ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 11, Issue, 06, pp. 47677-47681, June, 2021
https://doi.org/10.37118/ijdr.21775.06.2021

RESEARCH ARTICLE OPEN ACCESS

COMPUTERIZED STRUCTURAL MODELINGOF TAURINE AND ITS DERIVATIVES

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ARTICLE INFO

Article History:
Received 11th March, 2021
Received in revised form
17th April, 2021
Accepted 08th May, 2021
Published online 26th June, 2021

Key Words:

Taurine, Homotaurine, Glyciltaurine, Sulfonic group, Computerized modeling.

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ABSTRACT

Molecular modeling of taurine (TAU), homotaurine (HOTAU)) and glyciltaurine (GLYTAU) with a good approximation confirmed the structural data previously obtained by the X-ray technique for these compounds, thus confirming the suitability of the *Spartan* program to perform calculations with two amino acids and a dipeptide containing sulfonic radical SO_3H.The calculation of bond lengths and bond angles provided new structural information on TAU, HOTAU and GLYTAU in which selenium and tellurium were substituted for sulfur of the functional group. Common abbreviation for chalcogensS, Se and Te is Ch. The calculated bond lengths and bond angles of TAU and its derivatives with heavy chalcogens (Se, Te) were found to be similar, except for the remarkable elongation of the key distances Ch-O, Ch-O and Ch-C in proportion to the ionic radii of the substituents. The cumulative effect of such changes may result in significant structural alterations in the entire molecule, leading to promising drugs. It is assumed that the broader spectrum of clinical effects of HOTAU is associated with the existence of conformational isomers with slightly different values of potential energy. In this way, computerized modeling of virtual compounds will be able to provide insights into the viability of further laboratory synthesis and bioactivity tests.

Citation: Simone Cabral Monteiro Henrique, Petr Melnikov, Hector Marcell Guerreiro, Gabriel Augusto Wandekoken and Valter Aragão do Nascimento. 2021. "Computerized structural modelingof taurine and its derivatives", *International Journal of Development Research*, 11, (06), 47677-47681.

INTRODUCTION

Taurine, 2-aminoethanesulfonic acid (TAU) does not have the typical carboxyl group of other amino acids, but instead contains a sulfonate group SO_3H. It may be also considered a derivative of alanine, where the alanine acid group -COOH is exchanged with -SO_3H group. In the crystal it adopts a zwitterionic configuration with f high dipole moment. Much of the information may be summarized by suggesting that, to a large extent, all the biological properties of TAU in excitable tissues are related to a single phenomenon: the regulation of the excitation threshold (Jacobson *et al*., 1968; Oja *et al*., 2007). Homotaurine (HTA), 3-aminopropansulfonic acid is a derivative of taurine with an additional methylene group and at the same time is a structural analogue of γ-aminobutanoic acid (GABA). As a specific inhibitor of impulse transmission in the central nervous system it has more potent inhibitory effect than TAU. The anticonvulsant potency of HOTAU is also greater than that of TAU (Lajtha, 1982). As for its pharmacological properties, homotaurine under the name Tramiprosate is considered to be a promising agent for treating a number of neurodegenerative disease, especially in the elderly. Alzheimer's disease (Manzano *et al*., 2020). Glyciltaurine (GLYTAU), although being a close derivative of TAU is not an amino acid, but a dipeptide. It was chosen to represent compounds with both sulfonic and carboxyl groups with an amide bond in the middle of the structure.

This molecule possesses the zwitterion configuration with the formula NH_3^+-CH_2-CH_2-CO-N- $CH_2SO_3^-$. An intramolecular bond between the groups NH_3^+ and SO_3^- stabilizes the structural arrangement (Garrigou-Lagrange *et al*., 1977). At the same time virtually nothing is known about TAU and its derivatives containing heavy chalcogens (Ch) selenium and tellurium, although there are grounds to suggest that the substitution for sulfur in the state of oxidation 6^+ may lead to uncommon biochemical and physico-chemical properties. Obviously, their therapeutic and antitoxic potentials are promising and but largely underestimated (Soriano-Garcia, 2004). It is well known that the replacement, partial or complete, of one element by a close one within the same group of the Periodic table can significantly change the properties of the final product. An appreciation of the importance of sulfur chemistry to the function of amino acids and their derivatives is revealed by considering the roles of these compounds in proteins synthesis and how these would be affected if the sulfur atom were replaced by heavy chalcogens as trace elements selenium and tellurium (Masella *et al*., 2009). The purpose of this publication is to perform their structural simulations using the modern molecular modeling technique.

