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# Comparative Structural Modeling of Vitamin $D_3$ Containing Sulfur, Selenium and Tellurium

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**Abstract**

The comparative structural modeling of vitamins $D_3$ containing sulfur, selenium and tellurium in oxygen site has provided detailed information about the bond lengths and bond angles, filling the gap in the structural characteristics of virtual $VD_3$ variants. The investigation using the molecular mechanics technique with good approximation confirmed the information available on X-ray refinements for the natural $VD_3$. It was shown that Ch-H and Ch-C bond lengths grow in parallel with the increasing chalcogen ionic radii and practically insensitive to the presence of the organic moiety. These findings demonstrate a higher polarity of $VD_3$S-H, $VD_3$Se-H and $VD_3$Te-H as compared to $VD_3$. It maybe suggested that enhanced polarity can have a positive impact on hydroxylation processes.

**Keywords:** vitamin $D_3$, sulfur, selenium, tellurium, modeling

## 1. Introduction

Vitamin $D_3$ or $VD_3$ [cholecalciferol; 9,10-Secocholeasta-5,7,10(19) – trien-3β-ol)] is a truly remarkable compound as it is both an essential nutrient and steroid prohormone that has a wide variety of biologic effects on the human body as its receptors are present practically in every tissue and cell (Burtis, Ashwood, & Bruns, 2006). This is the parent member of the naturally occurring family of vitamins D, which are lipophilic molecules with low aqueous solubility that must be transported in the circulation bound to plasma proteins. $VD_3$ is produced in the skin on exposure of its precursors to the ultraviolet B portion of sunlight.

The complex network of roles, functions and effects makes this family a fascinating subject for protein chemists, biochemists, nutritionists and pathologists (Holick, 2010). Schematic representation of $VD_3$ molecular formula is given in Fig. 1

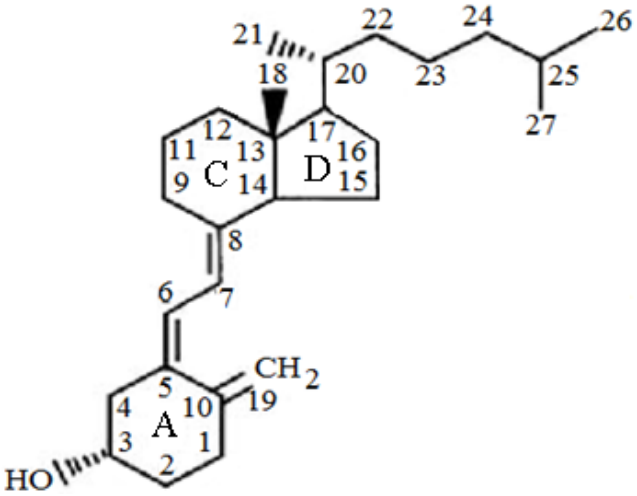


Figure 1. Schematic representation of $VD_3$ molecular formula (from (Holick, 2010) with modifications)

The structural formula of $VD_3$ contains four distinct moieties within the molecule: ring A (where a single O-H group is located), rings C and D, side chain and triene. In both the solid state and the solution the molecules are flexible and can

exist in many conformations at room temperature. In particular, ring A chair conformations are crucial for biological activity and mechanism of action of all D vitamins (Novak & Potts, 1997).

It is known that $VD_3$ exists as a dynamically equilibrating mixture of α and β chair conformers, the former with an equatorial disposition of the hydroxyl group and the latter with an axial orientation (Fig.2). The ratio between them was reported to be solvent and temperature dependent (Novak & Potts, 1997; Walsh et al., 2003).

