ISSN: 2230-9926

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

IJDR

International Journal of Development Research
Vol. 07, Issue, 08, pp.14510-14514, August, 2017

ORIGINAL RESEARCH ARTICLE

Open Access

COMPUTERIZED MODELING OF VITAMIN D_2 CONTAINING SULFUR, SELENIUM OR TELLURIUM IN OXYGEN SITE

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ARTICLE INFO

Article History:
Received 23rd May, 2017
Received in revised form
17th June, 2017
Accepted 22nd July, 2017
Published online 30th August, 2017

Keywords:
Vitamin D_2, Ergocalciferol, Sulfur, Selenium, Telluruim, Structural modeling.

ABSTRACT

The investigations using the molecular mechanics technique with good approximation confirmed structural X-ray data for vitamin D2. The calculation of bond lengths and bond angles provided new structural information for vitamin D2 derivatives containing chalcogens (sulfur, selenium or tellurium) in oxygen site. The comparison showed that most of the bond lengths of the substituted compounds are similar, with the exception of the key bonds Ch-H and Ch – C(3), which grow linearly with the ionic radii of chalcogens. 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 is suggested that increased polarity could significantly improve the metabolic functions of natural vitamin D_2.

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Citation: Petr Melnikov, Ana Nogueira Gaúna, Lourdes Z. Zanoni, Lincoln C.S. de Oliveira and Valter Aragão do Nascimento, 2017. "Computerized modeling of vitamin D_2 containing sulfur, selenium or tellurium in oxygen site", *International Journal of Development Research*, 7, (08), 14510-14514.

INTRODUCTION

The number of publications on vitamin D is constantly increasing and numbered over 4000 in 2014. The explanation for this increasing interest stems from the accumulative knowledge of this vitamin's mechanisms of action and from the parallel increase of potential clinical applications. Moreover, in recent years, we have begun to regard vitamin D as not just a simple vitamin but a hormone and component of a sophisticated 'vitamin D endocrine system' (Burtis *et al.,* 2006). Discovered as an anti-rachitic compound, vitamin D still represents the emblematic vitamin that fixes calcium to bone. However, epidemiologic and experimental data allow us to hypothesize numerous extra-skeletal effects (Mazzaferro and Pasquali, 2016). Indeed, observational studies link vitamin D deficiency with chronic illnesses like diabetes, cancer, infections, cardiovascular and autoimmune diseases. Its use may well prevent several degenerative diseases, and it may also play a role as an anticancer agent.

The complex network of roles, functions and effects makes vitamins D family a fascinating subject for protein chemists, biochemists, nutritionists and pathologists (DeLuca, 2004). Another important fact is that vitamin D is required throughout life. An overview of general physiologic features and functions of vitamins D family is given in (Vitamin, 2010). Five sterols belong to the vitamin D group (vitamins D_1, D_2, D_3, D_4 and D_5). The major role is played by two of them: vitamin D_2 (VD_2, ergocalciferol) and vitamin D3 (VD_3, cholecalciferol). The schematic representation of VD_2 molecular formula (3β, 5Z, 7E, 22E)-9, 10-secoergosta-5,7,10(19),22-tetraen-3-ol) is given in Fig. 1. As can be seen, the structural formula of VD_2 contains four distinct moieties within the molecule: ring A (where a single O-H group is located), rings C and D and side chain. In both the solid state and the solution the molecules are flexible and can exist in many conformations at room temperature. In particular, the cyclohexane-like ring A chair isomers are crucial for biological activity and mechanism of action of all D vitamins (Norman *et al.,* 1996).

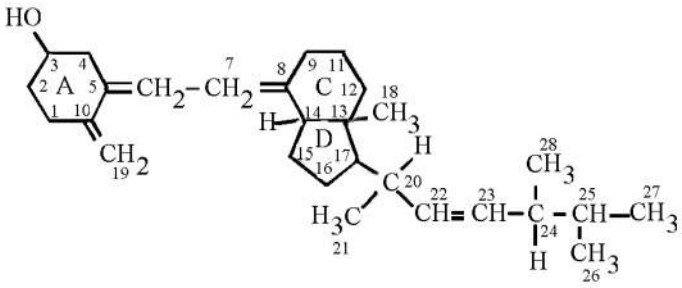

Fig. 1. Structural formula of vitamin VD_2

Similar to other vitamins of this group D, VD_2 exists as a dynamically equilibrating mixture of α and β chair conformations, 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 (Vitamin, 2010; Novak, 1997; Norman *et al.,* 1996).