METHODS

Various methods exist for calculating the potential energy of molecular systems as a function of the coordinates of their atomic

nuclei. All of them use empirical data to determine individuals force constants, in particular, bonds length and bond angles. In this work, the structure of substituted aminoacids were simulated employing the standard *Spartan 14* software for Windows, which uses MMF force field. As in previous publications on the structures of virtual bioactive compounds (Nascimento *et al.*, 2011; 2013; Melnikov *et al.*, 2013), the geometry optimization was carried out in Cartesian coordinates using the Berny optimization algorithm and adjusting the parameters until a stationary point on the potential energy 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 born in mind that no systematic energy sampling has been performed for searching conformational energy. 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, in particular, from the Cambridge Crystallographic Data Centre (CCDC, 2021) and FIZ Karlsruhe's free service to view and retrieve structures. Visualization of the crystal structure was performed using *Mercury*, a program attached to the CCDC. *Mercury* offers a comprehensive range of tools for 3D structure visualization and the exploration of crystal packing available in the aforementioned databases. The comparisons of the isolated models with their counterparts in solid state may prove useful for our general understanding of the structure of real compounds and our ability to assess their stability and chemical properties.

RESULTS AND DISCUSSION

The models obtained using the molecular modeling method are presented in Figures 1 - 5, all oriented in the same way. Figure 1 presents the TAU models obtained after virtual sulfur replacement by selenium and tellurium.

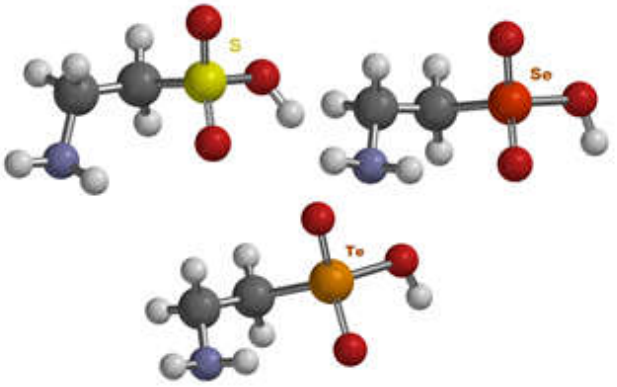

Figure 1. Models of TAU substituted for selenium and tellurium in SO_3H groups

The corresponding geometric parameters (bond lengths and bond angles) calculated for taurine are summarized in Tables1 and 2. First of all, we can see that the set of interatomic distances of the model molecule is very close to that of the structure previously refined by the X-ray technique (Sutherland *et al*., 1963). It should be also noted that the mean values of the calculated key sulfur-oxygen bond lengths are 1.462 and 1.502Å and the differences between these and the individual bond lengths are not significant. The Sulphur-carbon bond length is 1.805Å and both this value and the values of the Sulphur-oxygen bond lengths agree well with the mean values quoted for other compounds containing bonded sulfur, oxygen and carbon atoms (Rumble, 2020). It should be also noted that the mean values of the calculated key sulfur-oxygen bond lengths are 1.462 and 1.502Å and the differences between these and the individual bond lengths are not significant. The sulfur-carbon bond length is 1.805Å and both this value and the values of the sulfur-oxygen bond lengths agree well with the mean values quoted for other compounds containing bonded sulfur, oxygen and carbon atoms (Rumble, 2020).

Table 1. Bond lengths (Å) of TAU with selenium and tellurium compared to published data

BONDS	BOND LENGTHS			
	PUBLISHED *	MODELS		
		S	Se	Te
Ch - O1	1.453	1.615	1.825	2.043
Ch - O2	1.479	1.444	1.622	1.842
Ch - O3	1.463	1.446	1.622	1.842
Ch - C1	1.805	1.782	1.936	2.103
Ch - C2	2.760	2.729	2.867	3.007
C1 - C2	1.513	1.522	1.521	1.522
O1 - H1	0.971	0.982	0.972	0.973
C1 - H2	1.097	1.095	1.095	1.094
C1 - H3	0.934	1.095	1.095	1.095
C2 - H4	0.875	1.095	1.095	1.095
C2 - H5	0.987	1.096	1.094	1.094
N1 - C2	1.501	1.464	1.460	1.461
N1 - H6	1.079	1.024	1.022	1.022
N1 - H7	0.790	1.021	1.019	1.019

* [Sutherland, Young, 1963]

According to structural data the C atom and the three oxygen atoms form a tetrahedral group (Figure 2) with the sulfur atom at the center. Since in our case the distances are not equivalent this tetrahedron is not regular, and consequently this group must be more reactive. Both C-S distances are in accordance with the Cambridge Structural Database (CSD).

