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Structural Modeling of Glutathiones Containing Selenium and Tellurium

Valter A. Nascimento[1], Petr Melnikov[1], Andr é V. D. Lanoa[1], Anderson F. Silva[1], Lourdes Z. Z. Consolo[1]

[1]School of Medicine of the Federal University of Mato Grosso do Sul/UFMS, Brazil

Correspondence: Valter A. Nascimento, School of Medicine, Federal University of Mato Grosso do Sul/UFMS, Caixa Postal 549, Campo Grande/MS, Brazil. Tel: +55-67-3345-7805. E-mail: aragao60@hotmail.com

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Abstract

The comparative structural modeling of reduced and oxidized glutathiones, as well as their derivatives containing selenium and tellurium in chalcogen sites (Ch = Se, Te) has provided detailed information about the bond lengths and bond angles, filling the gap in the structural characteristics of these tri-peptides. The investigation using the molecular mechanics technique with good approximation confirmed the available information on X-ray refinements for the related compounds. It was shown that Ch-H and Ch-C bond lengths grow in parallel with the increasing chalcogen ionic radii. Although the distances C-C, C-O, and C-N are very similar, the geometry of GChChG glutathiones is rich in conformers owing to the possibility of rotation about the bridge Ch-Ch. It is confirmed that the distances Ch-Ch are essentially independent of substituents in most of chalcogen compounds from elemental chalcogens to oxydized glutathiones. The standard program Hyperchem 7.5 has proved to be an appropriate tool for the structural description of less-common bioactive compositions when direct X-ray data are missing.

Keywords: glutathione, selenium, tellurium, structural modeling

1. Introduction

Glutatione is a tri-peptide with a molecular mass 307.3 g mol^{-1} composed from the amino acids L-cysteine, L-glutamic acid and glycine (Figure 1). This is a major antioxidant acting as a free radical scavenger that protects the cell from reactive oxygen species (ROS). In addition, GSH is involved in nutrient metabolism and regulation of cellular metabolic functions, ranging from DNA and protein synthesis to signal transduction, cell proliferation, and apoptosis (Masella & Mazza, 2009).

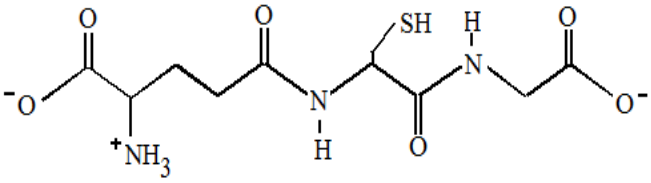
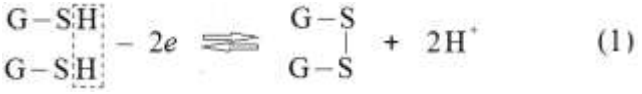


Figure 1. Schematic representation of GSH

This complex network of roles, functions, and effects makes GSH and sulfur amino acids a fascinating subject for protein chemists, biochemists, nutritionists, and pathologists. The sulfur atom of glutathione, being a good donor of electrons is responsible for its biochemical activity. Inside the cells, most of glutathione is in the cytosol, where it permanently exists in a reduced form, GSH. The latter can be reversibly transformed to form an oxidized derivative, GSSG. Their interrelationship is given by equation (1):



(1)

So it should be pointed out that GSSG is not really a “form” of GSH, but a product of condensation of the two GSH mol with the formation of S-S bridge (Figure 2). The interconversion between thiols and disulfide groups is a redox reaction, the thiol corresponding to the reduced state, and the disulfide to the oxidized. That is why the high GSH/GSSG ratio provides the essential reducing environment inside the cell (Reed et al., 2008). The S-S bond between the two divalent sulfur atoms plays an important role as the main stabilizer of the tertiary structure of many proteins.

