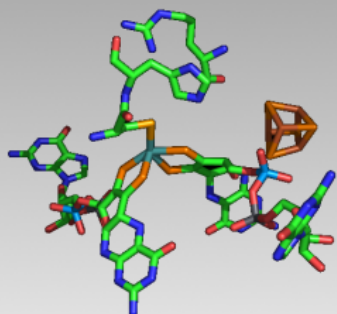
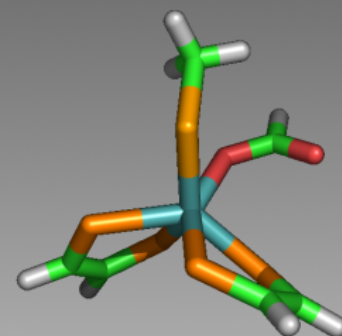


Estudi teòric de l'activitat bioquímica del seleni en la format deshidrogenasa H

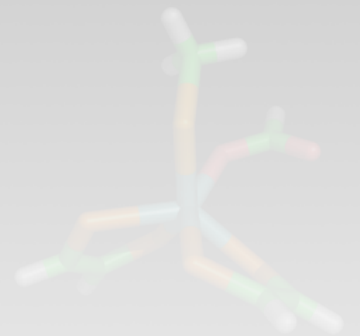
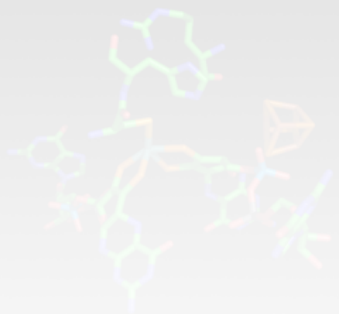
Alfons Nonell i Canals



Institut Català d'Investigació Química (ICIQ)
Tarragona

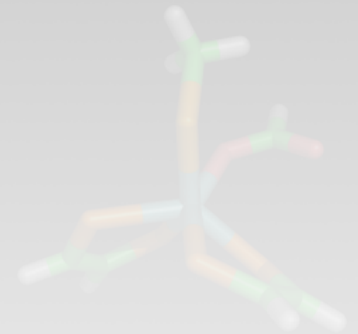
Tarragona, 10 de juliol de 2006

El seleni

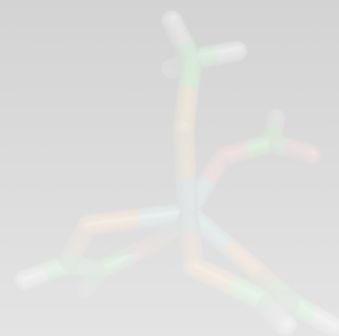
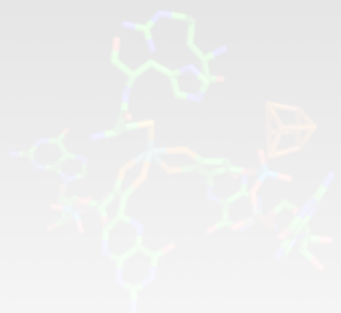


El seleni

- Descobert l'any 1817 per Jöns Jacob Berzelius
- Tòxic
- Micronutrient essencial
- Necessitats segons l'edat
- Forma part de la selenocisteïna (Sec)

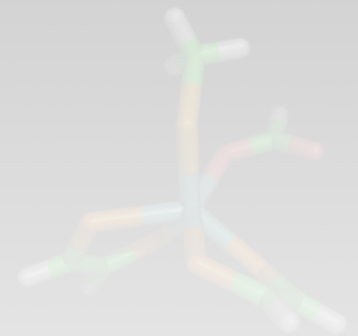
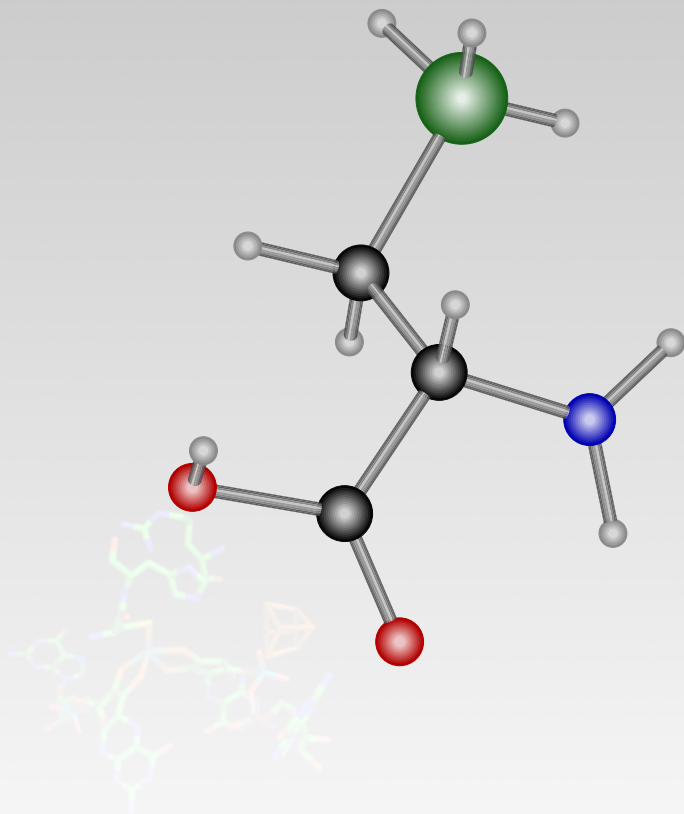


La selenocisteina



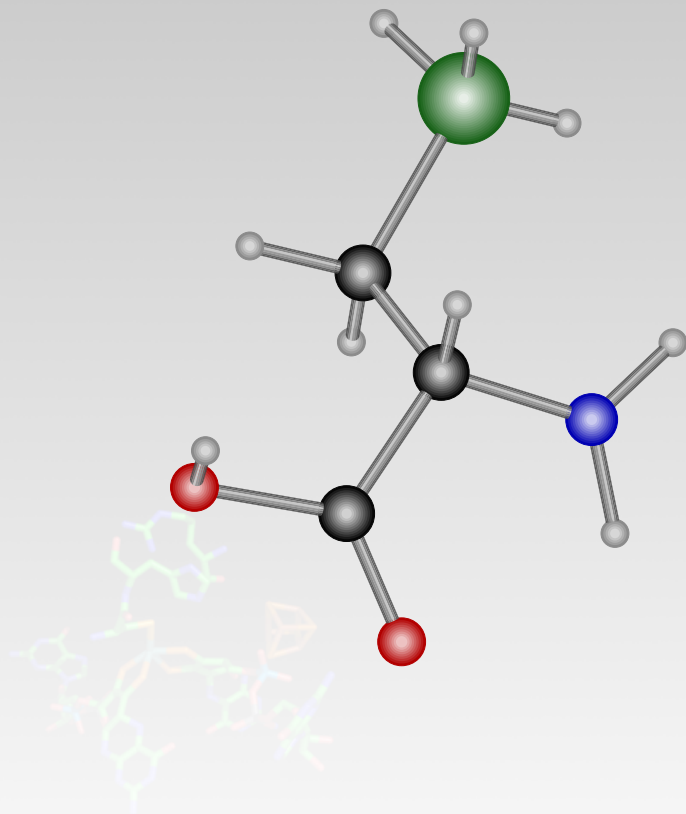
La selenocisteïna

- És un aminoàcid



La selenocisteïna

- És un aminoàcid



-Grup amino

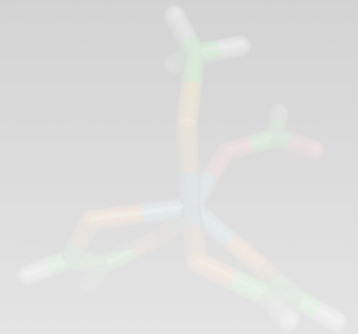
-Grup carboxílic

-No proteics

-Proteics

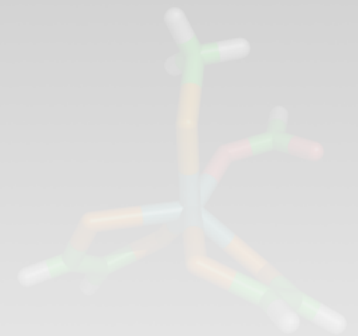
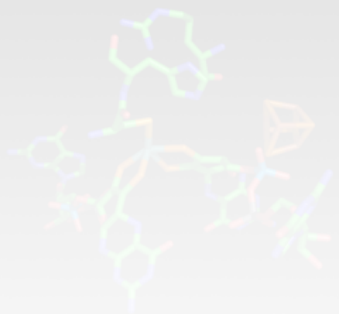
-Carboni α

-Cadena lateral



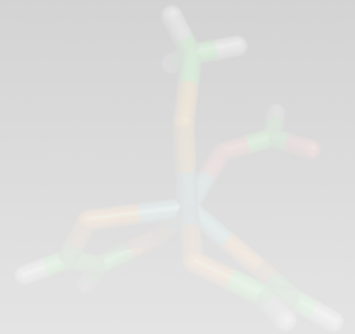
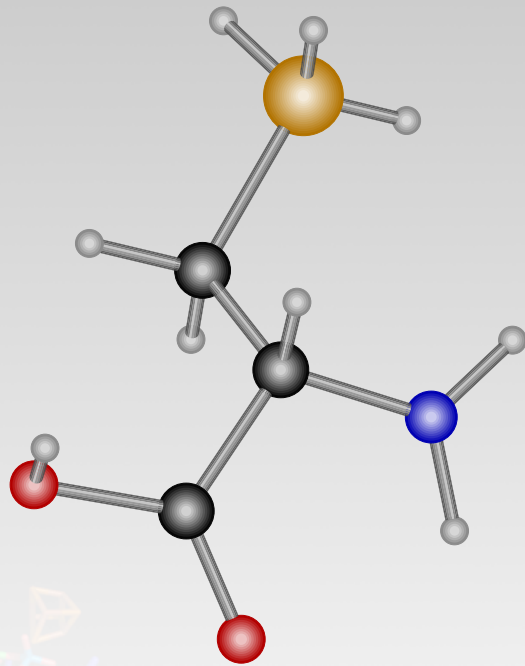
La selenocisteïna

L'aminoàcid 21



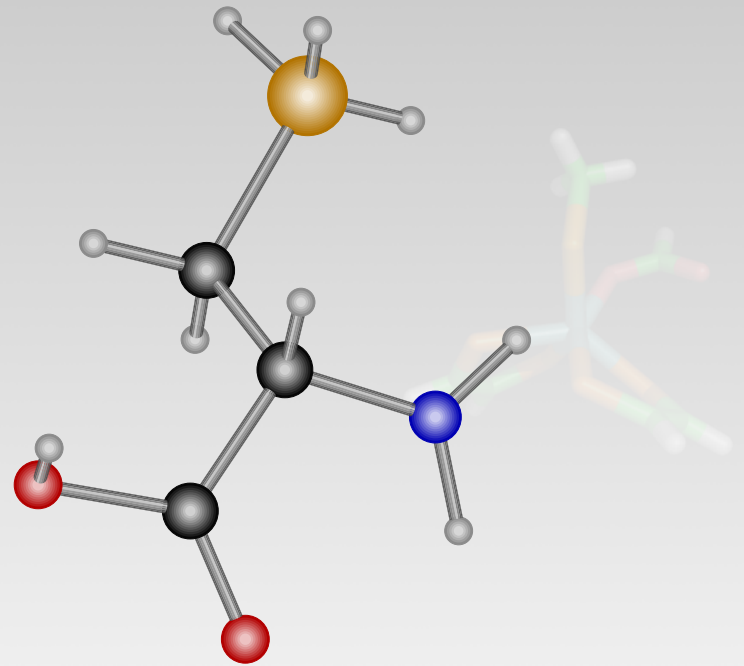
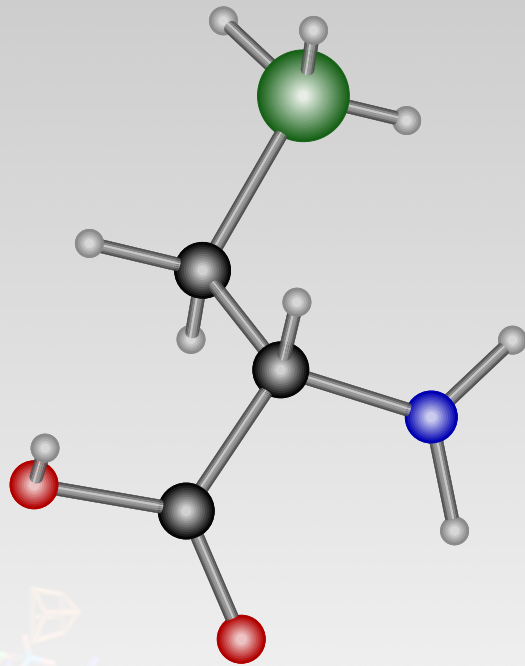
La selenocisteïna

L'aminoàcid 21



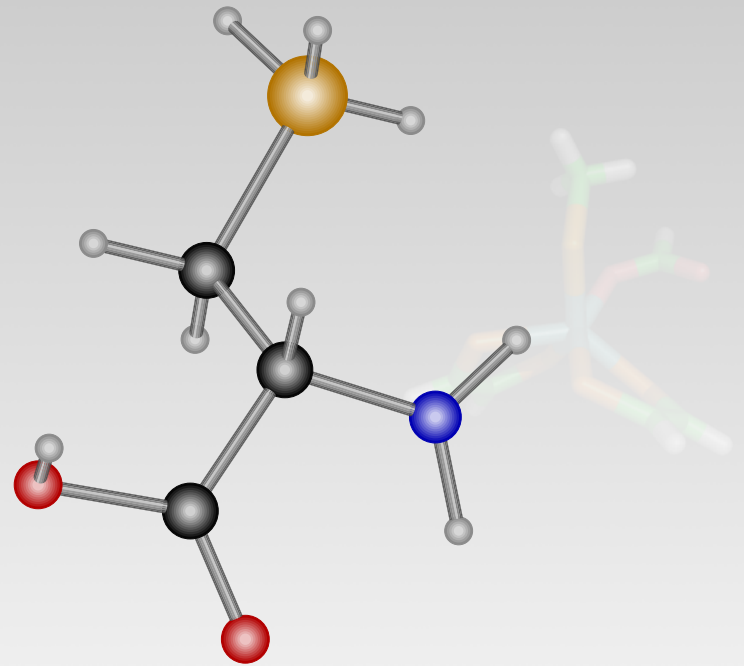
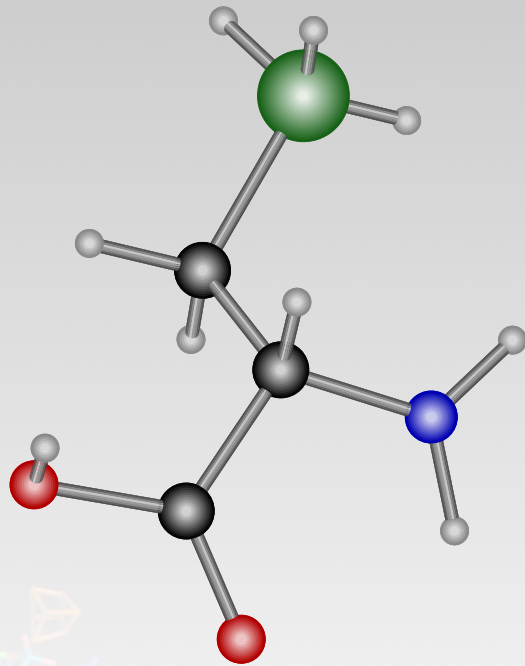
La selenocisteïna