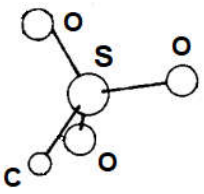

Figure 2. Tetrahedron SO_3C in TAU

The carbon-carbon bond length of 1.522Å is significantly shorter than the accepted value of 1.545Å of the carbon-carbon single bond. Meanwhile, in contrast to X-ray data (Sutherland, 1963) the single carbon-nitrogen bond of 1.464Å is not larger but closer to the accepted value of 1.475Å. The same can be said about the C - H bonds for which the model gives values closer to the generally accepted ones than to the X-ray data: 1.095 - 1.096Å instead of 0.875 - 0.987Å (Rumble, 2020). As for the angles, the model gives the mean oxygen-sulfur-oxygen bond angle as 108. 62° (Table 2), that is the regular tetrahedral angle, when all the three oxygen-sulfur-oxygen bond angles are essentially identical. It is much closer to the customary value than that of 112.13° obtained for the single crystal.

Table 2. Angles (°) of TAU with seleniumand telluriumcompared to published data

	ANGLES			
	PUBLISHED *	MODELS		
		S	Se	Te
O1 - Ch - O2	112.21	107.97	109.23	109.35
O1 - Ch - O3	113.94	105.64	108.93	109.23
O2 - Ch - C1	106.03	109.73	109.60	109.36
O3 - Ch - C1	105.90	110.07	110.13	109.79
O1 - Ch - C1	106.88	98.06	109.40	109.64
H1 - O1 - Ch	76.00	107.92	110.05	110.95

* [Sutherland, Young, 1963]

Finally, for OH groups there have been no differences detected between the model and X-ray results showing the normal value o 0.891 and 0.910Å. In all likelihood, the small deviations mentioned above in the structural parameters depend on the choice of a conformer with a lower potential energy level and bonds closer to those considered conventional. Therefore, as the computerized modeling renders the interatomic distances and angles, which with an error practically do not exceed the differences between the two columns of Table 1, the results, at least at the methodological level, can be considered to be convergent. It seems paradoxical, but SeTAU and TeTAU derivatives do not have a crystal structure determined even by X-ray powder diffraction despite the wide range of data available for TAU itself in other fields. As expected, the introduction of selenium and tellurium into the TAU matrix should have led to a shift in the main structural parameters. Simulation data shows that the distances S – O, Se – O and Te – O increase quite dramatically from sulfur to tellurium at the same rate for all the three oxygen anions. Moreover, when the bond lengths Ch - O are plotted*vs* the chalcogen anionic radii (Figure 3) the graph shows a net linear dependence on this parameter and practically coincide with the analogous dependence of Ch H_2 and gluitathioneChH on the same radii (Nascimento *et al.,* 2016).

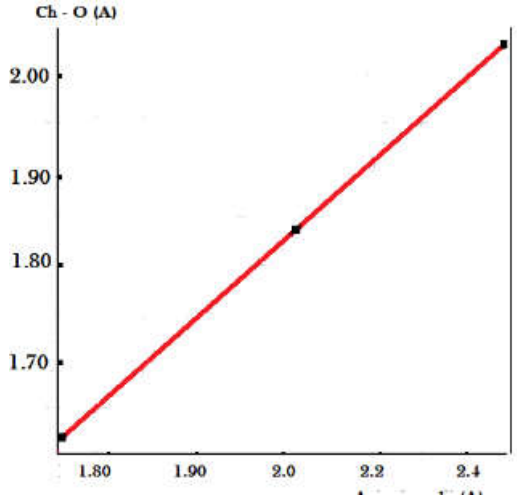

Figure 3. Dependence of the distancesCh-O in TAU, SeTAU and TeTAU onthe anionic radii

As a result of the heavier chalcogens intercalation the nearby distances Ch – C1, C – C2 and Ch – H1 are also enlarged, but always in a degree strongly proportional to the corresponding anionic radii. Comparisons show that in the rest of TAU and substitution models the distances C - C are identical. They are also invariable for the C-N, N-H and O-H bonds, their values being in accordance with the data published in the literature (NIST, 2018). Since, in the long term, computer modeling is aimed at identifying promising structures that are useful for a healthy and diseased organism, it seemed interesting to follow the evolution of TAU with the lengthening of its hydrocarbon chain. It cannot be said that there is little literary data on this subject. In contrast, there are informative reviews of TAU analogues and large experimental and epidemiological studies dedicated to new drugs but with no structural-clinical approach (Gupta *et al.*, 2005; Yamori *et al.*, 2010).