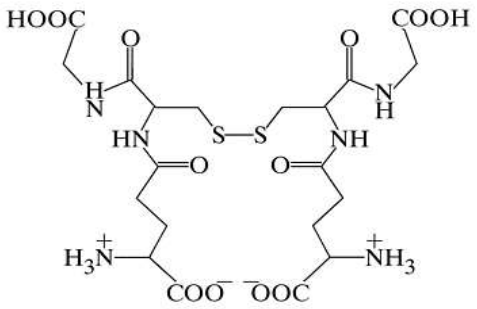


Figure 2. Schematic representation of GSSG

The crystal arrangement of both glutathione varieties has been the subject of several structural and spectroscopic studies at both room temperature (Nicolet, 1930; Qian & Krimm, 1994), and at 120 K (Gorbitz, 1987), in order to obtain further knowledge on hydrogen bonds involving the SH group. It was concluded that GSH and GSSG crystallize in the orthorhombic system, the space group $P2_12_12_1$. The latter contains a crystallographic twofold symmetry axis through the middle of the disulfide bridge. At the same time virtually nothing is known about glutathione analogs containing selenium and tellurium, although there are grounds to suggest that the substitution for sulfur may lead to uncommon biochemical and physico-chemical properties (Soriano-Garcia, 2004). Further, selenium-containing molecules might be expected to reduce H_2O_2 owing to their established anti-oxidant credentials (Ramoutar & Brumaghim, 2010). The simple di-selenide PhSeSePh proved more effective than sulfur derivatives against a panel of 116 pathogenic fungi with greatest inhibitory activity evident against *Candida albicans, Candida dubliniensis, Aspergillus spp.* and *Fusarium spp.* (Tiekink, 2012). Selenium can act as an effective radiosensitizer to enhance the anticancer efficacy through induction of cancer cell apoptosis (Xie, He, Lai, Zheng, & Chen, 2014). Motivated by the potential utility of selenium and tellurium against a number of diseases and pathological conditions, we have undertaken this study in order to fill the gap in structural characteristics of the two substituted tri-peptides. The purpose of this publication is to perform their structural simulations using the modern molecular modeling software to elucidate the similarities and differences between the substituted derivatives and natural glutathione. All methods use empirical data to determine individual force constants, in particular, bond lengths and bond angles. Herein we consider both glutathiones as independent unities, and not as a part of numerous enzymes they are attached to, particularly glutathione peroxidases, which contain selenium in the form of selenocysteine (SeCys), and their chemistry is still obscure.

2. Methods

The geometry optimization was carried out in Cartesian coordinates using the Berny optimization algorithm, adjusting the parameters until a stationary point on the potential surface was found. That means that for a small displacement the energy does not change within a certain amount, and the placements are successfully converged. It should be pointed out that we did not perform any systematic energy sampling for searching conformational energy space. Angles and interatomic distances were evaluated by using special features of the program. The experimental parameters used for comparisons were taken from databases and publications on structural X-ray refinements of related compounds containing sulfhydryl and selenohydril groups, as well as disulfide bridges.

3. Results and Discussion

A number of techniques exist for computerized modeling and calculating the potential energy of molecular systems as a function of coordinates of their atomic nuclei, neglecting explicit treatment of electrons. In this work, both varieties of glutathione were simulated using the standard HYPERCHEM 7.5 software package employing MM+ force field and PM3 semi-empirical (Hyperchem for windows, 2003). In vacuo calculations would bring out most of the underlying conformations without being side-tracked by the solvent used in the study or the limitations imposed by the densest packing. Strictly speaking, no conformational search routine guarantees that all conformers have been found, so the strategy chosen in this work was to study a reasonably representative set of the optimized geometries.

3.1 Reduced Form

To the best of our knowledge, glutathiones containing either selenium (GSeH) or tellurium (GTeH) have never been described. As a result, the reference compounds with the structural data available for comparisons are limited to GSH (Wright, 1958; Gorbitz, 1987), selenocysteine (Nascimento, Melnikov, & Zanoni, 2011) and, to some extent, to the simplest chalcogen hydrides H_2S, H_2Se and H_2Te (National Institute of Standards and Techonology [NIST], 2014). Three structurally similar conformers, one for each chalcogen, were built and oriented in a comparable way. The corresponding models are represented in Figure 3.

