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Molecular Mechanics-Based Conformational Analysis of Previtamin D and its A-Ring Analogues

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Summary. The ground-state conformational analysis of previtamin D and analogues with different substituents at C-3, C-1, and C-10 have been performed by force-field calculations. Differences in the photochemistry of these analogues are discussed in view of the concept of ground-state conformational control in photochemical reactions. The effect of complexes of previtamin D with silanol derivatives, formed *via* hydrogen bonds, on their conformational equilibrium has been calculated. An increase in the population of *cZc* conformers with increasing size of the silanol molecules (as a model for a heterogeneous silica surface) was observed.

Keywords. Previtamin D; Previtamin D analogues; Force-field calculations; Conformational equilibrium; Ground-state conformational control of photoreactions.

Konformationsanalyse von Previtamin D und seiner A-Ring-Analogen mit Hilfe von Kraftfeldrechnungen

Zusammenfassung. Eine Konformationsanalyse des Grundzustandes von Previtamin D and von an C-1, C-3 und C-10 substituierten Analogen wurde mit Hilfe von Kraftfeldrechnungen durchgeführt. Unterschiedliches Reaktionsverhalten bei den photochemischen Umsetzungen dieser Verbindungen werden unter dem Gesichtspunkt der Grundzustandskontrolle von photochemischen Reaktionen diskutiert. Der Einfluß von Komplexbildung über Wasserstoffbrücken von Previtamin D mit Silanolen wurde berechnet. Eine Zunahme der Population der *cZc*-Konformeren mit zunehmender Größe des Silanols (ein Modell für eine heterogene Kieselgeloberfläche) wurde dabei beobachtet.

Introduction

Previtamin D occupies the central position in the extended reaction network of vitamin D synthesis consisting of two stages: photosynthesis of previtamin D and its thermochemical conversion into vitamin D (Fig. 1).

The photochemical stage involves electrocyclic ring opening of the initial steroid diene previtamin D (*Pro*) to give previtamin D (*Pre*), which then undergoes a thermal [1, 7]-sigmatropic hydrogen shift producing vitamin D [1]. In contrast to the highly specific photoreaction *in vivo* [2], photosynthesis of previtamin D is complicated by a number of side-reactions *in vitro*, among which the undesired *cis-trans* isomerization into tachysterol (*T*) is most effective. Besides this *cis-trans* isomerization, photochemical formation of the so-called over-irradiation products (toxisterols, *Tox*) occurs [1]. This fact is a major drawback in the industrial production of

vitamin D, and several photochemical protocols have appeared in the literature to overcome the undesired side-reaction and improve the yield of previtamin D [1b]. One of the possible reasons of such non-selectivity of the process in organic media might share a conformational origin. *In vivo*, one can assume that the reaction occurs under a restricted molecular geometry. Therefore, due to the decrease of conformational space available for the previtamin D molecule, an inhibition of side-product formation should be expected. This fact has been examined in a number of experimental studies on provitamin D photoisomerization in heterogeneous reaction media. A significant inhibition of previtamin D *cis-trans* photoisomerization in organized reaction media has been revealed [3]. These studies demonstrated a dominant role of a conformational factor in previtamin D photochemistry and justify the application of the concept of ground-state conformational control in the photochemical reactions [4]. Since certain ground-state conformations of the triene determine reaction pathways and product distributions, a detailed knowledge of accessible conformations within a reasonable steric energy range is necessary to predict and control the outcome of this reaction.

Previtamin D possesses an exceptional internal flexibility caused by the oscillation around the C5–C6 and C7–C8 single bonds and the chair–chair interconversion of the A-ring [5]. It has been suggested that *cZc* conformations of previtamin D are precursors of ring-closed products, whereas *tZc* conformations lead to the *trans*-isomer tachysterol (*T*) [5, 6]. Therefore, varying the relative population of these conformations in some way, one might be able to influence the reaction kinetics and the final product distribution. The feasibility of this concept in previtamin D photochemistry has been examined theoretically on the basis of a simplified reaction model. An effective change in the previtamin D conformational equilibrium between *cZc* and *tZc* forms leading to a different temporal evolution and distribution of products has already been demonstrated [7].