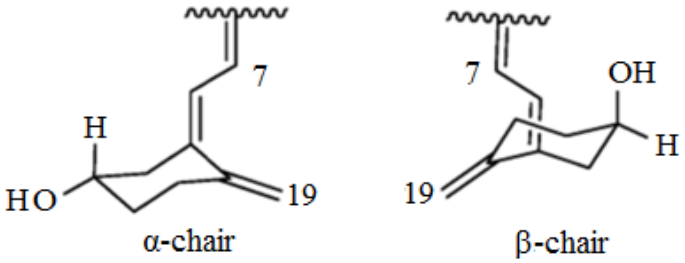


Figure 2. Two chairs conformations (from (Wang, Chun, Yu, & Mei, 2014) with modifications)

Although $VD_2$ has been known for almost ninety years (Blaner W. S.J Lipid Res. 2013; 54(7): 1716–1718, references therein), the structure of this important compound is not comprehensively characterized As for the crystal arrangement, it was concluded (Toan, Deluca, & Dahl., 1976) that $VD_3$ crystallizes in the orthorhombic system with the parameters given as ***a*** = 19.730Å; ***b*** = 7.340 Å and ***c*** = 35.716 Å. This crystalline compound exists in the form of a pseudo-homodimer and comprises a 1:1 complex of α- and β chairs. This modification has a close structural relationship with vitamin $VD_2$ (Hull, Leban, White, & Woolfson, 1976). In a recent structural studies (Wang, Zho, Qihui, & Mei, 2016), the hexagonal cell was proposed with the parameters given as ***a*** = ***b*** = 28.280Å and ***c*** = 5.932Å. The analysis of crystal structure data allowed suggesting that this polymorph contains exclusively α-chair conformation which is much prone to photo- or thermo-induced cyclization reactions than β conformer, and consequently it is more promising from the biochemical point of view (Wang, Chun, Yu, & Mei., 2014;). It should be born in mind that the value of the R factor that characterizes these investigations is of moderate accuracy, that is, 6.42 and 8.70%, respectively, and quite high even for large molecules.

At the same time, virtually nothing is known about $VD_3$ analogs containing the Ch-H group in which the oxygen analogs (Ch = sulfur, selenium and tellurium) replace this element in the classic hydroxyl group. Actually it was suggested elsewhere that such substitution may lead to uncommon biochemical and physico-chemical properties (Soriano-Garcia, 2004; Tiekink, 2012). In particular, selenium incorporated into natural bioactive compounds can act as an effective radiosensitizer to enhance the anticancer efficacy through induction of cancer cell apoptosis (Xie, He, Lai, & Zheng, 2014). Motivated by the potential utility of sulfur, 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 vitamins D. Such an approach enabled us in particular to perform modeling of glutathiones containing selenium and tellurium.

The purpose of this publication is to perform the structural simulations using the modern molecular modeling software to elucidate the similarities and differences between the substituted derivatives and natural compounds. All methods use empirical data to determine individual force constants, in particular, bond lengths and bond angles. Herein we consider $VD_3$ as an independent unit, and not as a part of numerous final metabolites like 25(OH) $D_3$ or $1,25(OH)_2D_3$ which act as circulating hormones.

## 2. Methods

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, the structure of $VD_3$ was simulated using the standard SPARTAN ‘14 for Windows, Macintosh and Cinox software package which employ MMFF force field (Halgren, 1996). 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, in particular related to the ring A.

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 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 the comparisons were taken from databases and publications on X-ray structural refinements of $VD_3$ molecule.

## 3. Results and Discussion

To the best of our knowledge, $VD_3$ containing sulfur ($VD_3S$-H), selenium ($VD_3Se$-H) or tellurium ($VD_3Te$-H) have never been described. As a result, the reference compounds with the structural data available for comparisons are limited to the orthorhombic and hexagonal polymorphs of $VD_3$ (Wang, Zho, Qihui, & Mei, 2016), orthorhombic $VD_2$ (Hull, Leban, White, & Woolfson, 1976) and, to some extent, to the simplest chalcogen hydrides $H_2S$, $H_2Se$ and $H_2Te$ (NIST, 2014). Three structurally similar conformers, one for each chalcogen, were constructed and oriented in a comparable manner, ie, a longitudinal view and a view allowing visualization at 45º. The corresponding models are represented in Figures 3 – 6.

