Dimer and Superstructure of the Active Form of a Vitamin D_3; 1α,24(*R*)Dihydroxy-vitamin D_3 Monohydrate, $C_{27}O_3H_{44}\cdot H_2O$

Kazuo KOYANO,*[a,1)] Yohichi SAITOH,[b] Jyunnichi OSHIDA,[b] and Midori TAKIMOTO-KAMIMURA[a]

Biomedical Research Institute, Teijin Ltd.,[a] 4–3–2 Asahigaoka, Hino, Tokyo 191–8512, Japan and Iwakuni Plant of Pharmaceuticals, Teijin, Ltd.,[b] 2–1 Hinodechoh, Iwakuni 740–8511, Japan.

Received October 11, 2000; accepted December 22, 2000

The crystals of 1α,24(*R*)dihydroxy-vitamin D_3 monohydrate, $C_{27}O_3H_{44}\cdot H_2O$ are orthorhombic in the space group $P2_12_12_1$ with cell dimensions a=25.719, b=42.572, c=9.851Å and Z=16. The asymmetric unit consists of two subunits with b/8, and each subunit contains a dimer in which two molecules are hydrogen-bonded through water molecules into non-crystallographical symmetry of C_2. The two-fold axes are the straight lines, x=1/2, z=0.256 and x=1/2, z=0.623. The two dimers are the same in the rigid ring part, but differ in the conformation of the flexible chains. The dimers further make C_2 symmetry between the rigid ring parts to form a superstructure, and the two-fold axis of the straight line, y=1/8, z=0.435 goes through a point that is a little apart from the hypercenter (1/2, 1/8, 1/2). The structure was solved by integrated Patterson and direct methods and refined on F_O^2 under restraints. The final R_1 is 0.228 on F_O for 1623 reflections with $F_O>3\sigma$, resolutions 1.0—3.0 Å, 313 restraints, 490 parameters and average U_{eq}=0.120. Not all the atoms of the chains appeared nor the hydrogen atoms. The missing atoms of the dimer were modeled from another pair molecule by C_2 symmetry and hydrogen atoms were added. The structure of the dimer was optimized by *ab initio* molecular orbital of HF/6-31G*.

Key words superstructure; vitamin D; dimer; crystal structure; active form; *ab initio* molecular orbital

The structure of vitamin D was first analyzed on calciferol by heavy atom method in 1948.[2)] In 1977, 25-hydroxy-vitamin D_3 (25(OH)-VD_3) was solved by direct method precisely.[3)] Until the analysis of calcipotriol mono-hydrate in 1993,[4)] the active form of vitamin D_3 in which the hydroxyl group is replaced at the 1α position by metabolism was not analyzed. Calcipotriol is a 1,24(*R*)$(OH)_2$-type VD_3, and has a rigid chain with a double bond and a terminal three-membered ring. In 1996, 1,25$(OH)_2$-VD_3 was analyzed[5)] as a trihydrate, of which two water molecules are disordered. The conformation of the A ring of both calcipotriol and 1,25$(OH)_2$-VD_3 is β-form, that is, 3-OH is axial.

1α,24(*R*)Dihydroxy-vitamin D_3 (1,24(OH)2-VD_3; Fig. 1) has a linear chain like 25(OH)-VD_3 and 1,25$(OH)_2$-VD_3. It has the same activity as 1,25(OH)-VD_3, and is especially applied to treat skin disease like psoriasis. It takes the crystal form of a superstructure, that is, its asymmetric unit consists of two subunits which are slightly different. The superstructure is difficult to solve, and only a few reports have been published on the subjects. In a centro-symmetrical crystal, it was solved using only reflections for the layers with subunits ("pseudo cell" in author's words) by direct method, but the accuracy is not good.[6)] In this case of an optically active molecule and a non centro-symmetrical crystal, reflections other than the layers of the subunits are not weak, nor absent. No direct method strategies were effective,[7,8)] though they only suggested the existence of pseudo translation and pointed out the incompatibility of symmetry. Another method of integrated Patterson and direct methods[9,10)] has been attempted here.

Experimental

Crystals of pharmaceutical from a methanol–water solution are too small for data collection; they were recrystallized from a dioxane–water (1 : 1) solution. Prismatic clear crystals 0.10×0.10×0.20 mm in size were obtained by slow evaporation. Crystal data from the different solutions are the same. Crystal data: $C_{27}O_3H_{44}\cdot H_2O$, M.W.=434.3, orthorhombic, a=25.719, b=42.572, c=9.851 Å, Z=16, V=10786.0 Å^3, D_c=1.070 g/cm^3, space group $P2_12_12_1$. The asymmetric unit contains 4 molecules. Data were collected by Rigaku automated four-circle diffractometer RASA-5R, with ω–2θ scan mode, Cu$K\alpha$ radiation and diffraction angle 2<2θ<105°. Intensities decrease rapidly at higher diffraction angle. As the crystal is degradative, it was changed at every 5% decrease of monitoring 3 reflections. Three crystals were used, and three data sets were processed by TEXAN.[11)] Of the 6659 independent reflections, 4506$F_O^2>0$ were observed. For $(0, k, 0)$ reflections, features other than systematic absence are, k=4n strong, k=2n−1 absent, k=4n−2 weak, indicative of a superstructure.

Structure Determination and Refinement. Preparation As the search fragment model, the more rigid ring part of the A ring to the condensed C,D ring through a conjugated diene was selected from 25(OH)-VD_3. The 1α oxygen atom was added and minimized by MM+force field.[12)] Super-sharpened Patterson function with coefficient $(E^3*F)^{1/2}$ and the largest 200 E-values were calculated by SHELXS-86.[13)]

Rotation Search[10)] Vectors shorter than 8Å were used. Of the 25000 random orientations tested, the one conspicuously highest value of rotational figure of merit 0.714 was obtained. A translation search which followed gave the solution of the largest overall combined figure of merit 1.470. Another fragment of which the conformation of the A ring is β-form, was also tested to give a much lower rotational figure of merit.

