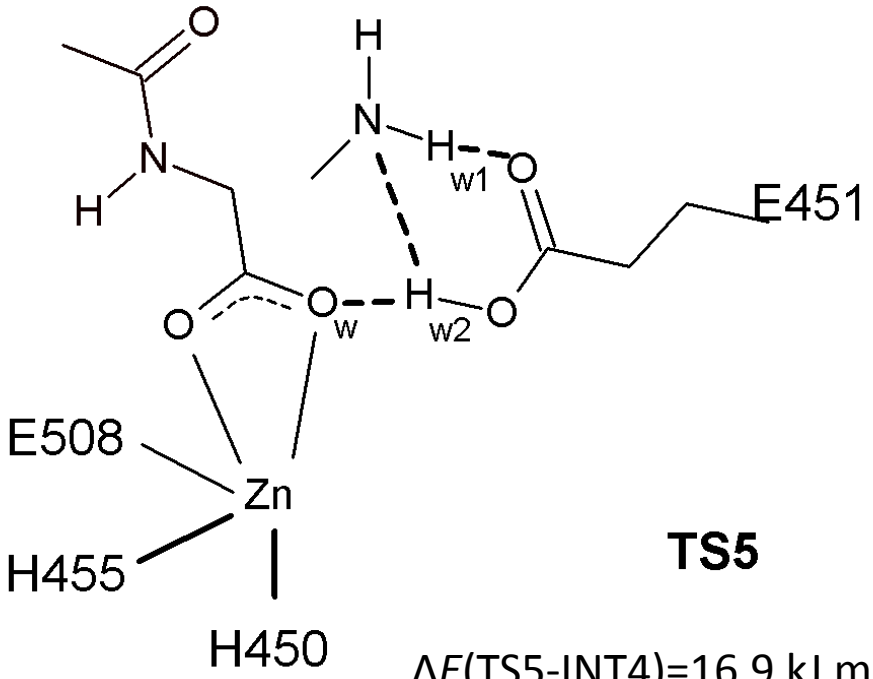
$d(C_s\text{-}N_s)$=2.82 Å

INT4



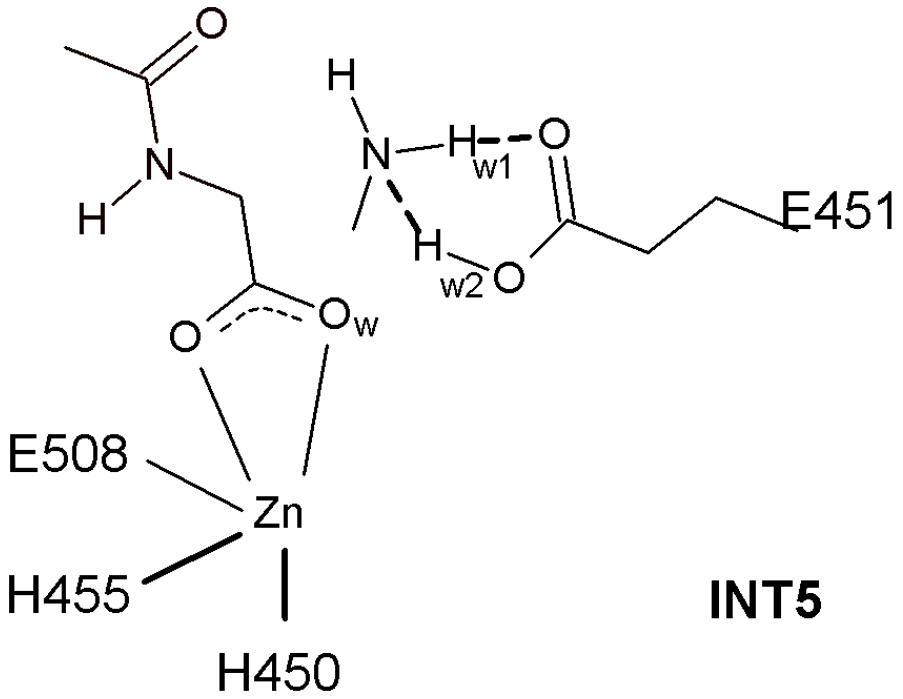
ΔE(INT4−ES)=8.3 kJ mol^{-1}



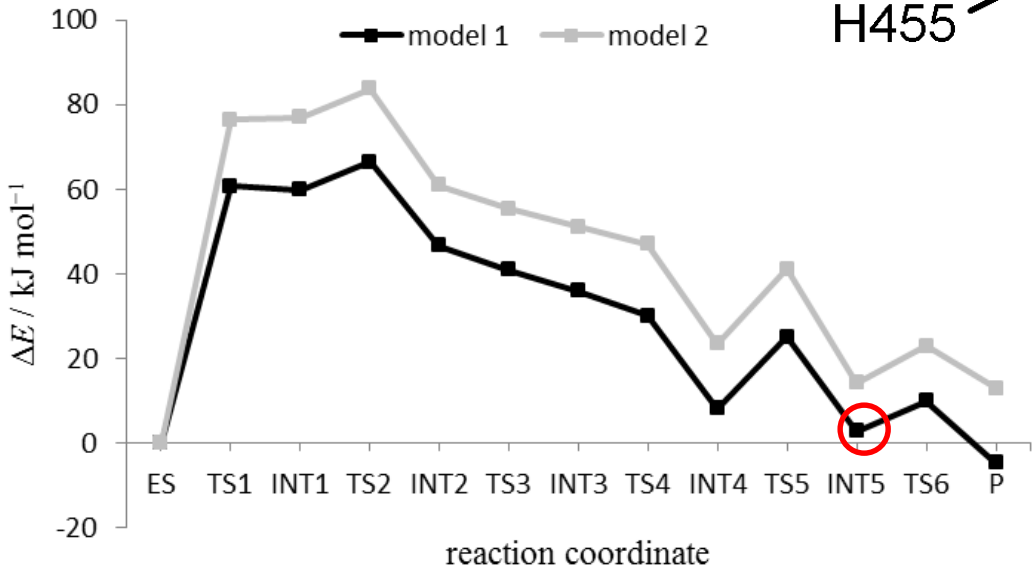