The geometries can be analyzed using the set of interatomic distances and angles listed in Table 1. Although the carbon atoms are connected in three "fused" rings, the interatomic distances for both single and double bonds are close to those calculated for the orthorhombic and hexagonal $DV_3$ from X-ray measurements (Wang, Zho, Qihui, & Mei, 2016; Toan, Deluca, & Dahl, 1976), which are our reference data. At the same time, and according to the Atlas of steroid structures (Griffin, Duax, & Weeks, 1984), they are also very similar to the distances found for a number of steroid arrangements with the group O-H attached to the ring A.

Figures 3-6 show that the main difference between the conformers containing O, S, Se and T is the torsion angle C (3) - Ch - H, thus reflecting the variety of distortions of the chairs A. At the same time, the angles in the main chain do not appear to be sensitive to the chalcogen nature, although the coincidences are not very precise. This feature can be easily explained by the existence of a number of conformational isomers with slightly different values of potential energy. In the solution and in the solid state, the degree of freedom may be to some extent limited due to the demands imposed by the formation of pseudo-homodimers. For example, for the orthorhombic form it was shown that the two conformers are alternately connected by a set of intermolecular O – H O – H interactions to form a one-dimensional chain arrangement [Wang, Chun, Yu, & Mei, 2014].

As concerns the key bonds Ch- H and Ch – C(3), they grow linearly with the Ch H distances in the simplest sulfides, selenides and tellurides (1.35, 1.46 and 1.69 Å, respectively) (Macyntyre, 1999), that is, are practically insensitive to the presence of the organic moiety. On the other hand, if the distances Ch – C(3) are arranged in a row S – Se – Te, there is a net linear dependence on this parameter (Fig. 7). These findings unequivocally demonstrate a higher polarity of $VD_3S$-H, $VD_3Se$-H and $VD_3Te$-H as compared to $VD_3$. So we can suggest that the improvement of polarity may have a positive impact on the processes of further hydroxylation, which culminate in the water soluble form suitable for the uptake by peripheral tissues (Quinn & Kagan, 1998; Jovičić, Ignjatović, & Majkić-Singh, 2012). Hence, selenium and tellurium analogs might enhance metabolic functions of natural $VD_3$.

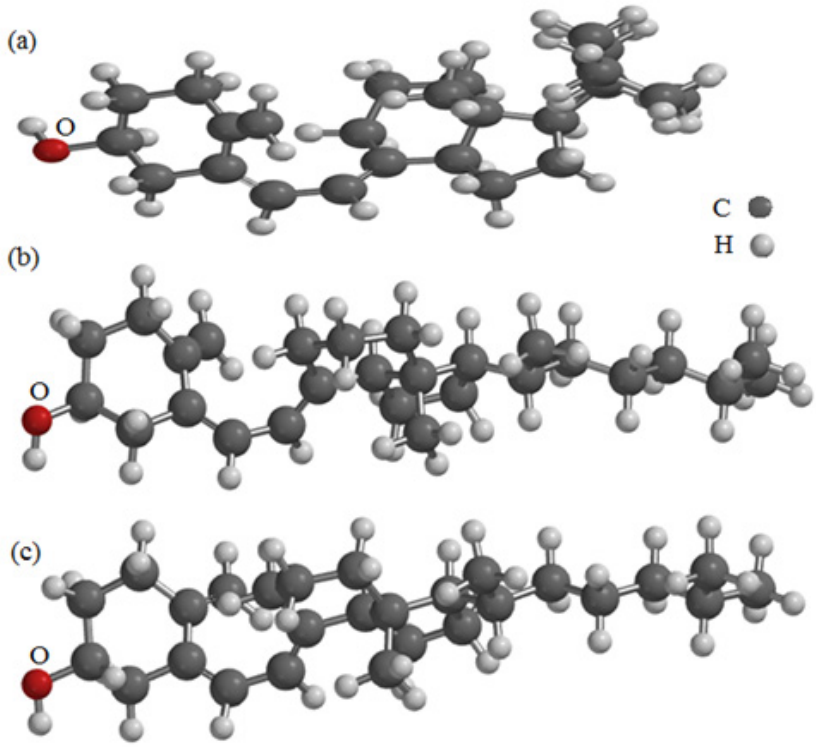


Figure 3. Structural models proposed for $VD_3O$-H, a – conformer 1, longitudinal view; b – conformer 2; longitudinal view; c – conformer 1, view permitting visualization at 45º