Partial Structure Expansion[13)] Fixing phases of 200 reflections, the fragment structure was expanded. Four molecules appeared in turn, but not all the atoms of the chains except those of the fragment molecule. Molecules were numbered as they appeared from molecule 1 to molecule 4.

Refinement The structure was refined on F_O^2 using SHELXL-93.[14)] As the number of reflections against atoms of the four molecules is small, refinement was done under restraints of the bond lengths and angles that conform to those of 25(OH)-VD_3. Both the bond lengths and angles were re-

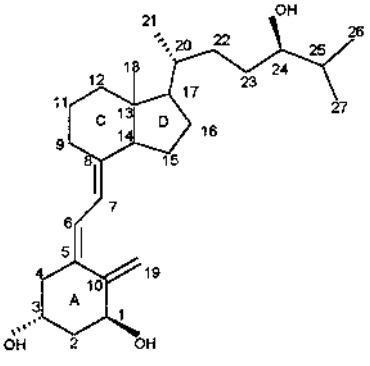


Fig. 1. Structural Formula of 1α,24(*R*)Dihydroxy-vitamin D_3

* To whom correspondence should be addressed. e-mail: kkoyano@cbi.or.jp

Table 1. Fractional Atomic Coordinates of Four Molecules

Atom	Dimer I						Dimer II					
	Molecule 1			Molecule 4			Molecule 2			Molecule 3		
	x_1	y_1	z_1	x_4	y_4	z_4	x_2	y_2	z_2	x_3	y_3	z_3
C1	0.4181	0.0808	0.1333	0.5818	0.0804	0.3792	0.4153	0.1654	0.7302	0.5843	0.1683	0.4896
C2	0.4560	0.0832	0.0136	0.5436	0.0839	0.4971	0.4531	0.1619	0.8464	0.5527	0.1654	0.3600
C3	0.4880	0.0547	−0.0097	0.5071	0.0552	0.5015	0.4906	0.1894	0.8579	0.5210	0.1945	0.3286
C4	0.4570	0.0249	−0.0030	0.5416	0.0265	0.5286	0.4615	0.2199	0.8661	0.5537	0.2237	0.3351
C5	0.4246	0.0223	0.1246	0.5794	0.0217	0.4116	0.4246	0.2240	0.7461	0.5836	0.2264	0.4670
C6	0.4131	−0.0064	0.1761	0.5726	−0.0019	0.3223	0.4249	0.2508	0.6760	0.5778	0.2505	0.5520
C7	0.3949	−0.0101	0.3185	0.6033	−0.0084	0.2026	0.3925	0.2579	0.5587	0.6098	0.2578	0.6697
C8	0.3847	−0.0393	0.3721	0.6021	−0.0351	0.1291	0.3848	0.2866	0.5033	0.6118	0.2857	0.7358
C9	0.4170	−0.0675	0.3428	0.5750	−0.0647	0.1668	0.4216	0.3137	0.5215	0.5802	0.3140	0.6963
C10	0.3907	0.0500	0.1466	0.6100	0.0503	0.3761	0.3894	0.1971	0.7241	0.6146	0.1979	0.4997
C11	0.4461	−0.0794	0.4673	0.5466	−0.0787	0.0451	0.4564	0.3166	0.3947	0.5401	0.3214	0.8079
C12	0.4102	−0.0830	0.5913	0.5815	−0.0826	−0.0793	0.4196	0.3229	0.2707	0.5688	0.3277	0.9420
C13	0.3858	−0.0506	0.6243	0.6093	−0.0522	−0.1163	0.3860	0.2941	0.2490	0.6016	0.3005	0.9834
C14	0.3535	−0.0423	0.4993	0.6381	−0.0408	0.0098	0.3514	0.2907	0.3796	0.6382	0.2904	0.8699
C15	0.3165	−0.0160	0.5459	0.6787	−0.0182	−0.0329	0.3131	0.2651	0.3375	0.6706	0.2645	0.9366
C16	0.3014	−0.0276	0.6891	0.6862	−0.0237	−0.1873	0.3056	0.2695	0.1836	0.6751	0.2743	1.0863
C17	0.3445	−0.0496	0.7381	0.6549	−0.0538	−0.2215	0.3397	0.2980	0.1414	0.6412	0.3044	1.1058
C18	0.4202	−0.0230	0.6749	0.5573	−0.0369	−0.1387	0.4228	0.2658	0.2438	0.5599	0.2760	1.0120
C19	0.3415	0.0484	0.1882	0.6615	0.0488	0.3544	0.3392	0.1987	0.6961	0.6626	0.1989	0.5490
C20	0.3611	−0.0433	0.8858	0.6391	−0.0542	−0.3748	0.3560	0.2961	−0.0095	0.6189	0.3061	1.2501
C21	0.3959	−0.0701	0.9348	0.6125	−0.0864	−0.4007	0.3904	0.3250	−0.0424	0.5880	0.3371	1.2650
C22	0.3154	−0.0460	0.9843	0.6884	−0.0551	−0.4609	0.3070	0.2958	−0.0987	0.6593	0.3043	1.3596
C23	0.2809	−0.0753	0.9705	0.7287	−0.0800	−0.4221	0.2829	0.3271	−0.1365	0.6456	0.3157	1.5038
C24	0.2334	−0.0731	1.0614				0.2256	0.3232	−0.1769	0.6913	0.3103	1.5997
C25	0.2429	−0.0715	1.2150				0.1958	0.3534	−0.2097	0.7350	0.3341	1.6066
C26	0.1915	−0.0663	1.2902							0.7747	0.3282	1.4916
C27	0.2689	−0.1018	1.2638							0.7636	0.3332	1.7424
O1	0.4500	0.0854	0.2567	0.5540	0.0865	0.2550	0.4403	0.1593	0.6029	0.5509	0.1641	0.6048
O2	0.1991	−0.0987	1.0339							0.7190	0.2826	1.5539
O3	0.5174	0.0553	−0.1329	0.4710	0.0597	0.6108	0.5221	0.1856	0.9770	0.4953	0.1919	0.2003
Ow	0.4093	0.1024	0.5157	0.6077	0.0856	−0.0031	0.4060	0.1554	0.3330	0.6050	0.1610	0.8788