TS5

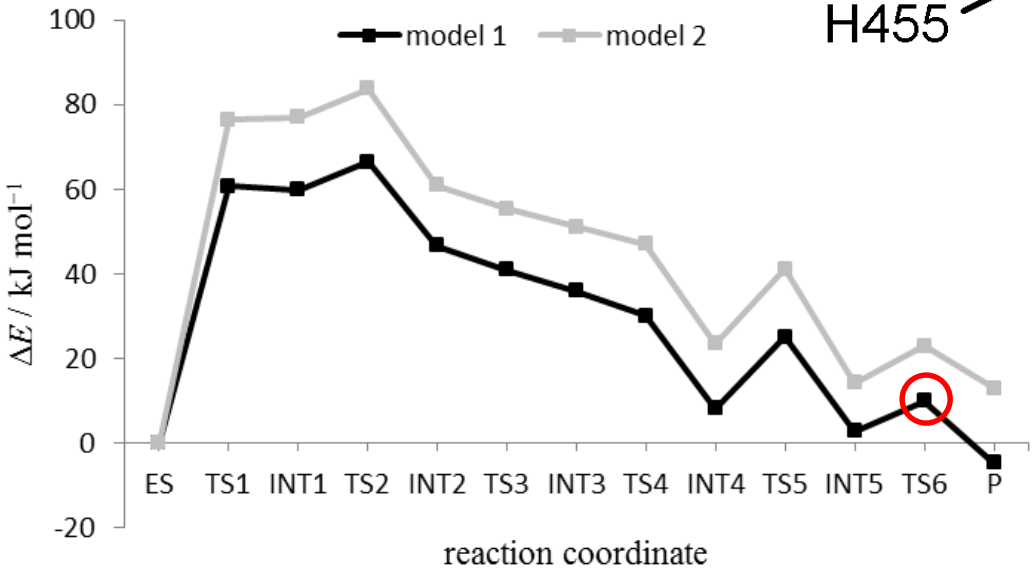
ΔE(TS5-INT4)=16.9 kJ mol^{-1}

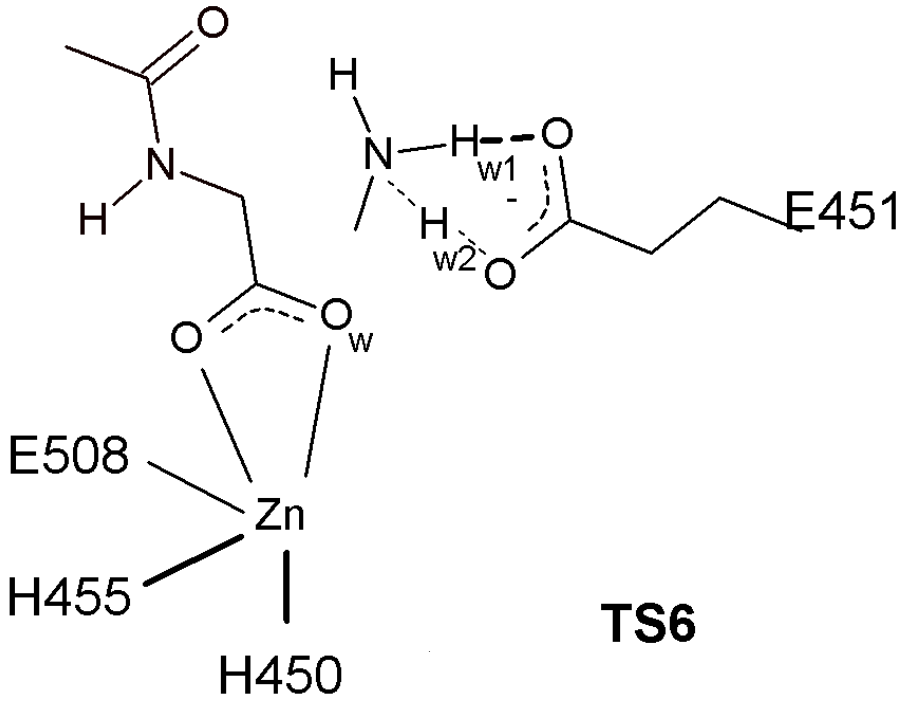


INT5



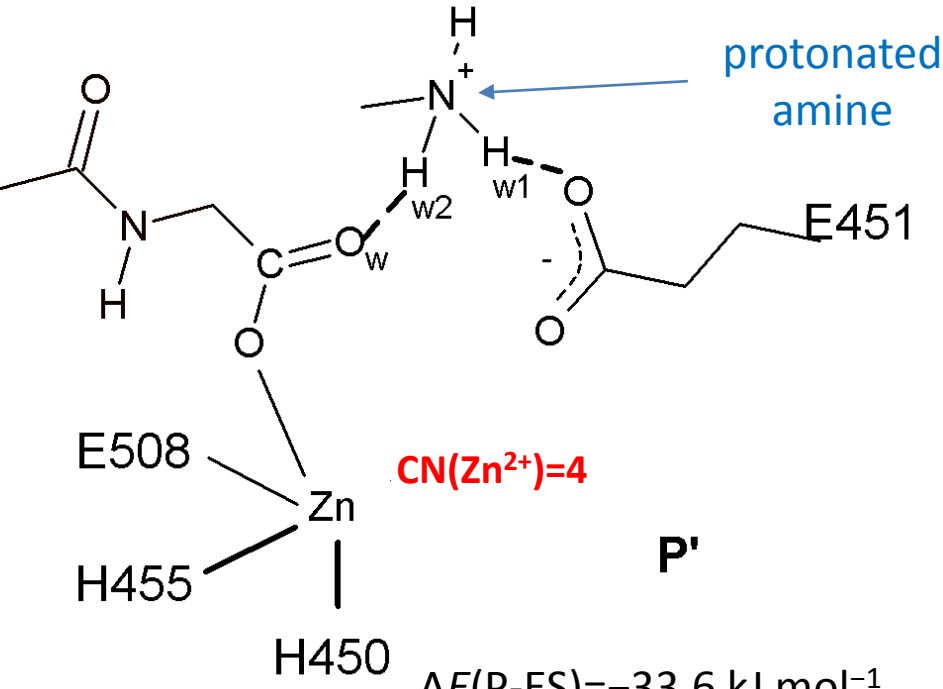
