# Sulfur containing amino acid oxidation by ·OH

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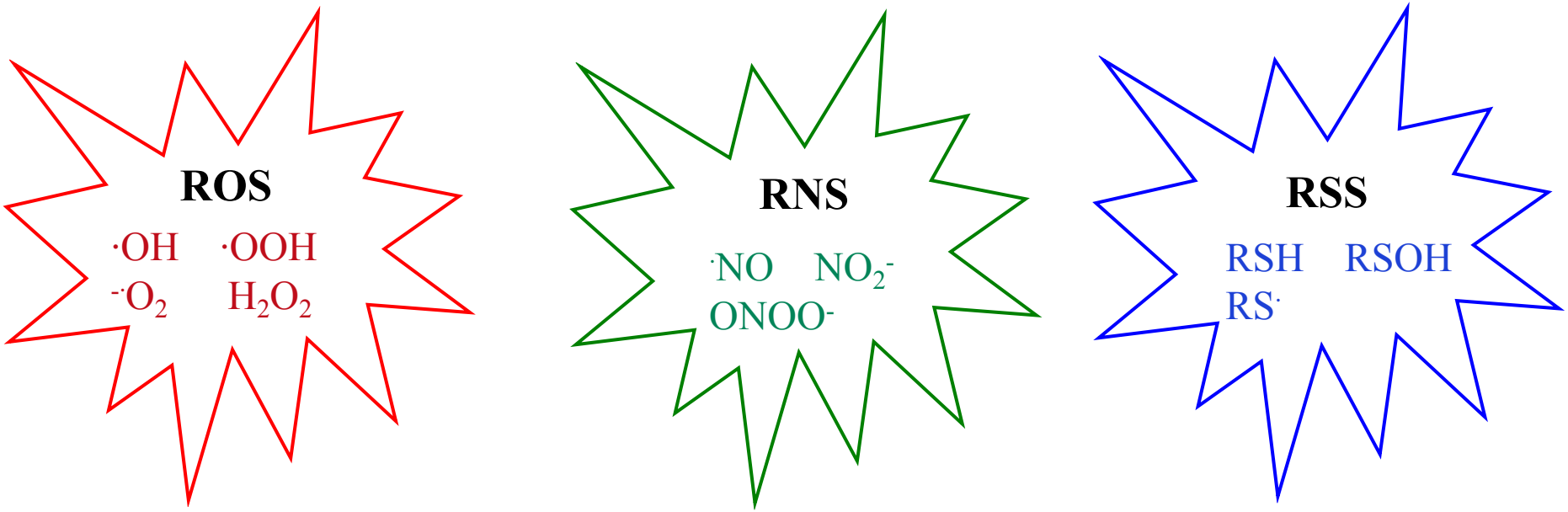
# 1.Introduction

# Introduction

- Production of free radicals:
  - Electromagnetic radiation expossure e.g. UV, γ
  - Mitochondrion dysfunctionallity
  - Fenton reaction
- Reactive radical species: ROS (oxygen), RNS (nitrogen), RSS (sulfur).



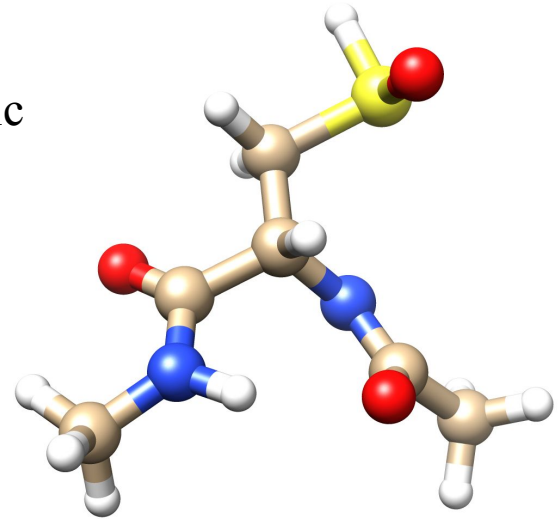
# Introduction

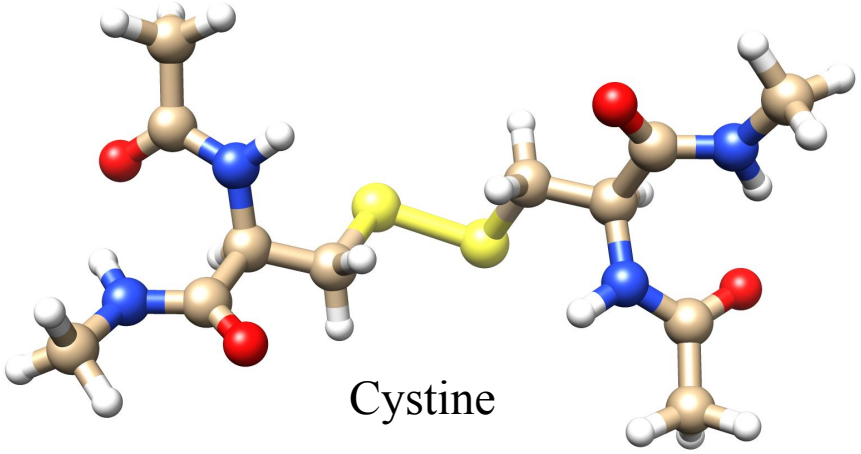
- Accomplish vital process in the cell e.g. apoptosis, homeostasis or cell signaling.
- A balance is requiered in the production of such species. Overproduction is known as oxidative stress.
- Excessive reactive species damage cell components, proteins are main target.
- Related with a wide variety of neurodegenerative disease: Parkinson, Alzheimer, Huntington, Jacob-Creutzfeld
- Also related with aging.
- Cell is provided with antioxidants in order to scavenge excess of radical species.
- Cysteine and Methionine are hypothesized to be free radical scavengers. Due to the reversibility of the process.
- The aim:
  - Analyse the possible reaction pathways for the oxidation of Met and Cys by ·OH.
  - Elucidate the key aspects of these reaction mechanisms.

