UNIVERSITY OF MISKOLC

Theoretical Investigations of Glutathione – A Unique Antioxidant

THESES OF THE DISSERTATION PRESENTED

BY

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Szeretteimnek.

For from him and through him and for him are all things. To Him be the glory forever! Amen.

<div align="center">Romans 11:36</div>

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Szerető Feleségemnek köszönöm, hogy mellettem áll mindenben, legyen szó utazásról vagy egy helyben maradásról, indulásról vagy érkezésről, doktori írásról vagy bármi másról * :}

Köszönöm a barátaimnak, hogy mindig számíthattam rájuk! Hálás vagyok mindenért!

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"Ford!" he said, "there's an infinite number of monkeys outside who want to talk to us about this script for Hamlet they've worked out."

— Douglas Adams,
The Hitchhiker's Guide to the Galaxy

I

Introduction

1. RADICALS AND LIFE

Free radicals are integral parts of life. Radicals play an important role in a number of biological processes (defense against infectious agents, ageing, oxidation processes, signaling etc.) [1–3], without some of which life would be impossible. From a biochemical point of view the radicals have a kind of duality: in addition to their positive attributes, they can be harmful. The free radical-induced oxidative or nitrosative stress (caused by reactive oxygen species (ROS) or reactive nitrogen species (RNS), respectively) is a significant factor in various diseases such as Alzheimer's disease, Parkinson's disease and carcinogenesis as well [4–6].

The ROS, as well as RNS, are products of normal cellular metabolism; therefore, in living organisms there is a so-called redox homeostasis, a number of mechanisms to regulate the amount of radicals [7, 8] to avoid adverse procedures.

1

2. RADICALS vs GLUTATHIONE

A CRUCIAL BIOMOLECULE in free radical regulation is the linear tripeptide glutathione (γ-L-glutamyl-L-cysteinyl-glycine), denoted as GSH (Figure 1). It is essential in a number of biochemical processes in living organisms, including repair of oxidative damage [9] and defense of the central nervous system against free radicals [10, 11]. It has also a role in apoptosis, signal transduction, and gene expression [12, 13].
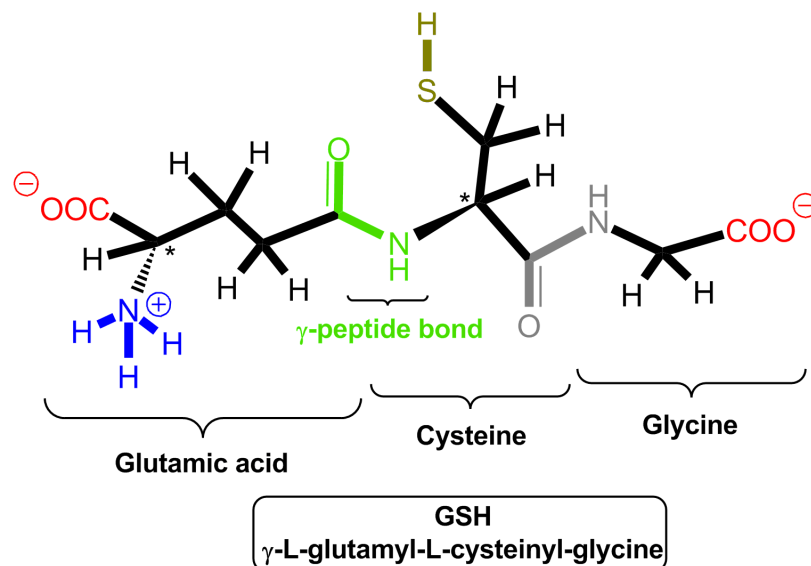

Figure 1: Glutathione (GSH) and its Building Blocks (Glutamic Acid, Cysteine and Glycine).

GSH exhibits antioxidant, radical scavenging activity by its electron donating ability [14, 15]. This enables GSH to neutralize free radicals, especially reactive oxygen species (ROS) such as the superoxide, hydroperoxyl, hydroxyl ($HO^\bullet$) radicals, having electron acceptor ability.

3. PERSPECTIVES & AIMS

The research presented here is focused on the different properties of glutathione which were studied by means of computational chemical tools (Figure 2).