Atoms of blank columns did not appear. Four molecules are divided into two dimers I and II, which are each paired by two molecules.

strained by fixing distance between the two atoms. Anti-bumping restraint was imposed on the water molecules that appeared. Refinement was dependent on resolution. The final R factor on F_O is 0.228 for 1623 reflections with $F_O > 3\sigma$, resolutions 1.0—3.0 Å, 313 restraints, 490 parameters and average $U_{eq}=0.120$. The atomic fractional coordinates of four molecules and crystal structures viewed from three orthogonal directions of the lattice planes are shown in Table 1 and Figs. 2a—d. Of the 124 heavy atoms, 8 atoms of the chains of two molecules were not found nor hydrogen atoms. As it is stated later in detail, the four molecules are grouped into two dimers in which two molecules are hydrogen-bonded through water molecules into non-crystallographical C_2 symmetry.

Optimization by *ab Initio* Molecular Orbital The missing atoms of the dimer were modeled from another pair molecule by C_2 symmetry and hydrogen atoms were added. The structure of the dimer was optimized by *ab initio* molecular orbital of HF/6-31G* under constraints of C_2 symmetry and the distance between 1α oxygen atoms to 2.7639 Å of this X-ray analysis so as to retain the relative disposition of two molecules. As the twofold axis is parallel to the b axis, the input was mixed coordinates of cartesian and internal, A rings near the axis were cartesian and the other part internal. There are 557 symmetry adopted basis functions. For the calculation Gaussian 98[15] was used. The optimized structure was fitted on the original in the asymmetric unit at the backbone C4–C5–C6–C7–C8–C14–C17 so as to minimize root mean square distances of the atom pairs, and the coordinates were reduced to crystal fractional coordinates. The atomic fractional coordinates and the optimized structure of the dimer are shown in Table 2 and Fig. 3.

Results and Discussion

As shown in Figs. 2a—d, the four molecules in the asymmetric unit are paired to two dimers which reside in two subunits with $b/8$. In each dimer two molecules are hydrogen-bonded through water molecules into non-crystallographical C_2 symmetry. The disposition of the dimers is further C_2 symmetry between the rigid ring parts to form a superstructure. The dimer which consists of molecule 1 and 4, and resides in the lower subunit of the asymmetric unit is designated as dimer I; that of 2 and 3 and resides in the upper subunit, is dimer II.

Hydrogen Bonds During refinement one water molecule per 1,24$(OH)_2$-VD_3 molecule, four water molecules in all appeared. It is equivalent to crystal water content of 4.147%, and the value of 4.2% by elemental analysis is near that. The water molecules mediate the head-to-head hydrogen bonding between 1OH– and 3OH– of the A rings of the two molecules to form non-crystallographical C_2 symmetry as further described below. As hydrogen atoms were not obtained, the mode of the hydrogen bonds was scrutinized in the optimized structure by *ab initio* molecular orbital of HF/6-31G* in Fig. 3 and Tables 3a—c. The 3OH– group donates a proton to the water molecule and the water molecule to the 1OH– group of the other molecule. The energy of hydrogen bond formation was obtained by calculating that of the monomer molecule and water separately.

	$2(C_{27}H_{44}O_3)$	+	$2H_2O$	→	$2(C_{27}H_{46}O_4)$
energy E (hartree)	$2(-1272.5844738)$		$2(-76.0107465)$		-2697.2241471

