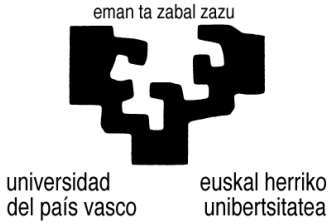
Natural Orbital Functional Theory Applied to Biologically relevant systems: Oxydative Stress in Amino Acid Side Chains

J. M. Matxain[1], X. Lopez[1], F. Ruipérez[1], J. M. Ugalde[1], M. Piris[1,2], E. Matito[3]

[1]Euskal Herriko Unibertsitatea / University of the Basque Country
[2]IKERBASQUE, Basque Foundation for Science
[3]University of Girona

Girona, January 17th 2013



PNOF5 Approach

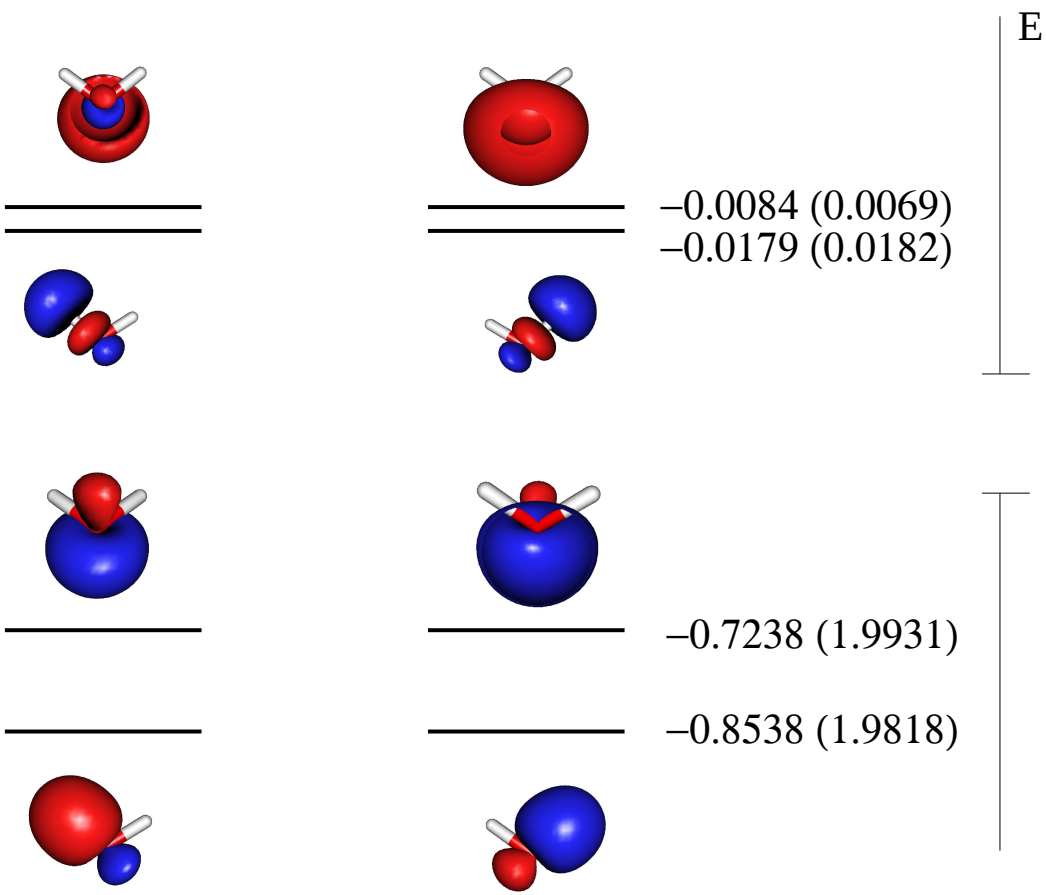
$$E^{PNOF5} = \sum_{p=1}^{N} \left[n_p \left(2H_{pp} + J_{pp} \right) - \sqrt{n_{\tilde{p}} n_p} K_{p\tilde{p}} \right] + \sum_{p,q=1}^{N}{}'' \; n_q n_p \left(2J_{pq} - K_{pq} \right) \qquad \left(\sum'' : q \neq p, \tilde{p} \right)$$