L'aminoàcid 21



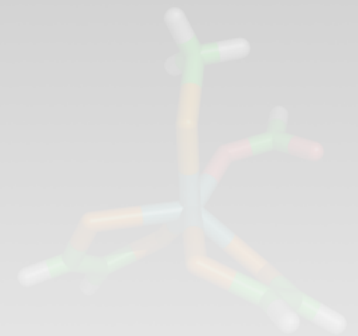
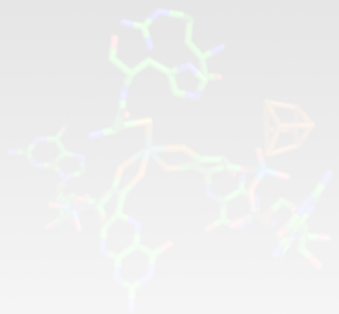
La selenocisteïna

L'aminoàcid 21

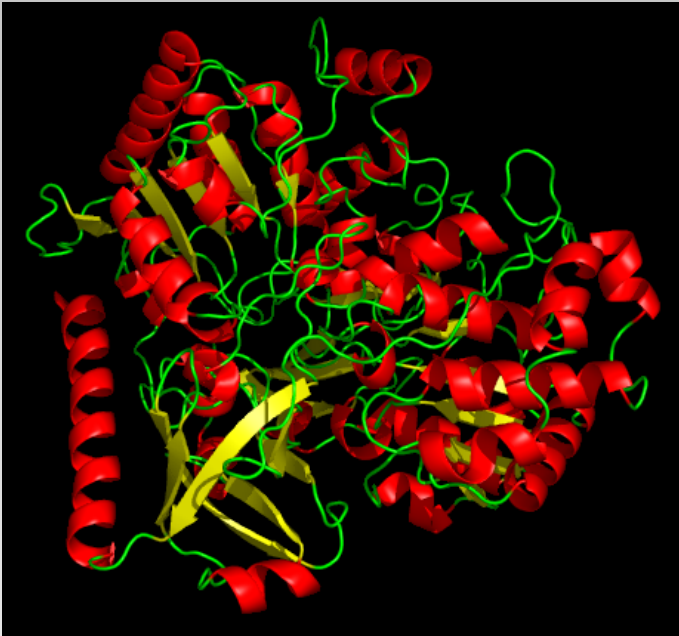


Sec: complicat mecanisme d'inserció

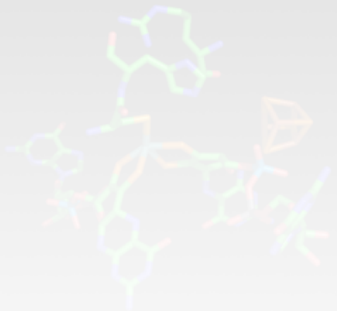
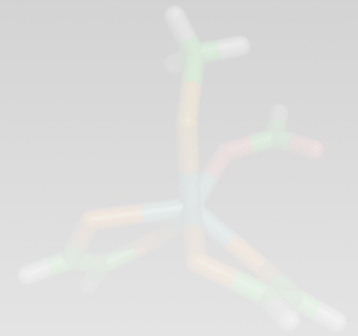
La Format deshidrogenasa H



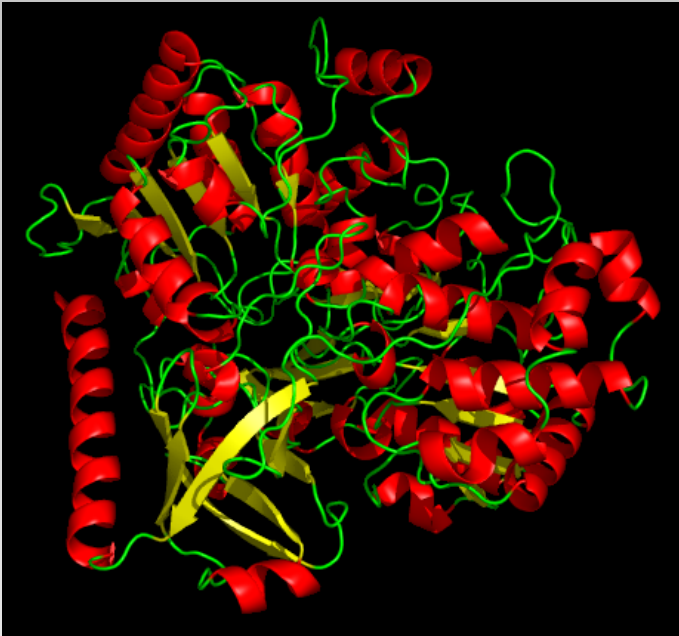
La Format deshidrogenasa H



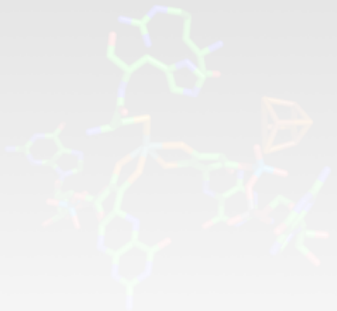
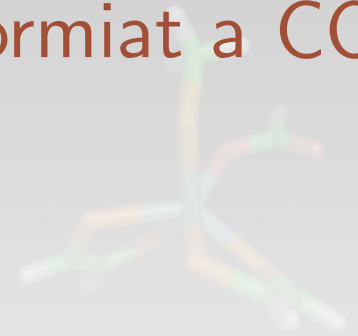
-Part del complex format hidrogen liasa



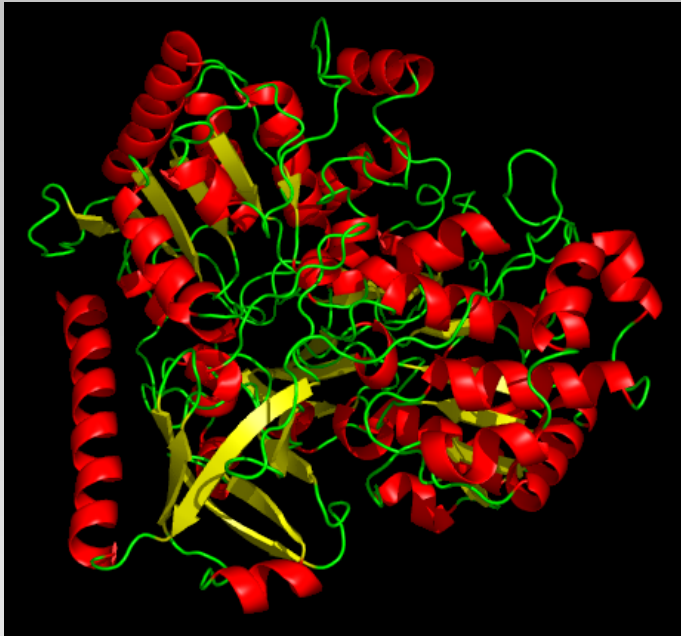
La Format deshidrogenasa H



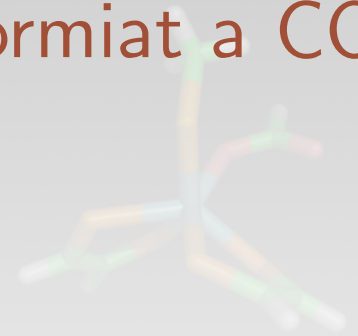
- Part del complex format hidrogen liasa
- El seu paper és oxidar formiat a CO_2



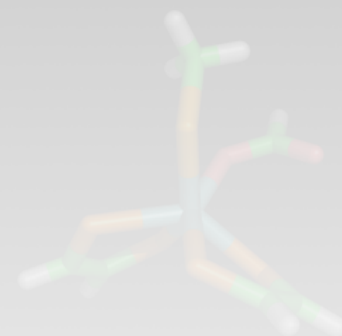
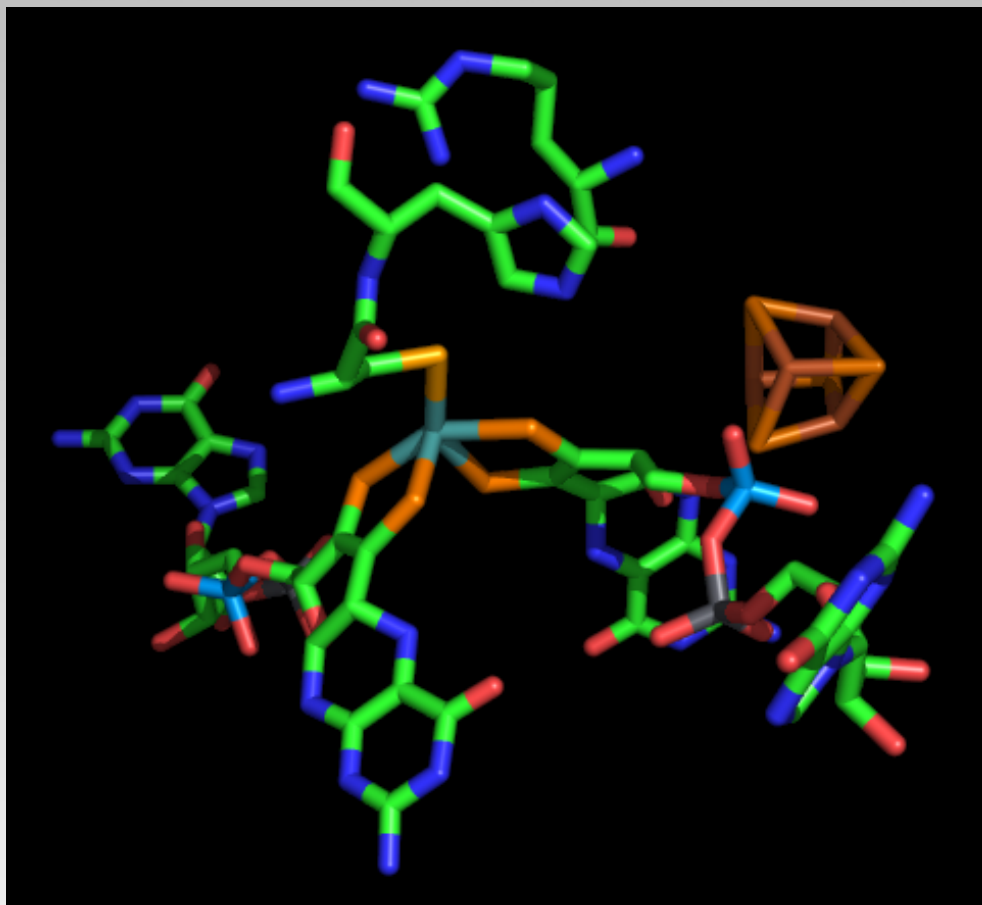
La Format deshidrogenasa H



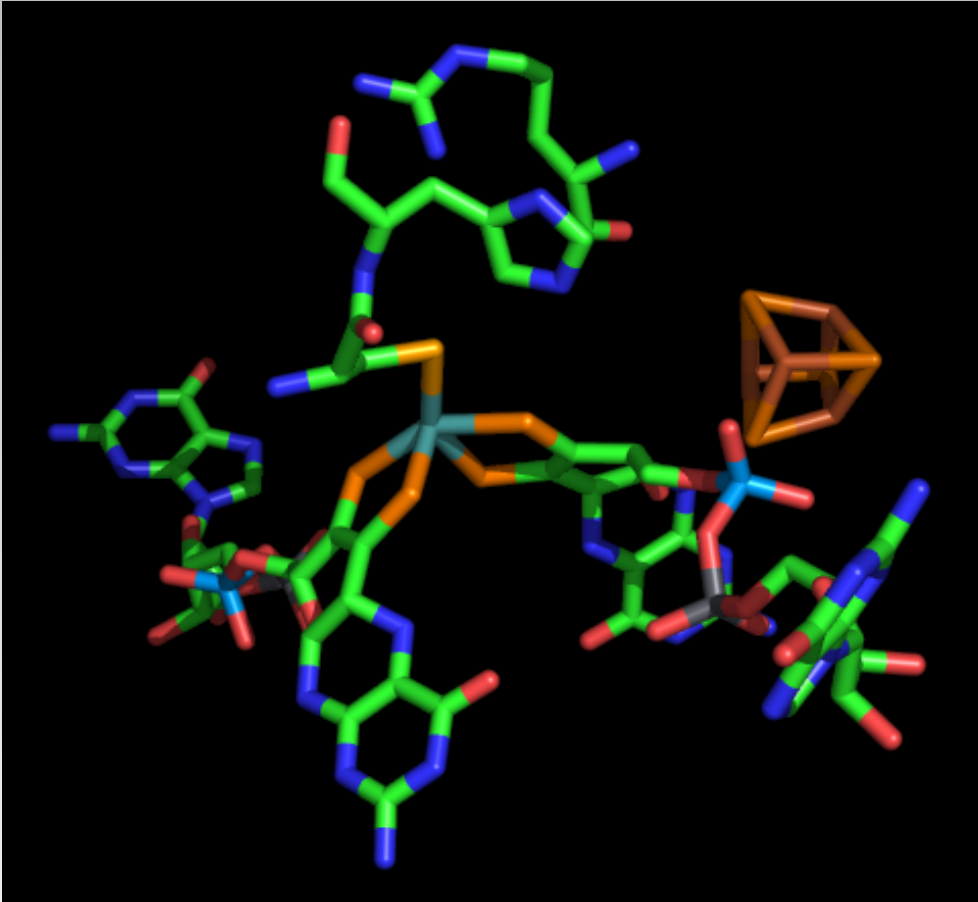
- Part del complex format hidrogen liasa
- El seu paper és oxidar formiat a CO_2
- Reacció redox ($2e^-$)