ΔE(INT5−ES)=2.9 kJ mol^{-1}

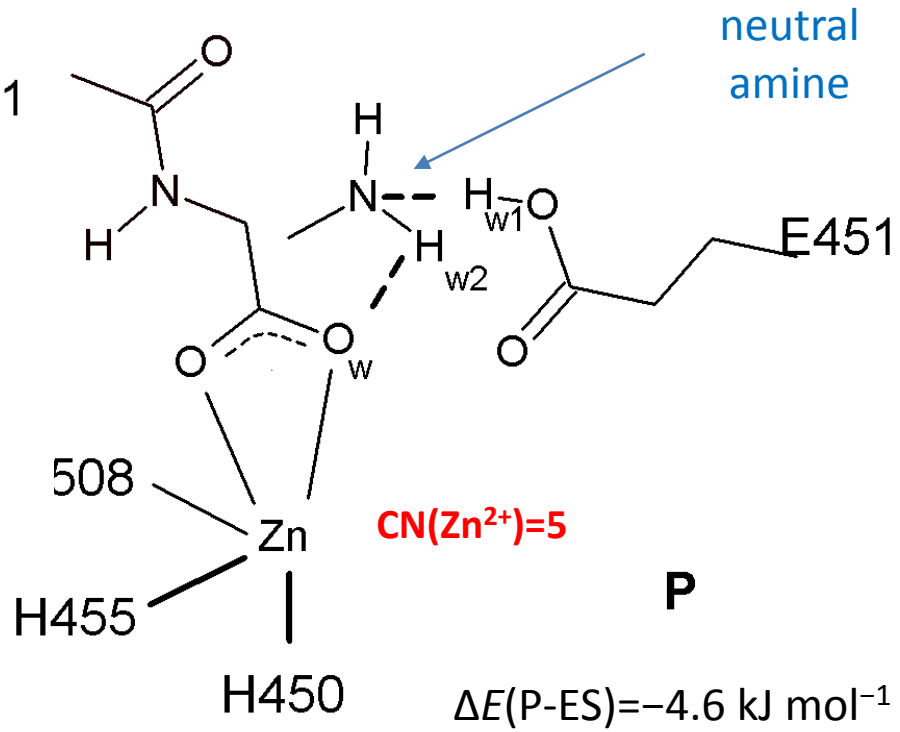




TS6

Δ*E*(TS6-INT5)=7.1 kJ mol^{-1}





ΔE(P-ES)=−33.6 kJ mol^{-1}

ΔE(P-ES)=−4.6 kJ mol^{-1}