# Introduction

## Cysteine experimental products

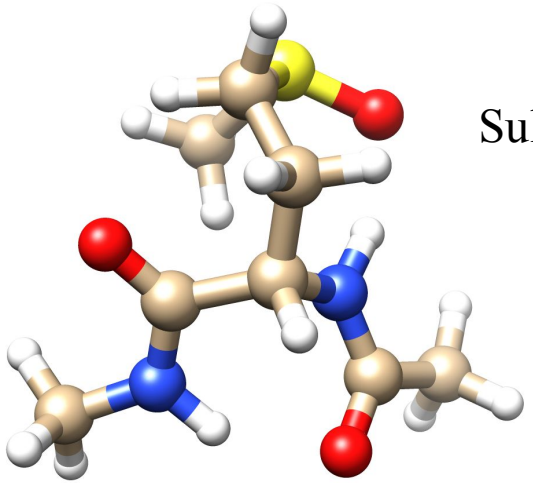
Sulfenic acid



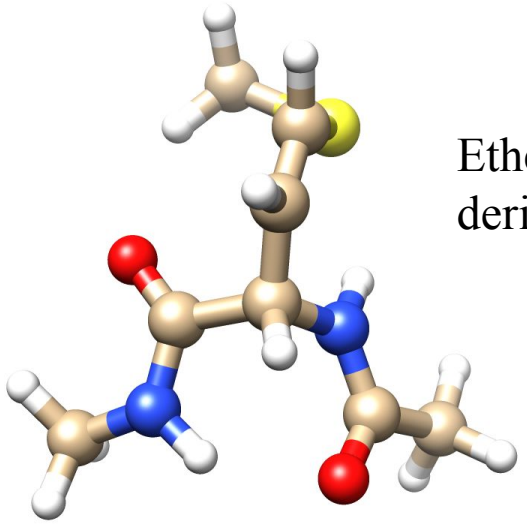


Cystine

## Methionine experimental products



Sulfoxide

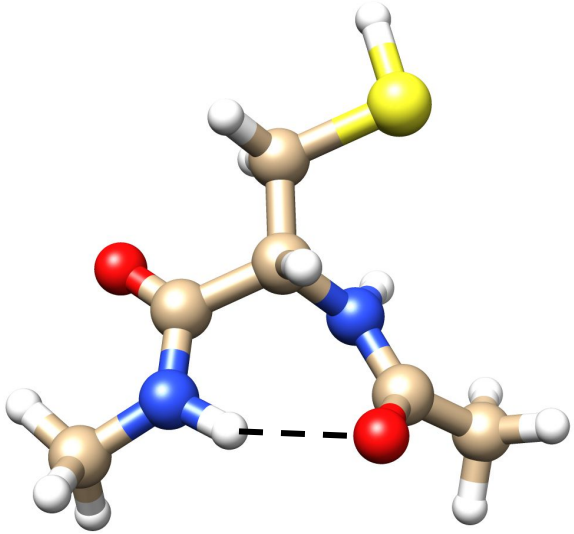


Ethene derivative

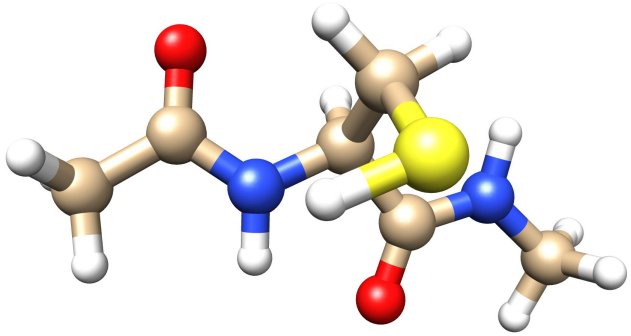
# 2.Methods and Model

# Methods and Model

- Studied structures  consist of two amide bonds.
- Dihedral angles oriented to simulate α-helix-like and β-sheet.



α-helix-like



β-sheet

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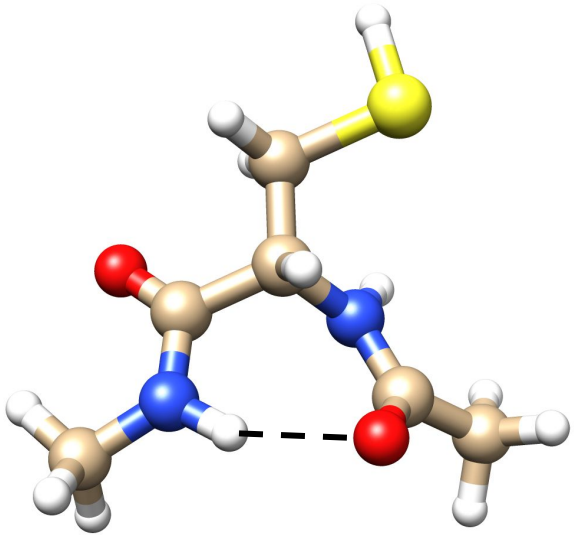
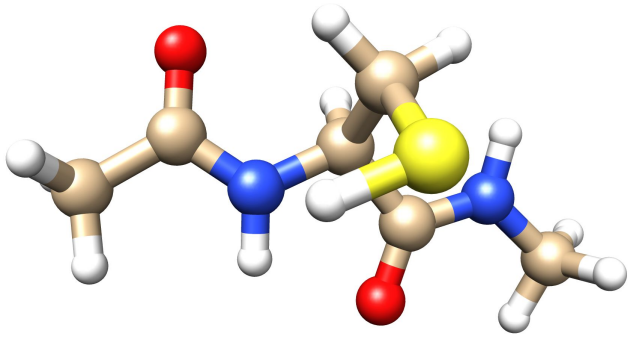