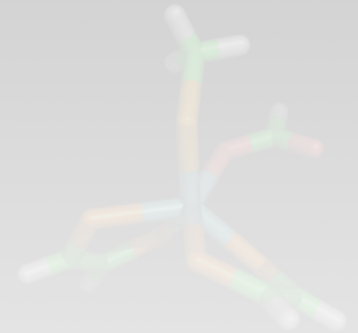
La Format deshidrogenasa H



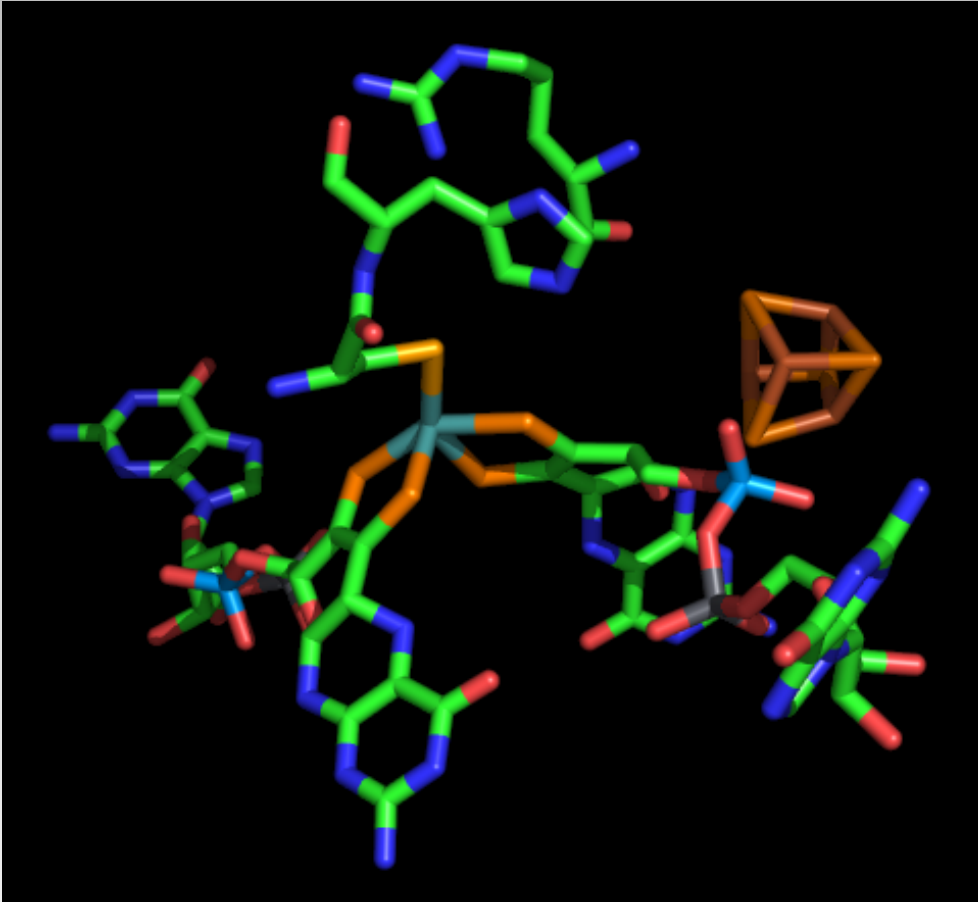
La Format deshidrogenasa H



-Selenocisteïna (Sec^{140})
(Crítica per la reacció)

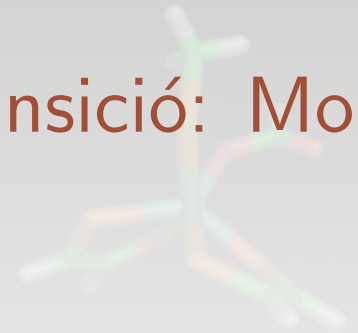


La Format deshidrogenasa H

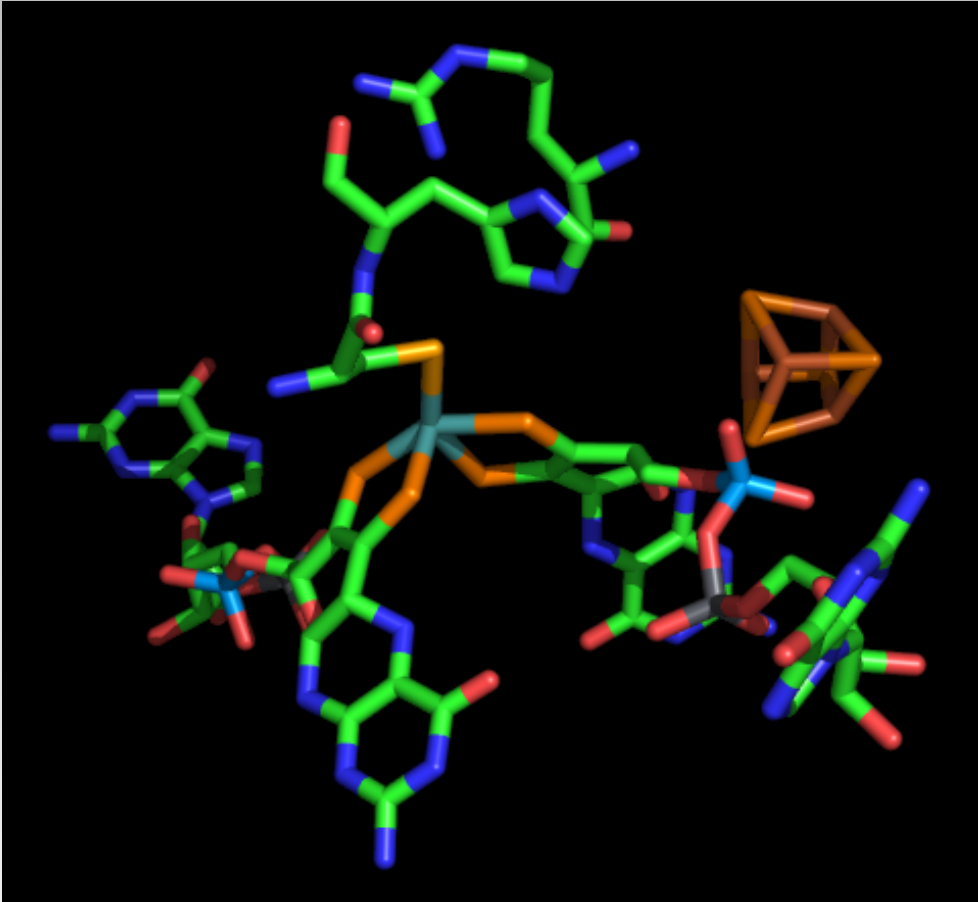


-Selenocisteïna (Sec¹⁴⁰)
(Crítica per la reacció)

-Metall de transició: Mo

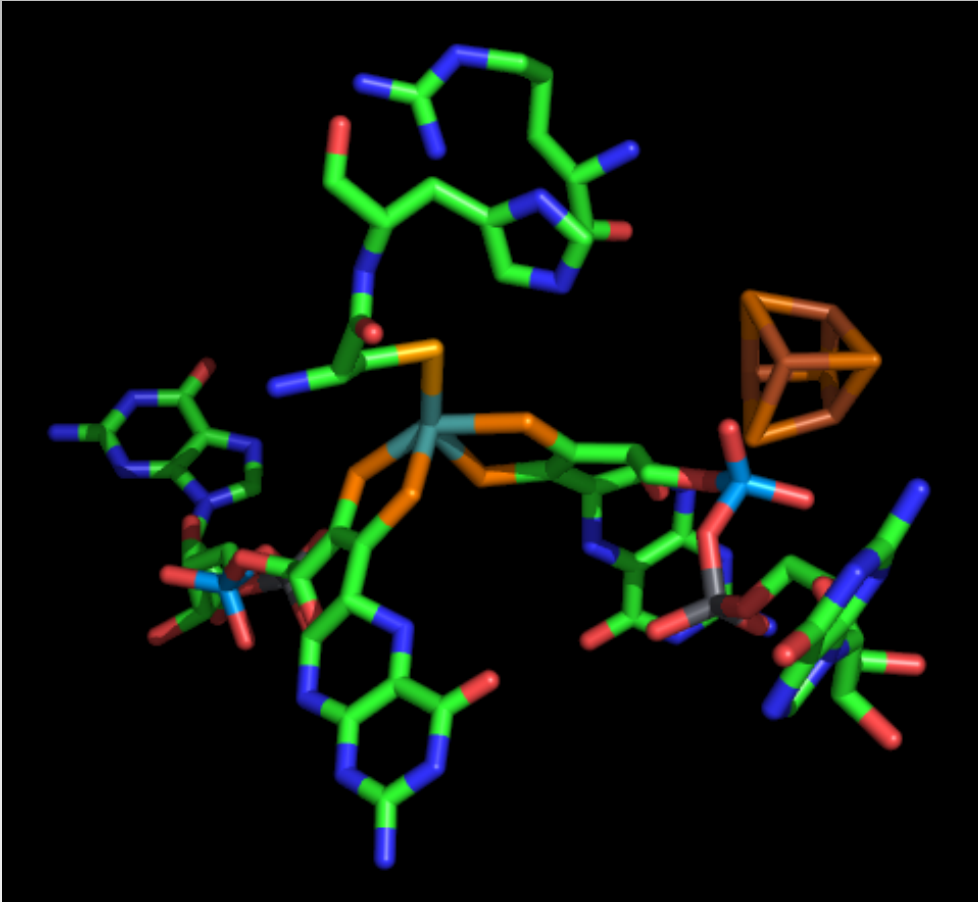


La Format deshidrogenasa H



- Selenocisteïna (Sec^{140})
(Crítica per la reacció)
- Metall de transició: Mo
- Acceptador d' e^- : Fe_4S_4

La Format deshidrogenasa H



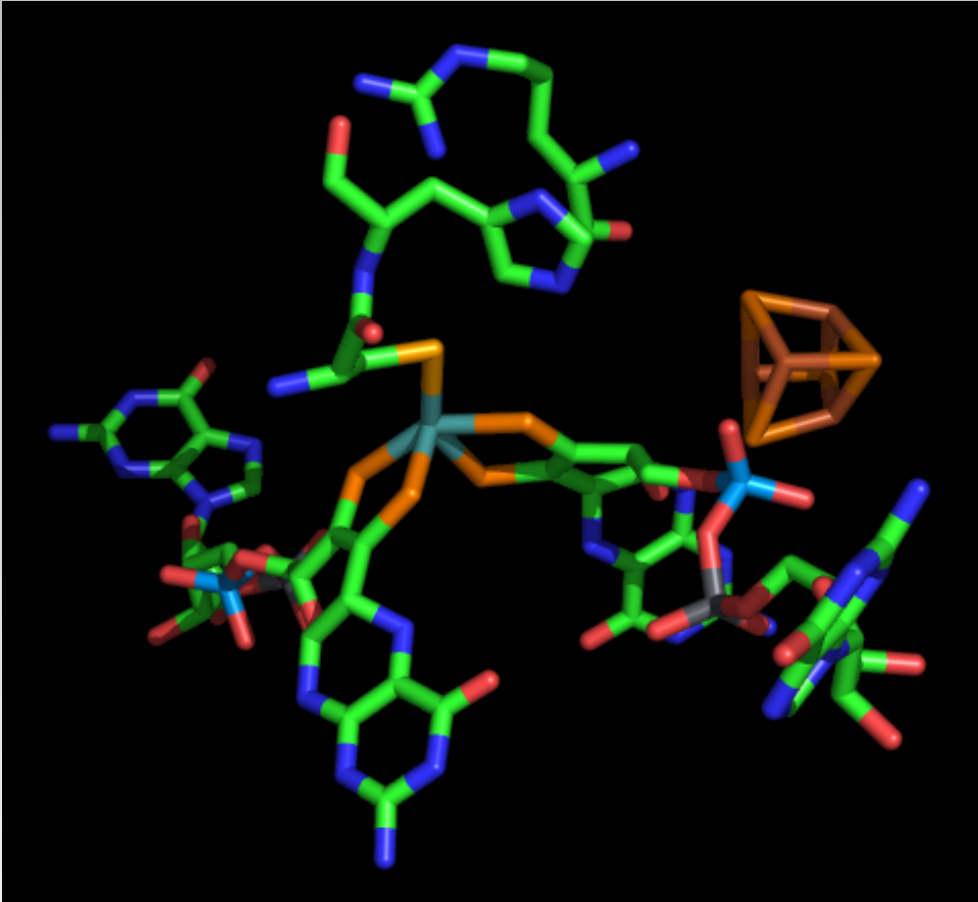
-Selenocisteïna (Sec^{140})
(Crítica per la reacció)

-Metall de transició: Mo

-Acceptador d' e^- : Fe_4S_4

-*Molybdopterin guanine dinucleotide cofactor* (MGDC)

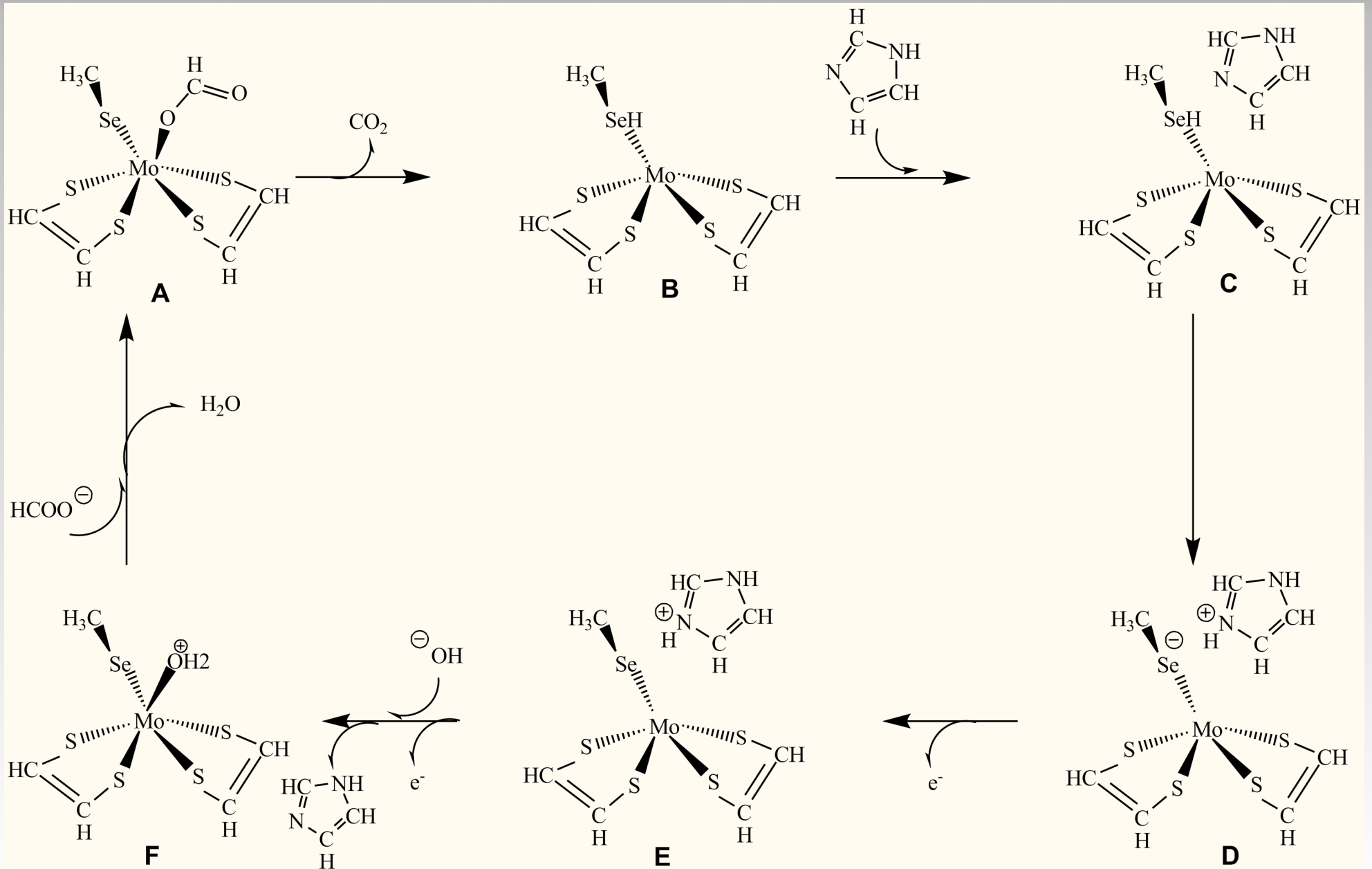
La Format deshidrogenasa H



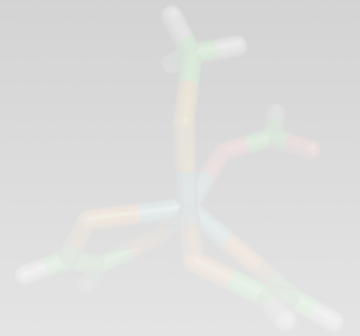
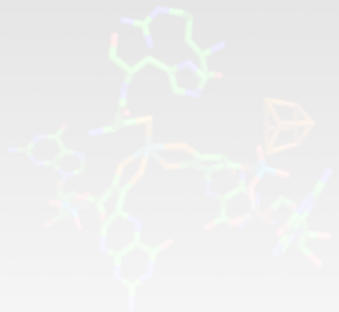
- Selenocisteïna (Sec¹⁴⁰)
(Crítica per la reacció)
- Metall de transició: Mo
- Accepter d'e⁻: Fe₄S₄