First, the radical forming ability of glutathione in a thermodynamic sense is determined by means of quantum chemical calculations (Figure 2, lightblue).
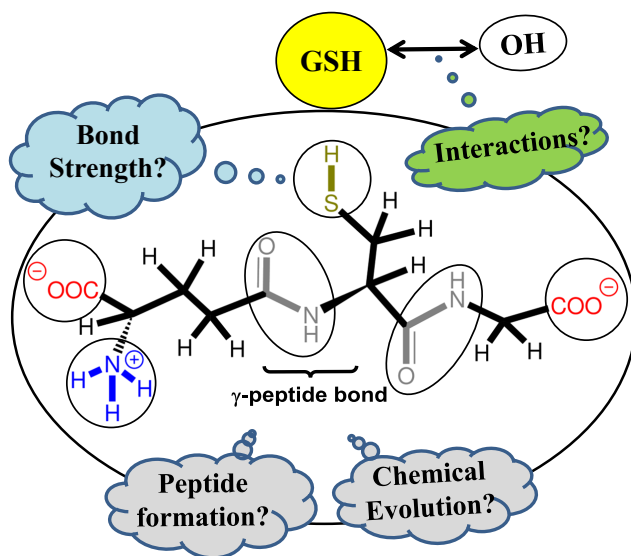
Figure 2: The Studied Properties of Glutathione.

Thereafter, the radical scavenging mechanism of glutathione was studied by combining molecular dynamics with quantum chemical calculations in order to shed light on the detoxification process (Figure 2, green). To overcome the limitation of the large flexibility of GSH, structures for further *ab initio* calculations were determined by non-reactive molecular dynamics (MD) simulations.

The evolutionary aspects of the unique structure of glutathione was also studied using quantum chemical methods. By this, we intend to contribute to the elucidation of the factors determining the strength of peptide bonds that may explain the preference of the *α*-peptide bond in proteins (Figure 2, gray).

II

Methods

1.   RADICAL FORMING ABILITY

The G3MP2B3 method can provide accurate thermochemical properties such as heat of formation or homolytic bond dissociation energy (BDE) [17] for radical systems. This method [18] has been chosen as a reference for calculating the BDEs and relative stability of the glutathione fragment radicals formed in gas and aqueous phases. As the first step in the G3MP2B3 procedure, the geometry optimizations were carried out using the B3LYP functional [19] as implemented in the Gaussian packages [20, 21] with the 6-31G(d) basis set [22]. Solvent effects were taken into account in optimizations at the same level of theory by applying the conductor-like polarizable continuum model (CPCM) [23, 24]. Normal mode analysis was carried out on each vacuum and solvent optimized structure at the B3LYP/6-31G(d) level of theory, and calculated harmonic frequencies were

scaled by a factor of 0.97 [25] to obtain thermochemical properties. To increase the accuracy of results, QCISD(FC,T)/6-31G(d) and MP2(FC)/G3MP2Large single point calculations were also performed as part of the G3MP2B3 procedure [17]. Since the computationally demanding part of the G3MP2B3 method is the calculation of accurate G3MP2 energy, the method is limited to medium-sized systems, preventing the accurate treatment of a tripeptide (such as the whole GSH). One can overcome this issue with the replacement of the G3MP2B3 calculation with an appropriately accurate functional. In order to find such a functional, results of the six metafunctionals MPWKCIS [26], MPWKCIS1K [26], M06 [27], TPSS1KCIS [28–30], TPSSh [31], and B3LYP, were tested on glutathione fragments against the G3MP2B3 values. These single point calculations were carried out using the 6-311++G(3df,2p) basis set [32] on structures obtained at the B3LYP/6-31G(d) level of theory, in both vacuum and solvent. The structural comparisons and the calculation of the root-mean-square-deviation (RMSD) values were carried out using the Molecular Operating Environment (MOE 2010.10) [33]. Calculations were performed on the whole glutathione in gas and solvent phase according to the same scheme as it was used for the fragments: DFT/6-311++G(3df,2p)//B3LYP/6-31G(d), where DFT can be any of the above mentioned density functional. The results were compared in order to gain further insights into the performance of the different density functionals.

2. RADICAL SCAVENGING MECHANISM

Five independent molecular dynamics (MD) simulations (5 x 240 ns) were performed for the GSH and GSH/OH$^\bullet$ systems, respectively. The structures were saved every 9.8 ps, which resulted in 25 000 frames for each simulation. GSH was solvated with TIP3P [34] water molecules and one Na$^+$ ion was also placed in the box in order to ensure the electro-neutrality of the system. The simulation box was cubic (37^3 Å^3), where the minimum distance between any atom of the GSH and the wall of the box was 12 Å. The simulations were conducted with the Desmond v. 30110 [35] software using the CHARMM22 [36] force field. The short range

van der Waals and electrostatic cut-off values were set to 9.0 Å and the long-range electrostatic interaction was calculated via the Particle Mesh Ewald [37] method. The missing bond parameters and charges for the OH radical were calculated with the Force Field Toolkit Plugin [38] implemented in Visual Molecular Dynamics (VMD) [39].