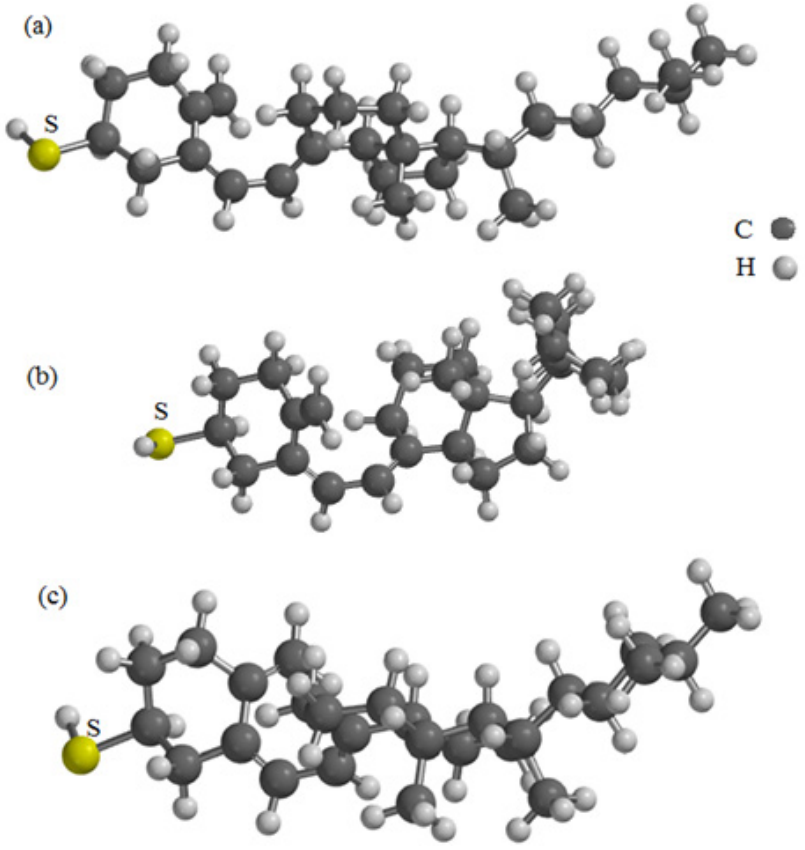


Figure 4. Structural models proposed for $VD_3S$-H, a – conformer 1, longitudinal view; b – conformer 2; longitudinal view; c – conformer 1, view permitting visualization at 45º