- Molybdopterin guanine dinucleotide cofactor* (MGDC)
- Histidina (His¹⁴¹) i Arginina (Arg³³³)

El cicle catalític

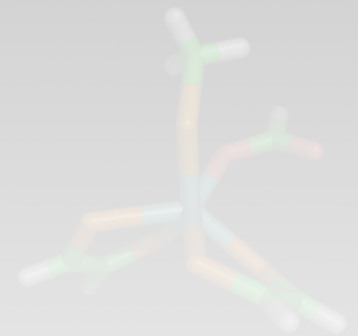
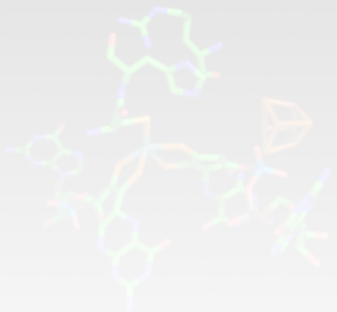


Objectius



Objectius

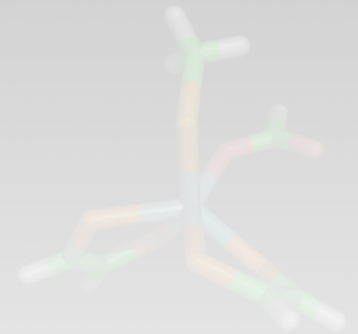
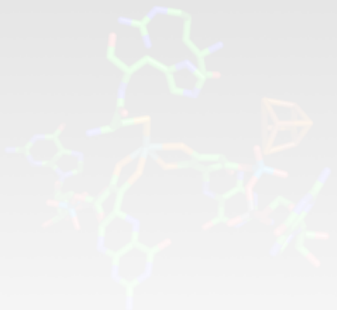
Per què es manté la selenocisteïna?



Objectius

Per què es manté la selenocisteïna?

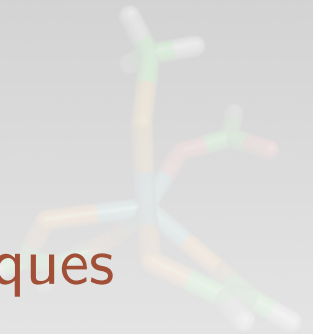
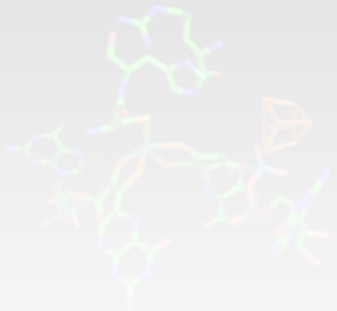
-Comprovar la validesa del mecanisme



Objectius

Per què es manté la selenocisteïna?

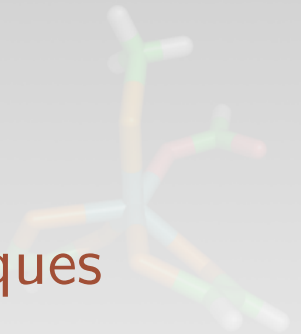
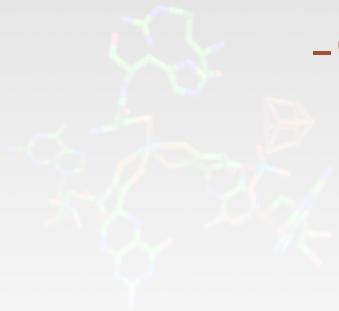
- Comprovar la validesa del mecanisme
- Analitzar el perfil i identificar les etapes crítiques



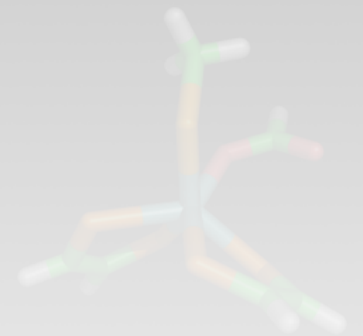
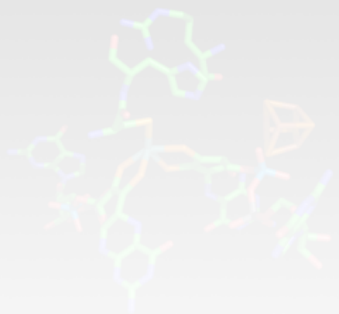
Objectius

Per què es manté la selenocisteïna?

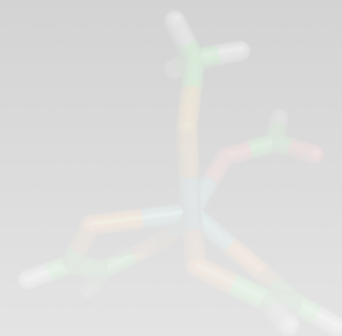
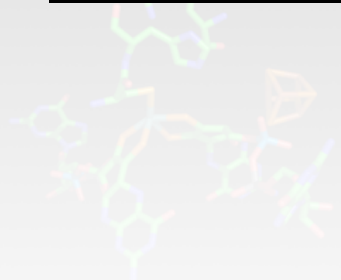
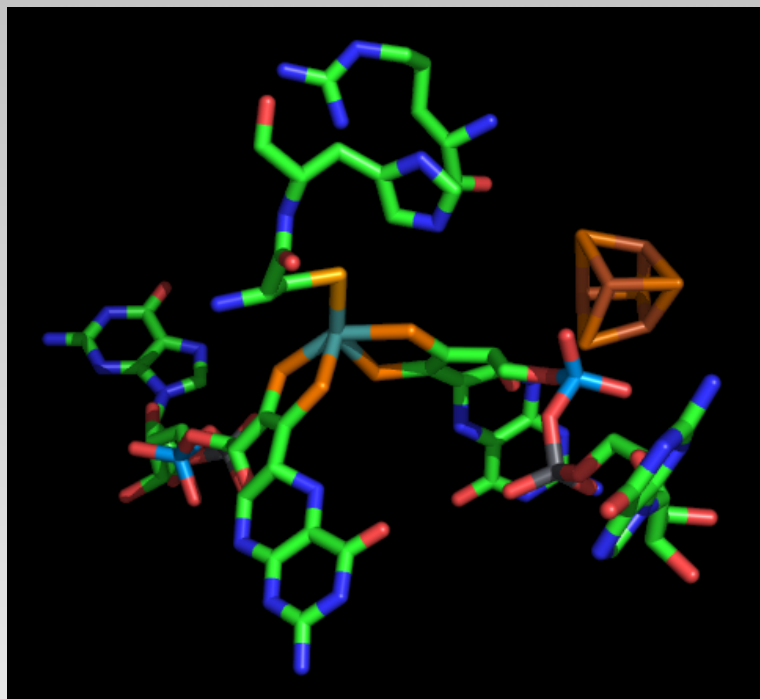
- Comprovar la validesa del mecanisme
- Analitzar el perfil i identificar les etapes crítiques
- Comparar la selenocisteïna amb la cisteïna



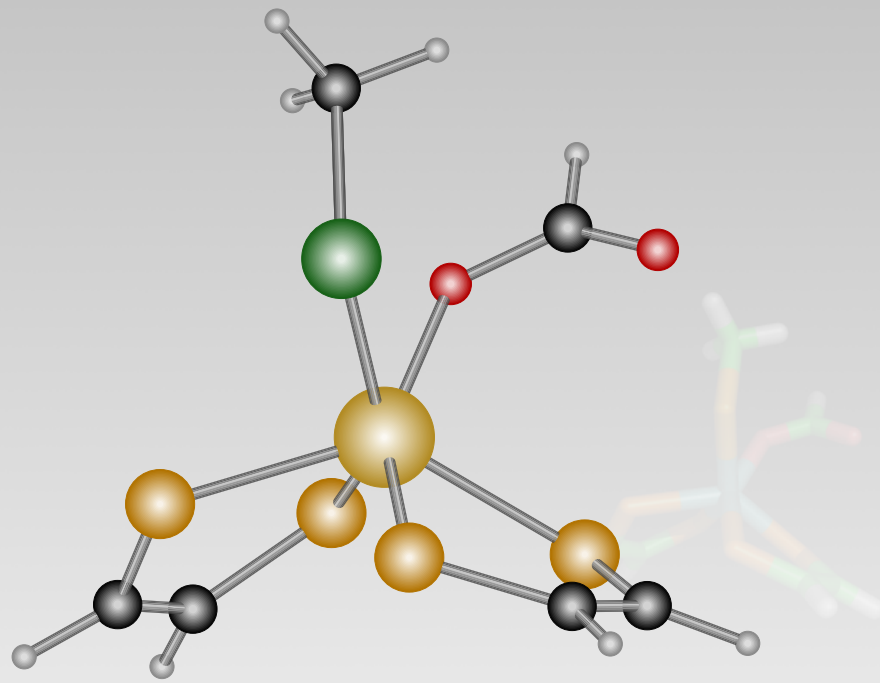
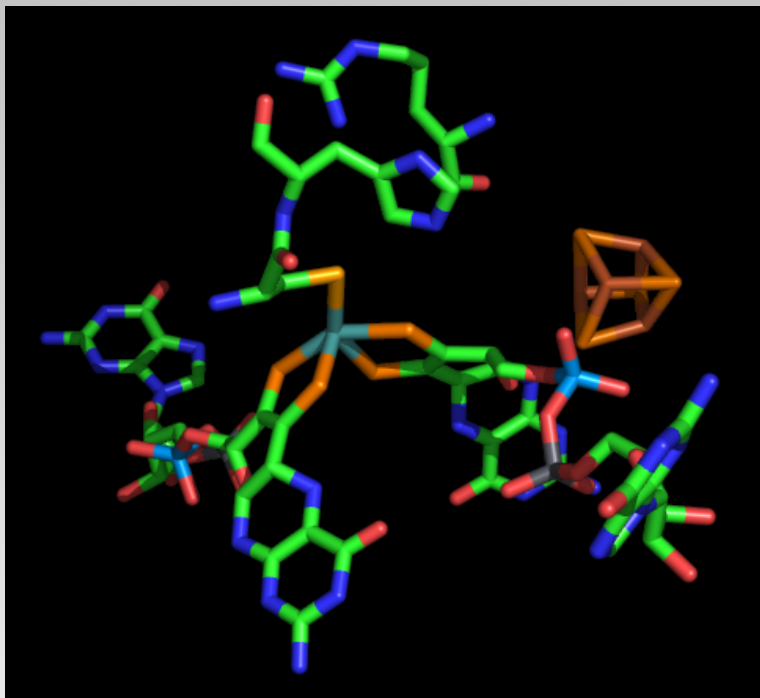
Procediment: model QM



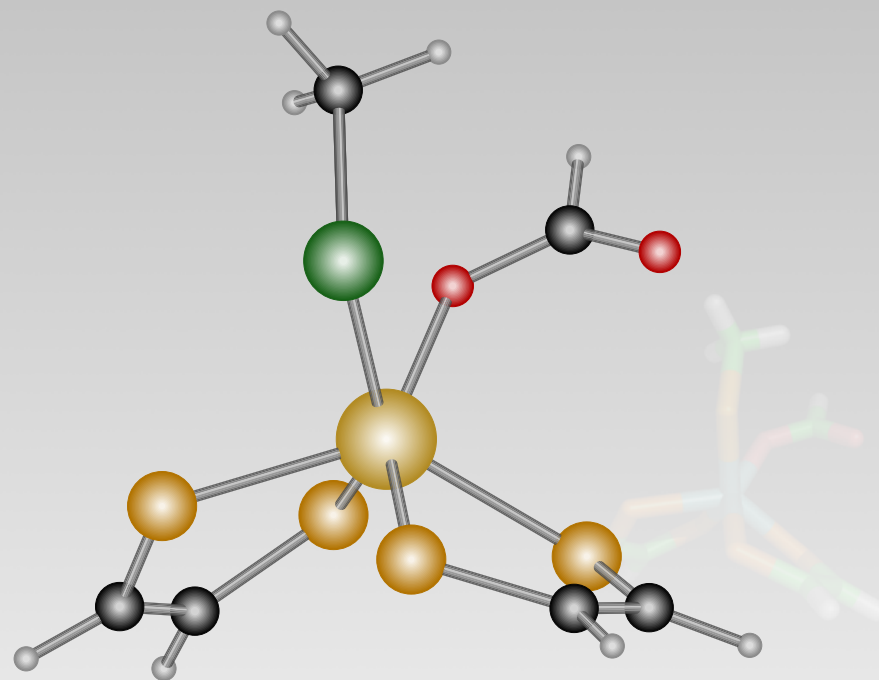
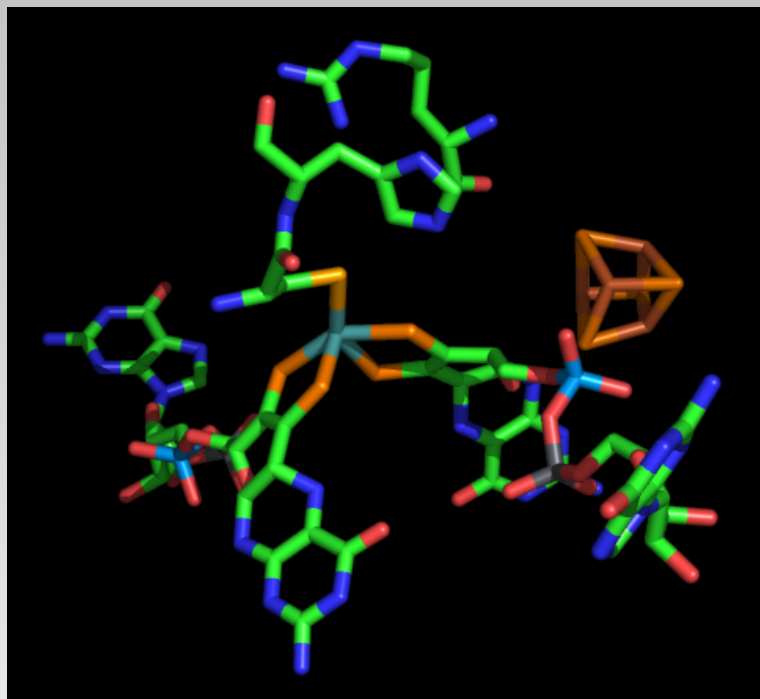
Procediment: model QM