α-helix-like



β-sheet

# Methods and Model

- DFT, MPB1WK functional.
- Geometry optimization and frequency calculation with 6-31+G(d,p) at vacuum. ( $H_{gas}^{corr}$ )
- Single point with IEFPCM at ε=4, ε=78 with 6-311++G(2df,2p). ( $E_{solv}$ )
- In order to perform the analysis we use the enthalpy difference. ($\triangle H$)

$$H_{solv} = E_{solv} + H_{gas}^{corr}$$

$$\triangle H_{solv} = H_{solv}^{i} - H_{solv}^{reactants}$$

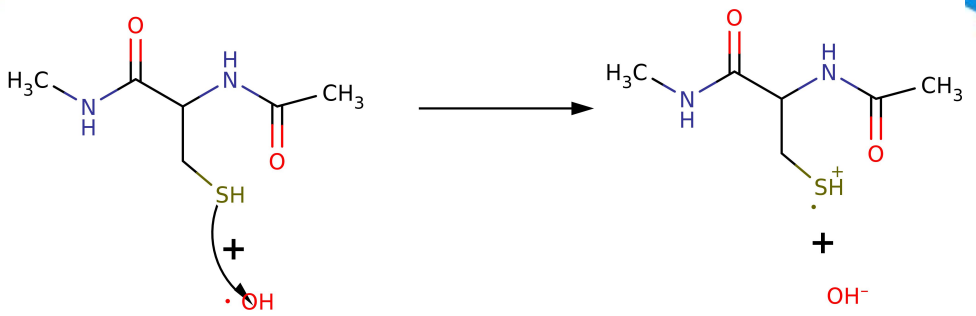
$$i = TS, Int, Prod$$

- The kinetic barriers found were very small and thereby not plotted in the examples, as the thermodynamic is considered as the driving force.

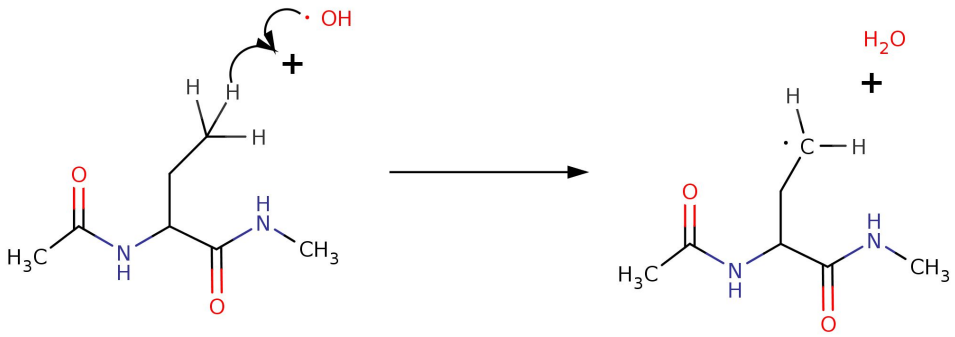
# 3.Results

# Results

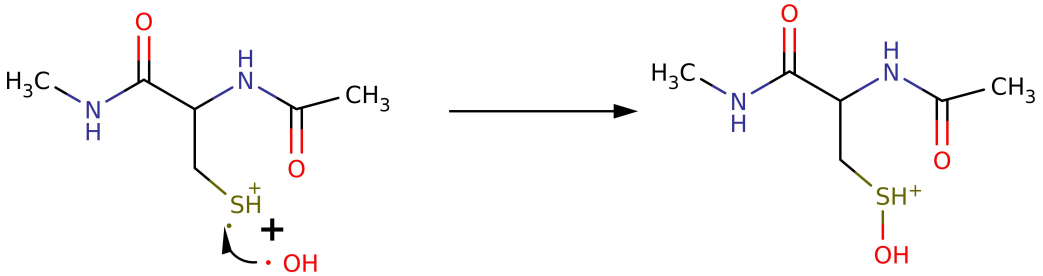
1. $e^-$ transfer.




2. H abstraction.



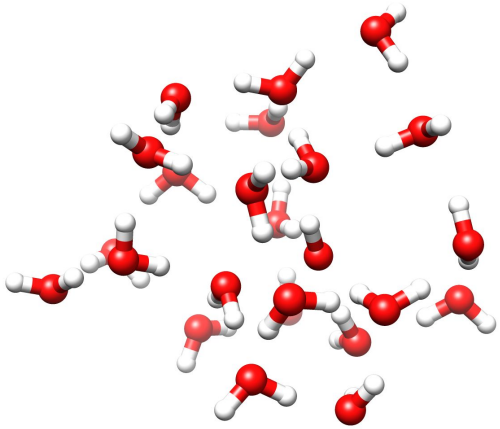

3. ·OH addition.