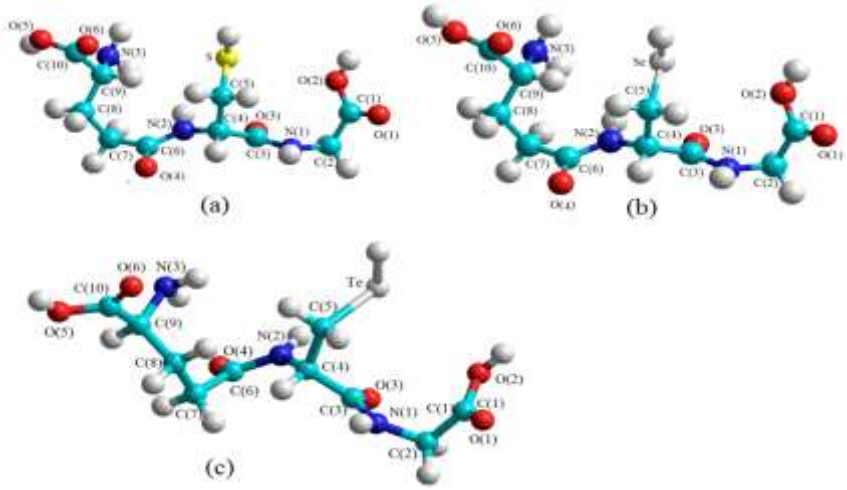


Figure 3. Structural models proposed for reduced glutathiones. (a) GSH; (b) GSeH; (c) GTeH

The geometries can be analyzed using the set of interatomic distances and angles listed in Table 1. Although the carbon atoms make an irregular chain, the interatomic distances C(1)-C(2), C(3)-C(4), C(4)-C(5), C(6)-C(7), C(7)-C(8), C(8)-C(9), C(9)-C(10), are the same (1.51−1.55 Å) as the typical C-C bond lengths in isolated molecules. They neither increase along the chain from C(1) to C(9) nor depart in a significant manner from the normal single-bond value of 1.542 Å as in the solid aminoacids and polypeptides (Protein Interatomic Distance Distribution Database [PIDD] (2014)). That is why they are not presented in Table 1. The same applies to the C-N and C-O bonds.

As for the key bonds Ch-H and Ch-C(5), the former are in good agreement with Se-H distance in SeCys, but larger than in crystalline GSH (Table 2), while the latter are practically the same as in SeCys and GSH. When plotted *vs* the chalcogen ionic radii the bond lengths Ch-H (Figure 4) showed a net linear dependence on this parameter and practically coincide with the analogous dependence of H_2Ch on the same radii (Figure 4). This finding unambiguously suggests that selenol GSeH and tellurol GTeH are polar compounds comparable to the simple hydrides, with all the biochemical consequences in regard to the reduction of cytosolic pH and protein glutathionylation. An important role of GSH is the detoxification of xenobiotics, electrophilic compounds which are eliminated by conjugation to GSH at sulfur site. Hence, selenium and tellurium analogs might enhance this function.

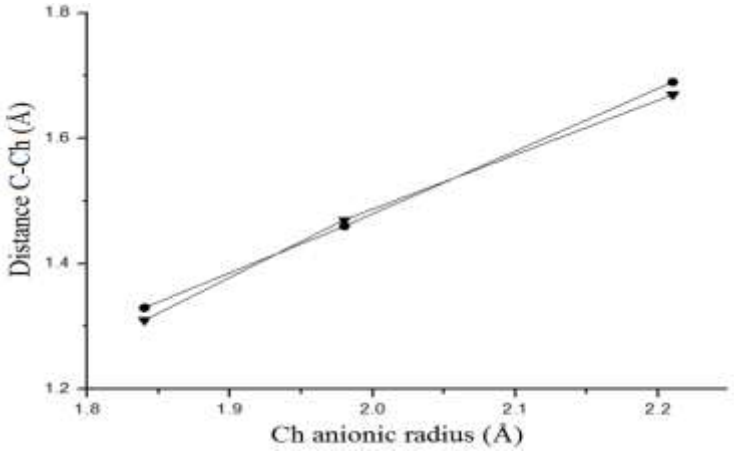


Figure 4. Dependence of the distances Ch-H in GChH (●) and in H_2Ch (▼) on the chalcogen ionic radii

It is worth noting that the calculated distance S-C(5) is practically the same as in the crystalline GSH, a fact which to a certain degree supports predictions made for Se-C and Te-C distances. If these distances are arranged in a row S-Se-Te, there is a similar parallelism with the ionic radii as in the case of the aforementioned Ch-H bond lengths. The comparison between the data obtained using MM+ force field and PM3 semi-empirical quantum mechanical methods shows that the former provides better approximations.