Procediment: model QM

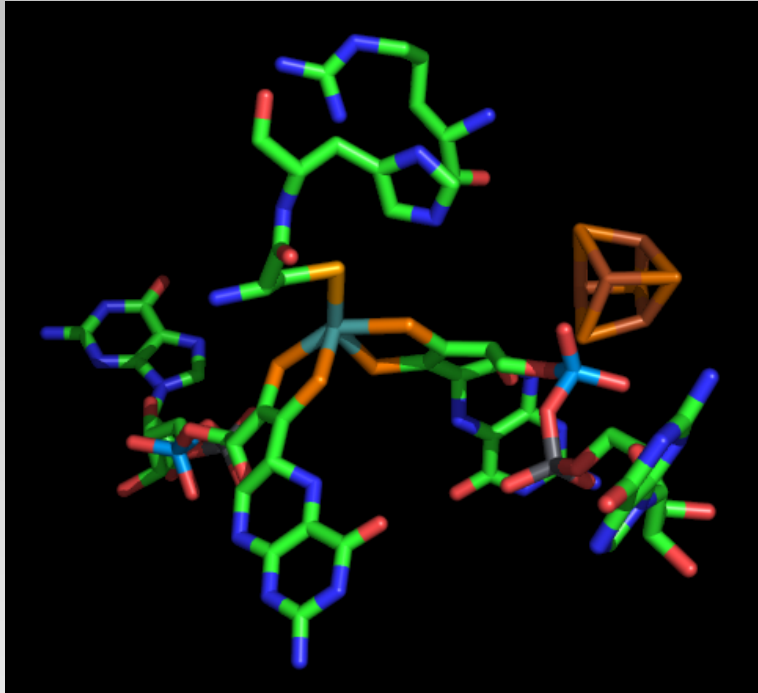


Procediment: model QM

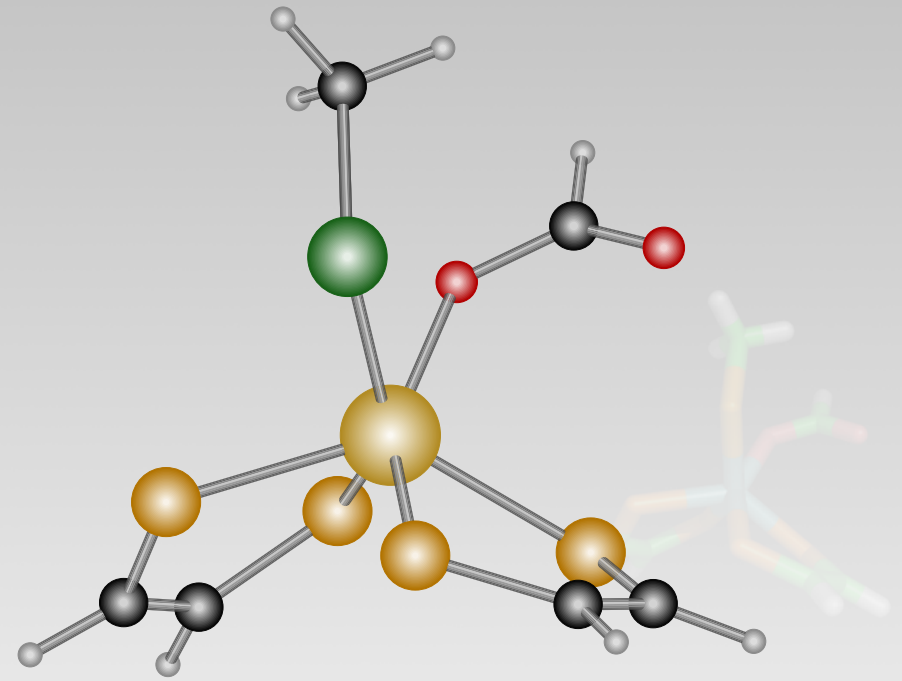


-Seleni/sofre

Procediment: model QM

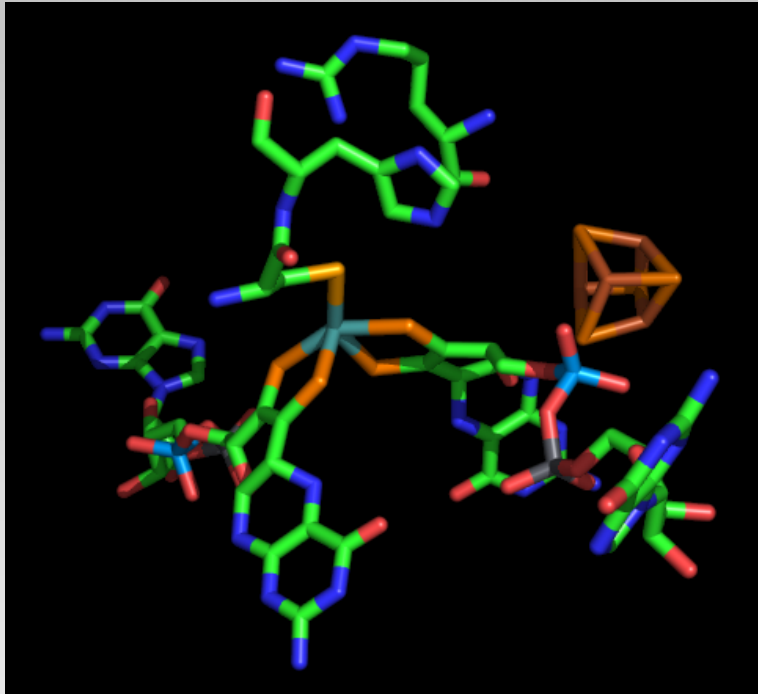


-Seleni/sofre



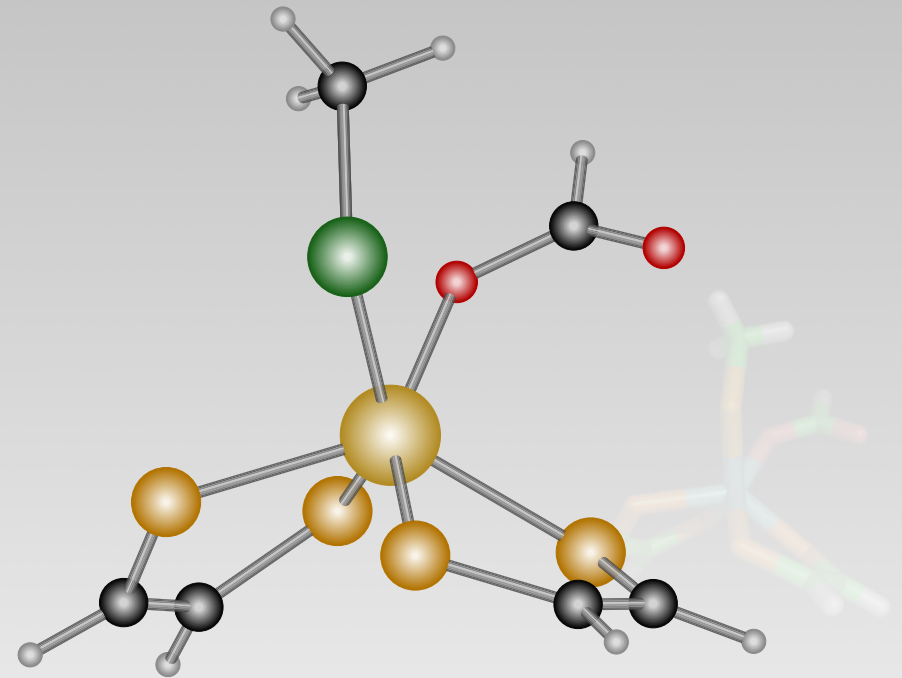
-Àtom de molibdè

Procediment: model QM



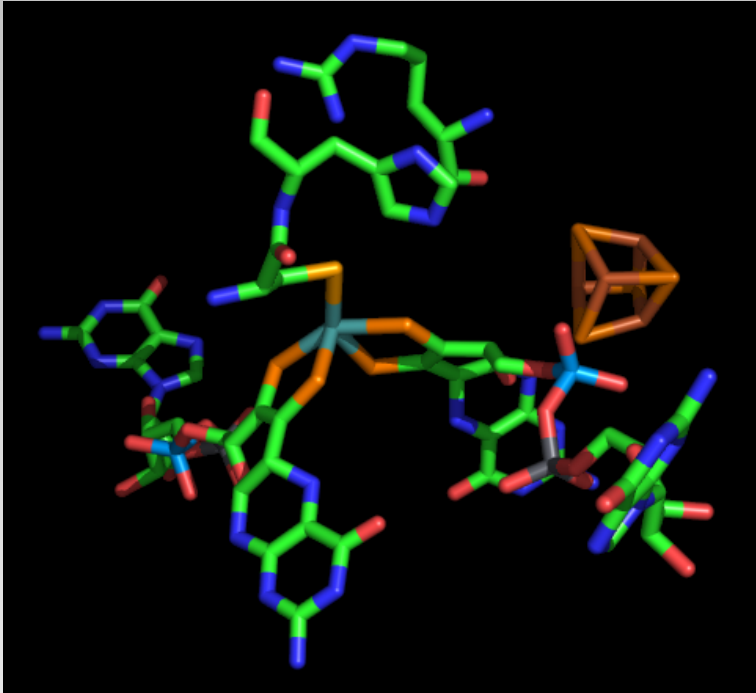
-Seleni/sofre

-4 sofres dels MGDC



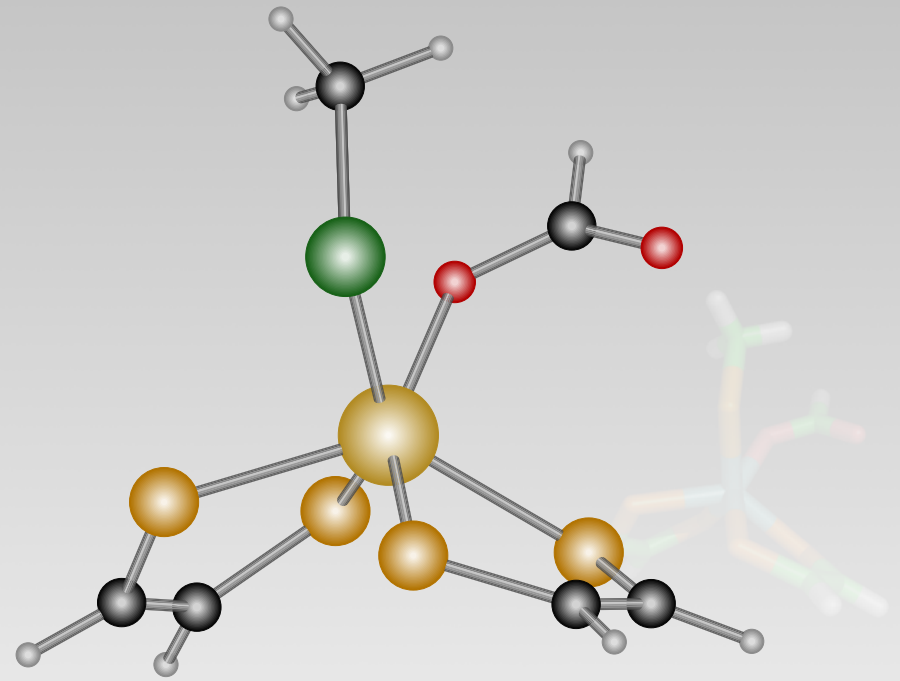
-Àtom de molibdè

Procediment: model QM



-Seleni/sofre

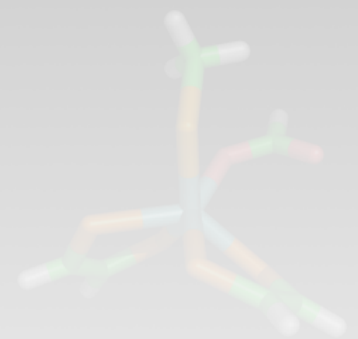
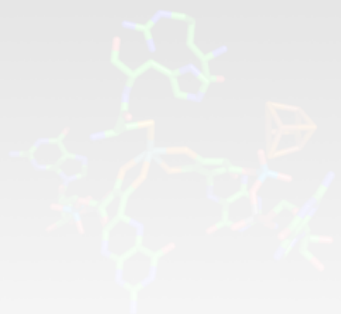
-4 sofres dels MGDC



-Àtom de molibdè

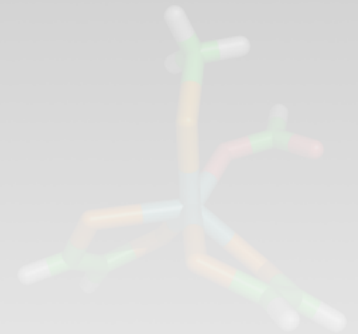
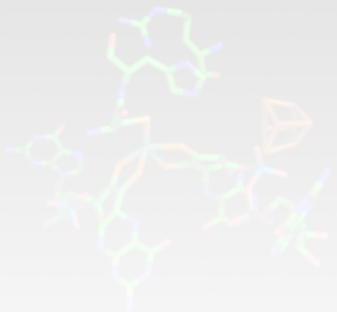
-Anell d'imidazol (His¹⁴¹)

Procediment



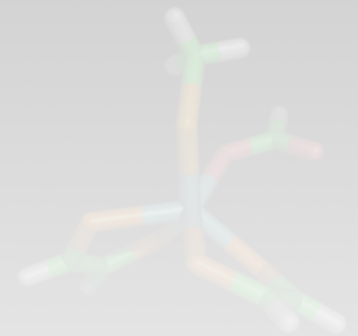
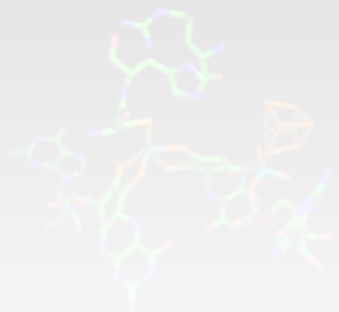
Procediment

-Optimització de les geometries (Se/S)



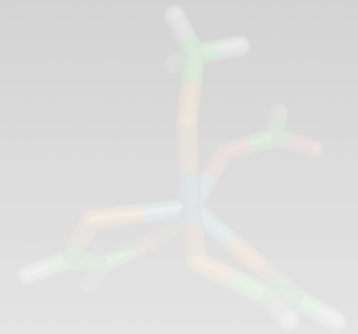
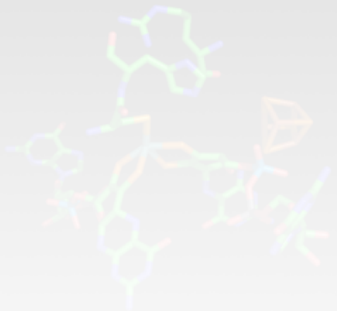
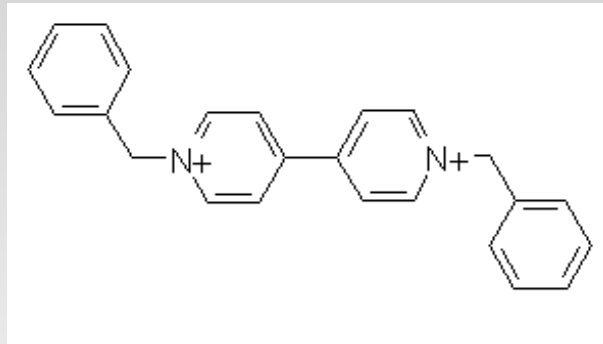
Procediment

- Optimització de les geometries (Se/S)
- Càlculs puntuals amb PCM. Acetonitril (ϵ 36.64)