Intra- and intermolecular interactions were identified by the geometric analysis using the following criteria: $d(A\times\times\times D)$ <3.5 Å and $a(A\times\times\times H\text{-}D)$ >100.0°. The structural analysis was performed with the ptraj module of the AmberTools 1.5 program package and Visual Molecular Dynamics [39] was used to prepare the 3D structures in the figures. To describe these interactions more in detail, electron density analyses (Atoms in Molecules, AIM) [40, 41] were carried out on some geometrically selected structures at the B3LYP/6-31G (d) level of theory. The AIM analysis was carried out with the AIM2000 program [42].

Geometry optimization were conducted on properly selected GSH/OH$^\bullet$ complexes and GSH conformers with the BHandHLYP density functional combined with the 6–31G(d) split valence basis set. To mimic the bulk water, the solvation model "D" (SMD) [43] was used. Normal mode analysis was also carried out at the same level of theory in order to confirm that the structures obtained are minima on the respective potential energy surface. The quantum chemical calculations were carried out using the Gaussian 09 program package [21].

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d - distance, a - angle, A - acceptor, D - donor, $\times\times\times$ - non-covalent interaction

3. Evolutionary Aspects

The thermodynamics of the peptide formation reaction

$$H_3^+N - Q - COO + H_3^+N - Q - COO$$
$$\rightarrow H_3^+N - Q - C(O)NH - Q - COO + H_2O$$
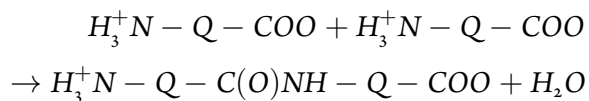
was studied using the G3MP2B3 method [17, 18] and two density functional sets, namely, B3LYP, as it is implemented in the Gaussian 09 program package [21], and the hybrid meta-GGA (generalized gradient approximation) functional M05-2X [44], combined with two split-valence basis sets, 6-31G(d) and 6-311+G(d,p). The G3MP2B3 method and each functional– basis-set pair was combined with two implicit water models, the conductor-like polarizable continuum model, CPCM [23, 24], and the continuum solvation model "D", SMD [43], to mimic the solvent effects of bulk water. All computations were carried out using the Gaussian 09 program package [21].

"What's new is old, and what's old is new again."

— Anonymous

III

New Scientific Results

As a consequence of our detailed computational study of the different properties of glutathione the following new scientific results were obtained:

1st Thesis

The radical forming ability of glutathione in a thermodynamic sense is determined by means of quantum chemical calculations. Bond dissociation energies, BDEs, have been calculated in both gas and aqueous phases for all X–H bonds (where X can be C, N, O, and S) of glutathione, and their values have been compared.

- The O–H bond dissociation of the carboxyl group has the smallest bond

dissociation energy in vacuum.

- In the aqueous phase, the weakest X–H bond is the N–H bond of the glutamine residue $(Q_{N_{1,2}}^b)$ in the vicinity of the negatively charged carboxyl group (Figure 3). In both cases, CO_2 formation (decarboxylation) can accompany the breaking of the X–H bond, making the dissociation energetically more favorable than the cleavage of the S–H bond.
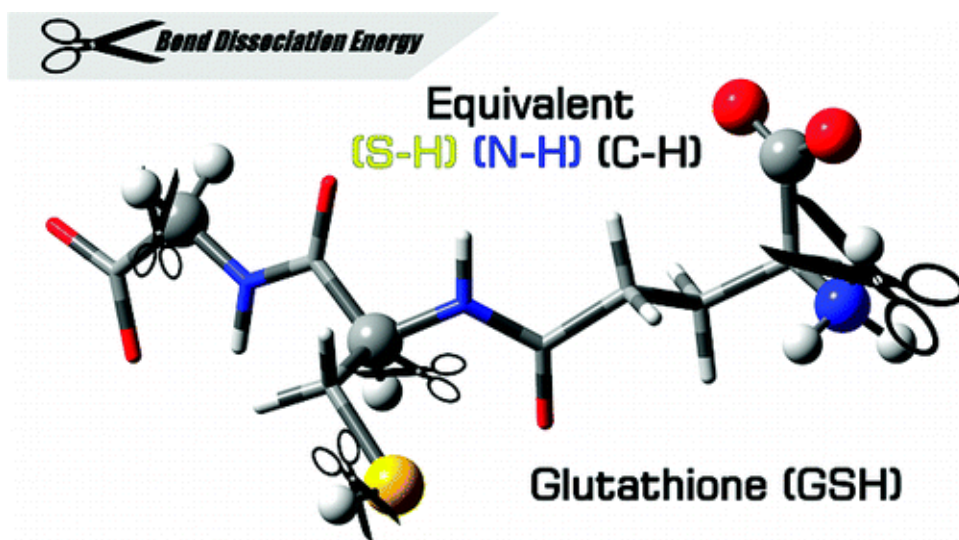
Figure 3: Competing Radical Forming Sites in Glutathione (GSH).