# Results

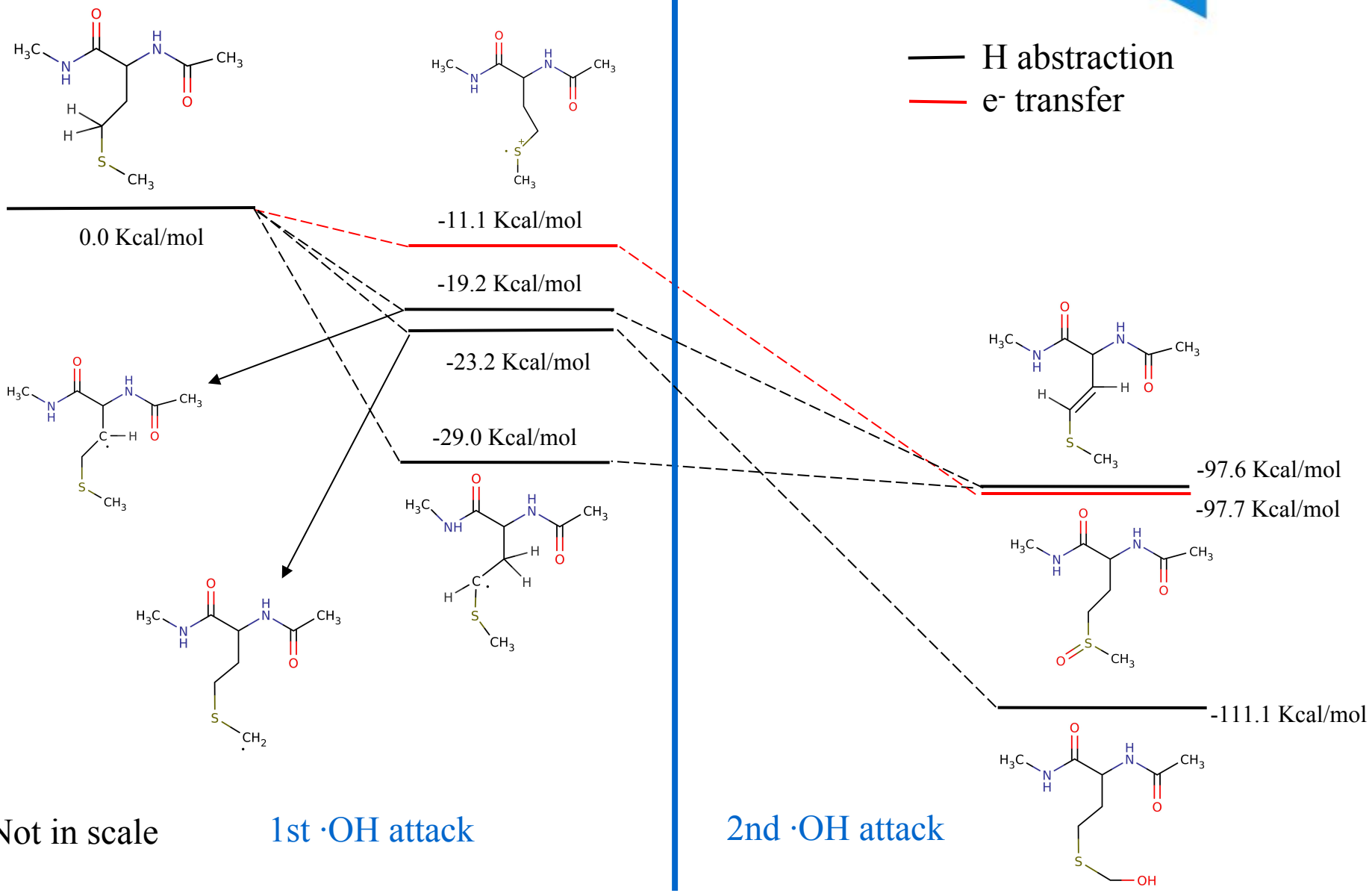
- For $e^-$ transfer: Reduction potential of ·OH was calculated to calibrate the methodology:
  - MPB1WK the best functional
  - Inclusion of explicit water molecules needed.