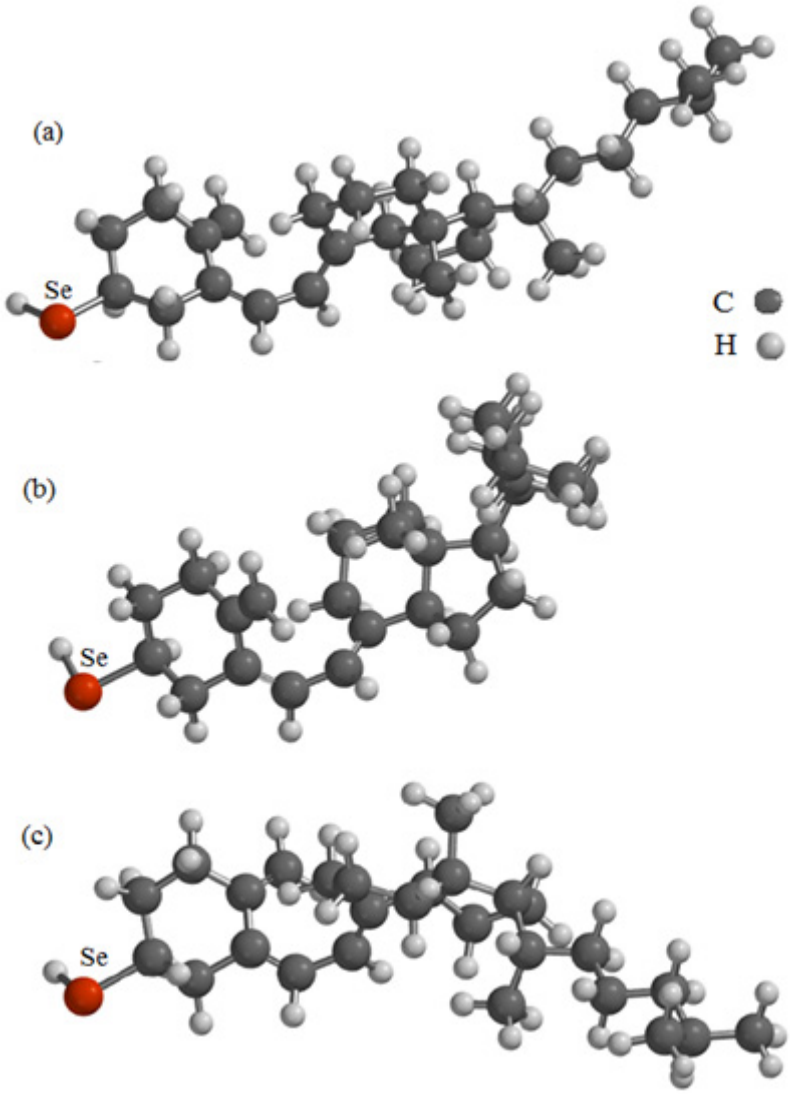


Figure 5. Structural models proposed for $VD_3Se$-H, a – conformer 1, longitudinal view; b – conformer 2; longitudinal view; c – conformer 1, view permitting visualization at 45º