- The N–H bond is stronger than the C–H bond in the gas phase, but protonation significantly weakens it. Furthermore, C–H bonds with a-carbons are found to be about as weak as the sulfhydryl bond of the cysteine residues.

- Electron delocalization was found to have an important influence on the antioxidant potential. As clearly evident from our results, glutathione has five possible positions to scavenge a free radical in biologically relevant conditions (3 a-C–H, S–H and N–H, Figure 3).

2nd Thesis

From a methodological point of view the following results were obtained:

- It was proved that the calculations using G3MP2B3 composite method provides bond dissociation enthalpy (DH$_{298}$) values consistent with the experimental ones. Therefore, it was concluded that the G3MP2B3 model chemistry is able to provide reasonable bond dissociation enthalpies for glutathione fragments as well.

- In order to reduce the cost of the calculations by the replacement of the G3MP2 energy with accurate single point calculations, six density functionals, namely, MPWKCIS, MPWKCIS1K, M06, TPSS1KCIS, TPSSh, and B3LYP, have been tested against G3MP2 for obtaining accurate bond dissociation energies. These single point calculations were carried out on optimized glutathione fragment structures obtained at the B3LYP/6-31G(d) level of theory in both vacuum and solvent.
The MPWKCIS1K/6-311++G(3df,2p)//B3LYP/6-31G(d) level of theory provides the best correlation with the G3MP2B3 method for BDEs in both phases, and therefore, this method is recommended for similar calculations.

3rd Thesis

Comparative MD simulations were conducted on GSH and GSH/OH$^\bullet$ systems. Based on these, the radical recognition process of GSH was described and the OH radical attractor regions of GSH were identified.

- Two main steps were identified during the radical recognition process, namely catching and steering (Figure 4). In ~78% of all interactions characterized, strong complexes were formed between anionic carboxyl groups and the OH radical (catching). After this catching step, the strong carboxyl-OH$^\bullet$ complexes could evolve additional interactions with the other parts of GSH, stabilized by both the donor and acceptor features of the OH radical.
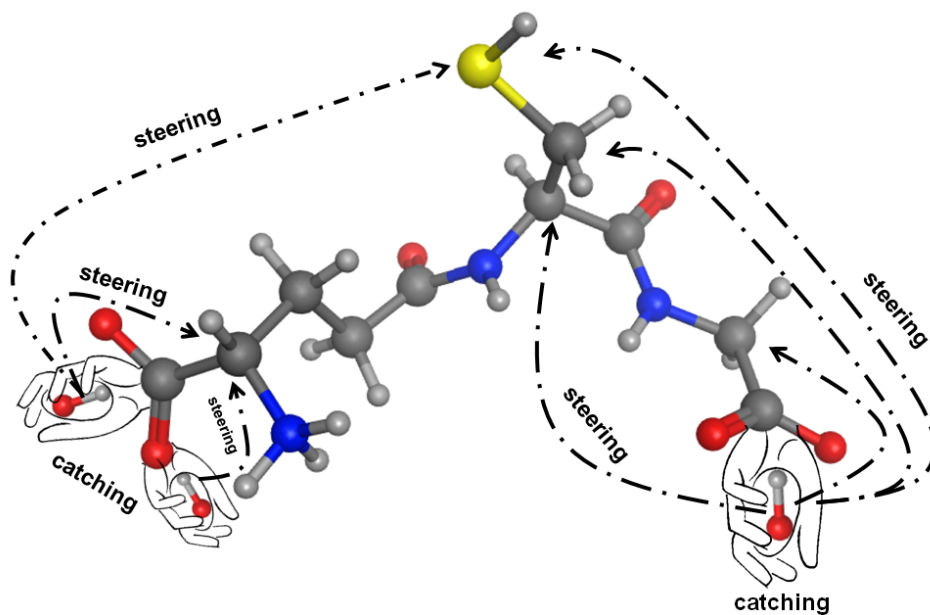

Figure 4: Radical Recognition Process of Glutathione: Catching and Steering.

- Glycine residue dominates the steering role in the recognition step, while the glycine-hydroxyl radical complexes could facilitate further interactions with the thiol group, α- and β-carbons of the cysteine residue via the OH$^\bullet$ lone pair electron. The glutamic acid residue does not show this property during the MD simulations.

