Vitamin D_1

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The X-ray crystallographic structure of vitamin D_1 reveals a sandwich-like 1 : 1 heterodimeric complex of lumisterol$_2$ and vitamin D_2 with the latter in its α-chair conformer.

Vitamin D_1, the very first anti-rachitic factor, which played a historical role in the development of the vitamin D field, was discovered by Windaus[1] with contributions from Askew and co-workers[2] and Reerink and Van Wijk[3] in 1931. This sharp melting, biologically active substance, produced photochemically from ergosterol (provitamin D_2, **3a**), was soon thereafter discovered to be a 1 : 1 crystalline heterodimer of lumisterol$_2$ (**4a**) and vitamin D_2 (**1a**).[1] This was all at a time when the involvement of previtamin D_2 (**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 D_2 were reported by Bernal in 1932[5] 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 D_2 was essentially the same as that in the very interesting finding in 1976[8] by Hull *et al.* that the crystalline orthorhombic form of pure **1a** (a feature also characteristic of **1b**, vitamin D_3[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 D_2 exists as a dynamically equilibrating mixture of the same α- and β-chairs and that this ratio is solvent dependent.[10]

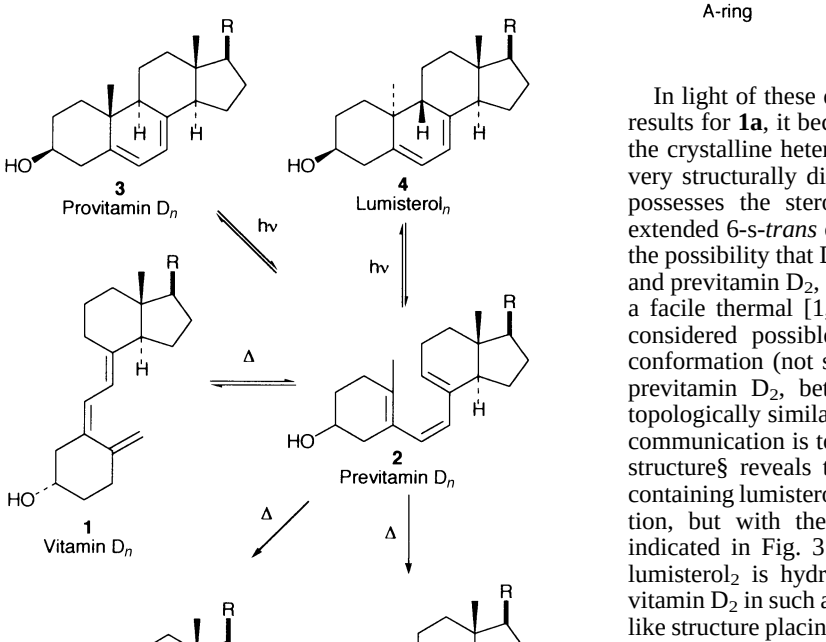

Fig. 1

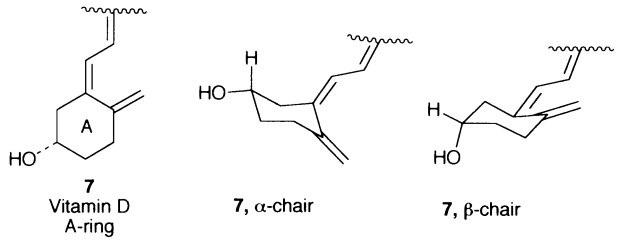

Fig. 2

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 D_1, 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 D_1 might in fact be a complex of lumisterol$_2$ and previtamin D_2, a substance related to vitamin D_2 by way of a facile thermal [1,7]-sigmatropic shift. Alternatively, it was considered possible that the D_2 might exist in its 6-s-*cis* conformation (not shown), thus rendering it, like the putative previtamin D_2, better able to co-crystallize with the more topologically similar lumisterol$_2$ molecule. The purpose of this communication is to report that in fact the single crystal X-ray structure§ reveals that vitamin D_1 is simply a 1 : 1 complex containing lumisterol$_2$ and vitamin D_2 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 lumisterol$_2$ is hydrogen bonded to the equatorial 3β-OH of vitamin D_2 in such a manner as to form a face to face sandwich-like structure placing the two C_{18} angular methyl group carbons in close proximity with one another.