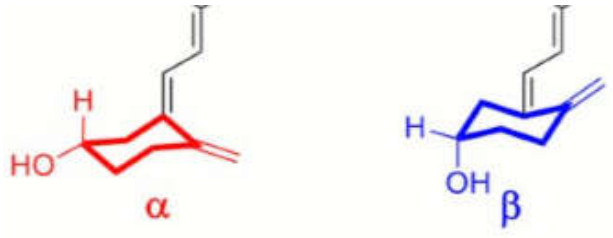

Figure 2. Two possible chair conformations of ring A

Due to its biological importance and its wide application in food, drug and nutrition industries, the related compound VD_3 has been widely covered in the literature, including its chemical, photochemical and thermal aspects. Meanwhile, although VD_2 has been known for almost ninety years, the structure of this important compound is not comprehensively characterized. There are two crystalline forms reported up to date: the orthorhombic polymorph with the parameters given ***a*** = 21.695Å; ***b*** = 6.857 Å and ***c*** = 35.320 Å (Hull *et al.,* 1976) and the monoclinic variety with the parameters ***a*** = 35.600Å; ***b*** = 7.200 Å; ***c*** = 20.500 Å and β = 102.00º (Bernal *et al.,* 1940). If one pays attention to the aforesaid parameters, this last modification seems to be simply a slightly distorted orthorhombic form. In addition, the two modifications also show a close structural relationship with vitamin VD_3 (Wang *et al.,* 2016). At the same time, practically nothing is known about VD_2 derivatives 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 *et al.,* 2000; Tiekink, 2012). In particular, selenium incorporated into natural bioactive compounds can act as an effective radio sensitizer to enhance the anticancer efficacy through induction of cancer cell apoptosis (Xie *et al.,* 2014). Motivated by the potential utility of sulfur, selenium and tellurium against a number of diseases and pathological conditions we performed this study to fill the gap in the structural characteristics of vitamin VD_2 derivatives. Recent research using this approach has enabled us, in particular, to perform modeling of glutathiones containing selenium and tellurium (Nascimento *et al.,* 2016). The purpose of this publication is to perform structural simulations of the aforementioned VD_2 derivatives using the modern molecular modeling software to elucidate possible similarities and differences between the substituted products and naturally occurring compound. All methods use empirical data to determine individual force constants, in particular, bond lengths and bond angles. Herein VD_2 is considered as an independent unit, and not as a part of its final metabolites.

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 MMFF94 (Merck Pharmaceuticals) force field (Spartan14v112, 2013). MMFF has been implemented for all elements in the table periodic. 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_2 molecule.

RESULTS AND DISCUSSION

Vitamin D molecule is characterized by unique dynamic properties and can sample numerous tridimensional shapes. To the best of our knowledge, VD_2 containing sulfur (VD_2S-H), selenium (VD_2Se-H) or tellurium (VD_2Te-H) have never been described. As a result, the reference compounds with the structural data available for comparisons are limited to the monoclinic (Hull *et al.,* 1976) and orthorhombic (Bernal *et al.,* 1940) polymorphs of VD_2 and, to some extent, to the simplest chalcogen hydrides H_2S, H_2Se and H_2Te (National Institute of Standards and Technology, 2014). Three structurally similar conformers, one for each chalcogen, were constructed and oriented in a comparable manner, i.e., 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 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_2 from X-ray measurements (Hull *et al.,* 1976; Bernal *et al.,* 1940), which are our aforementioned reference data. At the same time, and according to the Atlas of steroid structures (Griffin *et al.,* 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, for example 11β-methoxyestradiol. Figures 3-6 show that the main difference between the conformers containing O, S, Se and T is the angle

C(3) - Ch - H, thus reflecting the variety of distortions of the chairs A. Another characteristic is the small variability of the distance C7 – C19, which reflects differences in torsion angles due to the rotation above the bond C6 – C7. The side chain, which is the most dynamic region, can rotate 360 degrees around the single bond that links it to the C-D ring, and each carbon of the chain also has some flexibility. The number of tridimensional conformations that a metabolite can sample is thus very high (Mazzaferro and Pasquali, 2016).