$$E^0 = \frac{-\Delta G^0(X)}{F} - E^0_{SHE}$$

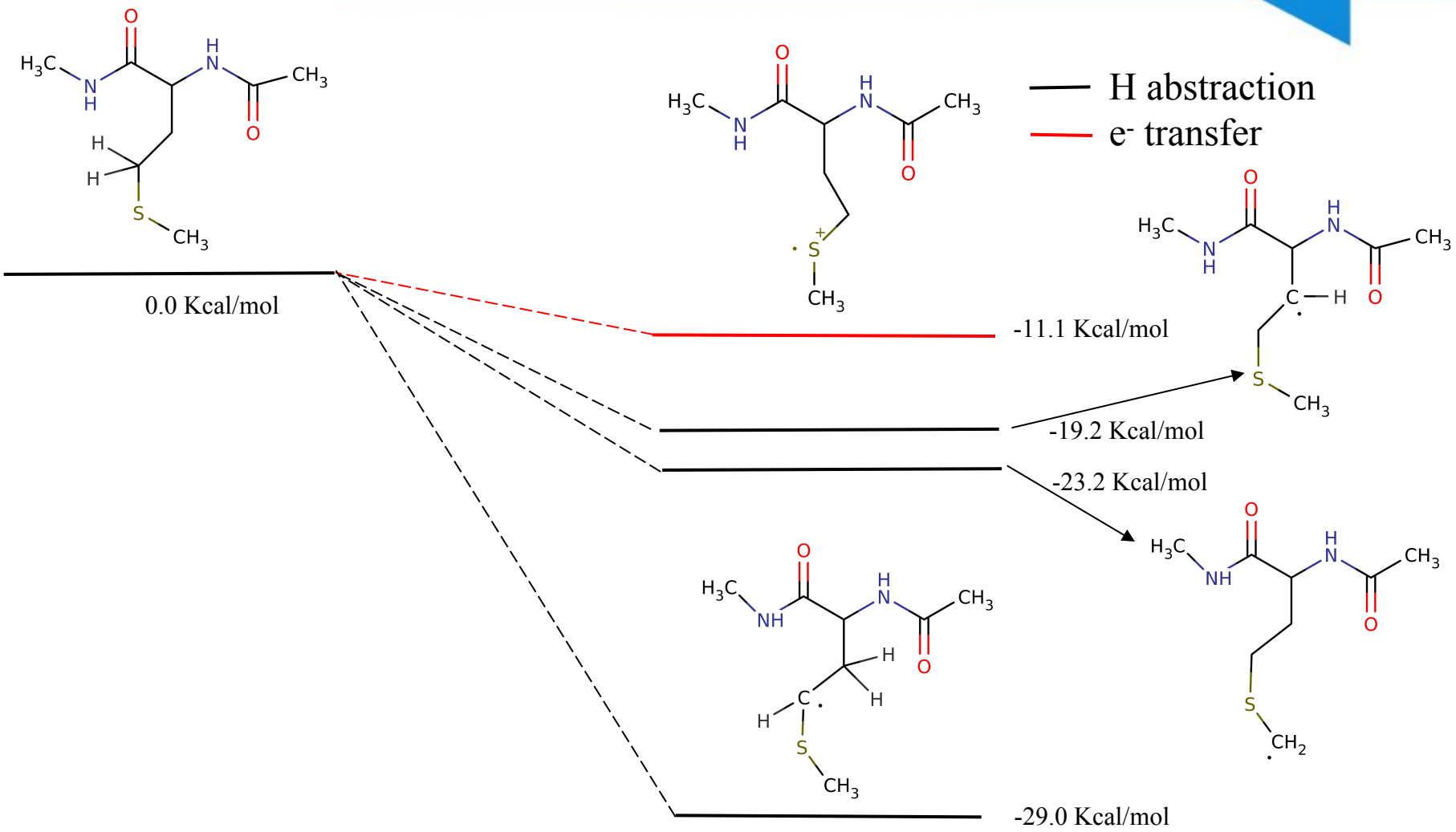


$E_{exp} = 1{,}9eV$
$E_{theo} = 1{,}8eV$

# Methionine-Results

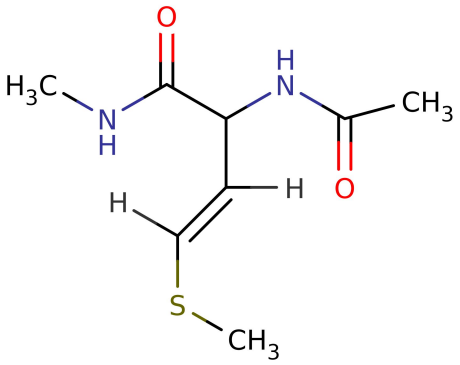


# Methionine-Results




1st ·OH attack Not in scale

# Methionine-Results

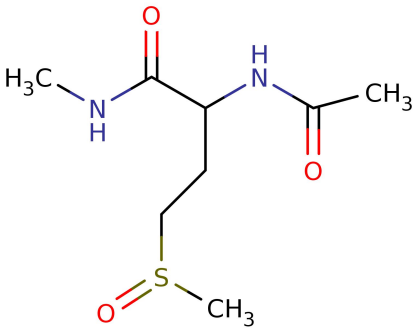


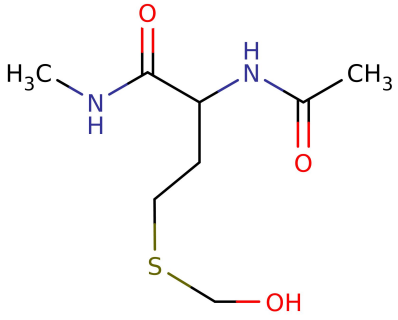
H abstraction

e- transfer

-97.6 Kcal/mol

-97.7 Kcal/mol

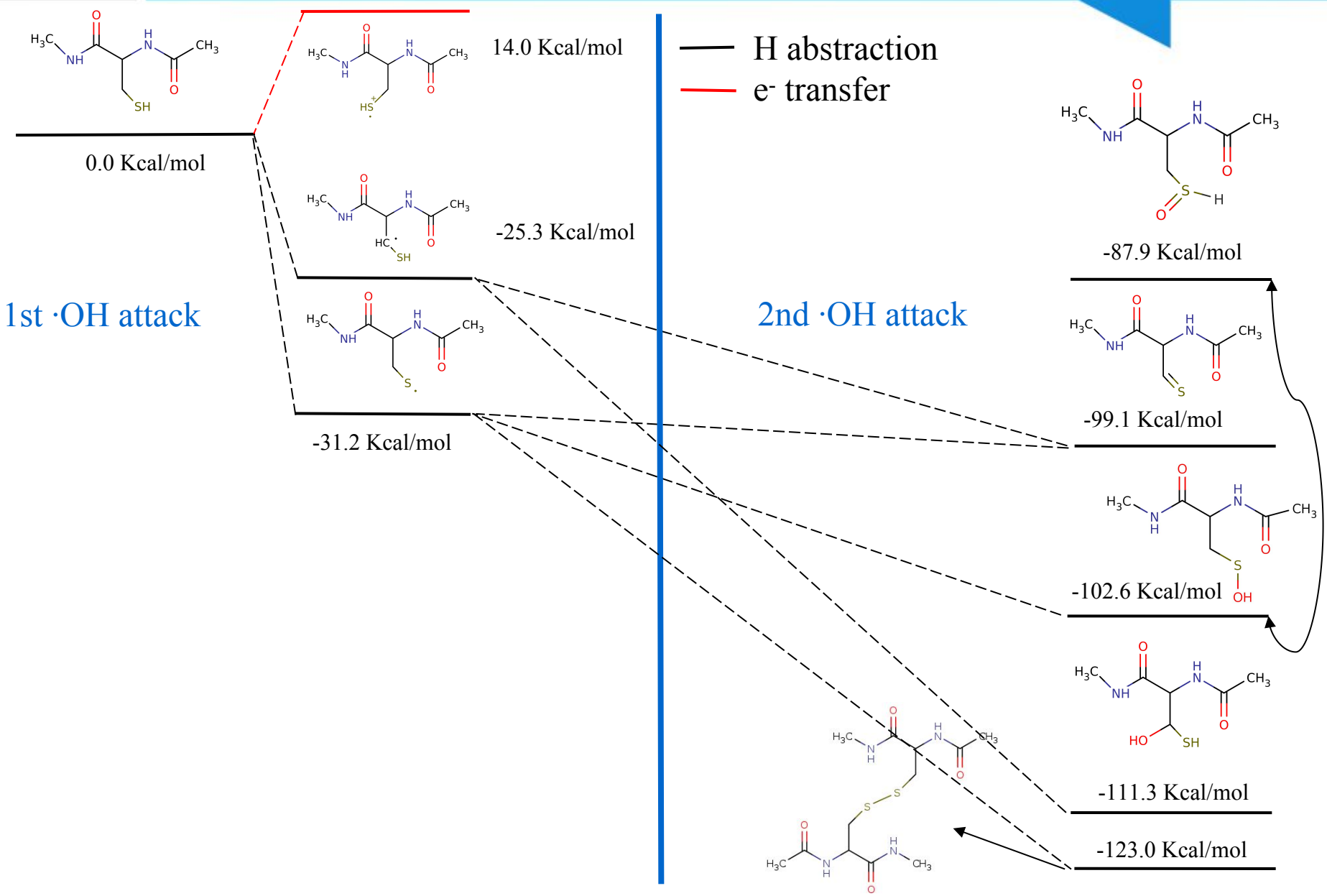




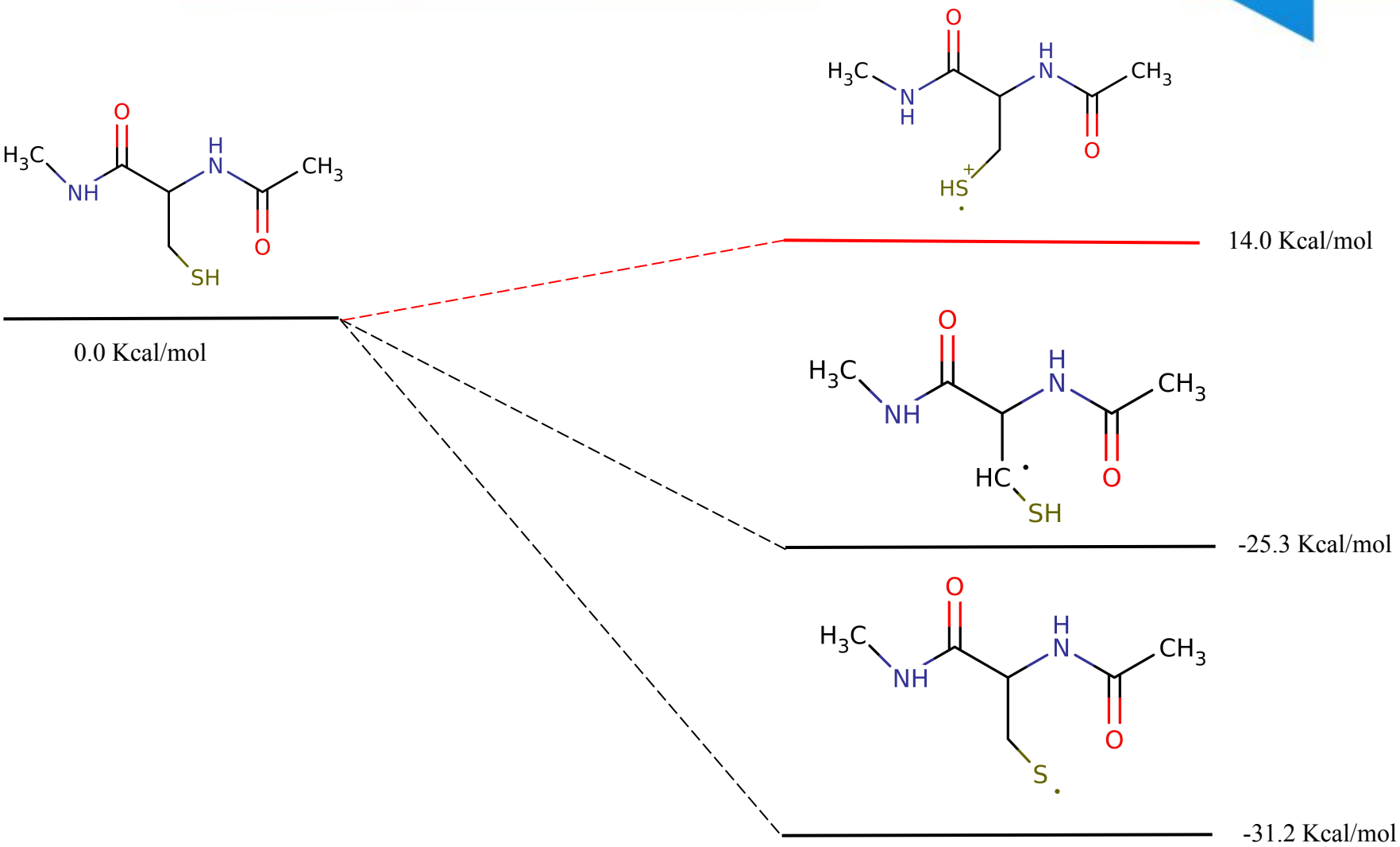
-111.1 Kcal/mol

2nd ·OH attack  Not in scale

# Cysteine-Results

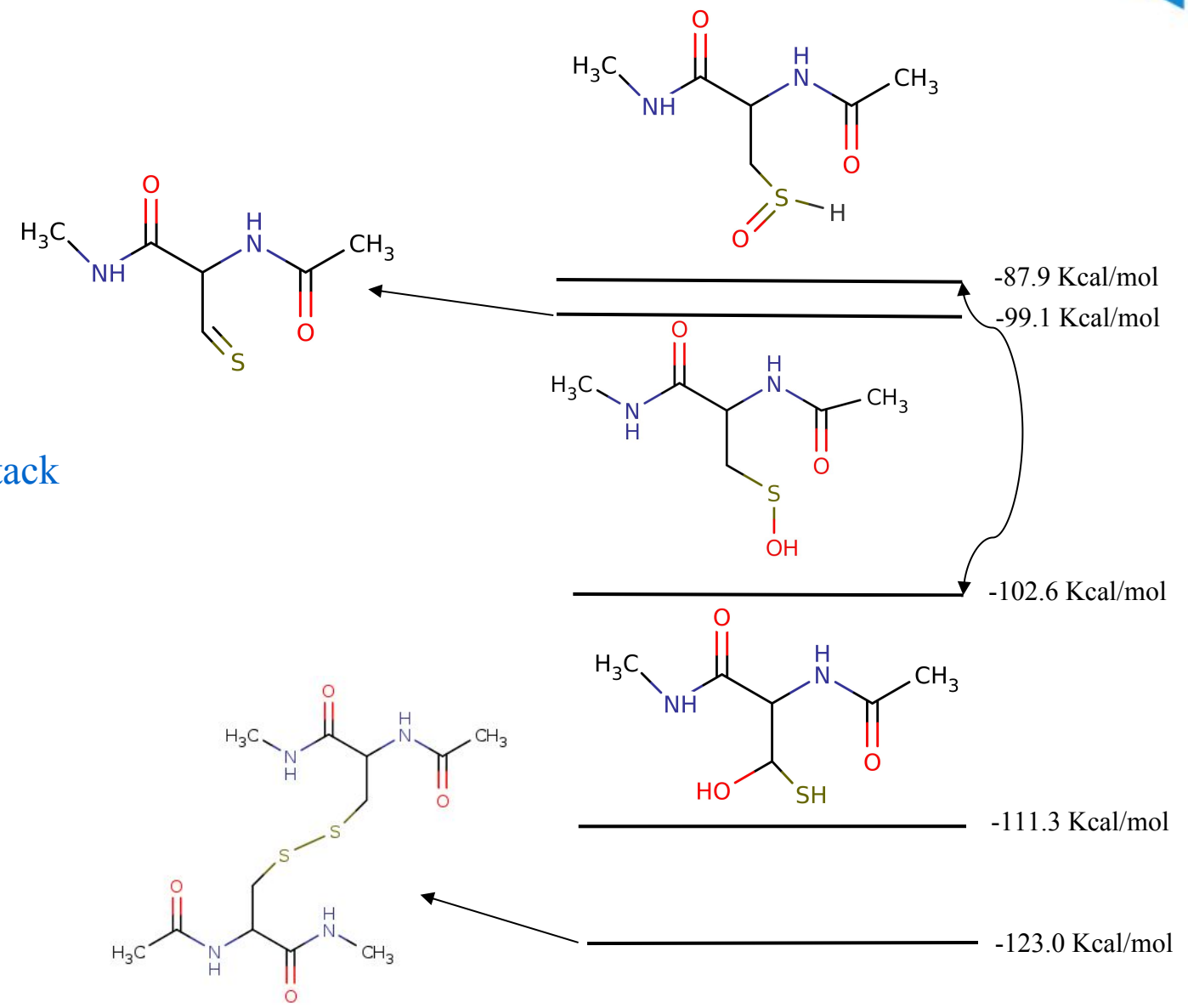