In this respect, HOTAU with sulfur substituted for heavy chalcogens is of undoubted interest. The calculated geometric parameters (bond lengths and angles) for homotaurine with selenium and tellurium are summarized in Figure 4 and Tables 3 and 4. Comparison of these data with the values for TAU shows striking similarities. Thus, the edge sizes of ChO3C tetrahedra coincide up to the third decimal place and the same behavior, with minimal differences, is observed with the distances O - H, C - H, N - C and N -H. Finally, the tgα (slope of the graph to the abscissa) for each sequence S - Se - Te is the same for each bond distance. As for the key bond angles, they are practically equal to the corresponding angles of TAU.

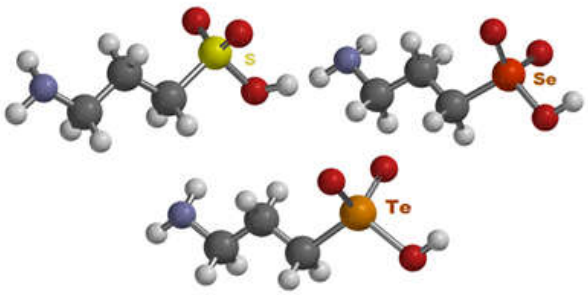

Figure 4. Models of HOTAU substituted or selenium and tellurium in SO_3H groups

Table 3. Bond lengths (Å) of HOTAUwith selenium and tellurium

BONDS	BOND LENGTHS		
	MODELS		
	S	Se	Te
Ch - O1	1.615	1.823	2.042
Ch - O2	1.444	1.622	1.842
Ch - O3	1.445	1.622	1.842
Ch - C1	1.786	1.931	2.101
Ch - C2	2.731	2.837	2.980
Ch - C3	4.108	4.235	4.391
C1 - C2	1.525	1.525	1.525
C2 - C3	1.522	1.519	1.519
O1 - H1	0.972	0.972	0.973
C1 - H2	1.095	1.094	1.094
C1 - H3	1.095	1.094	1.094
C2 - H4	1.097	1.097	1.097
C2 - H5	1.097	1.097	1.097
C3 - H6	1.096	1.096	1.096
C3 - H7	1.095	1.095	1.095
N1 - C3	1.455	1.458	1.458
N1 - H8	1.020	1.019	1.019
N1 - H9	1.020	1.019	1.019

Table 4. Bond angles of HOTAUwith selenium and tellurium

	ANGLES		
	MODELS		
	S	Se	Te
O1 - Ch - O2	105.44	109.14	109.40
O1 - Ch - O3	107.85	109.17	109.42
O2 - Ch - C1	109.99	109.72	109.44
O3 - Ch - C1	109.89	109.71	109.45
O1 - Ch - C1	97.73	109.56	109.66
H1 - O1 - Ch	107.73	109.79	110.61

As is known from numerous publications, HOTAU resembles TAU in its spectrum of biochemical activity, but its clinical indications are much more diverse, and a new drug Tramiprosate has been recently approved for clinical usage. Based on structural considerations, this difference can be explained, on the one hand, by the greater solubility and bioavailability of HOTAU and, on the other hand, by the

presence of an additional carbon atom. Indeed, the appearance of C3 makes the possibility of free or restricted rotation about the C2 - C3 bond and, consequently, the existence of conformational isomerisme. Conformational analysis can be an important contribution to the rational design of HOTAU drugs. In this regard, the special structural relationships of HOTAU and γ-aminobutanoic acid (GABA) should be kept in mind. In fact, it is not an amino acid but a carboxylic analogue of HOTAU with a missing sulfur group. This compound exists in two modifications, tetragonal and monoclinic, and in both phases the unique type of molecule assumes a partially folded zwitterionic form from the C2-C3 bond (Dobson *et al*., 1996). This molecule is believed to work as a neurotransmitter in the central nervous system of mammals that directly affects personality and stress management. In addition, it has hypotensive, tranquilizing, diuretic and anti-diabetic effects. Returning to HOTAU, it becomes clear that it is the C2 - C3 axis that is responsible for increasing the biological activity of the two related compounds, while γ-aminobutanoic acid appears to manifest itself as a more active neurotransmitter.