- Occupations coupled in pairs ($n_{\tilde{p}} + n_p = 1$)
- Coefficients of ϕ_i reorganized along the calculation
- Best results compared to other PNOF
  - Satisfy known N-representability conditions
    M. Piris et. al., J. Chem. Phys. 134, 164102 (2011)
  - Non-dynamical correlation (diradicals)
    M. Piris et. al., J. Chem. Phys. 134, 164102 (2011))
    X. Lopez et. al., J. Chem. Theor. Comput. 8, 2646 (2012)
  - Correct dissociation to integer number of electrons
    J. M. Matxain et. al., Phys. Chem. Chem. Phys., 13, 20129 (2011)

PNOF5 Orbital Interpretation

- Localized Orbital Picture (agree with VSEPR and Bent Rule)

  J. M. Matxain et. al., ChemPhysChem 13, 2297 (2012)
  J. M. Matxain et. al., Chem. Phys. Lett. 531, 272 (2012)



- ϕ_i reorganized
- O: 4 sp^3
  - 2 sp^3-s (σ)
  - 2 sp^3-s (σ^*)
  - 2 sp^3 (nb)
- Coupling scheme
  - σ / σ^*
  - nb / nb
- n_i (nb) > n_i (σ)

PNOF5 Radical Formation

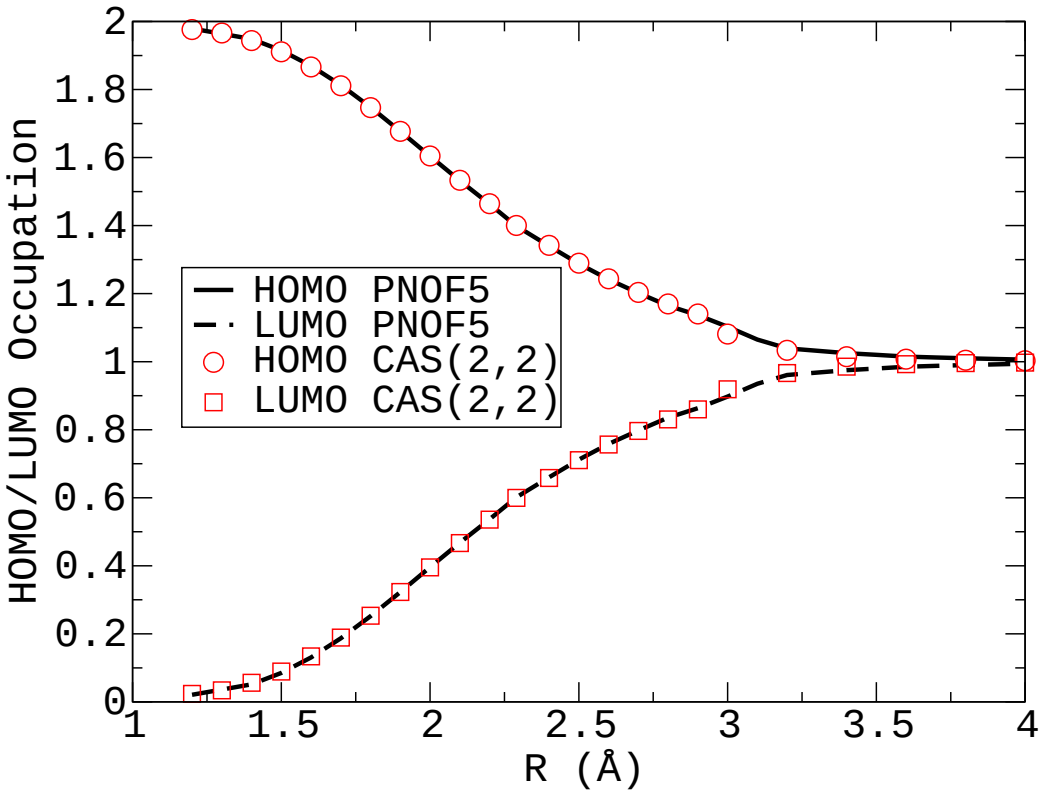
- H Abstraction and C—C and O—O Homolytic Bond Cleavage
  X. Lopez et. al., J. Chem. Theor. Comput. 8, 2646 (2012)