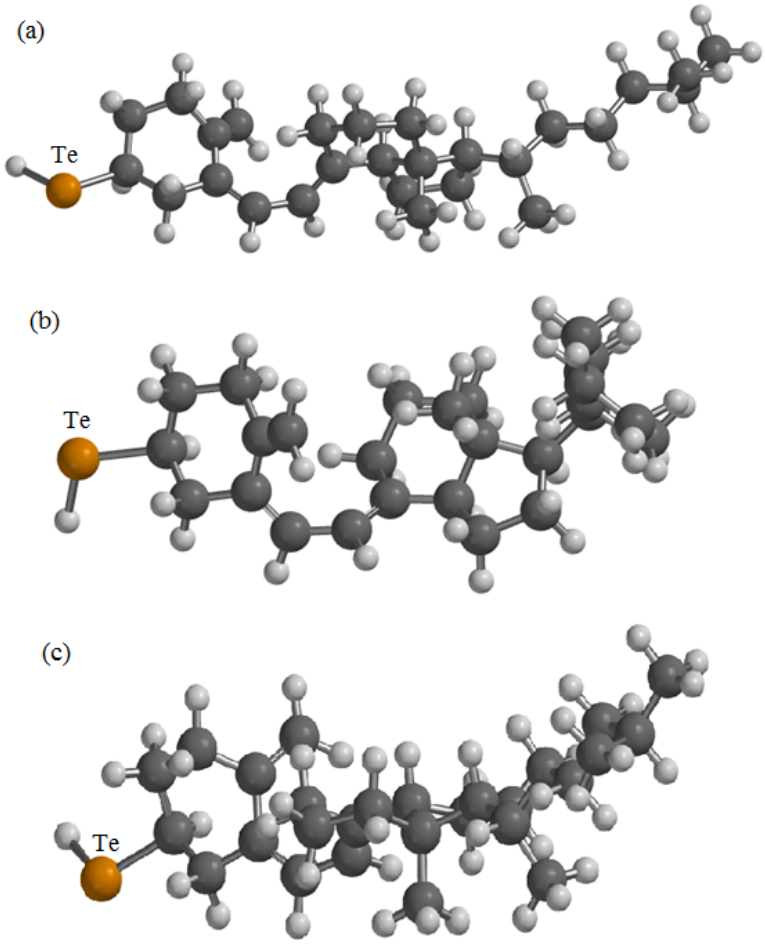


Figure 6. Structural models proposed for $VD_3Te$-H, a – conformer 1, longitudinal view; b – conformer 2; longitudinal view; c – conformer 1, view permitting visualization at 45º

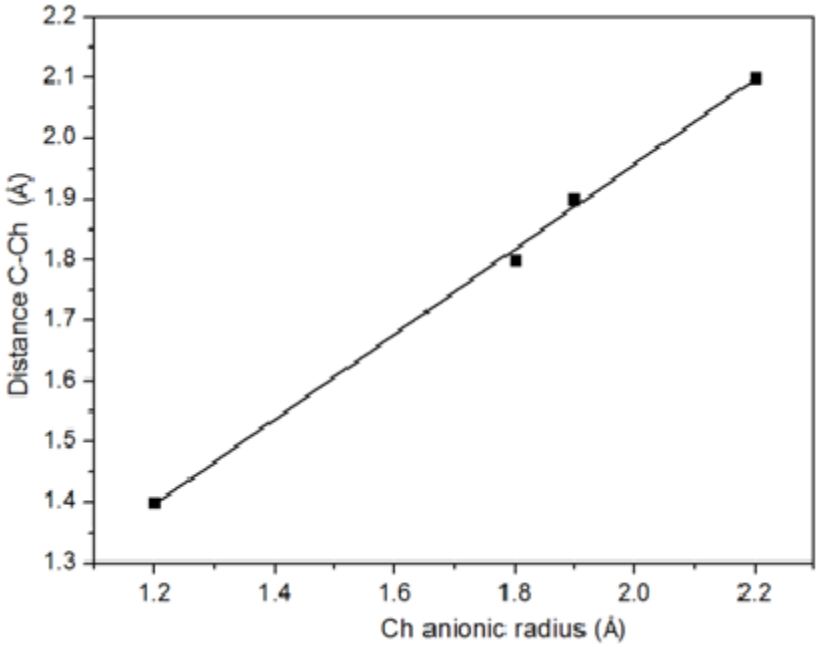


Figure 7. Dependence of the distances Ch-H on the chalcogen ionic radii

Table 1. Interatomic distances (Å) and potential energies (ua) calculated for substituted $VD_3$Ch-H