# Cysteine-Results




1st ·OH attack Not in scale

# Cysteine-Results




2nd ·OH attack

Not in scale

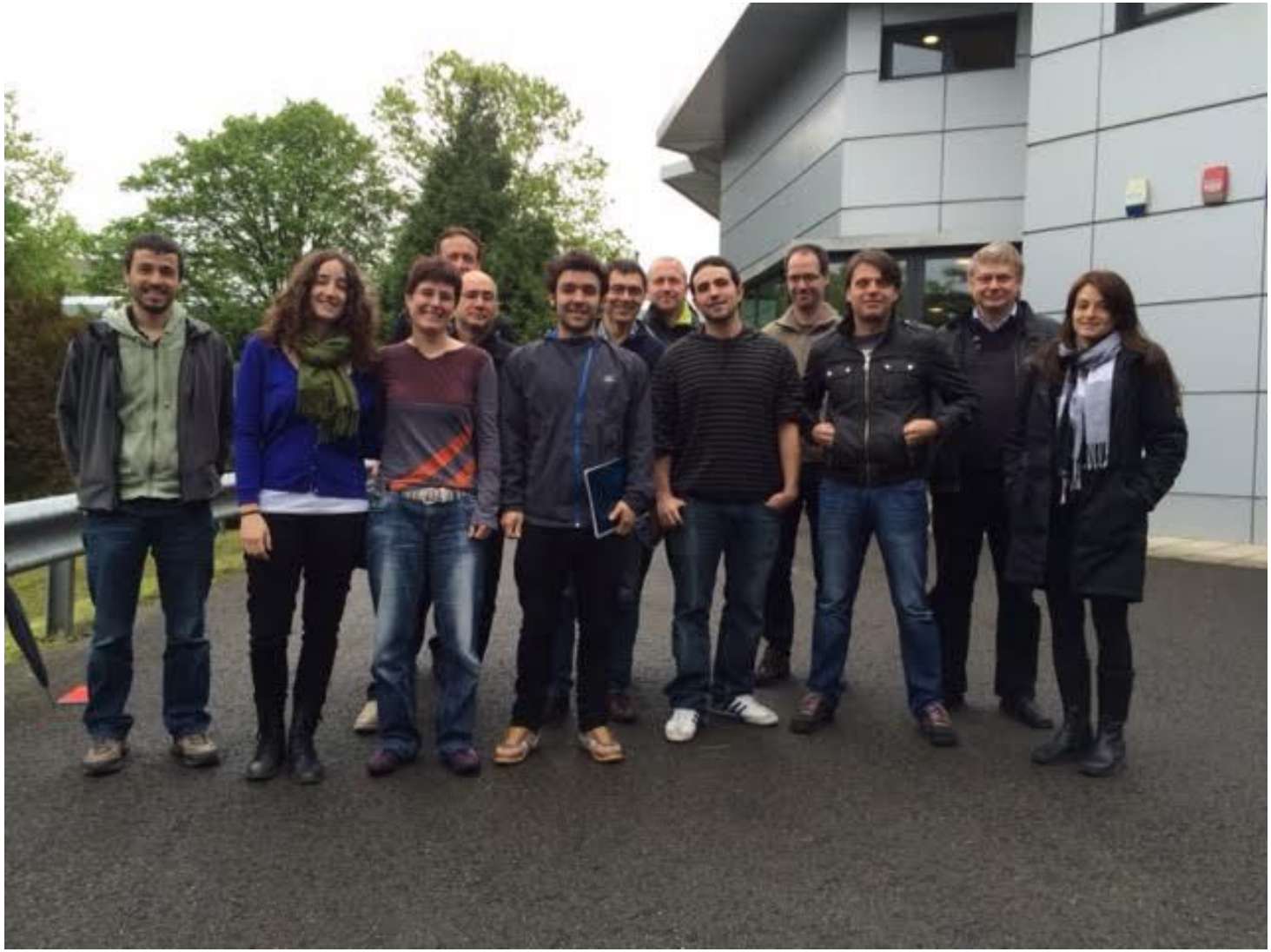
# 4.Summary

# Summary

- 3 ·OH attack mechanisms possible: H abstraction, $e^-$ transfer and addition.
- Attack first ·OH:
  - H abstraction to Cγ and Sγ favoured, but others can take place.
  - $e^-$ transfer: in Met, competitive, depending on the stability of the resulting S radical cation.
- Attack of second ·OH:
  - Met: H abstraction and addition possible.
  - Cys: Addition of ·OH or formation of S-S.
- Summary: Production of experimental products explained. New products predicted.