	PNOF5	CASSCF(2,2)	CASPT2(2,2)	exptl
$CH_4 \longrightarrow \cdot CH_3 + \cdot H$	98.9	98.0	109.6	113.0
$NH_3 \longrightarrow \cdot NH_2 + \cdot H$	97.9	93.3	111.5	115.9
$H_2O \longrightarrow \cdot OH + \cdot H$	106.1	92.9	122.8	126.0
$C_2H_6 \longrightarrow \cdot C_2H_5 + \cdot H$	98.9	89.2	106.0	109.4
$H_2O_2 \longrightarrow \cdot OOH + \cdot H$	86.6	81.3	91.0	92.7
$C_2H_6 \longrightarrow 2 \cdot CH_3$	83.1	74.2	96.6	96.6
$H_2O_2 \longrightarrow 2 \cdot OH$	32.6	19.4	53.7	55.1

- PNOF5 results between CASSCF and CASPT2
- Non-dynamical correlation like CASSCF, and part of dynamical correlation

PNOF5: Radical formation

- O–O Homolytic Bond Cleavage in H_2O_2
  X. Lopez et. al., J. Chem. Theor. Comput. 8, 2646 (2012)



PNOF5: Radical formation

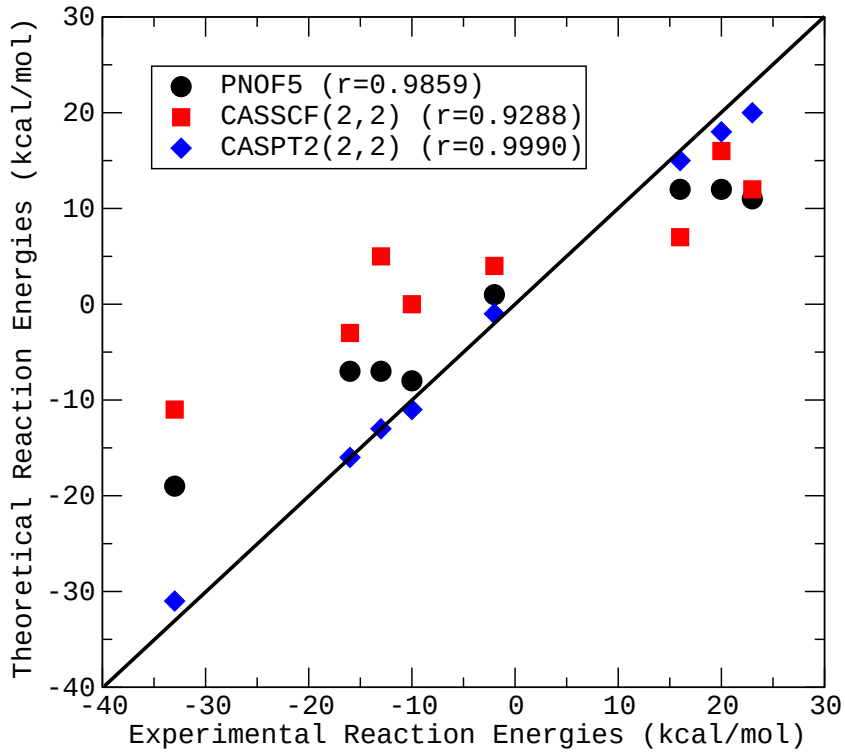
- Energetics of radical mediated reactions
  X. Lopez et. al., J. Chem. Theor. Comput. 8, 2646 (2012)

$$\begin{array}{cc} CH_4 \longrightarrow \cdot CH_3 + \cdot H & \Delta E_1 \\ \cdot OH + \cdot H \longrightarrow H_2O & \Delta E_2 \\ \hline CH_4 + \cdot OH \longrightarrow \cdot CH_3 + H_2O & \triangle E = \Delta E_1 + \Delta E_2 \end{array}$$