The dominant role of previtamin D ground-state geometry upon its photosynthesis makes it interesting to study the effects of various chemical modifications. The most pronounced effect should be expected for A-ring analogues, because changes in that part of the molecule have the strongest influence on the global energy of the molecule. In this paper we present our results on force-field calculations of previtamin D and analogues with substituents in the A-ring that do not change significantly the individual geometry of the conformers but effect their global population. In addition, we performed model calculations simulating the effect of a silica surface on the conformational equilibrium in previtamin D.

Results and Discussion

For the conformational analysis of previtamin D and its A-ring analogues, various force field programmes were used [8]. For simplicity, the side chain in all previtamins was substituted by a methyl group, since the side chain geometry does not play any role in the photochemical conversions of previtamin D [5]. Because rings C and D of the steroid skeleton are almost rigid [5], the main attention was paid to the geometry of the A-ring and the torsional angles C10-C5-C6-C7 and C6-C7-C8-C9.

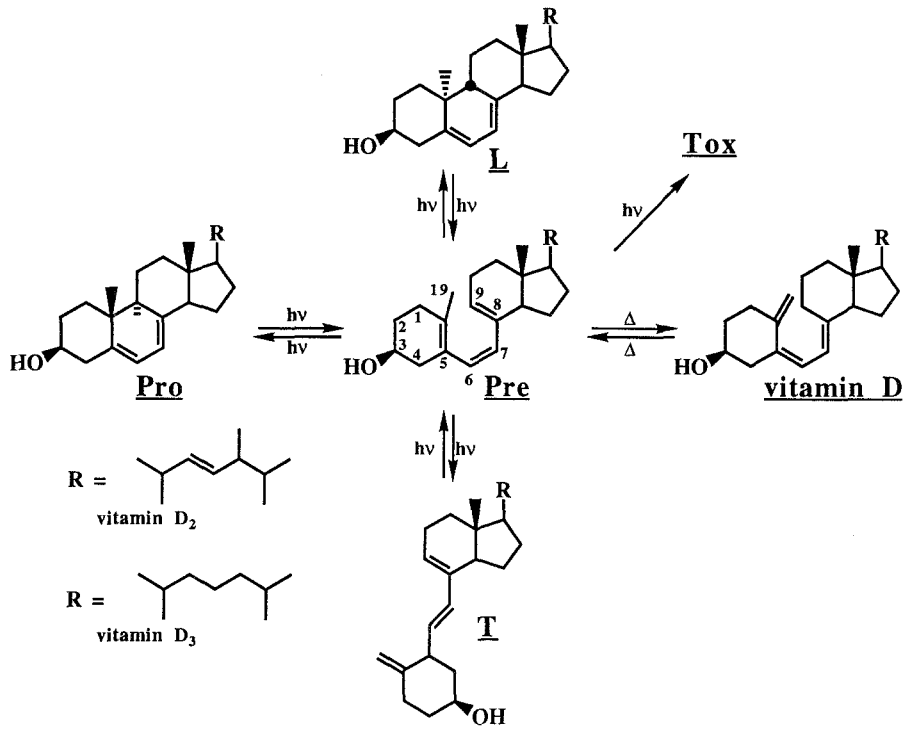

Fig. 1. Scheme of vitamin D synthesis

A conformational search for 3,4-dimethylcyclohex-3-en-1-ol (equivalent to the A-ring in previtamin D with the rest of the molecule replaced by a methyl group) revealed two low energy half-chair conformations with the OH group in *pseudo*-equatorial and *pseudo*-axial position [9]. In our analysis, the conformer with *pseudo*-axial OH orientation is only 0.26 kcal/mol higher in energy, in contrast to the value of 0.66 kcal/mol given in Ref. [5]. Different orientations of H-C3-O-H torsion (two *gauche*, one *anti*) results in a further splitting of the conformations, but, as it was noted in Ref. [10] for vitamin D, this is of no importance since there is no change in other geometric features. We have always chosen such *gauche* orientations of oxygen H that represent the energy minimum within a family. In contrast to vitamin D [10], this *gauche* orientation is the same in both half-chair forms. Within a steric energy range of 1.4 kcal, we found 12 stable and distinct conformations of previtamin D and its analogues. Moreover, conformations presented here have less planar structure, and the *cZc* geometry is more stable as will be shown below (Fig. 2).