- Additional quantum chemical calculations on appropriately selected GSH/OH$^\bullet$ complexes revealed exothermic heats of formations. These complexes, containing two or more intermolecular interactions (Figure 5), identified as the starting configurations for the hydrogen atom migration to quench the hydroxyl radical and to complete the radical scavenging mechanism *via* different reaction channels.
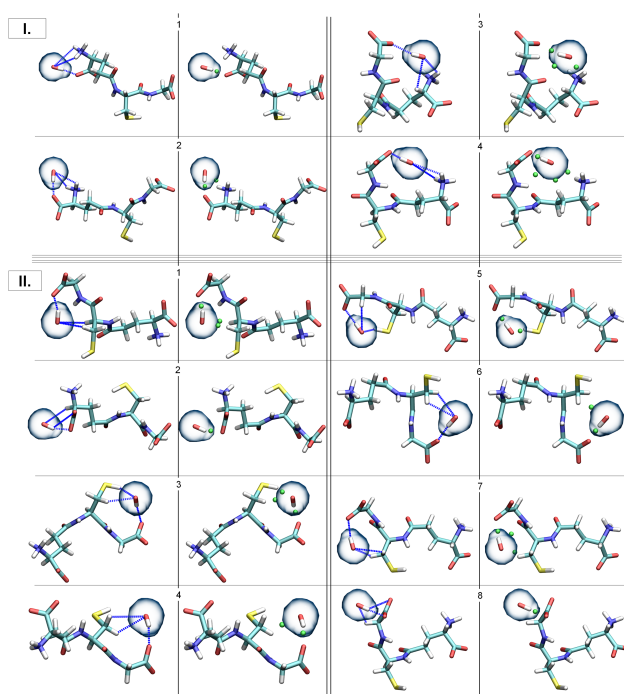
Figure 5: Structures Contained the Maximum (3) Number of GSH – OH$^\bullet$ Interactions (I. – Zwitterionic Group, II. – Anionic Group).

4th Thesis

By calculating the formation of glutathione, and its *a* analogue, L-glutamyl-L-cysteinyl-glycine along with similar systems, the thermodynamics of regular (*a*-) and isopeptide bond formation were described.

- The enthalpy of the peptide formation, reflecting the strength of peptide bonds, was shown to be linearly related to the acidity and basicity of the *N*- and *C*-terminal amino acids (Figure 6). The stronger acid the *N*-terminal and the weaker base the *C*-terminal amino acid, the weaker is the peptide bond. Since the γ-carboxyl group of glutamic acid is weaker than the *a*-COOH, the dipeptide γ-L-glutamyl-L-cysteine (γ-EC) and the tripeptide GSH are more stable than their regular, *a*-peptide isomers. The preference for formation of γ-EC and GSH is due to the enhanced stability of the γ-peptide bond. Therefore, the weak acid–strong peptide bond principle can also be considered as one of the factors why glutathione is still among the chemical agents of living organisms. At the beginning of chemical evolution, the larger exothermicity of the γ-dipeptide formation was probably one of the reasons why GSH has appeared, and when it successfully fulfilled its role as an antioxidant, it was retained in the redox arsenal of cells.
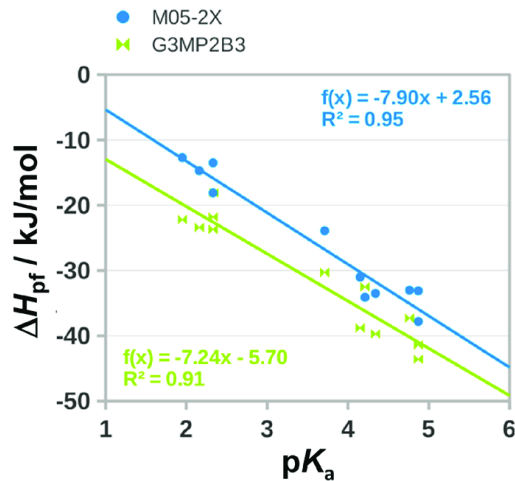
Figure 6: Correlation Between the Standard Reaction Enthalpies of Peptide Bond Formation ΔH_{pf} and the Experimental Acidity Constants pKa of the Bond-Forming *N*-Terminal Acids.