	PNOF5	CASSCF(2,2)	CASPT2(2,2)	exptl
$CH_4 + \cdot OH \longrightarrow \cdot CH_3 + H_2O$	-7.2	5.1	-13.2	-13.0
$CH_4 + \cdot NH_2 \longrightarrow \cdot CH_3 + NH_3$	1.0	4.7	-1.9	-2.9
$NH_3 + \cdot OH \longrightarrow \cdot NH_2 + H_2O$	-8.2	0.4	-11.3	-10.1
$C_2H_6 + \cdot OH \longrightarrow \cdot C_2H_5 + H_2O$	-7.2	-3.7	-16.8	-16.6
$H_2O_2 + \cdot OH \longrightarrow \cdot OOH + H_2O$	-19.5	-11.6	-31.8	-33.3
$CH_4 + \cdot OOH \longrightarrow \cdot CH_3 + H_2O_2$	12.3	16.7	18.6	20.3
$NH_3 + \cdot OOH \longrightarrow \cdot NH_2 + H_2O_2$	11.3	12.0	20.5	23.2
$C_2H_6 + \cdot OOH \longrightarrow \cdot C_2H_5 + H_2O_2$	12.3	7.9	15.0	16.7
Mean Absolute Error	7.4	11.8	1.3	

PNOF5: Radical formation

- Energetics of radical mediated reactions
  J. Chem. Theor. Comput. 8, 2646 (2012)



- Sign of reaction energetics improved from CASSCF to PNOF5

ROS and biomacromolecules

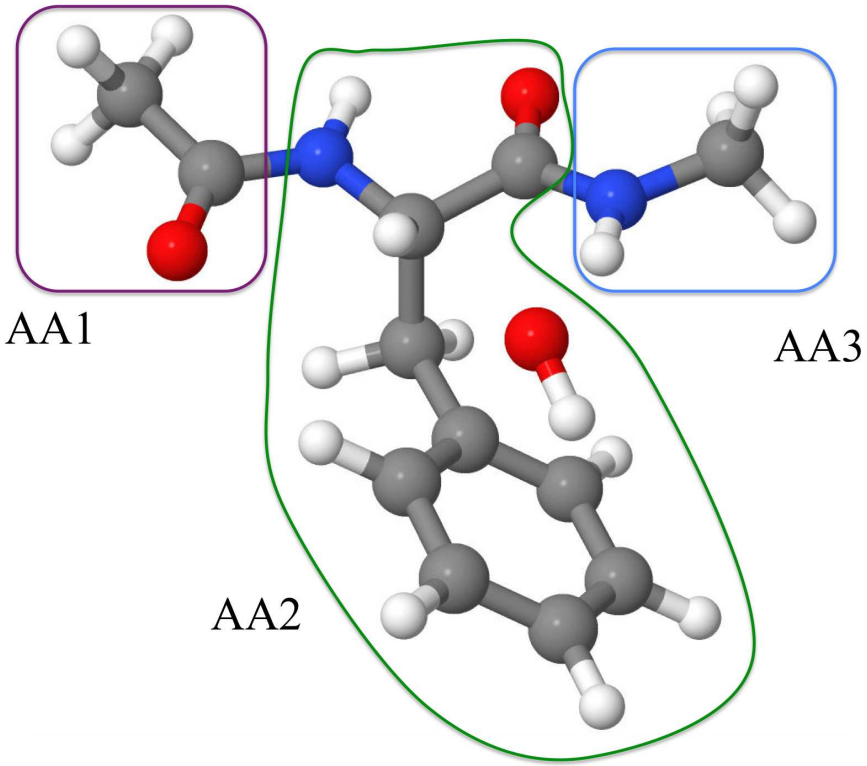
- ROS (Reactive Oxygen Species): abundant among radical species (RNS, RCS, RSS)
  - $\cdot OH$, $\cdot OOH$, $\cdot O_2^-$, $^1O_2$.
- Biomacromolecular targets:
  - Proteins, cell membrane phospolipids, DNA, RNA...
- Attack may cause...
  - Alteration of the function (function loss) of cell macromolecules
  - If not controlled, cell death
- Deseases
  - Alzheimer, Parkinson etc...
  - Among others, $\cdot OH$ Attack to proteins

Jump to Biologically relevant molecules?