Previtamin D

In our computational study of previtamin D, twelve distinct conformers have been localized. Wire frame representation of these conformations and their relative steric energies are shown in Fig. 2. The torsional angles C10-C5-C6-C7 and C6-C7-C8-C9 and the conformational population according to a *Boltzmann* distribution at 298 K are given in Table 1. The sign of the torsional angle follows the rules of *Klyne* and *Prelog* [11]. In contrast to Ref. [5], our analysis gives a *pseudo*-axial–*pseudo*-

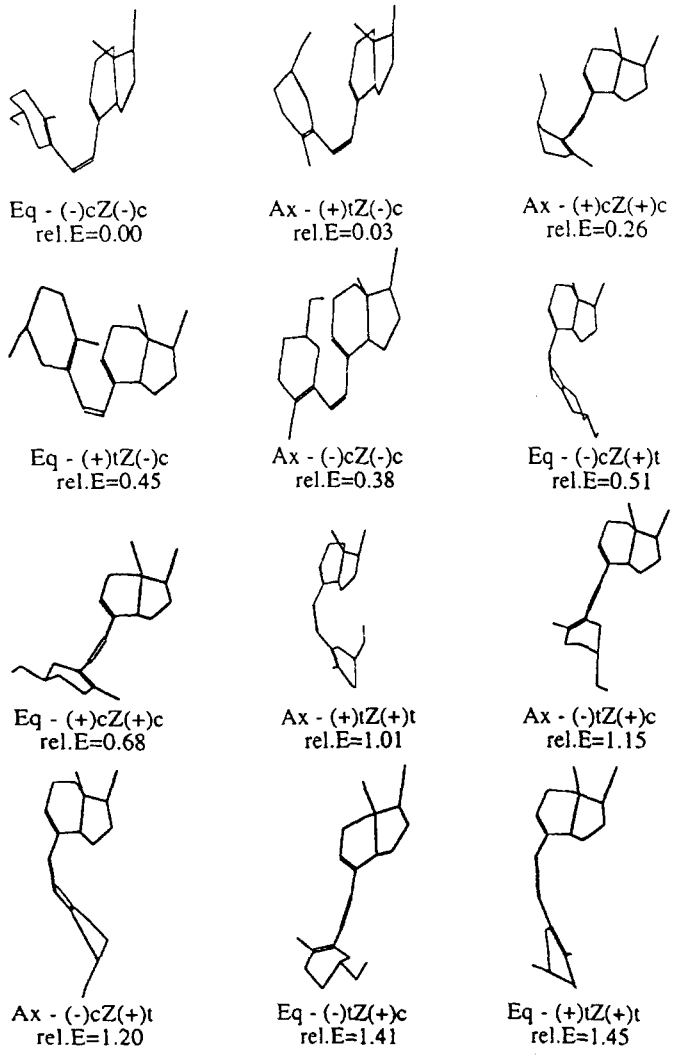

Fig. 2. Wire frame representations of the calculated conformations previtamin D

equatorial equilibrium of 53:47 and, in the *pseudo*-equatorial series, the global minimum is the *(−)cZ(−)c* form, whereas in the *pseudo*-axial series, it is the *(+)tZ(−)c* conformation. In our calculation, the conformational equilibrium is shifted in favour of the all-*cis* conformations. Our calculations have revealed that the population of the 7-*s*-*trans* conformations is not negligible and should be also taken into consideration for rationalizing the previtamin D photoconversions. In accordance with the new mechanistic scenario recently offered by *Bernardi et al.* [6], one can assume that excited 7-*s*-*trans* previtamin D conformers return to the ground state involving a passage through the $CI_{Z/E}$ conical intersection and producing tachysterol. The torsional angle C6-C7-C8-C9 of this conical intersection is 83° [6]; that is close to the 7-*s*-*trans* geometry in the ground state. Thus, for rationalization of previtamin D photoreactivity based on the concept of ground-state conformational control it seems to be convenient to determine the constant of the conformational equilibrium k which is defined as the ratio of the sum of the populations of *tZc*, *cZt*, and *tZt* conformers and the sum of the populations of *cZc* conformers. Therefore,