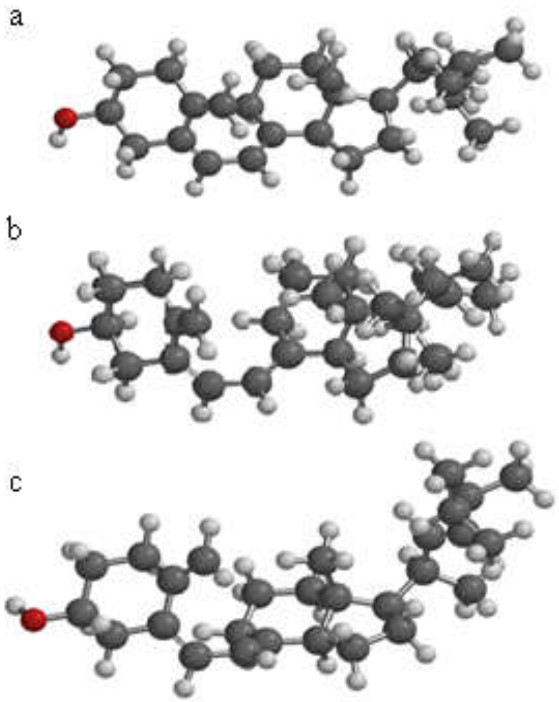

Fig. 3. Structural models proposed for VD_3O-H, a – conformer 1, longitudinal view; b – conformer 2, longitudinal view; c – conformer 1, view permitting visualization at 45º

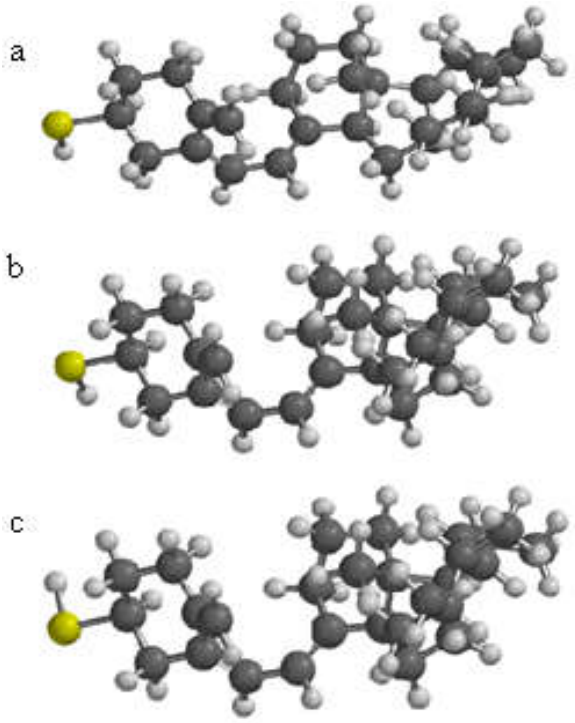

Fig. 4. Structural models proposed for VD_3S-H, a – conformer 1, longitudinal view; b – conformer 2, longitudinal view; c – conformer 1, view permitting visualization at 45º

At the same time, valence angles in the main chain (Table 2) 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 Jian-Rong *et al.,* 2014).

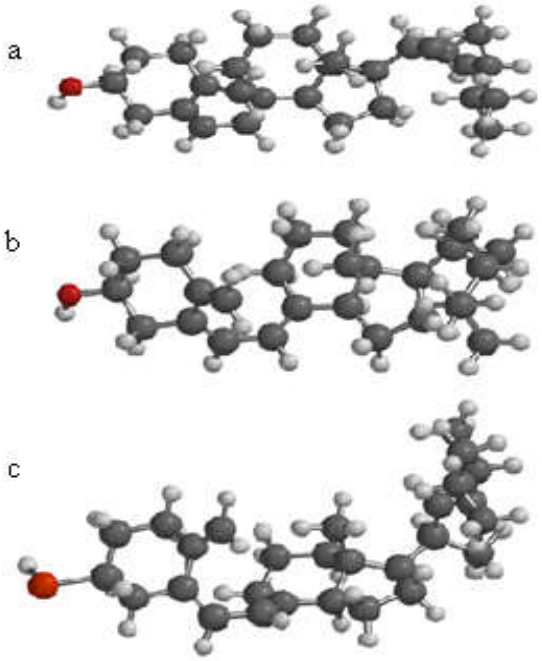

Fig. 5. Structural models proposed for VD_3Se-H, a – conformer 1, longitudinal view; b – conformer 2, longitudinal view; c – conformer 1, view permitting visualization at 45º