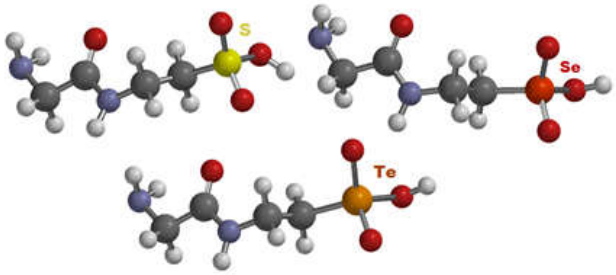

Figure 5. Models of glyciltaurine substituted for selenium and tellurium in SO_3H groups

Table 5. Structural parameters of glyciltaurine with selenium and tellurium

BONDS	BOND LENGTHS		
	MODELS		
	S	Se	Te
Ch - O1	1.614	1.823	2.042
Ch - O2	1.443	1.622	1.842
Ch - O3	1.446	1.622	1.842
Ch - C1	1.781	1.931	1.931
Ch - C2	2.698	2.839	2.986
Ch - C3	4.812	4.989	5.151
Ch - C4	6.262	6.392	6.563
C1 - C2	1.519	1.520	1.521
C3 - C4	1.534	1.534	1.534
C3 - O4	1.228	1.228	1.228
O1 - H1	0.981	0.981	0.973
C1 - H2	1.094	1.094	1.094
C1 - H3	1.095	1.095	1.095
C2 - H4	1.096	1.095	1.095
C2 - H5	1.095	1.095	1.095
N2 - H6	1.014	1.012	1.012
N2 - C2	1.456	1.449	1.449
N2 - C3	1.380	1.378	1.378
C4 - H7	1.094	1.094	1.094
C4 - H8	1.094	1.094	1.094
N1 - C4	1.469	1.471	1.470
N1 - H9	1.024	1.024	1.024
N1 - H10	1.023	1.024	1.024

Correlations between biochemical characteristics and physiological manifestations are expertly and in detail considered in the review, which still has not lost its relevance (Roberts *et al*., 1968). The next object of this study is GLYTAU, which was selected to follow the effect of the amide bond on the structural parameters of TAU derivatives. The calculated geometric parameters (bond lengths and angles) for GLYTAU with selenium and tellurium are summarized in Figure 5 and Tables 5 and 6. Comparison of these data with the values for TAU, as in the case of HOTAU, shows certain similarities of structural parameters. The S atom does not form any hydrogen bonds or polar interactions. Nevertheless, the linearity of the molecule is less pronounced, as can be judged from the significant increase in the S – C3 distance both in the original model and in the substituted structures. The N2 - C3 bonds are also remarkably larger than those reported for another small dipeptide, alanylmethionine (Guillot, Muzet, Dahaoui*et al.*, 2001).

Table 6. Bond angles of glyciltaurinewith selenium and tellurium

	ANGLES		
	MODELS		
	S	Se	Te
O1 - Ch - O2	108.14	109.15	109.39
O1 - Ch - O3	105.64	109.25	109.45
O2 - Ch - C1	110.26	109.70	109.40
O3 - Ch - C1	109.36	109.67	109.47
O1 - Ch - C1	98.25	109.57	109.65
H1 - O1 - Ch	108.18	110.04	110.86

The other parameters are within the range of published mean values. As to the angles, the coincidences are not so precise, but this finding can be easily explained by a large number of conformational isomers with slightly different values of potential energy.

CONCLUSIONS

Molecular modeling of taurine, homotaurine and glyciltaurine with a good approximation confirmed the structural data previously obtained by the X-ray technique for these compounds thus confirming the suitability of the *Spartan 14* program to perform calculations with two amino acids and a dipeptide containing sulfonic radical SO_3H. The calculation of bond lengths and bond angles provided new structural information on taurine, homotaurine and glyciltaurine in which selenium and tellurium were substituted for sulfur of the functional group. The calculated bond lengths and bond angles of taurine and its derivatives with heavy chalcogens were found to be similar, except for the remarkable elongation of the key distances Ch - O, Ch = O and Ch - C in proportion to the ionic radii of the substituents. The cumulative effect of such changes may result in significant structural alterations in the entire molecule, leading to promising drugs. It is assumed that the broader spectrum of clinical effects of homotaurine is associated with the existence of conformational isomers with slightly different values of potential energy. In this way, computerized modeling of virtual compounds will be able to provide insights into the viability of further laboratory synthesis and bioactivity tests. Further, organic molecules which contain heavy chalcogens might be expected to reduce hydrogen peroxide owing to their established antioxidant properties. An additional positive factor to improve the clinical effect is the structural commonality with active metabolites such taurine and its derivatives.

Acknowledgments: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

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