$$\Delta E_e^0 = -0.0337065 = -21.151149 \text{ kcal/mol}$$

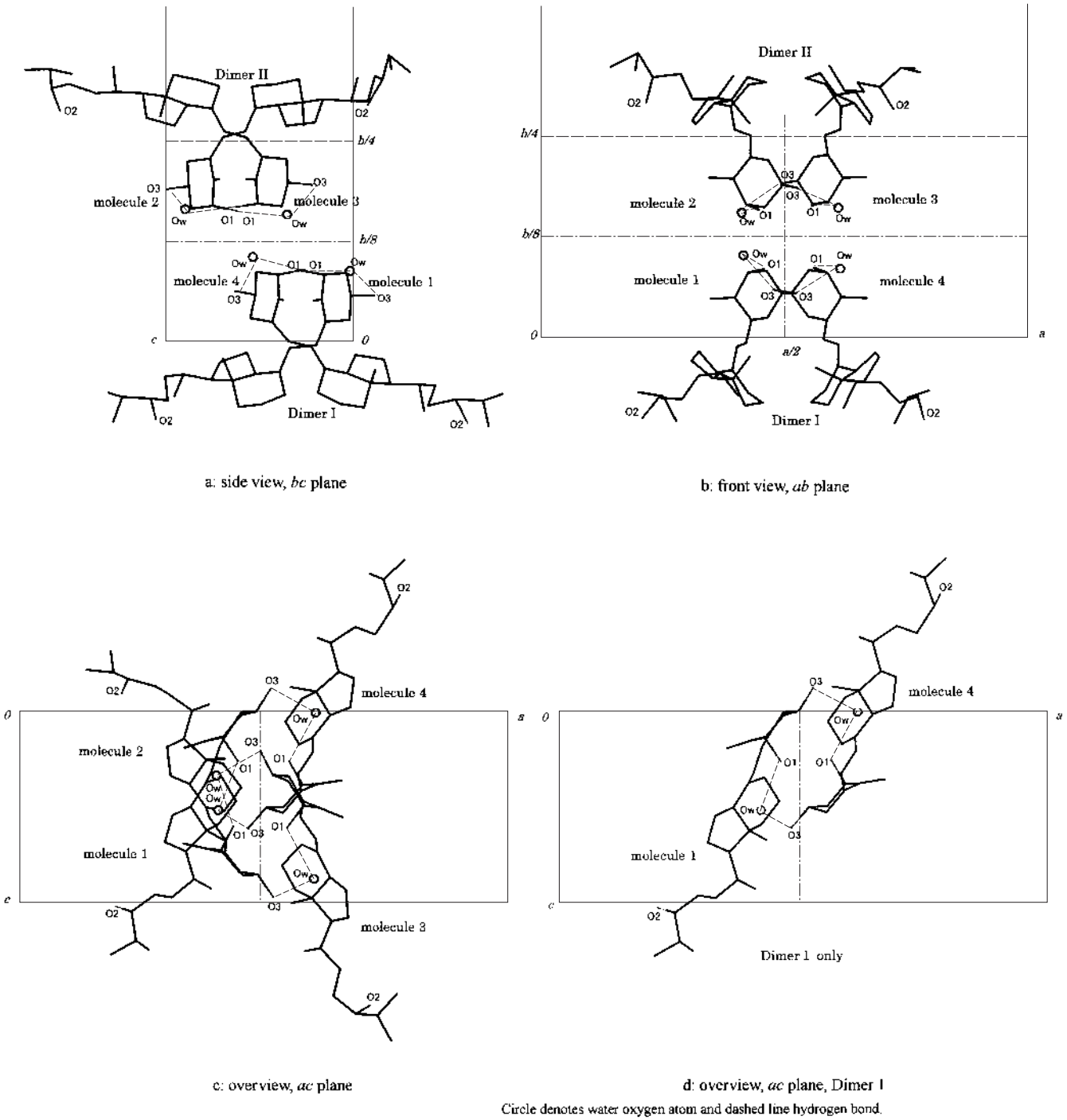


Fig. 2. Crystal Structure of 1α,24(*R*)Dihydroxy-vitamin D_3 Monohydrate; Viewed from Three Orthogonal Planes of Asymmetric Unit

The energy is 5.288 kcal/mol per hydrogen bond. The hydrogen bond in 25(OH)-VD_3[3] is head-to-tail type between the A ring and the chain terminal. There is a direct head-to-head type hydrogen bond between the 1OH– and 3OH– of the A rings in calcipotriol[4] and 1,25$(OH)_2$-VD_3.[5] In any case, no symmetrical dimer forms.

Symmetry of Dimers The two-fold axes of dimers are parallel to the *b* axis. Referring to Table 1, for molecule 1 and 4 of dimer I, $(x_1+x_4)/2 \fallingdotseq 0.500$, $y_1-y_4 \fallingdotseq 0.00$, $(z_1+z_4)/2 \fallingdotseq 0.256$, and for molecule 2 and 3 of dimer II, $(x_2+x_3)/2 \fallingdotseq 0.500$, $y_2-y_3 \fallingdotseq 0.00$, $(z_1+z_4)/2 \fallingdotseq 0.623$. The corresponding average values for all pairs of atoms are 0.4986, 0.0020, 0.2559 and 0.4938, −0.0021, 0.6225. Then the two-fold axis of dimer I is $x=1/2$, $z=0.256$ and that of dimer II is $x=1/2$, $z=0.623$.

Bond Lengths, Angles and Torsion Angles For molecule 1 of the four molecules , structural data are shown in Tables 3a—c with those of 25(OH)-VD_3[3] and optimized structure by HF/6-31G*. The data of molecule 1 deviate from those of 25(OH)-VD_3, though the restraints of refinement conformed to the latter. The angle at the double bond C5–C6–C7, for example, is 121.1° close to 120.0° of the force