- Based on the weak acid-strong peptide bond principle the role of formylmethionine (fMet) in the first step of the bacterial protein synthesis can also be viewed in a new way. According to this, fMet act as a catalyst or rather an activator (Figure 7). The acidic strength of methionine is reduced by formylation, enabling it to form a stronger peptide bond whose strength is similar to that of a-peptide bonds in a peptide chain. This way the "bottleneck of the first peptide bond" is circumvented and fMet can be released from the *N*-terminus.
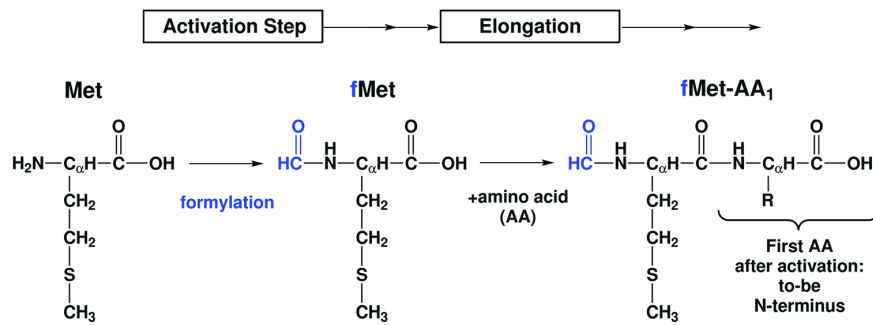
Figure 7: Initial Steps of the Bacterial Protein Synthesis.

- The correlation between the acid and base strength and the reaction enthalpy of peptide bond formation offers the possibility of being utilized in the design of new synthetic pathways for peptide synthesis, allowing one to control the steps of the process by varying the acidity and/or basicity of the amino acids.

5th Thesis

By our research, we contributed to the elucidation of the factors determining the strength of peptide bonds that may explain the preference of the α-peptide bond in proteins.

- The correlation between peptide bond strength and acidic strength proves to be a key factor in protein synthesis. Under thermodynamic control, the stronger the peptide bond the larger is the equilibrium concentration of the peptide. The closer the biosynthesis of proteins can follow the thermodynamics of the individual reaction steps the less effort and less smart technology is needed to make and break bonds efficiently. The energetics of peptide bond formation may also adds an item to the list why Nature relies on α-amino acids in proteins: β- or γ-peptide bonds are stronger than the α-peptide bond. While the enhanced strength is favorable in the first step of the synthesis, later too strong peptide bonds would be more difficult to manipulate in living organisms.

6th Thesis

A correction procedure is proposed for the calculation of the Gibbs free energy of peptide formation using standard quantum chemical techniques and continuum solvent models, but further verification necessary to prove its general applicability.

'The greatest desire of man is to contribute to the knowledge and beauty.'

Albert Szent-Györgyi (1893 – 1986)

IV

Summary

Glutathione (γ-L-glutamyl-L-cysteinyl-glycine, GSH) is essential in a number of biochemical processes in living organisms, including repair of oxidative damage and defense of the central nervous system against free radicals. It has also a role in apoptosis, signal transduction and gene expression.

Several research programs have been conducted to study the different properties of GSH. However, there are still blind spots, which are waiting to be elucidated. We tried to throw some light on these and as a result three papers have been published so far about glutathione (*J. Phys. Chem. B*, vol. 115(38), pp. 11269-11277, **2011**; *PLOS ONE*, vol. 8(9), pp. e73652, **2013**; *J. Phys. Chem. B*, vol. 119(10), pp. 3940-3947, **2015**), which form the basis of my dissertation and the theses presented here.

In our earliest work the radical forming ability of GSH in a thermodynamic sense is determined by means of quantum chemical calculations. Furthermore,

the radical scavenging ability of the neutral and anionic GSH was compared (*J. Phys. Chem. B*, vol. 115(38), pp. 11269-11277, **2011**).

Thereafter, we tried to shed light on the radical scavenging mechanism of glutathione. To overcome the limitation of the large flexibility of GSH, structures for further *ab initio* calculations were determined by non-reactive molecular dynamics (MD) simulations. A long comparative MD simulation were set for the solvated GSH and GSH/HO$^\bullet$ as model systems. Based on the MD trajectories the different interactions between GSH and HO$^\bullet$ were characterized. Moreover, the non-reactive MD trajectories combined with *ab initio* calculations allow us to describe a detailed free radical recognition and radical scavenging process (*PLOS ONE*, vol. 8(9), pp. e73652, **2013**). Based on these findings, new better antioxidant molecules can be designed.

The formation of α- and isopeptide bonds were in the focal point of our most recent work. The stability of GSH and its α analogue, ECG (L-glutamyl-L-cysteinyl-glycine) and other isopeptide-normal peptide pairs were computed and compared using quantum chemical methods. The obtained results showed that special peptides can be formed before the appearance of living organisms (*J. Phys. Chem. B*, vol. 119(10), pp. 3940-3947, **2015**).