The angles of the main chain in ɣ-L-glutamyle residue do not appear to be sensitive to the chalcogen nature, being within a range of 111.1–114.7 °for C(6)-C(7)-C(8) and C(7)-C(8)-C(9). The angles C(8)-C(9)-C(10) are always smaller, that is 108.3–109.7 °. The remaining calculated angles of GSH are similar, but not identical with those determined by X-ray diffraction. A more pronounced dispersion in angles can be easily explained by the existence of a number of

conformationl isomers with slightly different values of potential energy (Table 1) due to the simultaneous rotation about the bonds C(1)-C(2), C(3)-C(4), C(4)-C(5), C(6)-C(7) and C(8)-C(9). It is to be born in mind that only the energies calculated using identical techniques can be compared. Naturally, all these considerations are true for isolated molecules as in the solid state such rotation is hindered.

Table 1. Interatomic distances (Å), angles (°) and minimal potential energies (kcal/mol) calculated for GSH, GSeH and GTeH

Parameters	MM+			PM3		
	S	Se	Te	S	Se	Te
Distances	1. 35	1.354	1.35	1.33	1.35	1.35
O(2)-C(1)	1.79	1.934	2.13	1.82	1.95	2.22
S/Se/Te-C(5)	1.46	1.461	1.45	1.51	1.48	1.48
C(4)-N(2)	1.41	1.41	1.42	1.50	1.42	1.42
N(2)-C(6)	1.33	1.480	1.68	1.34	1.46	1.67
Bond angles	120.22	120.22	118.87	123.50	116.60	116.48
O(1)-C(1)-O(2)	119.58	119.58	121.22	121.50	127.90	116.56
O(2)-C(1)-C(2)	120.18	120.18	119.89	114.86	115.38	126.94
O(1)-C(1)-C(2)	109.51	109.50	109.54	109.43	112.43	115.50
C(1)-C(2)-N(1)	112.99	112.61	111.43	108.29	103.22	112.96
C(4)-C(5)-S(Se)	111.11	110.88	112.01	111.70	109.40	107.14
C(3)-C(4)-C(5)	120.91	120.90	117.47	121.42	116.01	115.79
N(2)-C(6)-O(4)	120.22	120.24	124.41	118.82	119.98	120.39
N(2)-C(6)-C(7)	122.62	122.59	124.83	110.84	119.60	120.56
Energy	-15.74	-15.75	-15.82	-3619.9	-3624.7	-3611.3

Table 2. Main literature data on interatomic distances (Å) and angles (°) in SeCys and GSH

Parameters	Reference compounds			
	Glutathione [4]	Glutathione [7]	Cysteine and selenocysteine [13]	
	S	S	S	Se
O(2)-C(1)	1.30	1.30	1.35	1.35
S/Se/-C(5)	1.78	1.82	1.79	1.93
C(4)-N(2)	1.46	1.45	1.48	1.48
N(2)-C(6)	1.31	1.34	-	-
S/Se/-H	-	1.21	1.34	1.47
O(1)-C(1)-O(2)	122.8	123.1	119.71	119.74
O(2)-C(1)-C(2)	121.5	121.2	120.44	120.40
O(1)-C(1)-C(2)	115.6	115.6	119.68	119.71
C(1)-C(2)-N(1)	109.4	116.8	110.71	110.61
C(4)-C(5)-S(Se)	116.7	114.7	113.65	112.39
C(3)-C(4)-C(5)	109.1	109.6	111.18	110.54
N(2)-C(6)-O(4)	122.6	121.1	-	-
N(2)-C(6)-C(7)	117.9	117.1	-	-
C(4)-N(2)-C(6)	121.9	120.9	-	-

3.2 Oxidized Form

Hitherto, oxidized glutathiones containing either selenium (GSeSeG) or tellurium (GTeTeG) have never been described. As a result, the reference compounds with the structural data available for comparisons are limited to GSSG [5], cysteine (Chaney & Steinrauf, 1974; Hameka, Jensen, Ong, Samuels & Vlahacos, 1998) and, to some extent, to the simplest chalcogen hydrides H_2S_2, H_2Se_2 and H_2Te_2 (Boyd, Perkyns & Ramani, 1983; Elemental., 2003). Three structurally similar conformers, one for each chalcogen, were built and oriented in a comparable way. Calculations were carried out by analogy with the reduced form. The corresponding models are represented in Figure 5 showing the upper and lower moieties of glutathiones under consideration.