Table 2. Fractional Atomic Coordinates of Molecule 1 in Dimer I

Atom	x_1	y_1	z_1	H-atom	x_1	y_1	z_1
C1	0.41992	0.08010	0.14186	H1	0.39287	0.09975	0.14144
C2	0.45654	0.08325	0.02060	HO1	0.42966	0.07771	0.33729
C3	0.49091	0.05438	0.00492	H21	0.48052	0.10389	0.03491
C4	0.45802	0.02462	−0.00975	H22	0.43396	0.08634	−0.07173
C5	0.42140	0.02110	0.10981	H3	0.51575	0.05235	0.09304
C6	0.42073	−0.00479	0.18553	HO3	0.54343	0.04131	−0.12665
C7	0.39040	−0.00971	0.31006	H191	0.31576	0.07056	0.15282
C8	0.38438	−0.03662	0.37703	H192	0.31593	0.02786	0.13007
C9	0.40532	−0.06837	0.33387	H41	0.48300	0.00412	−0.01817
C10	0.38912	0.04968	0.13316	H42	0.43593	0.02642	−0.10371
C11	0.43540	−0.08479	0.44858	H6	0.44614	−0.02356	0.15474
C12	0.40547	−0.08570	0.58355	H7	0.37222	0.01096	0.35044
C13	0.38605	−0.05298	0.62691	H91	0.42964	−0.06683	0.24448
C14	0.35370	−0.03938	0.50725	H92	0.37228	−0.08305	0.30591
C15	0.32569	−0.01100	0.56767	H111	0.47249	−0.07304	0.46290
C16	0.31444	−0.02111	0.71557	H112	0.44454	−0.10867	0.41763
C17	0.34407	−0.05245	0.74120	H121	0.43018	−0.09618	0.66023
C18	0.43229	−0.03153	0.66260	H122	0.37207	−0.10119	0.57236
C19	0.33777	0.04929	0.13905	H141	0.32382	−0.05703	0.48747
C20	0.36105	−0.05612	0.89088	H151	0.29050	−0.00540	0.51201
C21	0.39048	−0.08676	0.92028	H152	0.34985	0.00981	0.56574
C22	0.31510	−0.05247	0.99106	H161	0.27310	−0.02407	0.73322
C23	0.27280	−0.07776	0.98276	H162	0.32741	−0.00309	0.78578
C24	0.22523	−0.07130	1.07146	H181	0.45641	−0.02714	0.57441
C25	0.23567	−0.06857	1.22497	H182	0.45665	−0.04218	0.73988
C26	0.18546	−0.06071	1.30196	H183	0.41963	−0.00890	0.70081
C27	0.26118	−0.09796	1.28501	H17	0.31772	−0.07168	0.71792
O1	0.45076	0.08088	0.25888	H20	0.38731	−0.03683	0.91419
O2	0.18989	−0.09579	1.04254	H211	0.42888	−0.08678	0.87530
O3	0.52218	0.05921	−0.11235	H212	0.36989	−0.10719	0.88216
Ow	0.40945	0.06907	0.53233	H213	0.39561	−0.08987	1.02893
				H221	0.29733	−0.02955	0.97721
				H222	0.33154	−0.05224	1.09270
				H231	0.28835	−0.10066	1.00874
				H232	0.25835	−0.07973	0.87971
				H24	0.20838	−0.04906	1.03846
				HO2	0.15652	−0.09055	1.07602
				H25	0.26192	−0.04881	1.23896
				H261	0.15836	−0.08029	1.30099
				H262	0.16599	−0.04036	1.25880
				H263	0.19372	−0.05544	1.40757
				H271	0.29961	−0.10204	1.24328
				H272	0.23774	−0.11863	1.26507
				H273	0.26543	−0.09560	1.39423
				Hw1	0.40134	0.08629	0.58946
				Hw2	0.44255	0.06149	0.56215

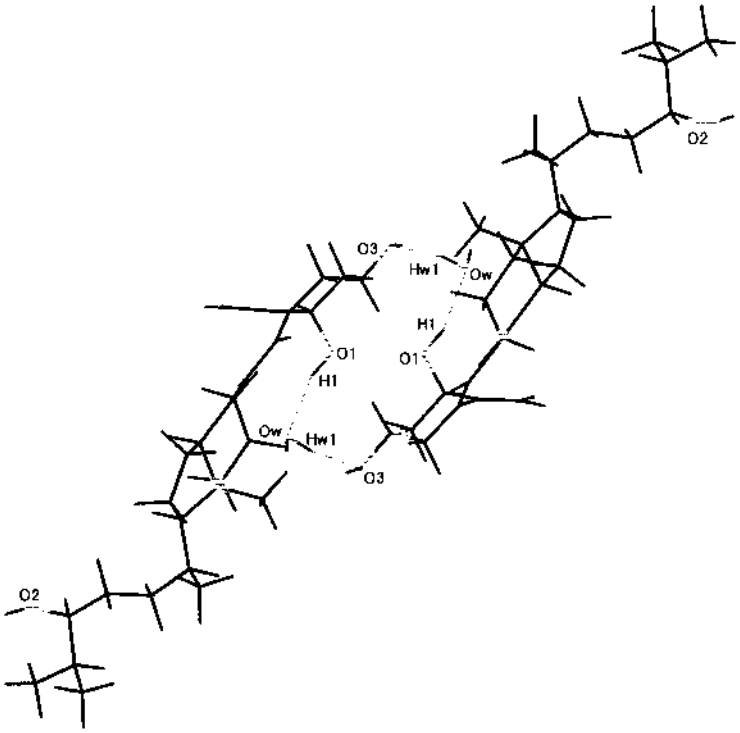
Optimized by *ab initio* molecular orbital of HF/6-31G*.

field parameter, but smaller than 126.8° of 25(OH)-VD_3 and 126.40° of the optimized structure. The data of 25(OH)-VD_3 are close to those of the optimized structure.

Triene Conjugated System Bond lengths of single bonds C10–C5 and C6–C7 in the triene conjugated system C19–C10–C5–C6–C7–C8 are 1.460—1.491 Å, a little longer than 1.460 Å of bond order 1.5. The planeness of the diene connecting the A ring to the C, D condensed ring of molecule 1, 3 and the optimized structure are curved a little, estimated from torsion angles in Table 3c, ϕ(7–6–5–10), ϕ(8–7–6–5), ϕ(6–7–8–9), and (4–5–6–7) which are to be 0 or $\pm$180.0° if planar. The diene of 25(OH)-VD_3 is almost planar.