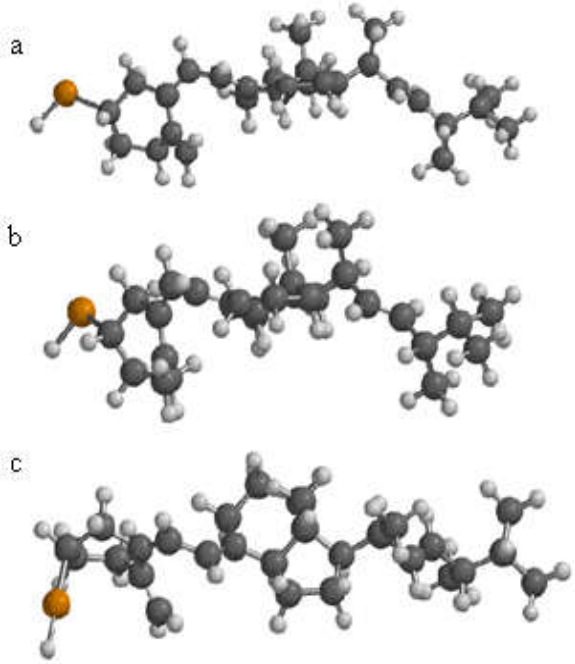

Fig.6. Structural models proposed for VD_3Te, a – conformer 1, longitudinal view; b – conformer 2, longitudinal view; c – conformer 1, view permitting visualization at 45º

Tabel 1. Interatomic distances (Å) and potential energies (a.u.) calculadas for V_3 Ch - H (Ch = O, S. Se and Te)

Distance	Ch				
	O	S	e	Te	O ;[6]
H-O	0.972	1.341	1.507	1.692	-
O-C3	1.427	1.827	1.936	2.103	1.446
C3-C2	1.531	1.534	1.527	1.530	1.448
C2-C1	1.528	1.532	1.529	1.532	1.534
C1-C10	1.510	1.510	1.510	1.509	1.433
C10-C19	1.342	1.342	1.342	1.342	1.349
C10-C5	1.461	1.461	1.461	1.466	1.448
C3-C4	1.534	1.537	1.530	1.528	1.504
C4-C5	1.514	1.517	1.514	1.520	1.498
C5-C6	1.347	1.347	1.347	1.349	1.348
C6-C7	1.447	1.447	1.447	1.447	1.488
C7-C8	1.346	1.346	1.346	1.346	1.322
C8-C9	1.520	1.521	1.521	1.521	1.500
C9-C11	1.537	1.537	1.537	1.538	1.478
C11-C12	1.538	1.538	1.538	1.537	1.590
C12-C13	1.542	1.542	1.542	1.543	1.515
C13-C17	1.536	1.556	1.556	1.556	1.563
C13-C18	1.546	1.546	1.546	1.545	1.523
C13-C14	1.554	1.554	1.554	1.551	1.529
C14-C8	1.512	1.512	1.512	1.512	1.530
C14-C15	1.531	1.531	1.531	1.531	1.522
C15-C16	1.541	1.540	1.541	1.541	1.547
C16-C17	1.550	1.549	1.550	1.548	1.525
C17-C20	1.552	1.551	1.552	1.550	1.541
C20-C21	1.540	1.540	1.540	1.532	1.516
C20-C22	1.515	1.515	1.516	1.518	1.529
C22-C23	1.344	1.344	1.345	1.343	1.350
C23-C24	1.515	1.516	1.521	1.514	1.541
C24-C28	1.532	1.534	1.537	1.532	1.467
C24-C25	1.554	1.555	1.558	1.554	1.606
C25-C26	1.533	1.534	1.534	1.533	1.488
C25-C27	1.533	1.535	1.536	1.533	1.407
C7-C19	3.308	3.308	3.309	3.226	3.155
Energy	380.35	371.51	360.55	376.53	-

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 that is 1.35, 1.46 and 1.69 Å, respectively (Macyntyre, 1999); they 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 O → S → Se → Te, there is a net linear dependence on this parameter. These findings unequivocally demonstrate a higher polarity of VD_2S-H, VD_2Se-H and VD_2Te-H as compared with the initial VD_2. Ring A is the primary site for the interaction with nuclear receptor (VDR) that regulates the transcription of several target cells. So we can expect that changes in the shape of the ring will modify a specific step in the VD_2 metabolism or receptor interaction.