Table 1. Calculated geometries and *Boltzmann* distribution at 298 K of previtamin D conformations

Geometry	Torsion angle (deg) C10-C5-C6-C7	Torsion angle (deg) C6-C7-C8-C9	Percentage (%)
		OH *pseudo*-equatorial	
(−)cz(−)c	−69.50	−43.44	20
(+)cZ(+)c	56.64	41.18	6
(−)tZ(+)c	−122.81	43.39	2
(+)tZ(−)c	148.69	−45.11	9
(+)tZ(+)t	132.78	124.50	2
(−)cZ(+)t	−51.03	132.41	8
		OH *pseudo*-axial	
(−)cZ(−)c	−65.92	−42.57	11
(+)cZ(+)c	60.64	44.53	13
(−)tZ(+)c	−146.75	54.01	3
(+)tZ(−)c	116.35	−38.09	19
(+)tZ(+)t	135.63	134.33	4
(−)cZ(+)t	−46.91	132.81	3

from the data presented in Table 1 we define $k = 1$ for previtamin D. We will use this constant further on for an estimation of the conformational effect observed or expected. Thus the greater k, the more efficient is the Z/E isomerization into tachysterol and the less probable is the ring-closing reaction.

1α-Hydroxy-previtamin D

The 1α-hydroxyl group in vitamin D is essential for biological activity, and detailed knowledge about its influence on structural features in previtamin D is mandatory. The results of the conformational search are summarized in Table 2.

When the 3β-hydroxyl group has a *pseudo*-equatorial orientation, 1α-hydroxyl occupies the *pseudo*-axial position (*ea* conformation of the A-ring). In the opposite case, we have the *ae*-form of the A-ring [9]. It should be noted that the *Boltzmann* distribution calculated by us is approximately the same as the one presented by *Okamura* [12]. Thus, in our analysis, 1α-OH substitution results in a more pronounced shift of the conformational equilibrium in favour of *cZc* conformers in comparison with the parent previtamin D. The conformational equilibrium constant k is equal to 0.72. This fact has to effect the photochemistry of this analogue. The *cis-trans* isomerization should be relatively inhibited, and one can expect an increase in the efficiency of formation of ring-closure products.

10-Desmethyl-previtamin D

The photochemistry of this analogue has been investigated in detail [13] and compared with the 10-methyl series. More effective accumulation of the *trans*-isomer (10-desmethyl-tachysterol) has been observed. To explain the relative increase in the

Table 2. Calculated geometries, relative energies, and *Boltzmann* distribution at 298 K of conformations of 1α-hydroxylated previtamin D

Geometry	Torsion angle (deg) C10-C5-C6-C7	Torsion angle (deg) C6-C7-C8-C9	ΔE (kcal/mol)	Percentage (%)
		pseudo-equatorial position of 3β-OH group		
(−)cZ(−)c	−68.18	−40.43	0.00	28
(+)cZ(+)c	56.53	42.04	1.40	2
(−)tZ(+)c	−124.51	42.44	2.10	1
(+)tZ(−)c	149.55	−43.62	1.37	3
(+)tZ(+)t	130.63	124.43	2.05	1
(−)cZ(+)t	−50.97	133.17	0.84	7
		pseudo-axial position of 3β-OH group		
(−)cZ(−)c	−65.80	−41.01	0.25	19
(+)cZ(+)c	63.02	48.54	0.64	9
(−)tZ(+)c	−147.55	54.01	0.76	8
(+)tZ(−)c	113.4	−38.63	0.35	16
(+)tZ(+)t	134.33	135.02	1.30	3
(−)cZ(+)t	−46.75	133.51	1.32	3