- Based on success on the study of radical mediated reactions, want to study radical reactions with larger systems: proteins.
- Parallelization of PNOFID program carried out by E. Matito
- Tests on Arina (Supercomputer at UPV/EHU) Successfull
- Possible to jump to larger systems? Let us try!
- Very Challenging in NOFT!!
- Project to carry out at BSC Mare Nostrum supercomputer
  - QCM-2012-2-0011: PNOF theory: Towards biological applications
  - QCM-2012-1-0019: PNOF theory: Towards biological applications

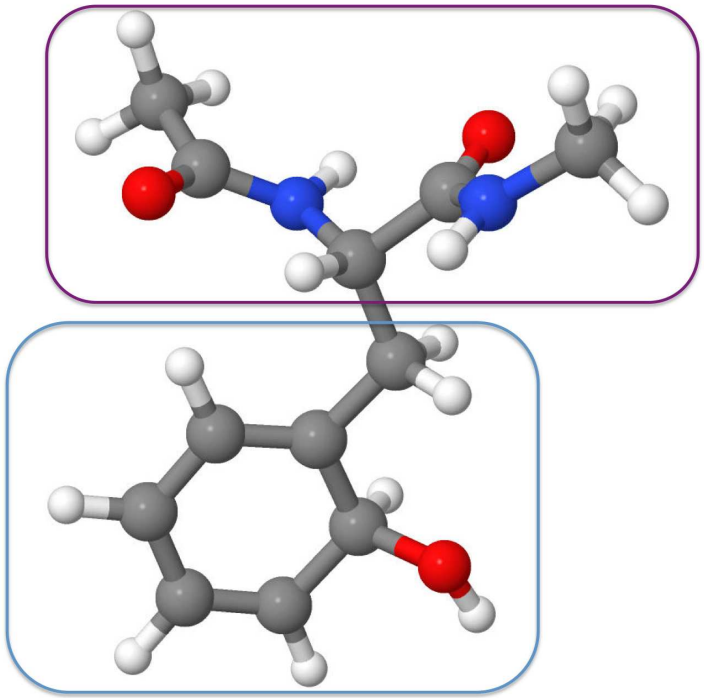
·OH Radical + Protein Model

- Model: Tripeptide model, R only at the central amino acid.



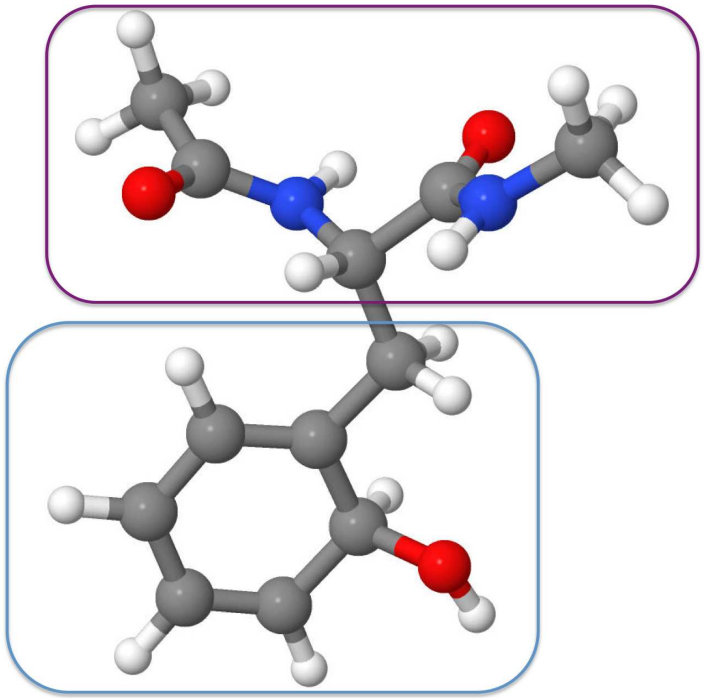
·OH Radical + Protein Model

- Modelize the two peptide bonds of a full amino acid
- Model the back-bone and amino acid side chains.