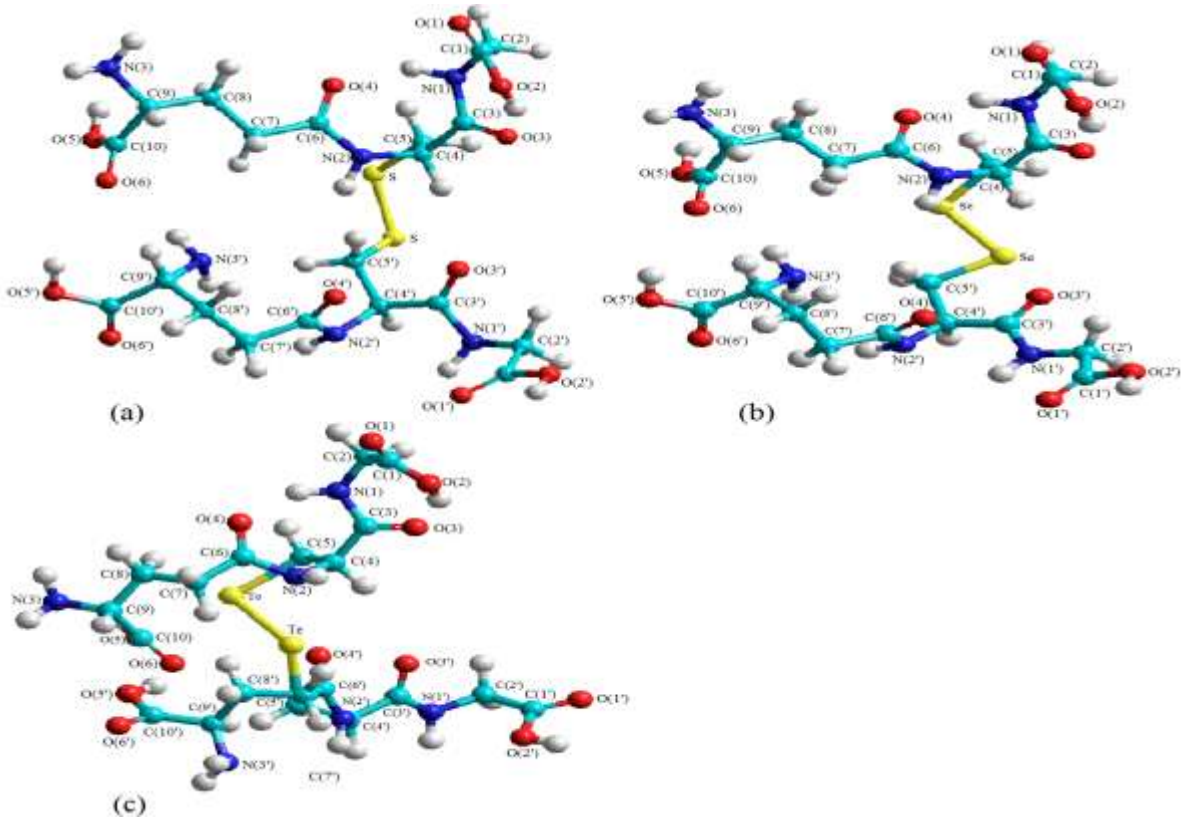


Figure 5. Structural models proposed for oxydized glutathiones. (a) GSSG; (b) GSeSeG; (c) GTeTeG

As can be seen from Table 3, the interatomic distances in both parts of the molecules practically coincide with each other, and simultaneously with those in the reduced portion of glutathione, including the distances Ch-C(5). As for the angles, the coincidences are not so precise, but that fact can be easily explained by the existence of a number of conformational isomers. First of all we are interested in the newly formed bridge Ch-Ch which connects the starting molecules. These distances (means calculated by MM+ and PM3), as obtained in this work are 2.02, 2.35 and 2.72 Å for GSSG, GSeSeG and GTeTeG, respectively. At the same time, the bond length within the S-S bridge as determined from X-ray diffraction for the oxidized form of glutathione is 2.043 Å (Jelsh & Didierjean, 1999). Moreover, the same distance in the H_2S_2 calculated using Gaussian programs is 2.065Å, so our value for GSSG must be correct. As concerns the values calculated for GSeSeG and GTeTeG in the present work, they match the corresponding distances determined experimentally for eight-membered homocycles S_8 and Se_8 which are a common structural motif of the chalcogens (Handbook., 2007), as well as for a number of related organic compounds (Allen et al., 1987): 2.34 for Se-Se and 2.704 Å for Te-Te, respectively. These comparisons suggest that the distances Ch-Ch are essentially independent of substituents in most of chalcogen compounds from elemental chalcogens oxydized glutathiones.