| Distance | Ch | | | | | |
|---|---|---|---|---|---|---|
| | O | S | Se | Te | O [6] | O [7] |
| Ch - H | 0.973 | 1.341 | 1.507 | 1.692 | 0.840 | 0.961 |
| Ch-C3 | 1.427 | 1.828 | 1.937 | 2.103 | 1.433 | 416 |
| C3-C2 | 1.533 | 1.537 | 1.530 | 1.530 | 1.503 | 1.564 |
| C2-C1 | 1.532 | 1.535 | 1.532 | 1.532 | 1.540 | 1.527 |
| C1-C10 | 1.509 | 1.508 | 1.509 | 1.509 | 1.496 | 1.479 |
| C10-C19 | 1.342 | 1.342 | 1.342 | 1.342 | 1.339 | 1.329 |
| C10-C5 | 1.466 | 1.465 | 1.466 | 1.466 | 1.483 | 1.448 |
| C3-C4 | 1.533 | 1.536 | 1.529 | 1.528 | 1.519 | 1.508 |
| C4-C5 | 1.521 | 1.524 | 1.520 | 1.320 | 1.515 | 1.506 |
| C5-C6 | 1.349 | 1.349 | 1.349 | 1.349 | 1.341 | 1.338 |
| C6-C7 | 1.447 | 1.447 | 1.447 | 1.447 | 1.454 | 1.436 |
| C7-C8 | 1.347 | 1.347 | 1.347 | 1.348 | 1.325 | 1.336 |
| C8-C9 | 1.519 | 1.519 | 1.519 | 1.513 | 1.515 | 1.572 |
| C9-C11 | 1.534 | 1.534 | 1.534 | 1.532 | 1.526 | 1.518 |
| C11-C12 | 1.537 | 1.538 | 1.538 | 1.532 | 1.522 | 1.559 |
| C12-C13 | 1.546 | 1.546 | 1.546 | 1.543 | 1.530 | 1.532 |
| C13-C17 | 1.563 | 1.563 | 1.563 | 1.577 | 1.554 | 1.523 |
| C13-C18 | 1.548 | 1.548 | 1.548 | 1.555 | 1.520 | 1.537 |
| C13-C14 | 1.556 | 1.556 | 1.556 | 1.570 | 1.557 | 1.518 |
| C14-C8 | 1.513 | 1.513 | 1.513 | 1.525 | 1.550 | 1.548 |
| C14-C15 | 1.525 | 1.525 | 1.525 | 1.533 | 1.525 | 1.502 |
| C15-C16 | 1.532 | 1.532 | 1.532 | 1.518 | 1.538 | 1.533 |
| C16-C17 | 1.558 | 1.558 | 1.558 | 1.536 | 1.550 | 1.572 |
| C17-C20 | 1.559 | 1.559 | 1.559 | 1.564 | 1.546 | 1.512 |
| C20-C21 | 1.532 | 1.532 | 1.532 | 1.533 | 1.530 | 1.547 |
| C20-C22 | 1.554 | 1.554 | 1.554 | 1.554 | 1.520 | 1.522 |
| C22-C23 | 1.535 | 1.535 | 1.535 | 1.534 | 1.610 | 1.514 |
| C23-C24 | 1.534 | 1.534 | 1.534 | 1.533 | 1.415 | 1.533 |
| C24-C25 | 1.540 | 1.540 | 1.540 | 1.540 | 1.514 | 1.258 |
| C25-C26 | 1.531 | 1.531 | 1.531 | 1.531 | 1.516 | 1.569 |
| C25-C27 | 1.529 | 1.529 | 1.529 | 1.529 | 1.518 | 1.489 |
| C7-C19 | 3.232 | 3.230 | 3.226 | 3.322 | 3.232 | 3212 |
| Energy | 353.51 | 347.28 | 329.30 | 358.53 | | |

Modeling is increasingly used in all aspects of drug candidates' with desired properties. Naturally, its results make 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. Its objective is to draw attention to the possibility of changing the properties of vitamin D by means of the substitution of S, Se and Te for oxygen. Thus our data appear to be appropriate to fill the gap in structural characteristics of virtual $VD_3$ variants for further research.

## 4. Conclusions

For the first time, the comparative structural modeling of vitamin $D_3$ containing sulfur, selenium and tellurium in oxygen site has been carried out. It provided detailed information about the bond lengths and bond angles, filling the gap in the structural characteristics of virtual $VD_3$ variants. The investigation using the molecular mechanics technique with good approximation confirmed the information previously available on X-ray refinements for the natural $VD_3$. It was shown that Ch-H and Ch-C bond lengths grow in parallel with the increasing chalcogen ionic radii and practically insensitive to the presence of the organic moiety. These findings demonstrated a higher polarity of $VD_3$S-H, $VD_3$Se-H and $VD_3$Te-H as compared to $VD_3$. The main difference between the derivatives containing O, S, Se and T is the angle C (3) - Ch - H, thus reflecting a variety of distortions of α and β chairs. It may be suggested that increased polarity could significantly improve the metabolic functions of natural $VD_3$.

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