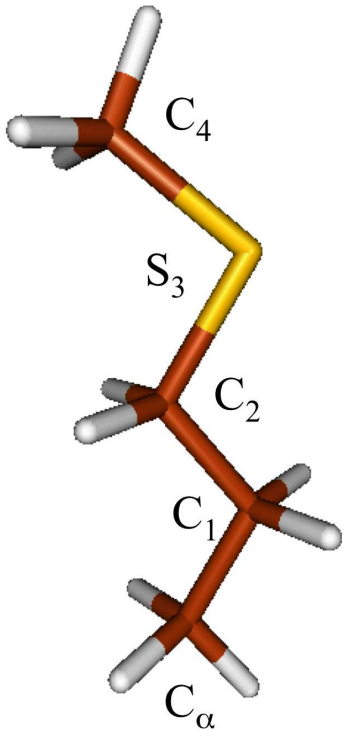
·OH Radical + Protein Model

- First Idea: Study H Abstraction from C_α, as a function of R



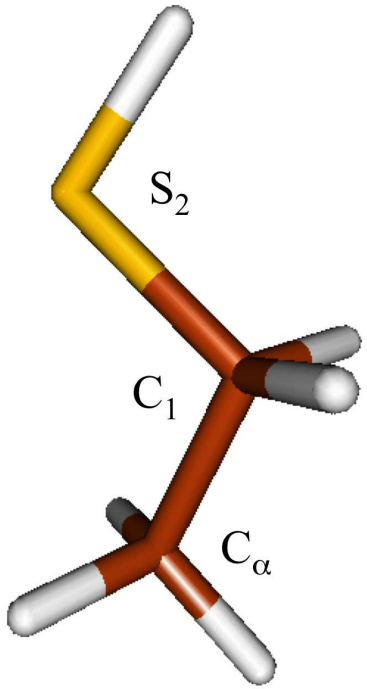
·OH Radical + Protein Model

- Convergence problems.
  - Multiple minima problem (difficult to converge to the minimum)
  - Try to converge faster
  - Collaboration with P. Salvador, E. Matito and E. Ramos to try to solve this.
- Necessary to choose smaller system to be practical.
- Attack to amino acid side chains: C_α modelized by $-CH_3$ group.



·OH Radical + AA side chains

- First, X-H dissociation from possible targets

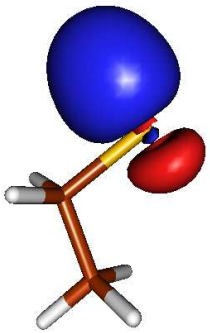


- Then reaction energetics combining reaction ΔE

Cysteine

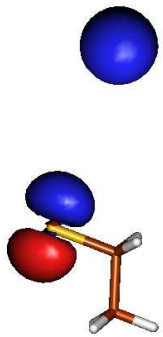
- Geometry optimizations using DFT
- Single points at the minimum and X-H dissociated at 5 Å
- Obtained NO and (ON) for the S-H dissociation in Cysteine

Minimum



1.983

Dissociation



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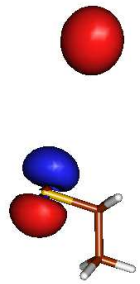

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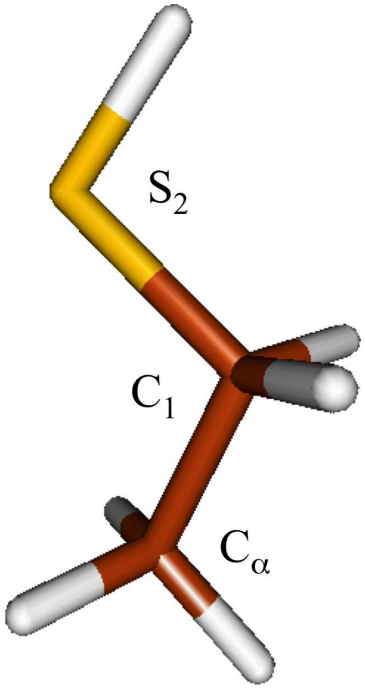
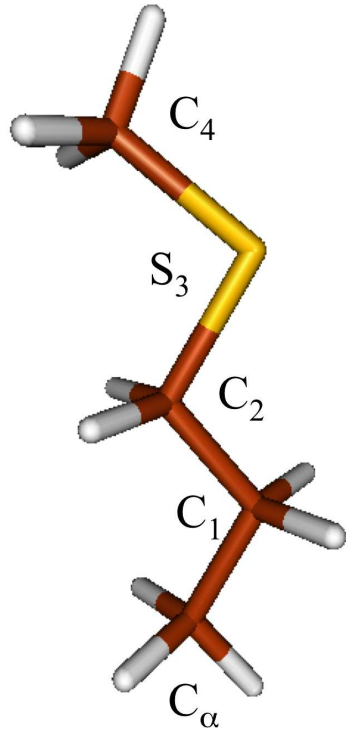
Sulfur containing side chains