Table 3. Calculated geometries, relative energies, and *Boltzmann* distribution at 298 K of conformations of 10-desmethyl-previtamin D

Geometry	Torsion angle (deg) C10-C5-C6-C7	Torsion angle (deg) C6-C7-C8-C9	ΔE (kcal/mol)	Percentage (%)
		pseudo-equatorial position of 3β-OH group		
(−)cZ(−)c	−53.56	−44.63	0.33	17
(+)cZ(+)c	46.09	39.48	0.63	10
(−)tZ(+)c	−135.17	43.26	1.75	2
(+)tZ(−)c	163.18	−51.22	0	29
(−)cZ(+)t	−42.22	135.67	0.67	9
		pseudo-axial position of 3β-OH group		
(−)cZ(−)c	−51.43	−40.93	0.64	10
(+)cZ(+)c	47.41	43.12	1.05	5
(−)tZ(+)c	−135.17	43.26	0.88	7
(+)tZ(−)c	163.18	−51.22	0.96	6
(+)tZ(+)t	140.13	135.00	1.69	2
(−)cZ(+)t	−38.42	136.47	1.36	3

quantum yield of formation of the provitamin D analogue, it was suggested that the absence of the 10-methyl group will reduce the preference for the (+)cZ(+)c conformation [13]. As can be seen from Table 3, our calculations are in good agreement with the above mentioned experimental results. According to our computational results, the value of the conformational equilibrium constant is 1.38. That value allows to predict a very efficient *cis-trans* isomerization as it was actually

observed in [13]. The population of the *(+)cZ(+)c* conformation is indeed reduced with respect to previtamin D. Thus, we conclude that our calculations have sufficiently good prognostic force.

3-Desoxy-previtamin D

To understand the role of the OH group in the 3β-position, we have removed this hydroxyl group in each of the previtamin D conformers and minimized the structures obtained. Analysis of the structures has revealed a significant depopulation of *tZc* forms in favour of *cZc* conformations. The conformational equilibrium constant in the considered case is equal to 0.64. This allows us to predict efficient ring-closure conversions and less efficient *cis-trans* isomerization for 3-desoxy-previtamin D.

Effects of bulky substituents in position 3β

As our calculations have shown, such a substitution does not lead to significant changes in the geometry of the conformers, but effects the steric energies and, as a consequence, results in the redistribution of conformational populations. The data collected in Table 4 give a clear idea about the influence of the 3β-substitution.

From these calculations one can expect a significant difference in the efficiencies of photochemical conversions as compared to previtamin D itself. The more bulky this substituent is, the more the conformational populations are shifted in favour of effective *cis-trans* isomerization to tachysterol.

As will be discussed below, there is the possibility to effect the opposite direction (which is of practical interest) and to reach a ground-state conformational distribution similar to 3-desoxy-previtamin D.

Complexes of previtamin D with the simplest possible models of surface silanol groups

As has been shown [3a, c], adsorption of previtamin D on a SiO_2 surface decreases the efficiency of the previtamin D *cis-trans* isomerization. We attribute this to a conformational shift in favour of *cZc* previtamin D conformations caused by

Table 4. Abundance (%) of the calculated conformers according to a *Boltzmann* distribution at 298 K and conformational equilibrium constants *k*

Substituent at C-3	*cZc*	*tZc*	7-*s*-*trans*	axial	equatorial	*k*
OH (*Pre*)	50	33	17	53	47	1.00
CH_3	55	26	19	7	93	0.82
CH_2OH	56	29	15	5	95	0.79
$OSiH_3$	45	35	20	30	70	1.22
$OSi(OH)_3$	37	30	33	35	65	1.70
$OSi(CH_3)_3$	25	58	17	55	45	3.00

Table 5. Abundance (%) of the calculated conformers and conformational equilibrium constant (k) for previtamin D in complexes with model silanol groups

Cluster	*cZc*	*tZc*	*7-s-trans*	axial	equatorial	k
Shell-1	57	24	19	67	33	0.75
Shell-2	61	22	17	55	45	0.64

hydrogen bonding to the surface. To support this view, we have undertaken a conformational analysis of previtamin D complexes with simple model clusters, simulating a silica surface such as Shell-1 ($(HO)_3SiOH$) and Shell-2 ($(H_3SiO)_3SiOH$) [14]. These complexes were formed *via* hydrogen bonds between the previtamin D hydroxyl group and the hydroxyls of the silanols, then optimized, and the steric energies of the conformers were calculated. The data on the conformational populations and the constants of conformational equilibrium are summarized in Table 5.