# Acknowledgement

Thank you for your attention!



# Supplement

- Infinitely separated reactants and products are taken.
- This leads to an entropic overestimation.
- Therefore, enthalpy values were employed for discussion.

| Reaction | Computed | Experimental | Difference |
|---|---|---|---|
| *Bond dissociation* | | | |
| $CH_4 \rightarrow CH_3^{\bullet} + {}^{\bullet}H$ | 112.4 | 113.0 | −0.6 |
| $NH_3 \rightarrow NH_2^{\bullet} + {}^{\bullet}H$ | 114.2 | 115.9 | −1.7 |
| $H_2O \rightarrow {}^{\bullet}OH + {}^{\bullet}H$ | 122.3 | 126.0 | −3.7 |
| $C_2H_6 \rightarrow C_2H_5^{\bullet} + {}^{\bullet}H$ | 107.9 | 109.4 | −1.5 |
| $H_2O_2 \rightarrow HOO^{\bullet} + {}^{\bullet}H$ | 89.1 | 92.7 | −3.6 |
| $C_2H_6 \rightarrow 2\,CH_3^{\bullet}$ | 98.7 | 96.6 | 2.1 |
| $H_2O_2 \rightarrow 2\,{}^{\bullet}OH$ | 49.4 | 55.0 | −5.6 |
| MAD | | | −2.1 |
| *H abstraction* | | | |
| $CH_4 + {}^{\bullet}OH \rightarrow CH_3^{\bullet} + H_2O$ | −9.9 | −13.0 | 3.1 |
| $NH_3 + {}^{\bullet}OH \rightarrow NH_2^{\bullet} + H_2O$ | −8.2 | −10.1 | 1.9 |
| $C_2H_6 + {}^{\bullet}OH \rightarrow C_2H_5^{\bullet} + H_2O$ | −14.4 | −16.6 | 2.2 |
| $H_2O_2 + {}^{\bullet}OH \rightarrow HOO^{\bullet} + H_2O$ | −33.3 | −33.3 | 0.0 |
| MAD | | | 1.8 |

Computed with MPWB1K functional.