OH Radical Attack on amino acid side chains

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Introduction

OH radical attack in proteins, to the side chains and α carbon of the amino acids.

1. Addition of OH radical.
2. Hydrogen abstraction.

- Side chains under study: Ser, Thr, Cys, Met.

Aminoacid side chain:

- Abstraction from: All heavy atoms of the side chain and the Cα.
- Kinetics and Thermodynamics studied.
- Protein enviroment:

We have considered solvent effects at different dielectrics:

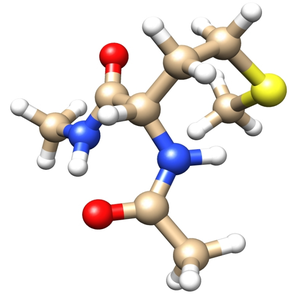
a) ε=4 for inner aminoacids (far from water)

b) ε=20 intermediate

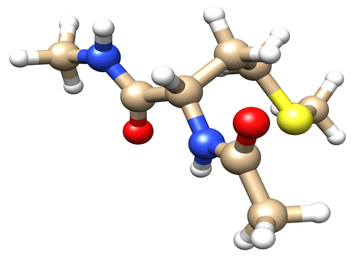
c) ε=78 for outter aminoacids (close to water)

Backbone Moldels

- Tripeptide (AA1-AA2-AA3). AA2 complete (side chains mentioned in the introduction), AA1, AA3 cut at Cα.
- For backbone: two types of folding: α helix and β sheet.



α helix (Met)

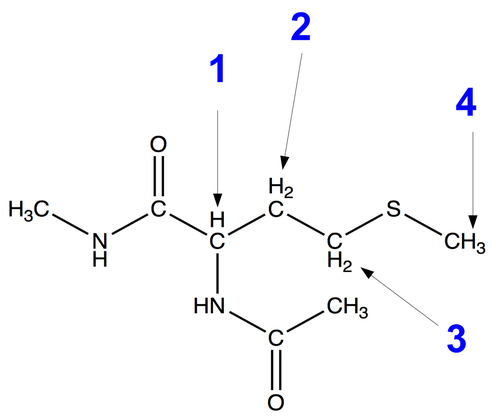


β sheet (Met)

Methods

- Optimization and Frequencies in gas phase: MPWB1K/6-31+G(d,p).
- Single points at ε=4, ε=20, ε=40 and ε=80: MPWB1K/6-311++G(2df,p).
- $H_{sol}^{298}=E_{sol}+H(cont)_{gas}^{298}$. IRC for Transition States.

Side Chains



- Methionine as example.
- Labelling: 1 for Cα then increasing. The further from Cα, the larger the number.

Results

	α-helix					
	ΔH_4^{TS}	ΔH_{20}^{TS}	ΔH_{water}^{TS}	ΔH_4^{Prod}	ΔH_{20}^{Prod}	ΔH_{water}^{Prod}
Cys1	-3.0	-2.2	-2.0	-30.5	-28.5	-31.3
Cys2	-4.4	-3.5	-3.3	-24.6	-22.6	-25.1
Cys3	-1.4	-1.0	-0.9	-30.9	-31.2	-31.2
Met1	-3.1	-2.6	-2.5	-30.4	-31.1	-31.2
Met2	1.1	1.4	1.4	-18.7	-19.1	-19.2
Met3	-1.0	-0.9	-0.9	-28.4	-28.9	-29.0
Met4	-3.3	-3.2	-3.2	-23.0	-23.1	-23.2
Ser1	-1.3	-0.8	-0.7	-24.8	-25.8	-26.0
Ser2	8.9	8.8	8.7	-22.1	-22.6	-22.7
Ser3	-2.0	-1.7	-1.6	-11.1	-12.0	-12.2
Thr1	-1.4	-0.7	-0.6	-23.8	-24.8	-25.0
Thr2	-2.8	-2.4	-2.3	-23.9	-24.4	-24.5
Thr3	2.9	3.4	3.5	-10.2	-10.6	-10.6
Thr4	1.0	1.2	1.2	-14.7	-14.9	-15.0

	β-sheet					
	ΔH_4^{TS}	ΔH_{20}^{TS}	ΔH_{water}^{TS}	ΔH_4^{Prod}	ΔH_{20}^{Prod}	ΔH_{water}^{Prod}
Cys1	-3.9	-2.9	-2.6	-32.2	-32.1	-32.0
Cys2	2.1	1.8	1.7	-23.1	-23.0	-23.0
Cys3	9.5	9.8	9.8	-30.3	-30.7	-30.7
Met1	-4.4	-3.2	-2.9	-33.0	-33.4	-33.5
Met2	-3.8	-3.3	-3.1	-19.7	-20.0	-20.1
Met3	-3.7	-2.7	-2.5	-19.7	-20.0	-20.1
Met4	-4.9	-4.3	-4.2	-27.0	-27.1	-27.2
Ser1	-2.5	-1.7	-1.5	-34.6	-34.3	-34.2
Ser2	2.5	3.5	3.8	-14.3	-14.3	-14.7
Ser3	-3.9	-3.7	-3.6	-21.8	-21.9	-21.9
Thr1	-3.4	-2.2	-1.9	-32.5	-32.2	-32.1
Thr2	-4.5	-4.1	-4.1	-26.0	-26.4	-26.5
Thr3	1.6	2.8	3.0	-14.1	-14.4	-14.5
Thr4	0.6	1.2	1.3	-16.1	-16.1	-16.1

- In α helix

- **Cys2, Met4, Ser3 and Thr2 are kinetically favoured.**
- **Cys1/2, Met1, Ser1 and Thr1/2 are thermodinamically favoured.**

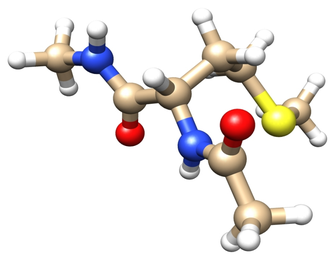
- In β sheet.

- **Cys1, Met2/4, Ser1/3 and Thr2 are kinetically favoured.**
- **Cys1/2, Met1, Ser1 and Thr1 are thermodinamically favoured.**

- β sheet conformation favors the attack in Cα, both thermodinamically and kinetically.

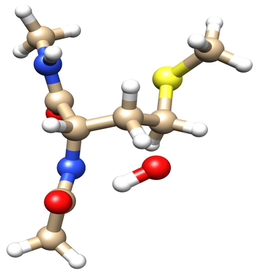
Attack to the Side Chain (Met2)

Reactant



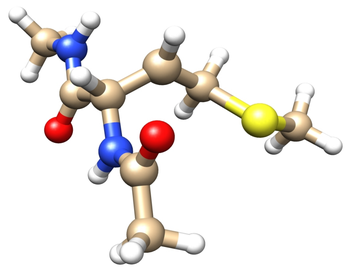
0.0 Kcal/mol

TS



-3.1 Kcal/mol

Product



−20.1 Kcal/mol

Acknowledgements

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