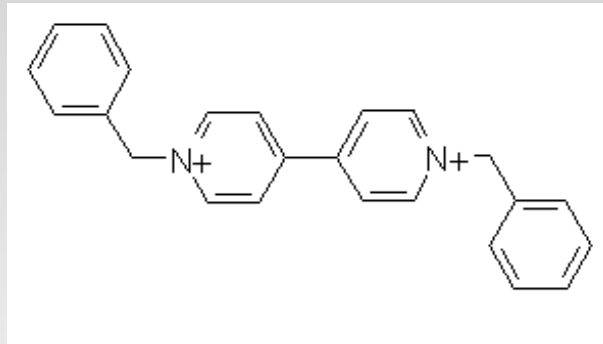
Procediment

- Optimització de les geometries (Se/S)
- Càlculs puntuals amb PCM. Acetonitril (ϵ 36.64)
- Acceptador d'electrons: Benzil viologen

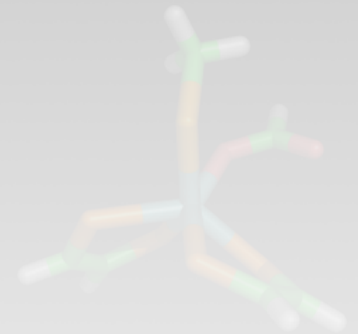


Procediment

- Optimització de les geometries (Se/S)
- Càlculs puntuals amb PCM. Acetonitril (ϵ 36.64)
- Acceptador d'electrons: Benzil viologen

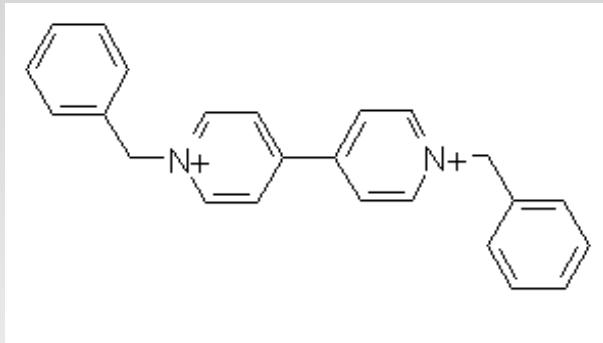


-Gaussian 03



Procediment

- Optimització de les geometries (Se/S)
- Càlculs puntuals amb PCM. Acetonitril (ϵ 36.64)
- Acceptador d'electrons: Benzil viologen

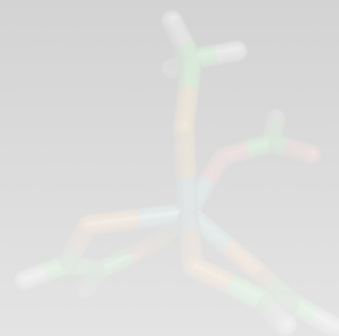
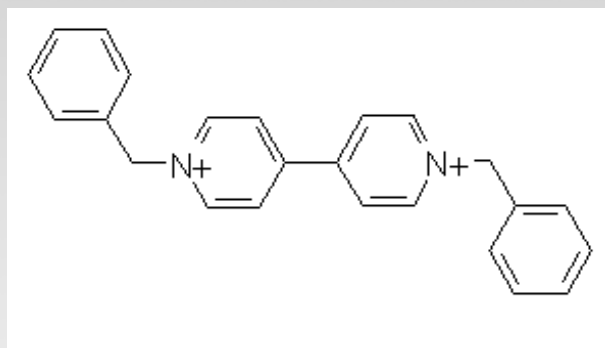


-Gaussian 03

-DFT B3LYP

Procediment

- Optimització de les geometries (Se/S)
- Càlculs puntuals amb PCM. Acetonitril (ϵ 36.64)
- Acceptador d'electrons: Benzil viologen



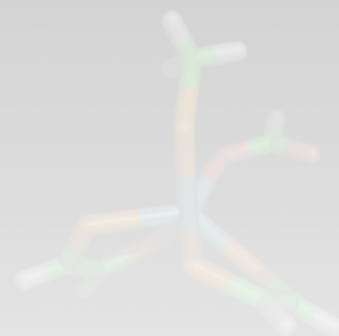
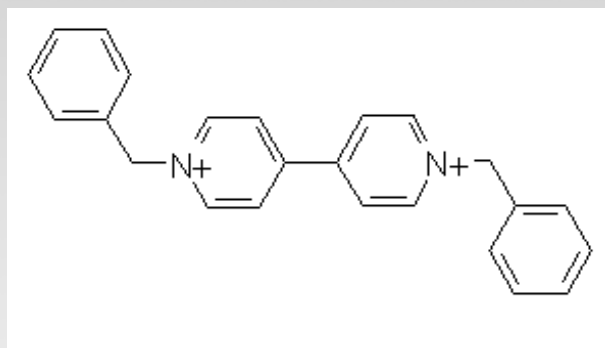
-Gaussian 03

-DFT B3LYP

-**LANL2DZ:** Mo, Se i S **6-31+G(d):** C, H, N

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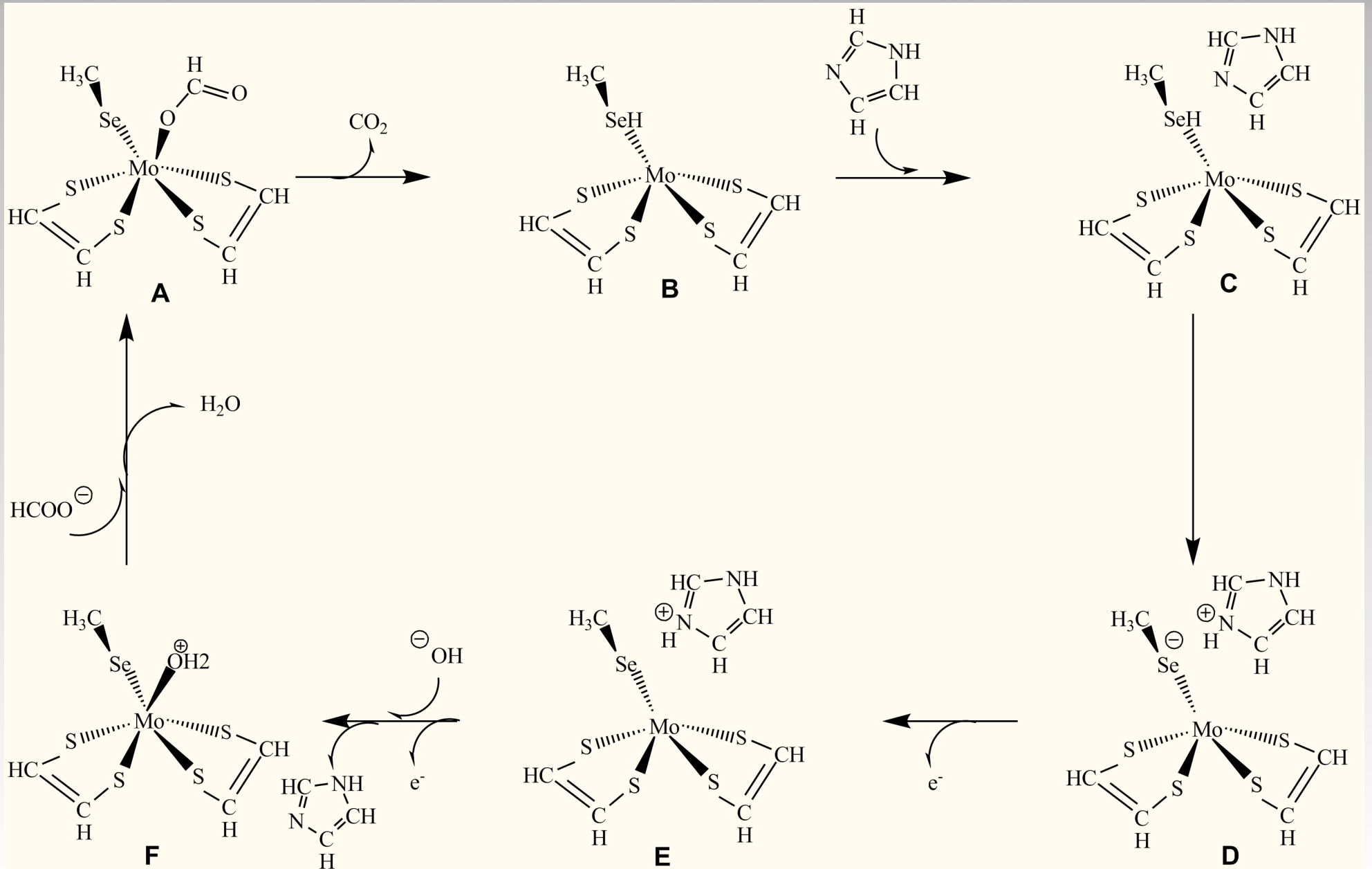
-Gaussian 03

-DFT B3LYP

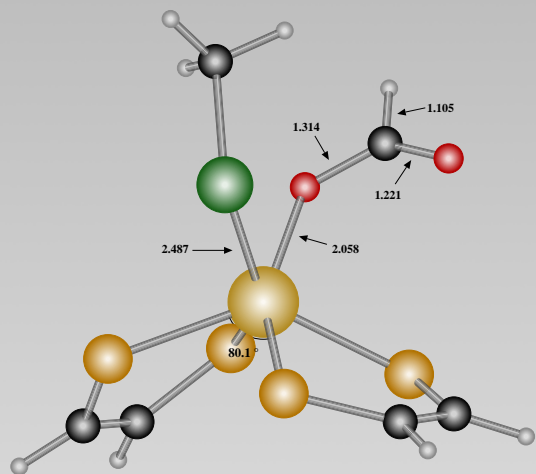
-**LANL2DZ**: Mo, Se i S **6-31+G(d)**: C, H, N

-Capa de funcions de polarització d al seleni i sofre

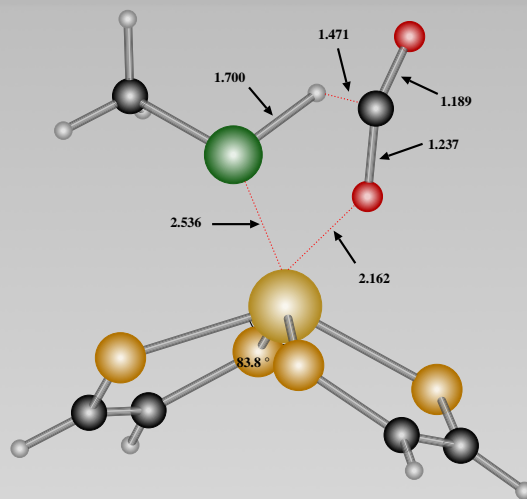
El cicle catalític



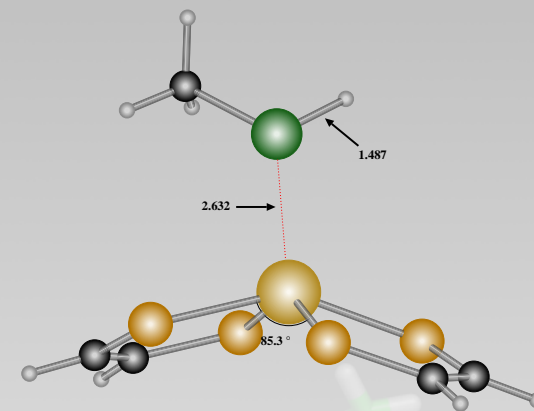
Desprotonació del formiat



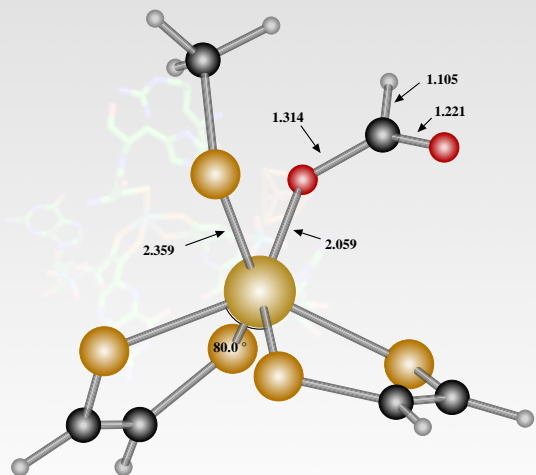
Se(kcal/mol) A: 0



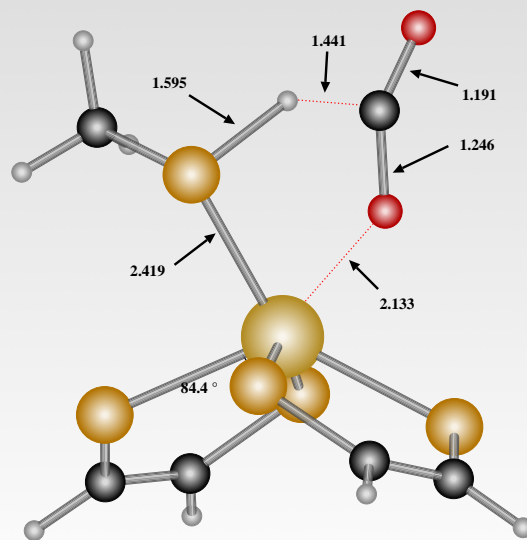
tsAB: 22.5



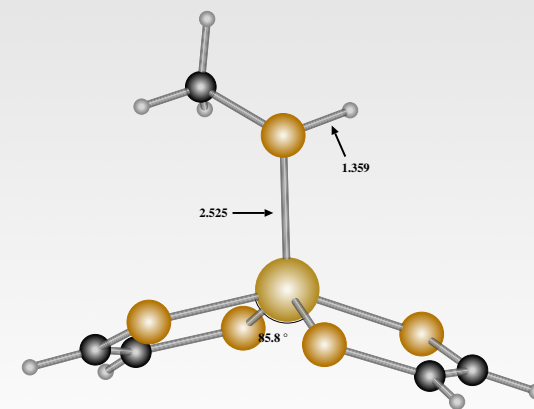
B: 1.9



S(kcal/mol) A: 0

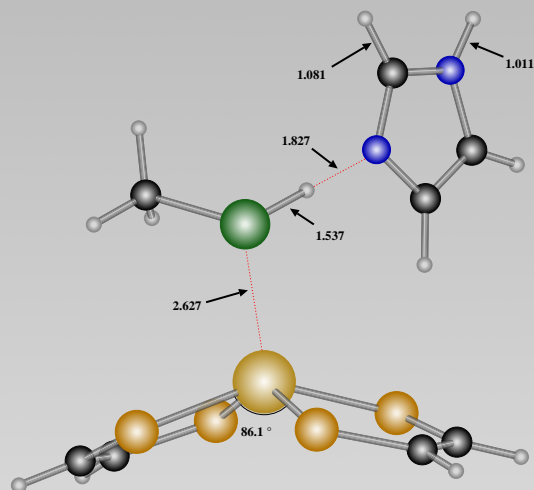


tsAB: 19.0

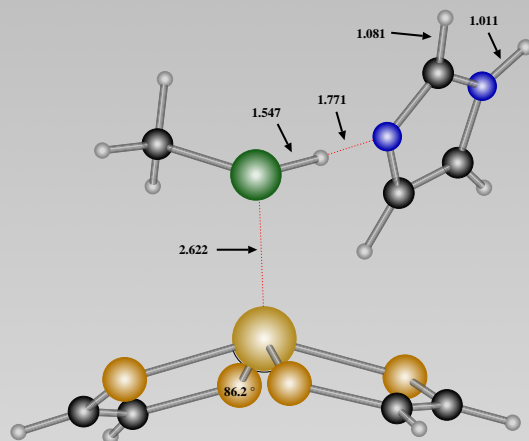


B: -5.9

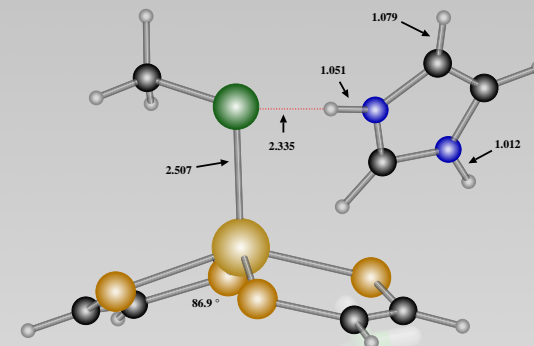
Desprotonació del seleni/sofre



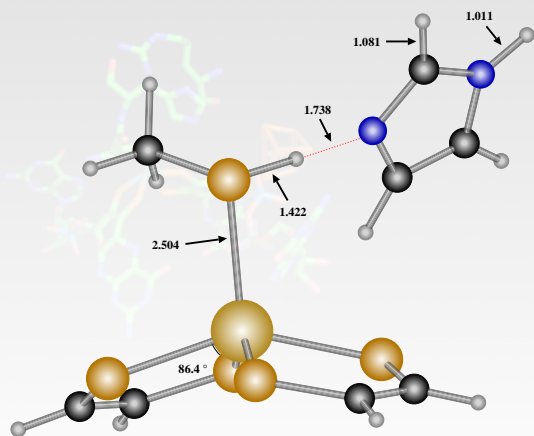
Se(kcal/mol) C: 0



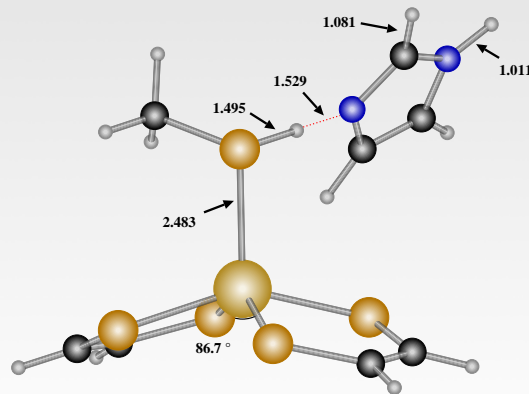
tsCD: -0.7(*)