Table 3. Selected interatomic distances (Å) and minimal potential energies (kcal/mol) calculated for the "upper" moiety of GSSG, GSeSeG and GTeTeG

Parameters	MM+			PM3		
	S	Se	Te	S	Se	Te
O(1)-C(1)	1.20	1.20	1.20	1.21	1.21	1.21
O(2)-H	0.96	0.96	0.96	0.96	0.96	0.96
O(2)-C(1)	1.33	1.33	1.33	1.34	1.34	1.34
C(1)-C(2)	1.52	1.52	1.52	1.52	1.52	1.52
C(2)-N(1)	1.44	1.44	1.44	1.47	1.47	1.48
C(3)-N(1)	1.37	1.37	1.37	1.41	1.40	1.37
C(3)-C(4)	1.53	1.53	1.53	1.54	1.53	1.52
C(3)-O(3)	1.20	1.20	1.20	1.22	1.23	1.26
C(4)-C(5)	1.54	1.54	1.54	1.52	1.51	1.51
S/Se/Te-C(5)	1.82	1.93	2.13	1.82	1.94	2.19
C(4)-N(2)	1.45	1.45	1.45	1.48	1.48	1.48
N(2)-C(6)	1.37	1.37	1.37	1.41	1.42	1.42
N(3)-H	1.01	1.01	1.01	0.99	0.99	0.99
Energy	-34.63	-34.76	-34.60	-7118.1	-7186.6	-7150.6

Table 4. Selected interatomic distances (Å) and minimal potential energies (kcal/mol) calculated for the "lower" moiety of GSSG, GSeSeG and GTeTeG

Parameters	MM+			PM3		
	S	Se	Te	S	Se	Te
O(1')-C(1')	1.20	1.20	1.20	1.21	1.21	1.21
O(2')-H	0.97	0.97	0.97	0.95	0.95	0.95
O(2')-C(1')	1.33	1.33	1.33	1.35	1.34	1.35
C(1')-C(2')	1.52	1.52	1.52	1.51	1.52	1.51
C(2')-N(1')	1.44	1.44	1.44	1.47	1.48	1.47
C(3')-N(1')	1.37	1.37	1.37	1.42	1.37	1.39
C(3')-C(4')	1.53	1.53	1.53	1.54	1.53	1.54
C(3')-O(3')	1.20	1.20	1.20	1.21	1.26	1.25
C(4')-C(5')	1.53	1.53	1.53	1.53	1.51	1.50
S/Se/Te-C(5')	1.82	1.96	2.14	1.83	1.97	2.203
C(4')-N(2')	1.45	1.45	1.45	1.49	1.48	1.49
N(2')-C(6')	1.38	1.38	1.38	1.44	1.44	1.43
N(3')-H	1.01	1.01	1.01	0.99	0.99	1.007
Energy	-34.63	-34.76	-34.60	-7118.1	-7186.6	-7150.6

From a comparison of Tables 3 and 4 follows that the main interatomic distances in both parts of the models are identical. It should also be remembered that after condensation this system is provided with a new degree of freedom due to free rotation about the bond Ch-Ch. This enables the oxydized form with the possibility of *cis-trans* isomerism in respect to the glutathione moieties. Naturally, this ability makes available a large population of intermediate conformers. However, it is not the aim of this article to give an overview of their geometry and stabilities since these aspects have been extensively considered in the work dedicated to conformations of simple disulfides and L-cystine (Boyd et al., 1983). Thus our data appear to be appropriate to fill the gap in structural characteristics of seleno–and telluroglutathiones.

4. Conclusion

The comparative structural modeling of reduced and oxidized glutathiones and their derivative containing selenium and tellurium in chalcogen sites (Ch = Se, Te) has provided detailed information about the bond lengths and bond angles, filling the gap in the structural characteristics of these tri-peptides. The investigation using the molecular mechanics technique with good approximation confirmed the available information on X-ray refinements for the related compounds. It was shown that Ch-H and Ch-C bond lengths grow in parallel with the increasing chalcogen ionic radii. Although the distances C-C, C-O, and C-N are very similar, the geometry of GChChG conformers is richer in conformers owing to the possibility of rotation about the bridge Ch-Ch. It is confirmed that the distances Ch-Ch are essentially independent on substituents in most of chalcogen compounds from elemental chalcogens to oxidized glutathiones. The standard program Hyperchem has proved to be an appropriate tool for the structural description of less-common bioactive compositions when direct X-ray data are missing.

Acknowledgments

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