

Vitamin D₁Edwin S. Tan,[†] Fook S. Tham,[‡] and William H. Okamura*

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The X-ray crystallographic structure of vitamin D₁ reveals a sandwich-like 1 : 1 heterodimeric complex of lumisterol₂ and vitamin D₂ with the latter in its α -chair conformer.

Vitamin D₁, the very first anti-rachitic factor, which played a historical role in the development of the vitamin D field, was discovered by Windaus¹ with contributions from Askew and co-workers² and Reerink and Van Wijk³ in 1931. This sharp melting, biologically active substance, produced photochemically from ergosterol (provitamin D₂, **3a**), was soon thereafter discovered to be a 1 : 1 crystalline heterodimer of lumisterol₂ (**4a**) and vitamin D₂ (**1a**).¹ This was all at a time when the involvement of previtamin D₂ (**2**), pyrocalciferol (**5**) and isopyrocalciferol (**6**) in the now well accepted scheme (Fig. 1) was not yet recognized.⁴ Early unsuccessful attempts to obtain the X-ray structure of crystalline, monoclinic D₂ were reported by Bernal in 1932⁵ and by Bernal and Crowfoot in 1935,⁶ but interestingly, the successful completion of the structure was not completed until 1994!⁷ The X-ray structure of the monoclinic

isomorph revealed that the D₂ was essentially the same as that in the very interesting finding in 1976⁸ by Hull *et al.* that the crystalline orthorhombic form of pure **1a** (a feature also characteristic of **1b**, vitamin D₃)⁹ exists as a pseudo-homodimer. What is novel about **1a** (and also **1b**) is that it crystallizes as a 1 : 1 complex of α - and β -A-ring chairs (Fig. 2), the former with an equatorial disposition of the C-3 hydroxy and the latter with an axial orientation of the same hydroxy. Not surprising is that in solution vitamin D₂ exists as a dynamically equilibrating mixture of the same α - and β -chairs and that this ratio is solvent dependent.¹⁰

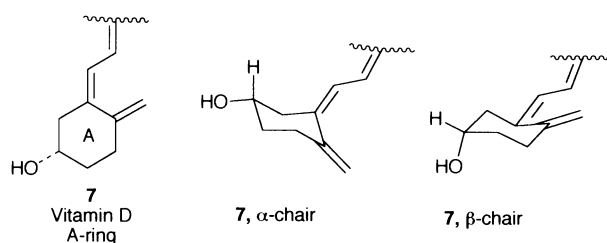


Fig. 2

In light of these divergent solid state and solution structural results for **1a**, it became of interest to consider the structure of the crystalline heterodimeric D₁, a complex of two seemingly very structurally dissimilar molecules **4a** and **1a**. The former possesses the steroid skeleton, but the latter exists in an extended 6-*s-trans* conformation. It was intriguing to entertain the possibility that D₁ might in fact be a complex of lumisterol₂ and previtamin D₂, a substance related to vitamin D₂ by way of a facile thermal [1,7]-sigmatropic shift. Alternatively, it was considered possible that the D₂ might exist in its 6-*s-cis* conformation (not shown), thus rendering it, like the putative previtamin D₂, better able to co-crystallize with the more topologically similar lumisterol₂ molecule. The purpose of this communication is to report that in fact the single crystal X-ray structure⁸ reveals that vitamin D₁ is simply a 1 : 1 complex containing lumisterol₂ and vitamin D₂ in its 6-*s-trans* conformation, but with the A-ring in the α -chair conformation as indicated in Fig. 3. It is interesting that the axial 3β -OH of lumisterol₂ is hydrogen bonded to the equatorial 3β -OH of vitamin D₂ in such a manner as to form a face sandwich-like structure placing the two C₁₈ angular methyl group carbons in close proximity with one another.