Conformation of A Ring The conformation of the A ring is α-form as 25(OH)-VD_3. This was tested at the first stage of the rotation search. Those of calcipotriol and 1,25$(OH)_2$-VD_3 are β-form, the inverted conformation of α-form. In solution, equimolar of α-form and β-form of 1,25$(OH)_2$-VD_3 exists from NMR measurement.[16] It was shown that the difference in energy of α-form and β-form is small by molecular mechanics calculation.[17]

Conformation of Chain The two dimers have the same rigid part from the A ring *via* diene to the condensed C, D ring, but differ in the chain conformation. The chain conformations of the dimers are not extended all-*trans* type as in 25(OH)-VD_3, but take mixed *trans*, *gauche*+ and *gauche*− warped conformations. The conformation of a chain C22–C23–C24–C25 beginning from the string 13–17–20 in the D ring is, from torsion angles in Table 3c approximately 22(t)–23(g+)–24(t)–25(g−) for dimer I, and 22(t)–23(t)–24(t)–25(g+) for dimer II. In 1,25$(OH)_2$-VD_3 there are several conformers around the all-*trans* type having the lowest energies comparable to that of all-*trans* type.[17] The energy by MM+ force field in this 1,24$(OH)_2$-VD_3 are as follows;



Gray stick denotes oxygen atom and dashed line hydrogen bond.

Fig. 3. Structure of 1α,24(*R*)Dihydroxy-vitamin D_3 Monohydrate Dimer I, Optimized by *ab Initio* Molecular Orbital of HF/6-31G*

molecule 1, in dimer I	22(t)–23(g+)–24(t)–25(g−)	44.4023 kcal/mol
molecule 3, in dimer II	22(t)–23(t)–24(t)–25(g+)	46.6458
extended all *trans*	22(t)–23(t)–24(t)–25(t)	44.0799

The energy difference between molecule 1 and 3 is not so large.

The Disposition of Dimers For $(0, k, 0)$ reflections, conspicuous features other than systematic absence are, $k=4n$, strong, $k=2n-1$, absent, $k=4n-2$, weak. At the centro-symmetrical crystal, in which the asymmetric unit contains 2 subunits that are related by centro-symmetry, it was shown that structure factor F_h is written[18)]

$$F_h=4\sum_{j=1}^{N/4} f_j[\cos(2\pi\mathbf{h}\cdot\mathbf{r}_j')\cos(2\pi\mathbf{h}\cdot\mathbf{d})]$$

where **h** is reciprocal lattice vector, **d** is the positional vector of the hypercenter, that is the center of the asymmetric unit (taking the inversion center of the space group as origin), and $\mathbf{r}_j'$ is the position of an atom to the hypercenter. Then, reflections of **h** satisifying $2\mathbf{h}\cdot\mathbf{d}=n$ (n: integer) are strengthened and those of $2\mathbf{h}\cdot\mathbf{d}=(2n+1)/2$ absent. In the case of a subunit with $b/8$, **d** is $(0, 1/8, 0)$ and $\mathbf{h}(h, k, l)$ reflections with $k=4n$ of subunits' layer lines are strengthened, and others are absent. In the case of the non-centro-symmetrical space group $P2_12_12_1$ of 1,24$(OH)_2$-VD_3, summing up the structure factors of 4 equivalent points, it is shown for $\mathbf{h}(0, k, 0)$ reflections;

$$F_h=8\sum_{j=1}^{N/8} f_j\cos(2\pi ky')\cos(2\pi kd)$$

where (x', y', z') is the coordinates of an atom to the hypercenter, and d is the position of the hyper center. Intensities of $(0, k, 0)$ reflections satisfying $2kd=n$ (n: integer) are strengthened and those of $2kd=(2n+1)/2$ absent. For a subunit with $b/8$, d is 1/8, and if $k=4n$, intensities of $(0, k, 0)$ reflections are also conspicuously strong and others absent. It holds only if y' is centro-symmetrical as below $y_1'=-y_2'$ and $y_3'=-y_4'$. In Fig. 2a and Table 1, taking the correspondence of the rigid parts of molecules 1, 2 and 3, 4, then $y_1'=-y_2'$ ($(y_1+y_2)/2\fallingdotseq 1/8$), $x_1'=x_2'$ ($x_1-x_2\fallingdotseq 0$), $z_1'=-z_2'+0.870$ [$(z_1+z_2)/2=0.435$], $y_3'=-y_4'$ and so on. In Fig. 2b taking the correspondence of molecules 1, 3 and 2, 4, then $y_1'=-y_3'$ and $y_2'=-y_4'$ and so on.

Symmetry between Dimers Dimer I and dimer II which reside in each subunit with $b/8$, form further C_2 symmetry as to the rigid part from the A ring *via* diene to the C, D condensed ring. Referring to Fig. 2a and Table 1, $x_1=x_2$, $x_3=x_4$, $(y_1+y_2)2\fallingdotseq 1/8$, $(y_3+y_4)/2\fallingdotseq 1/8$, and average $[(z_1+z_2)/2]=0.435$, average $[(z_3+z_4)/2]=0.435$, so the two-fold axis is $y=1/8$, $z=0.435$ parallel to the a axis. The axis goes through a point that is a little apart from the hypercenter (1/2, 1/8, 1/2), that is, the center of the asymmetric unit. The two dimers of C_2 symmetry, which have the same rigid part in common but differ in conformation of the chain of which the energy difference is small, make further C_2 symmetry to form a superstructure.

Receptors of a steroid hormone like the vitamin D_3 receptor[19)] exist as a dimer in the physiological state. It has been shown a ligand of pharmaceutical vitamin D_3 also exists as a dimer. Its stability in hydrophilic and lipophilic environment and its mode of action are subjects for further research.