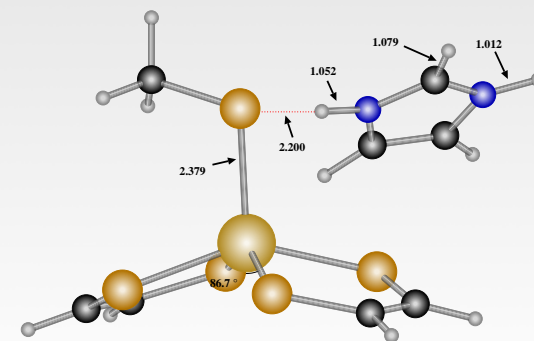
D: -22.5



S(kcal/mol) C: 0

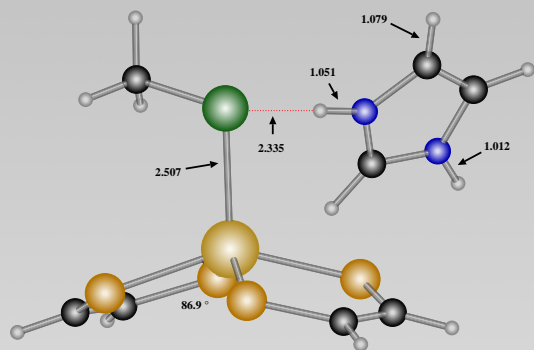


tsCD: -1.4(*)

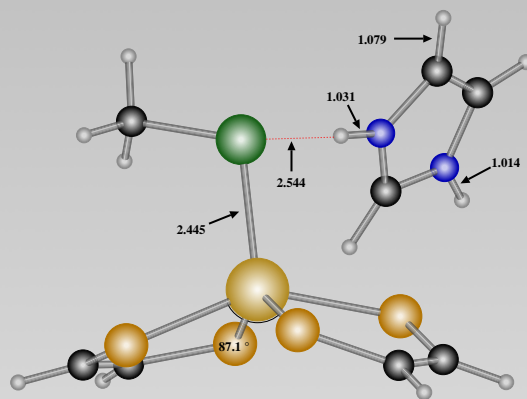


D: -19.8

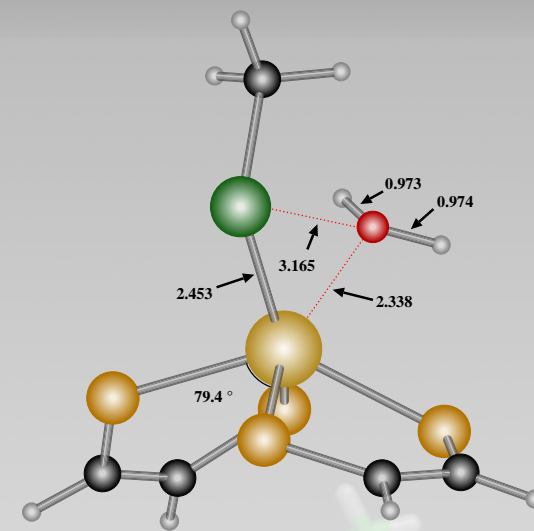
Oxidació del molibdè



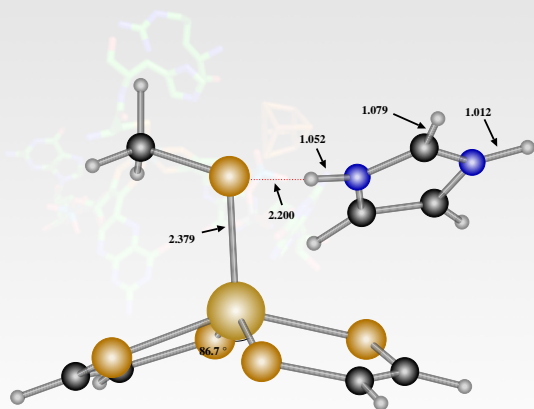
Se(kcal/mol) D: 0



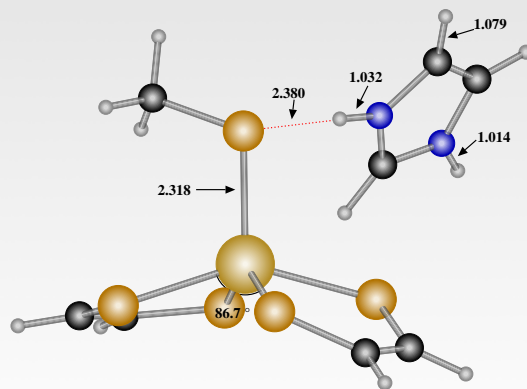
E: 13.7



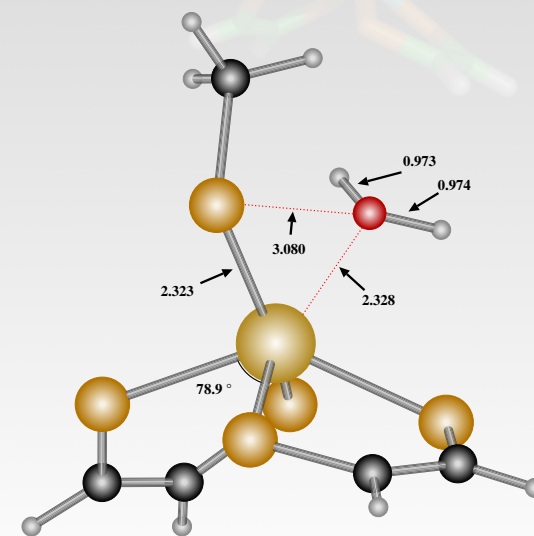
F: 35.8



S(kcal/mol) D: 0

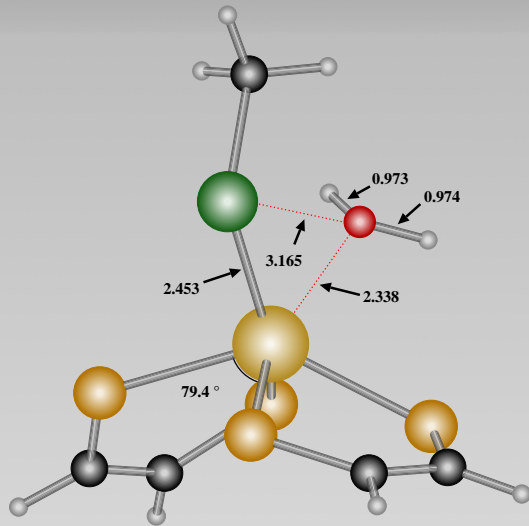


E: 19.9



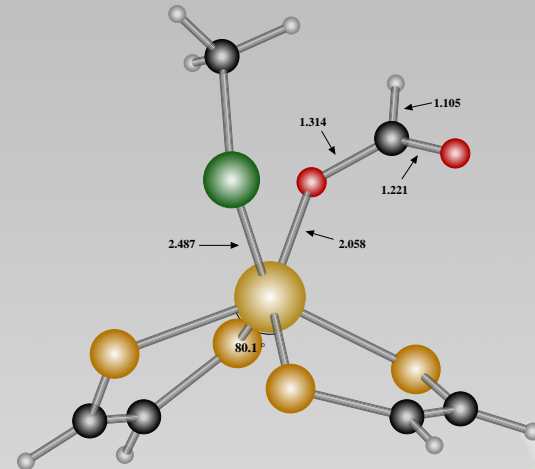
F: 38.7

Incorporació d'un nou formiat

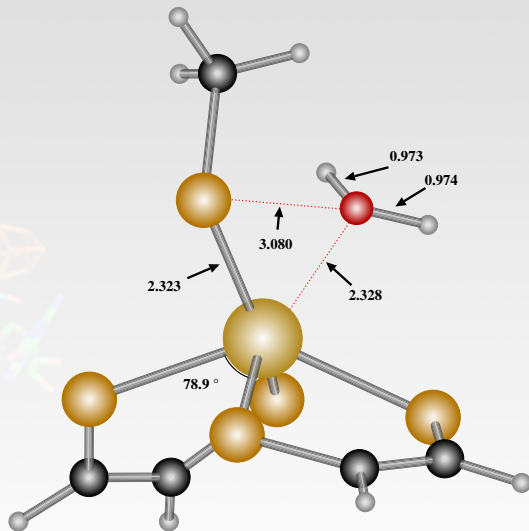


Se(kcal/mol)

F: 0

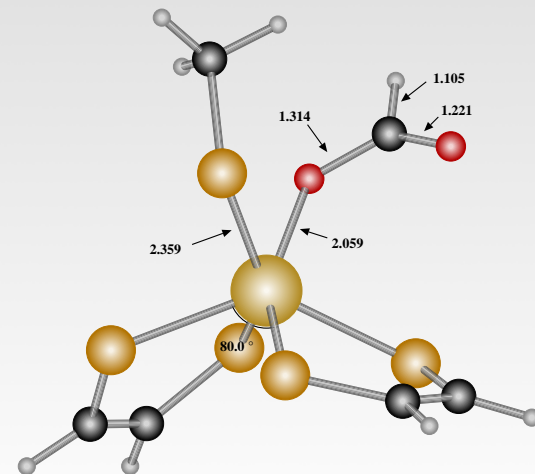


A: -27.7



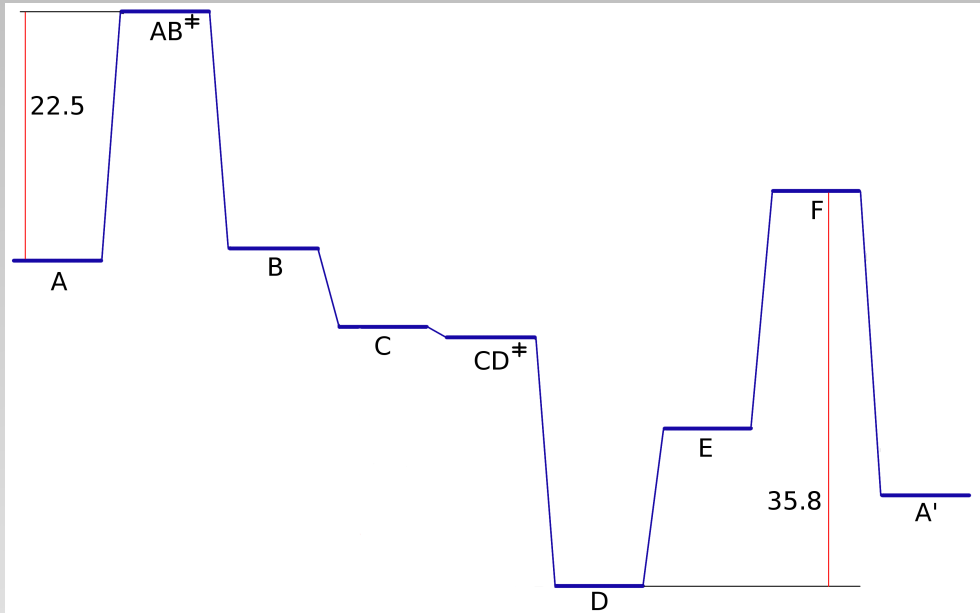
S(kcal/mol)