Therefore the improvement of polarity might have a positive impact on the processes of further hydroxylation, which culminates in the water soluble form suitable for the uptake by peripheral tissues (Quinn and Kagan, 1998; Jovičić *et al.,* 2012). In this way, sulfur, selenium and tellurium located at oxygen sites could significantly enhance the metabolic functions of natural VD_2.The next stage should be the attempts to synthesize such products and check their biological activity. The above considerations are made on the basis of at least 10 conformers. Those whose data are given in the Figures and Tables are only representative examples having close potential energies. It is clear that these energies, calculated by the means of molecular mechanics do not necessarily have any physical meanings in themselves. However, when analyzing a family of closely related structures, they are useful for the sake of comparisons.

Table 2.Angles (°) calculated for V_3Ch - H (Ch = O, S, Se and Te)

Angle	Ch				
	O	S	Se	Te	O[6][x].
H-CH-C3	107.47	96.61	95.15	109.35	-
CH-C3-C2	109.52	109.73	109.13	109.32	109.30
C3-C2-C1	111.28	110.73	111.28	113.36	108.66
C2-C1-C10	111.50	111.54	111.50	111.44	112.91
C1-C10-19	122.33	122.34	122.35	121.52	123.51
C1-C10-C5	114.95	114.94	114.91	113.85	114.04
C5-C4-C3	111.52	110.90	111.41	112.71	113.10
C5-C10-19	122.61	122.62	122.64	124.46	122.22
C4-C5-C6	120.94	121.06	120.95	118.98	119.02
C10-C5-C6	125.95	125.87	125.93	126.98	126.41
C5-C6-C7	127.65	127.57	127.65	128.55	124.81
C6-C7-C8	126.36	126.33	126.35	126.66	125.04
C7-C8-C9	125.04	125.07	125.02	124.94	127.83
C8-C9-C11	112.94	112.97	112.95	113.00	112.59
C9-C11-C12	113.08	113.09	113.08	113.49	113.66
C11-C12-C13	111.68	111.67	111.67	111.81	109.29
C12-C13-C18	109.47	109.45	109.46	109.60	112.00
C12-C13-C14	108.33	108.33	108.32	108.18	109.49
C13-C14-C8	112.33	112.32	112.33	111.94	110.61
C14-C8-C7	123.53	123.50	123.54	123.59	121.63
C13-C14-C15	103.09	103.02	103.09	103.32	105.84
C14-C15-C16	104.43	104.33	104.43	104.62	101.51
C15-C16-C17	106.26	106.32	106.27	106.28	107.97
C16-C17-C13	103.59	103.77	103.58	103.72	105.50
C18-C13-C17	113.17	113.26	113.21	112.65	107.64
C13-C18-C14	112.34	112.26	112.32	112.76	111.23
C13-C17-C20	119.86	120.07	119.92	118.14	119.84
C16-C17-C20	116.03	115.95	115.98	116.85	112.76
C17-C20-C21	109.71	109.77	109.66	116.60	116.20
C17-C20-C22	115.94	116.52	115.94	109.15	109.12
C20-C21-C22	112.16	112.03	112.32	107.25	110.63
C20-C22-C23	127.11	127.36	127.18	123.82	124.48
C22-C23-C24	123.64	123.74	126.81	123.80	127.41
C23-C24-C25	111.13	111.67	111.12	111.34	110.22
C24-C25-C26	111.49	112.23	112.14	114.29	111.19
C28-C24-C25	114.18	112.58	112.36	114.10	116.45
C25-C26-C27	109.42	108.56	108.44	109.37	110.07
C28-C24-C23	109.19	107.84	112.71	109.10	113.79

[x] Hydrogens not localized

Conclusion

The investigations using the molecular mechanics technique with good approximation confirmed structural X-ray data for vitamin D_2. The calculation of bond lengths and bond angles provided new structural information for vitamin D_2 derivatives containing chalcogens (sulfur, selenium or tellurium) in oxygen site. The comparison showed that the bond lengths of the substituted compounds are similar, with the exception of the key bonds Ch-H and Ch – C(3), which grow linearly with the ionic radii of chalcogens. 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 is suggested that increased polarity could significantly improve the metabolic functions of natural VD_2.

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