Table 3. Bond Lengths, Angles and Torsion Angles

a) Bond lengths (Å)

	25(OH)VD_3	Molecule 1	*ab Initio* MO		25(OH)VD_3	Molecule 1	*ab Initio* MO
C1–O1		1.479	1.3997	C13–C17	1.570	1.545	1.5601
C24–O2		1.430	1.4000	C13–C18	1.527	1.552	1.5401
C25–O2	1.451			C14–C15	1.523	1.539	1.5274
C3–O3	1.444	1.431	1.4226	C15–C16	1.537	1.554	1.5465
C1–C2	1.533	1.533	1.5271	C16–C17	1.543	1.529	1.5572
C2–C3	1.512	1.484	1.5220	C17–C20	1.524	1.540	1.5457
C3–C4	1.515	1.500	1.5301	C20–C21	1.529	1.531	1.5357
C4–C5	1.512	1.512	1.5155	C20–C22	1.547	1.529	1.5474
C5–C10	1.486	1.481	1.4907	C22–C23	1.519	1.536	1.5328
C10–C19	1.324	1.333	1.3221	C23–C24	1.535	1.517	1.5284
C5–C6	1.339	1.355	1.3314	C24–C25	1.514	1.534	1.5403
C6–C7	1.444	1.487	1.4687	C25–C26	1.522	1.530	1.5344
C7–C8	1.344	1.379	1.3308	C25–C27	1.533	1.530	1.5317
C8–C9	1.490	1.486	1.5161	O3···O25	2.871		
C9–C11	1.520	1.525	1.5375	O25···Ow	2.910		
C11–C12	1.530	1.539	1.5369	Ow···O3		2.588	2.8919
C12–C13	1.522	1.553	1.5403	Ow···O1		2.852	2.9390
C13–C14	1.543	1.527	1.5547	O1···O1		2.677	2.7639
O1–H1			0.9536	O25–H25	0.90		
O2–H2			0.9462	Ow–Hw1	0.98		
O3–H3	1.06		0.9485	Ow–Hw2	1.10		
O3···H25	2.00			Ow···H3	1.65		
O25···Hw1	2.03			Ow···H1			2.0242
O25···Hw2	1.86			O3···Hw1			1.9456
C1–H11	1.03		1.0880	C18–H181	0.98		1.0852
C1–H12	0.97			C18–H182	0.85		1.0838
C2–H21	1.04		1.0827	C18–H183	0.98		1.0842
C2–H22	0.88		1.0871	C19–H191	0.91		1.0766
C3–H31	1.05		1.0813	C19–H192	1.00		1.0751
C4–H41	0.93		1.0871	C20–H20	1.05		1.0881
C4–H42	0.98		1.0888	C21–H211	1.03		1.0824
C6–H61	1.02		1.0760	C21–H212	0.87		1.0865
C7–H71	0.97		1.0733	C21–H213	0.91		1.0853
C9–H91	1.06		1.0821	C22–H221	1.04		1.0868
C9–H92	0.95		1.0900	C22–H222	0.95		1.0861
C11–H111	0.99		1.0863	C23–H231	1.00		1.0842
C11–H112	0.94		1.0868	C23–H232	1.05		1.0844
C12–H121	1.02		1.0864	C24–H241	0.93		1.0910
C12–H122	1.02		1.0885	C24–H242	0.97		
C14–H141	1.00		1.0922	C25–H25			1.0873
C15–H151	1.02		1.0846	C26–H261	0.84		1.0852
C15–H152	0.96		1.0828	C26–H262	0.94		1.0867
C16–H161	0.99		1.0846	C26–H263	0.95		1.0873
C16–H162	0.88		1.0854	C27–H271	1.00		1.0845
C17–H171	1.01		1.0874	C27–H272	0.99		1.0861
				C27–H273	0.99		1.0844

b) Bond angles (°)

	25(OH)VD_3	Molecule 1	*ab Initio* MO		25(OH)VD_3	Molecule 1	*ab Initio* MO
C2–C1–C10	111.7	115.3	110.61	C8–C14–C13	112.1	113.8	113.16
C2–C1–O1		105.7	107.02	C8–C14–C15	121.5	121.4	121.04
C10–C1–O1		107.7	111.21	C13–C14–C15	104.2	105.3	104.57
C1–C2–C3	111.9	114.6	111.51	C14–C15–C16	103.8	101.3	103.62
C2–C3–C4	110.9	113.0	110.93	C15–C16–C17	107.9	107.6	107.43
C2–C3–O3	110.8	114.3	107.09	C13–C17–C16	103.4	106.6	103.54
C4–C3–O3	108.5	109.4	110.83	C13–C17–C20	120.2	120.0	119.43
C3–C4–C5	113.2	113.0	110.61	C16–C17–C20	112.6	113.1	112.31
C4–C5–C6	122.4	119.8	121.70	C17–C20–C21	112.5	109.3	113.90
C4–C5–C10	113.4	112.8	112.67	C17–C20–C22	110.1	111.9	112.49
C6–C5–C10	124.1	122.3	125.61	C21–C20–C22	108.8	101.0	109.97
C5–C6–C7	126.8	121.1	126.37	C20–C22–C23	116.4	116.8	115.63
C6–C7–C8	127.2	121.1	126.77	C22–C23–C24	110.9	111.2	114.28
C7–C8–C9	125.6	123.2	125.96	C23–C24–C25	118.4	117.2	115.81
C7–C8–C14	122.8	120.0	123.28	C23–C24–O2		109.6	105.49

Table 3. (Continued)

b) Bond angles (°)