F: 0

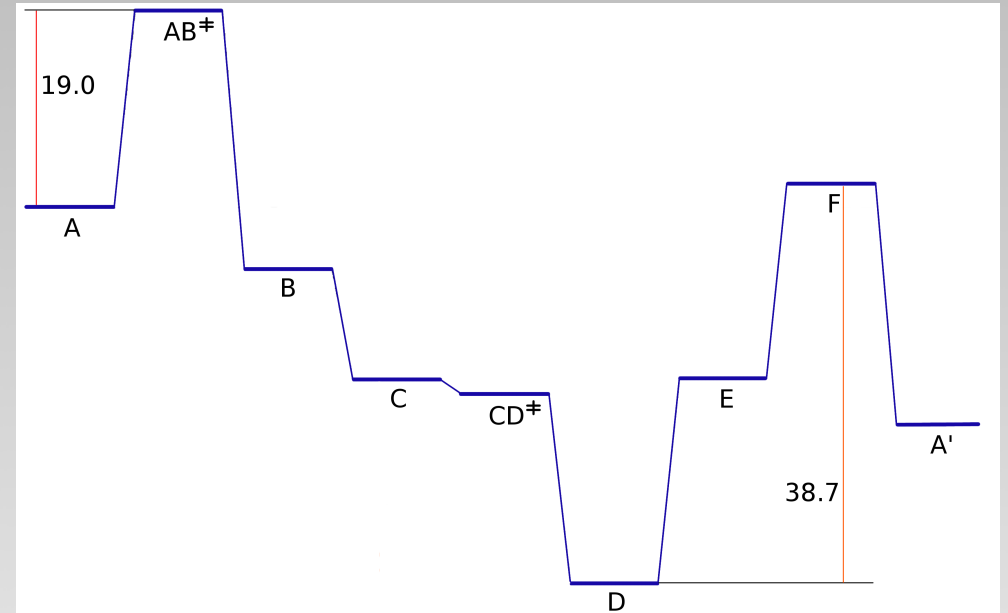


A: -23.7

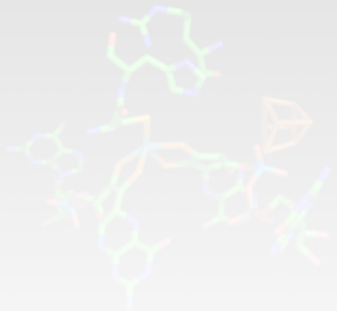
Anàlisi global d'energies



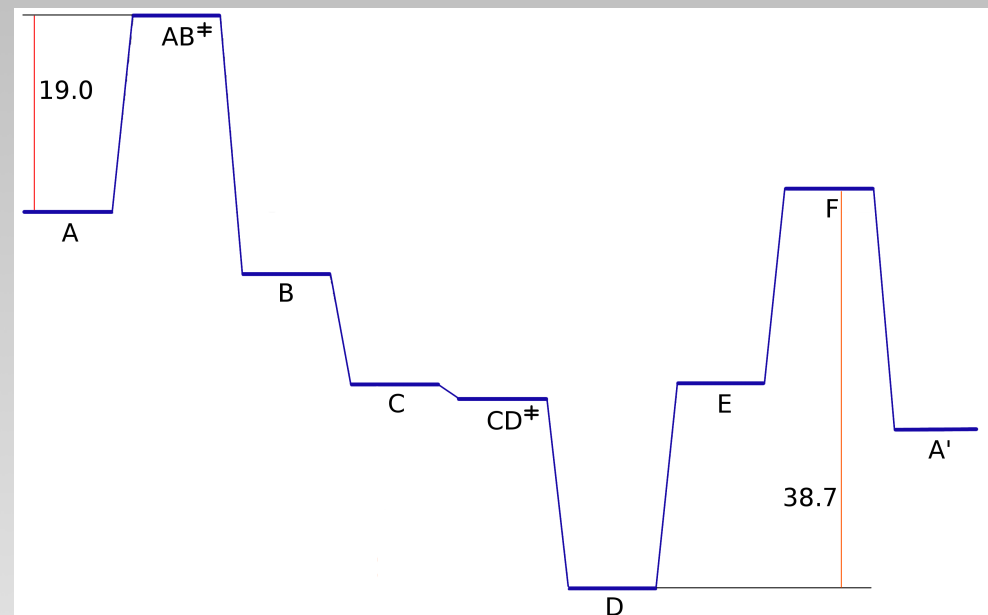
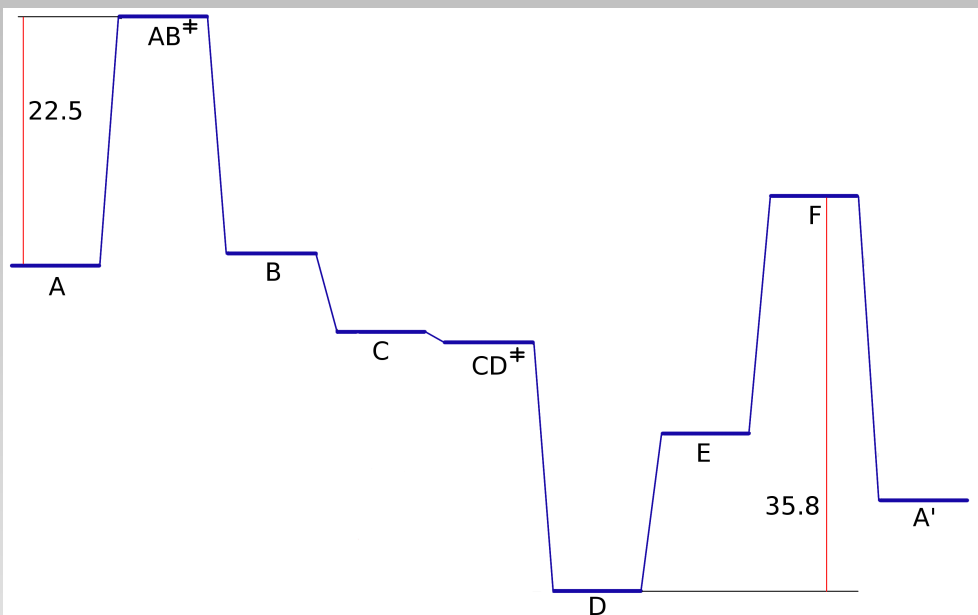
Se



S



Anàlisi global d'energies

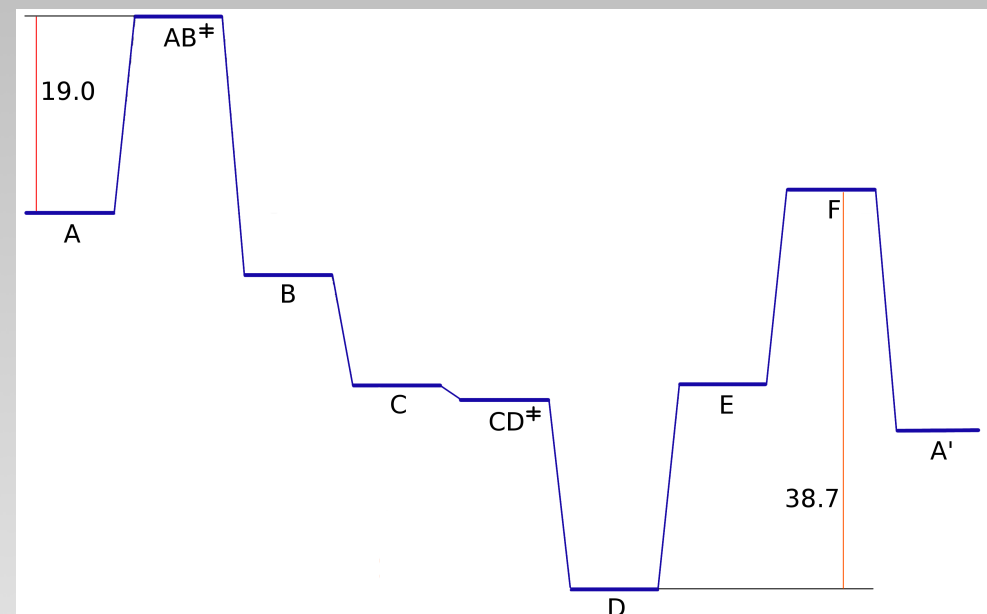
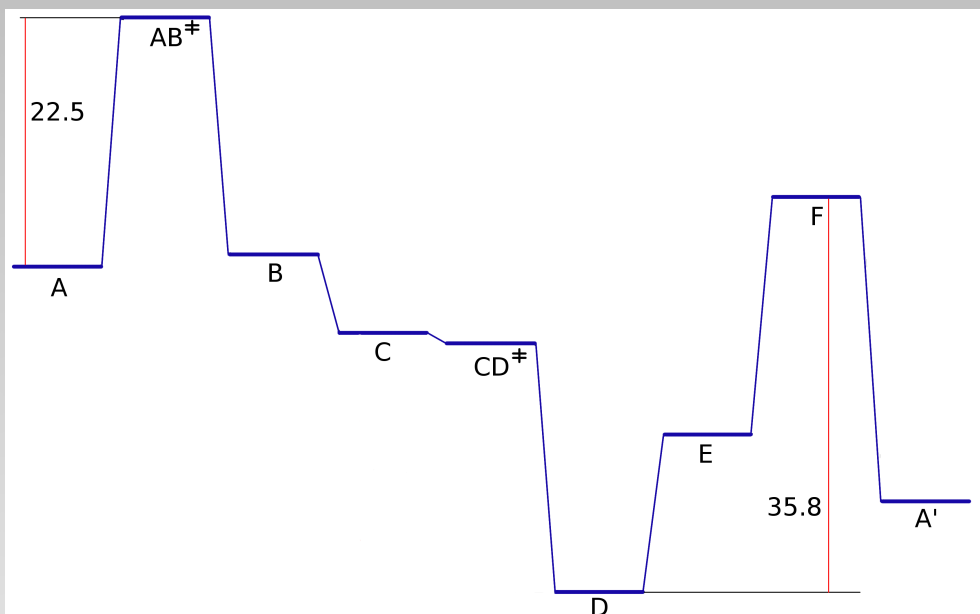


Se

S

Intermedi	Se	S	Se-S
A	0.0	0.0	0.0
tsAB	22.5	19.0	+3.5
B	1.9	-5.9	+7.8

Anàlisi global d'energies



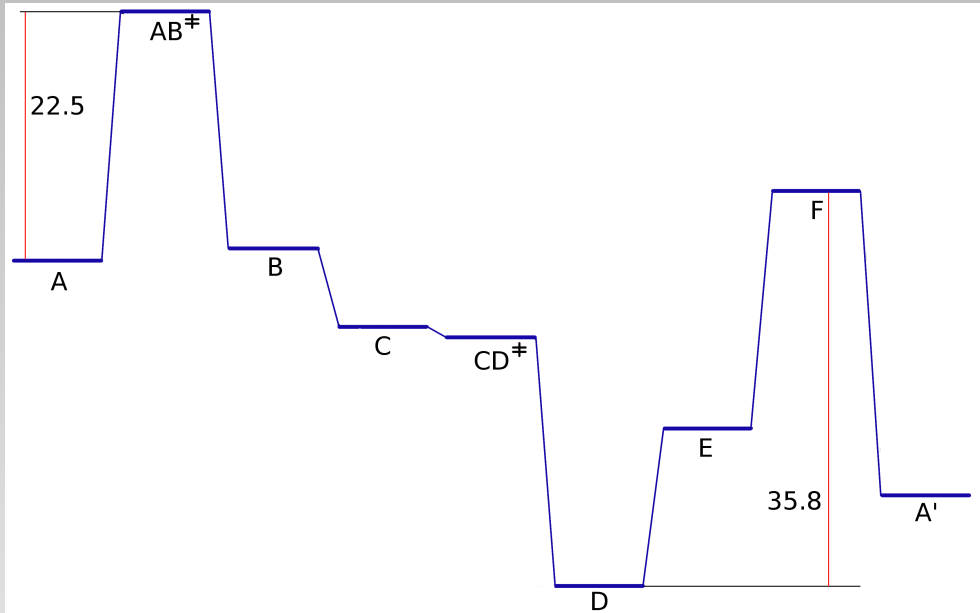
Se

Intermedi	Se	S	Se-S
A	0.0	0.0	0.0
tsAB	22.5	19.0	+3.5
B	1.9	-5.9	+7.8

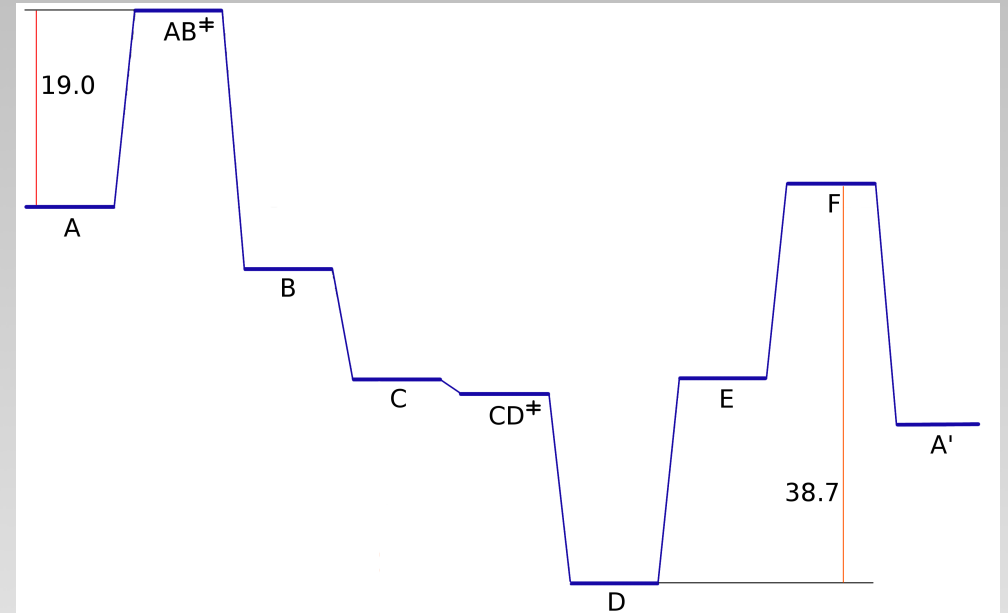
S

Intermedi	Se	S	Se-S
D	0	0	0
E	13.7	19.9	-6.2
F	35.8	38.7	-2.9
A'	8.1	14.9	-6.8

Anàlisi global d'energies



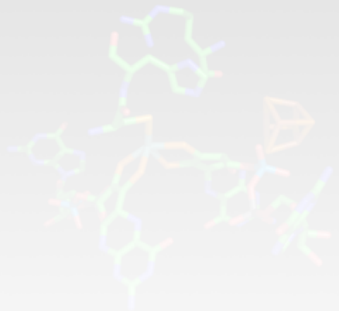
Se



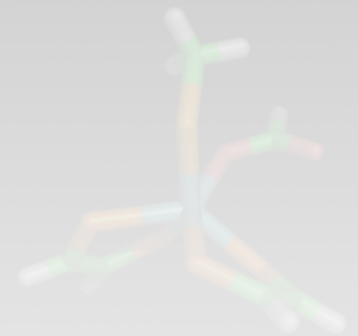
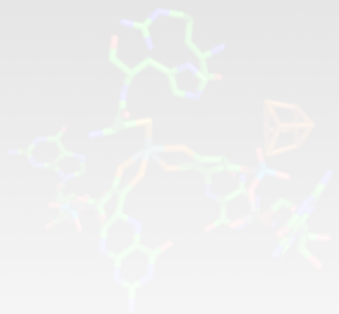
S

-Àcid - base

-Redox

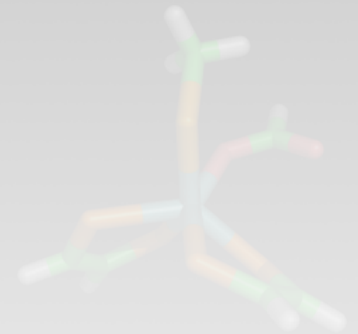
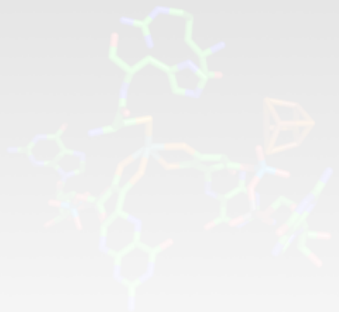


Conclusions



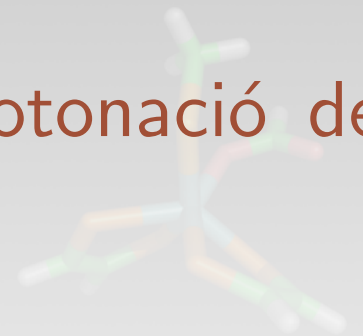
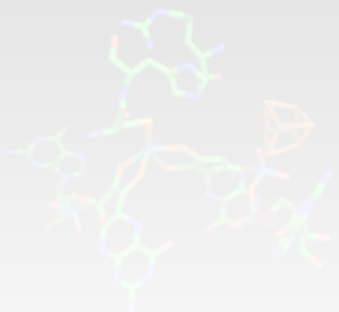
Conclusions

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- El sistema té dues etapes crítiques, la protonació del seleni i l'oxidació del molibdè.
- La presència de selenocisteïna s'explica per què la reacció amb seleni té una barrera més baixa en l'etapa crítica.