We are aware that application of these small clusters in the modeling of previtamin D adsorbed on a silica surface is quite critical. Nevertheless, our results allow to conclude that H-bonding with the silanol groups present on the surface causes a redistribution of the previtamin D conformer population in favour of the *cZc* forms. The larger the model cluster used, the more pronounced is this effect. It is worth mentioning that in the case of the *Pre*-Shell-2 complex the redistribution occurs only between *zZc* and *tZc* conformers as compared to previtamin D itself (see data for *Pre* in Table 4). Therefore, the main effect expected is the inhibition of the previtamin D *cis-trans* isomerization which has been already observed experimentally [3a, c].

Conclusions

The calculations presented here clearly demonstrate the effect of various A-ring substituents on the previtamin D ground-state conformational distribution and present the basis for further photochemical studies which may shed light on the nature of the formation of toxisterols.

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References

[1] a) Jacobs HJC, Havinga E (1979) Adv Photochem **11**: 305
b) Braun M, Fuss W, Kompa KL, Wolfrum J (1991) J Photochem Photobiol A: Chem **61**: 15
[2] Holick MF, Richtand NM, McNeil SC, Holick SA, Frommer JE, Henley W, Potts JT (1979) Biochemistry **18**: 1003

[3] a) Moriarty RM, Schwartz RN, Lee C, Curtis JV (1980) J Am Chem Soc **102**: 4257
b) Yamamoto JK, Borch RF (1985) Biochemistry **24**(13): 3338
c) Terenetskaya IP, Perminova OG, Yeremenko AM (1990) J Mol Struc **219**: 359
d) Terenetskaya IP, Perminova OG, Yeremenko AM (1992) J Mol Struc **267**: 93
[4] a) Pfoertner K (1972) Helv Chim Acta **55**: 937
b) Dauben WG, Rabinowitz J, Vietmeyer ND, Wendschun P (1972) J Am Chem Soc **94**: 4285
[5] Dauben WG, Funhoff DJH (1988) J Org Chem **53**: 5070
[6] Bernardi F, Olivucci M, Ragazos IN, Robb MA (1992) J Am Chem Soc **114**: 8211
[7] a) Dmitrenko OG, Terenetskaya IP (1993) Teor i Eksper Khim **29(4)**: 326 (translated in English)
b) Terenetskaya IP, Dmitrenko OG, Eremenko AM (1995) Res Chem Intermed **21(6)**: 653
[8] G-MMX and PC-MODEL (Serena Software, Bloomington, Indiana) for SGI Indigo 2. – MMP2 (QCPE 395) for the IBM 3090 mainframe computer. – Allinger NL, Flanagan HL (1983) J Comput Chem **4**: 399
[9] Eliel EL, Allinger NL, Angyal SJ, Morrison GA (1965) Conformational Analysis. Interscience, New York, p 102
[10] Hofer O, Kählig H, Reischl W (1993) Monatsh Chem **124**: 185
[11] Klyne W, Prelog V (1960) Exerientia **12**: 521
[12] Okamura WH, Midland MM, Hammond MW, Rahman NA, Dormanen MC, Nemere IN, Norman AW (1994) In: Norman AW, Bouillon R, Thomasset M (eds) Vitamin D. Pluripotent Steroid Hormone: Structural Studies. Molecular Endocrinology and Clinical Applications. Walter de Gruyter, New York, p 12
[13] Koolstra RB, Cornelisse J, Jacobs HJC (1987) Recl Trav Chim Pays-Bas **106**: 526
[14] Sauer J, Ugliengo P, Garrone E, Saunders VR (1994) Chem Rev **94**: 2095

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