V

Összefoglaló

Az élő szervezetekben előforduló szabadgyökök regulációjában fontos szerepet tölt be a glutation (GSH, L-γ-glutamil-L-ciszteinilglicin, γ-ECG), egy glutaminsavból, ciszteinből és glicinből álló antioxidáns lineáris γ-tripeptid. Ezen felül a GSH számos biokémiai folyamatban vesz részt, például az élő szervezetek központi idegrendszerének oxidatív stressz elleni védelmében, az apoptózisban, jelátvitelben és a gének expressziójában is. Összefüggés mutatható ki a glutation ideálistól eltérő koncentrációja és a Parkinson és Alzheimer-kór kialakulása között is. Ez az egyszerű tripeptid tehát kulcsfontosságú az élő szervezetek egészséges működése szempontjából. A GSH különböző tulajdonságait számos kutatási programban vizsgálták már, de maradtak még vakfoltok, amelyek felderítésre várnak. Ezekkel foglalkoztunk az utóbbi években, s eredményeinkből eddig három publikáció született (*J. Phys. Chem. B*, vol. 115(38), pp. 11269-11277, **2011**; *PLOS ONE*, vol. 8(9), pp. e73652, **2013**; *J. Phys. Chem. B*,

vol. 119(10), pp. 3940-3947, **2015**), amelyek a disszertációm és az abban foglalt tézisek alapját képezik.

Legkorábbi munkánkban számításos kémiai módszerekkel összehasonlítottuk a glutationban esetlegesen kialakuló gyökcentrumok képződésének termodinamikai valószínűségeit és meghatároztuk a molekula gyökökkel szemben legfogékonyabb csoportjait. Ezen túlmenően, összehasonlítottuk a GSH anionos és semleges formájának szabadgyök semlegesítési potenciálját is (*J. Phys. Chem. B*, vol. 115(38), pp. 11269-11277, **2011**).

Ezután a glutation szabadgyök semlegesítési mechanizmusának részleteire próbáltunk fényt deríteni. A GSH flexibilitásából eredően csak *ab initio* módszerek alkalmazásával nem deríthető fel ez a folyamat. Ezért elegendően hosszú, összehasonlító molekula dinamikai (MD) szimulációkat indítottunk szolvatált GSH és GSH/HO$^\bullet$ rendszerekre. A molekula dinamikai számolások eredményeit elemezve a GSH és HO$^\bullet$ között kialakuló kölcsönhatásokat sikerült meghatároznunk. Ezután az MD trajektóriákból kiválasztott szerkezeteken *ab initio* számolásokat végeztünk, s ezzel a kombinált eljárással részletesen sikerült a glutation szabadgyök felismerő mechanizmusát feltárni (*PLOS ONE*, vol. 8(9), pp. e73652, **2013**). Erre alapozva reményeink szerint a jövőben akár új, hatékonyabb antioxidáns molekulák tervezhetők.

Legutóbbi vizsgálódásaink középpontjában az *a*- és izopeptid kötések kialakulásának összehasonlítása állt. Ezt a glutationra és a megfelelő *a* analóg tripeptidre (L-glutamil-L-ciszteinilglicini, ECG) épülő esettanulmányon keresztül végeztük el. A GSH és ECG peptidek stabilitásának kvantum kémiai módszerekkel történő vizsgálatával meghatároztuk azokat a faktorokat, amelyek szerepet játszanak a peptid kötések kialakulásában. Eredményeink arra utalnak, hogy egyes speciális peptidek létrejöhettek az élet kialakulása előtt (*J. Phys. Chem. B*, vol. 119(10), pp. 3940-3947, **2015**).

If I have seen further, it is by standing on ye shoulders of giants.

— Isaac Newton,
Letter to Robert Hooke (1675)

VI
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'It does not, therefore, depend on human desire or effort, but on God's mercy.'

Romans 9:16

VII

List of Publications

List of Publications

Articles Related to the Thesis Points

Σ IF ∼ 10.417

[1] <u>B. Fiser</u>, M. Szőri, B. Jójárt, R. Izsák, I. G. Csizmadia, and B. Viskolcz, "Antioxidant potential of glutathione: A theoretical study," *The Journal of Physical Chemistry B*, vol. 115, pp. 11269–11277, 2011. **IF = 3.696**.

[2] <u>B. Fiser</u>, B. Jójárt, I. G. Csizmadia, and B. Viskolcz, "Glutathione – hydroxyl radical interaction: A theoretical study on radical recognition process," *PLoS One*, vol. 8, p. e73652, 2013. **IF = 3.534**.