Cysteine



	CASSCF	CASPT2	PNOF5
C_1	94.31	98.37	99.32
S_1	77.34	85.08	78.77

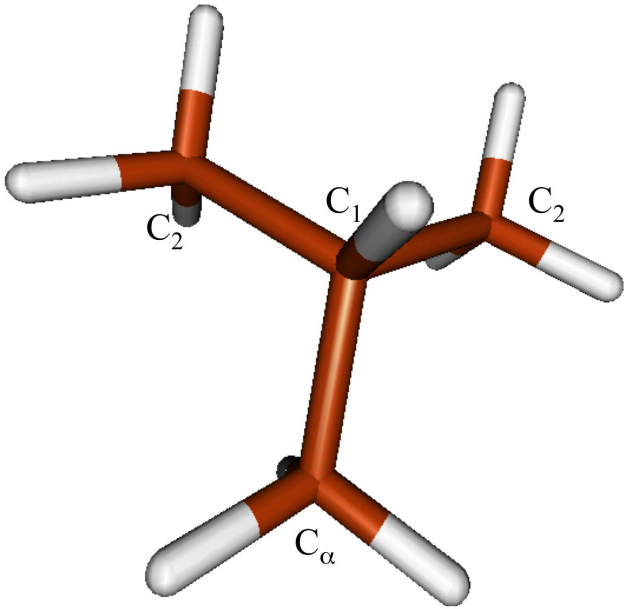
Methionine



	CASSCF	CASPT2	PNOF5
C_1	93.44	100.73	96.66
C_2	91.48	96.28	95.80
C_3	96.69	103.85	102.26

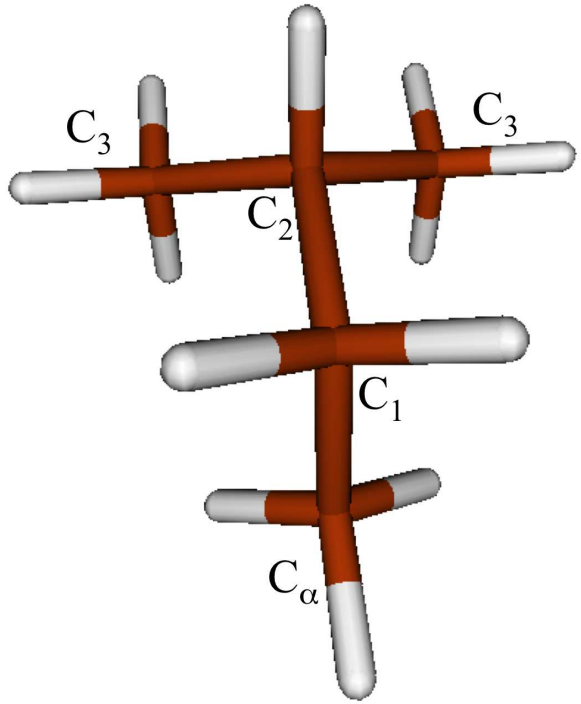
Alyphatic side chains

Valine



	CASSCF	CASPT2	PNOF5
C_1	93.68	101.05	98.71
C_2	97.07	105.42	99.62

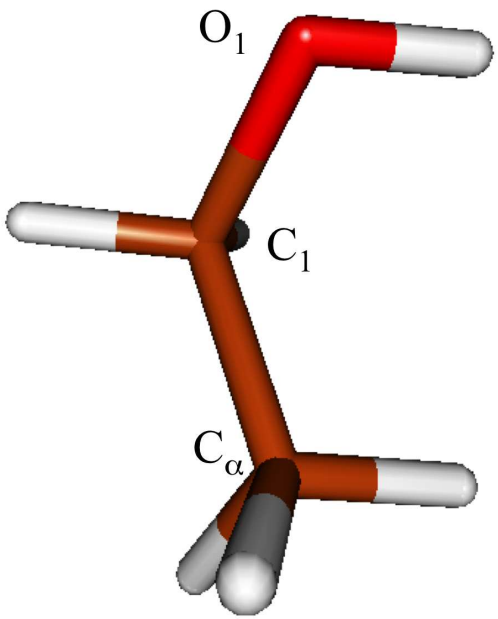
Leucine / Isoleucine



	CASSCF	CASPT2	PNOF5
C_1	117.32	102.35	97.14
C_2	117.40	105.28	98.98
C_3	113.57	107.54	99.74
C_α	110.65	105.49	98.42

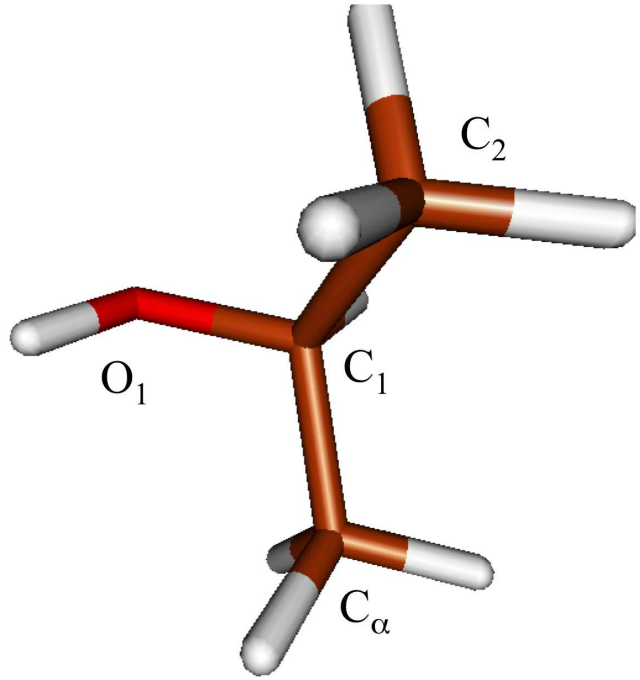
Alcohol containing side chains

Serine



	CASSCF	CASPT2	PNOF5
C_1	95.41	101.05	102.20
O_1	97.98	111.03	101.70

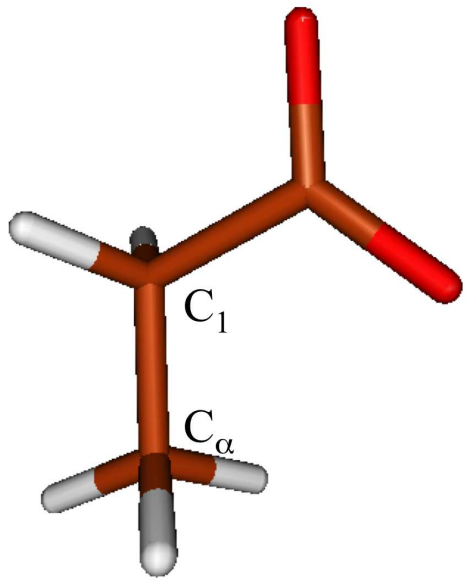
Threonine



	CASSCF	CASPT2	PNOF5
C_2	97.45	106.35	100.06
C_1	96.26	101.90	103.42
O_1	99.28	111.68	108.84

Aspartic acid and summary

Aspartic acid



	CASSCF	CASPT2	PNOF5
C_1	115.84	99.75	100.53

Summary

C-H, O-H and S-H dissociations

	Strength	Av. Dev.
CASSCF	C-H > O-H > S-H	~ 10
CASPT2	O-H > C-H > S-H	-
PNOF5	O-H > C-H > S-H	~ 5

Concluding Remarks

- Parallelization good. It could be improved.
- Need of an improved convergence for large systems.
- Possible to study large systems with PNOF5.
- Results in between CASSCF and CASPT2.
- A step forward in Natural Orbital Functional Theory

Acknowledgments

Theoretical Chemistry Group

Supercomputing Resources

- The SGI/IZO–SGIker (UPV/EHU)
  - Arina supercomputer
- BSC
  - Mare Nostrum supercomputer