Samples of vitamin D_1 were prepared by collecting crystals (mp, 119–121 °C; literature[2] mp 124–125 °C) from a slowly evaporating solution containing a 1 : 1 mixture of lumisterol$_2$ and vitamin D_2 (acetone). Similar attempts to obtain crystalline

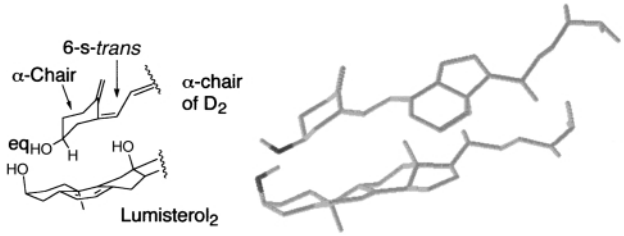

Fig. 3

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material from a 1 : 1 mixture of previtamin D_2 (**2a**) and vitamin D_2, lumisterol$_3$ (**4b**) and vitamin D_3 (**1b**), or previtamin D_3 (**2b**) and vitamin D_3 failed. Lumisterol$_2$ and previtamin D_2 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 D_2 could also prepared by thermal equilibration with vitamin D_2 followed by HPLC separation.[11] Lumisterol$_3$ and previtamin D_3 were prepared in a similar way from 7-dehydrocholesterol or from vitamin D_3 as appropriate. The X-ray structures of pure lumisterol$_2$ and lumisterol$_3$ have been previously reported[12] as have vitamin D_2 and D_3.[7–9] Thus, the vitamin D_1 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*: $C_{56}H_{88}O_2$, 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 $C2$, 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 [$I > 2\sigma(I)$] were $R1$ = 0.0497, $wR2$ = 0.1147; R indices (all data) were $R1$ = 0.0725, $wR2$ = 0.1249. There was one lumisterol$_2$ and one vitamin D_2 molecule present in the asymmetry unit. The side chain attached to $C_{23'}$ of vitamin D_2 and C_{23} of lumisterol$_2$ were refined as individual disordered-side chains (the site occupancy ratio for disordered-side chains was 56 : 44% and 52 : 48% for vitamin D_2 and lumisterol$_2$, respectively). The DELU, SIMU, and DFIX restrains (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).

1 A. Windaus, A. Luttringhaus and M. Deppe, *Liebigs Ann. Chem.*, 1931, **489**, 252. See also: A. Windaus, *Proc. R. Soc. London, Ser. B*, 1931, **108**, 568; A. Windaus, O. Linsert, A. Luttringhaus and G. Weidlich, *Liebigs Ann. Chem.*, 1932, **492**, 226.
2 F. A. Askew, H. M. Bruce, R. K. Callow, J. St. L. Philpot and T. A. Webster, *Nature*, 1931, **128**, 758. See also: T. C. Angus, F. A. Askew, R. B. Bourdillon, H. M. Bruce, R. K. Callow, C. F. Fischmann, J. St. L. Philpot and T. A. Webster, *Proc. R. Soc. London, Ser. B*, 1931, **108**, 340; F. A. Askew, R. B. Bourdillon, H. M. Bruce, R. K. Callow, J. St. L. Philpot and T. A. Webster, *Proc. Royal Soc. B*, 1932, **109**, 488.
3 E. H. Reerink and A. Van Wijk, *Biochem. J.*, 1931, **25**, 1001.
4 P. Karlson, *Trends Biochem. Sci.*, 1981, 29.
5 J. D. Bernal, *Nature*, 1932, **129**, 277.
6 J. D. Bernal and D. Crowfoot, *Chem. Ind.*, 1935, **54**, 701.
7 I. Leban, R. A. G. De Graaf, R. De Gelder, J. Turkenburg, K. S. Wilson and Z. Dauter, *The Collected Works of Dorothy Crowfoot Hodgkin: Volume-III, General Crystallography and Essays*, eds. G. G. Dodson, J. P. Glusker, S. Ramaseshan and K. Venkateran, Interline Pub., Bangalore, India, 1994, pp. 43–51.
8 S. E. Hull, I. Leban, P. Main, P. S. White and M. M. Woolfson, *Acta Cryst. B*, 1976, **32**, 2374.
9 Trinh-Toan, H. F. DeLuca and L. F. Dahl, *J. Org. Chem.*, 1976, **41**, 3476.
10 R. M. Wing, W. H. Okamura, M. R. Pirio, S. M. Sine and A. W. Norman, *Science*, 1974, **186**, 939; R. M. Wing, W. H. Okamura, A. Rego, M. R. Pirio and A. W. Norman, *J. Am. Chem.Soc.*, 1975, **97**, 4980; G. N. LaMar and D. L. Budd, *J. Am. Chem. Soc.*, 1974, **96**, 7317; B. Helmer, H. K. Schnoes and H. F. DeLuca, *Arch. Biochem. Biophys.*, 1985, **241**, 608; W. H. Okamura and G.-D. Zhu, *Vitamin D*, eds. D. Feldman, F. H. Glorieux and J. W. Pike, Academic Press, San Diego, 1997, pp. 939–971.
11 W. H. Okamura, H. Y. Elnagar, M. Ruther and S. Dobreff, *J. Org. Chem.*, 1993, **58**, 600.
12 D. C. Hodgkin and P. Sayre, *J. Chem. Soc.*, 1952, 4561; A. J. De Kok and C. Romers, *Acta Cryst. B*, 1974, **30**, 1695.