[3] <u>B. Fiser</u>, B. Jójárt, M. Szőri, G. Lendvay, I. G. Csizmadia, and B. Viskolcz, "Glutathione as a prebiotic answer to *α*-peptide based life," *The Journal of Physical Chemistry B*, vol. 119, pp. 3940–3947, 2015. **IF = 3.187**.

List of Publications

Poster and Oral Presentations Related to the Thesis Points

[1] <u>B. Fiser</u>, B. Jójárt, M. Szőri, B. Viskolcz, I. G. Csizmadia, and E. Gómez-Bengoa, "Glutathione – a versatile antioxidant." **poster presentation**, DYNAPEUTICS, International Summer School, Donostia, Spain, 25 - 30 September 2016.

[2] <u>B. Fiser</u>, B. Jójárt, M. Szőri, I. G. Csizmadia, and B. Viskolcz, "Theoretical study of the structural properties of glutathione." **oral presentation**, KeMoMo–QSAR 2012 Symposium, Szeged, Hungary, 20 September 2012.

[3] <u>B. Fiser</u>, B. Jójárt, M. Szőri, I. G. Csizmadia, and B. Viskolcz, "Glutathione as an ancient prebiotic peptide – a theoretical study." **oral presentation**, Conference on Bile Acids – Modelling, Chemistry and Pharmacy I, Palics, Serbia, 6 - 7 September 2012.

[4] <u>B. Fiser</u>, B. Jójárt, M. Szőri, I. G. Csizmadia, and B. Viskolcz, "Glutathione as an ancient prebiotic peptide." **poster presentation**, ESF-LFUI Conference, Energy Landscapes, Obergurgl, Austria, 16 - 21 July 2012.

[5] <u>B. Fiser</u>, B. Jójárt, M. Szőri, I. G. Csizmadia, and B. Viskolcz, "The evolution of the structural properties of an antioxidant molecule - glutathione." **oral presentation**, VIII. Conference of Young Hungarian Scientists from Transcarpathia, Beregszász, Transcarpathia, Ukraine, 19 May 2012.

[6] <u>B. Fiser</u>, M. Szőri, B. Jójárt, R. Izsák, B. Viskolcz, and I. G. Csizmadia, "Antioxidant potential of glutathione - theoretical study." **poster presentation**, 4th

31

European Conference on Chemistry for Life Sciences (4ECCLS), Budapest, Hungary, 31 August - 3 September 2011.

[7] B. Fiser, M. Szőri, B. Jójárt, B. Viskolcz, and I. G. Csizmadia, "Stability of glutathione radicals." **oral presentation**, Celebration of the Hungarian Science, Szeged, Hungary, 11 November 2010.

List of Publications

Articles *not* Related to the Thesis Points

Σ **IF** ∼ **96.968**

[1] S. P. J. T. Bachollet, D. Volz, <u>B. Fiser</u>, S. Münch, F. Rönicke, J. Carrillo, H. Adams, U. Schepers, E. Gómez-Bengoa, S. Bräse, and J. Harrity, "A modular class of fluorescent difluoroboranes: Synthesis, structure, optical properties, theoretical calculations and applications for biological imaging," *Chemistry - A European Journal*, vol. 22, pp. 12430–12438, 2016. **IF = 5.771**.

[2] D. Scarpi, M. Petrović, <u>B. Fiser</u>, E. Gómez-Bengoa, and E. G. Occhiato, "Construction of cyclopenta [b] indol-1-ones by a tandem gold(I)-catalyzed rearrangement/Nazarov reaction and application to the synthesis of Bruceolline H," *Organic Letters*, vol. 18, pp. 3922–3925, 2016. **IF = 6.732**.

[3] P. Ramírez-López, A. Ros, B. Estepa, R. Fernandez, <u>B. Fiser</u>, E. Gómez-Bengoa, and J. M. Lassaletta, "A dynamic kinetic C–P cross–coupling for the asymmetric synthesis of axially chiral P,N ligands," *ACS Catalysis*, vol. 6, pp. 3955–3964, 2016. **IF = 9.307**.

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[5] <u>B. Fiser</u>, Z. Mucsi, E. Gómez-Bengoa, B. Viskolcz, S. J. K. Jensen, and I. G. Csizmadia, "Reply to comment on "Radicalicity: A scale to compare reactivities of radicals"," *Chemical Physics Letters*, vol. 654, p. 141, 2016. **IF = 1.860**.

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[15] B. Fiser, Z. Mucsi, E. Gómez-Bengoa, B. Viskolcz, S. J. K. Jensen, and I. G. Csizmadia, "Radicalicity: A scale to compare reactivities of radicals," *Chemical Physics Letters*, vol. 618, pp. 99–101, 2015. **IF = 1.860**.

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