	25(OH)VD_3	Molecule 1	*ab Initio* MO		25(OH)VD_3	Molecule 1	*ab Initio* MO
C9–C8–C14	111.7	113.3	110.74	C25–C24–O2		108.6	111.47
C8–C9–C11	111.0	112.7	112.21	C24–C25–C26	113.1	110.3	110.80
C1–C10–C5	113.4	114.1	114.44	C24–C25–C27	109.8	110.0	113.09
C1–C10–C19	122.2	121.3	121.92	C24–C25–O25	107.1		
C5–C10–C19	124.3	124.2	123.56	C26–C25–C27	110.4	110.4	110.36
C11–C12–C13	112.1	108.6	112.30	C26–C25–O25	108.3		
C12–C13–C14	107.1	104.9	107.46	C27–C25–O25	108.0		
C12–C13–C17	117.1	117.1	115.95	O3–H3···Ow	171.1		
C12–C13–C18	111.0	120.5	110.45	O25–H25···O3	162.7		
C14–C13–C17	100.2	117.1	99.87	O1–H1···Ow			160.18
C14–C13–C18	111.0	113.3	111.44	Ow–Hw1···O3			169.75
C17–C13–C18	109.9	97.9	111.17				

c) Torsion angles (°)

	25(OH)VD_3	Molecule 1	Molecule 3	*ab Initio* MO
ϕ(6–5–10–19)	−56.7	−16.8	−49.1	−56.91
ϕ(7–6–5–10)	2.6	−44.6	17.9	−3.43
ϕ(8–7–6–5)	−177.0	−178.1	163.2	171.02
ϕ(6–7–8–9)	1.8	39.0	0.1	−3.68
ϕ(4–5–6–7)	178.7	162.5	−170.1	174.30
ϕ(6–7–8–14)	−178.6	−163.6	169.1	178.07
ϕ(13–17–20–22)	−177.1	−175.0	170.2	175.54
ϕ(17–20–22–23)	−163.8	48.1	161.2	65.27
ϕ(20–22–23–24)	−172.4	−172.7	177.4	−173.30
ϕ(22–23–24–25)	−171.4	−62.8	83.7	−60.18
ϕ(23–24–25–27)	−178.0	−63.2	155.1	−57.92
ϕ(23–24–25–26)	58.2	174.8	−83.4	177.59

Acknowledgment The authors are indebted to Dr. Akiko Sekine, Faculty of Science, Tokyo Institute of Technology, for her help, and Japan Science and Technology Corp. for use of a supercomputer to calculate *ab initio* molecular orbital.

References and Notes

1) *Present address: Division of Chem-Bio Informatics, National Institute of Health Sciences*, *1–18–1 Kamiyoga, Setagaya-ku, Tokyo 158–8501, Japan*.
2) Crowfoot D., Dunitz J. P., *Nature* (London), **162**, 608—609 (1948).
3) Trinh-Toan, Ryan R. C., Simon G. L., Calabrese J. C., Dahl L. F., DeLucal H. F., *J. Chem. Soc. Perkin Trans. II*, **1977**, 393—401.
4) Larsen S., Hansen E. T., Hoffmeyer L., Rastrup-Andersen N., *Acta Cryst*., **C49**, 618—621 (1993).
5) Suwinska K., Kutner A., *Acta Cryst*., **B52**, 550—554 (1996).
6) Karle I. L., Karle J., *Acta Cryst*., **16**, 969 (1963).
7) Fan Hai-fu; R-SAPI85 (Rigaku Version of Structure Analysis Programs with Intelligent Control) Inst. of Physics, Academia Sinica, Beijing, China.
8) Giacovazzo C., SIR97 (Semi-Invariants Representation) Inst. of Mineralogy and Petrography, The University, Bari, Italy.
9) Ernst E., Sheldrick G. M., *Acta Cryst.*, **A41**, 262—268 (1985).
10) Ernst E., PATSEE, Institute für Organisch Chemie, Universität Frankfurt, D-60439, Frankfurt, Germany.
11) TEXAN, Molecular Structure Corporation, 3200A Research Forest Drive, The Woodlands, Texas 77381.
12) HyperChem, Release 6.0,2000; Hypercube, Inc., 1115 NW 4th Street, Gainesville, Florida 32601–4256.
13) Sheldrick G. M., SHELXS-86, Institute für Anorganische Chemie, Universität Göttingen, D-3400, Göttingen, Germany.
14) Sheldrick G. M., SHELXL-93, Institute für Anorganische Chemie, Universität Göttingen, D-3400, Göttingen, Germany.
15) Gaussian 98, Revision A.7, Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Zakrzewski V. G., Montgomery J. A., Jr., Stratmann R. E., Burant J. C., Dapprich S., Millam J. M., Daniels A. D., Kudin K. N., Strain M. C., Farkas O., Tomasi J., Barone V., Cossi M., Cammi R., Mennucci B., Pomelli C., Adamo C., Clifford S., Ochterski J., Petersson G. A., Ayala P. Y., Cui Q., Morokuma K., Malick D. K., Rabuck A. D., Raghavachari K., Foresman J. B., Cioslowski J., Ortiz J. V., Baboul A. G., Stefanov B. B., Liu G., Liashenko A., Piskorz P., Komaromi I., Gomperts R., Martin R. L., Fox D. J., Keith T., Al-Laham M. A., Peng C. Y., Nanayakkara A., Gonzalez C., Challacombe M., Gill P. M. W., Johnson B., Chen W., Wong M. W., Andres J. L., Gonzalez C., Head-Gordon M., Replogle E. S., Pople J. A., Gaussian, Inc., Pittsburgh PA, 1998.
16) Wing R. M., Okamura W. H., Rego A., Pirio M. R., Norman A. W., *J. Am. Chem. Soc*., **97**, 4980—4985 (1975).
17) Koyano K., Ishizuka S., Abstracts, 16th Symposium on Chemical Information and Computer Science, Tokushima, Japan, 1993, pp. 45—48.
18) Giacovazzo C., Direct Methods in Crystallography, Academic Press, 1980, p. 36.
19) Rochel N., Eurtz J. M., Mitschler A., Klaholz B., Moras D., *Molecular Cell*, **5**, 173—179 (2000).