Samples of vitamin D₁ were prepared by collecting crystals (mp, 119–121 °C; literature² mp 124–125 °C) from a slowly evaporating solution containing a 1 : 1 mixture of lumisterol₂ and vitamin D₂ (acetone). Similar attempts to obtain crystalline

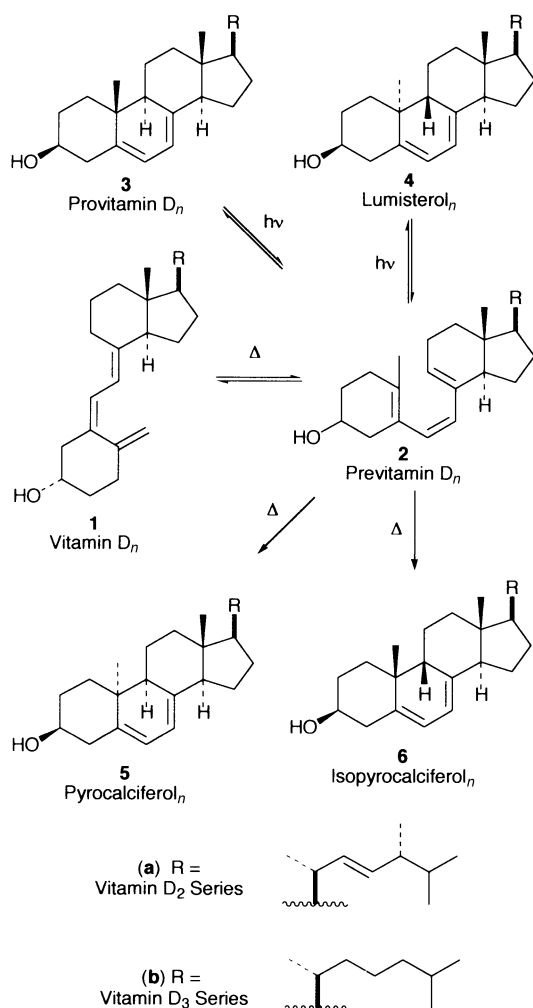


Fig. 1

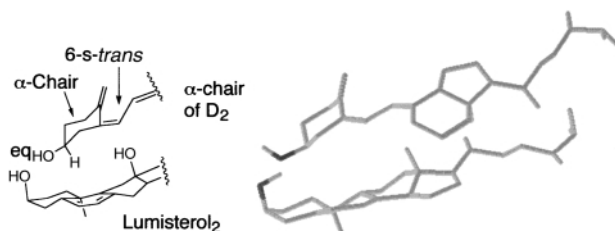


Fig. 3

material from a 1:1 mixture of previtamin D₂ (**2a**) and vitamin D₂, lumisterol₃ (**4b**) and vitamin D₃ (**1b**), or previtamin D₃ (**2b**) and vitamin D₃ failed. Lumisterol₂ and previtamin D₂ were prepared by photochemical irradiation of **3a** (Hanovia 450 W medium pressure mercury lamp, pyrex vessel, EtOH) followed by HPLC purification (20% EtOAc–hexanes, silica column). Previtamin D₂ could also be prepared by thermal equilibration with vitamin D₂ followed by HPLC separation.¹¹ Lumisterol₃ and previtamin D₃ were prepared in a similar way from 7-dehydrocholesterol or from vitamin D₃ as appropriate. The X-ray structures of pure lumisterol₂ and lumisterol₃ have been previously reported¹² as have vitamin D₂ and D₃.^{7–9} Thus, the vitamin D₁ result reported herein represents a unique combination of these earlier crystallographic results.

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Notes and references

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§ *Crystal data*: C₅₆H₈₈O₂, *M* = 793.26, monoclinic, *a* = 20.1072(13), *b* = 7.2481(5), *c* = 35.858(3) Å, β = 94.091(2)°, *V* = 5212.6(6), *T* = 213(2) K, space group *C*2, *Z* = 4, μ(Mo–Kα) = 0.059 mm^{−1}, 16502 reflections measured, 9692 unique (*R*_{int} = 0.0262) which were in all calculations. The final *R* indices [*I* > 2σ(*I*)] were *R*1 = 0.0497, *wR*2 = 0.1147; *R* indices (all data) were *R*1 = 0.0725, *wR*2 = 0.1249. There was one lumisterol₂ and one vitamin D₂ molecule present in the asymmetry unit. The side chain attached to C_{23'} of vitamin D₂ and C₂₃ of lumisterol₂ were refined as individual disordered-side chains (the site occupancy ratio for disordered-side chains was 56:44% and 52:48% for vitamin D₂ and lumisterol₂, respectively). The DELU, SIMU, and DFIX restraints (SHELXTL software) were used to

model the disorder, where the C–C and C=C–C single bond distances were restrained to 1.53 and 1.51 Å, respectively. Full details have been deposited at the Cambridge Crystallographic Data Centre, Cambridge, UK CB2 1EZ (CCDC 182/1825).

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