Effect of Solvents on the Thermal Isomerization of 1α -Hydroxyprevitamin D_3 Diacetate to 1α -Hydroxyvitamin D_3 Diacetate*

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Summary The thermal conversion of 1α -hydroxyprevitamin D_3 (1α -OH-previtamin D_3) diacetate to 1α -hydroxyvitamin D_3 (1α -OH-vitamin D_3) diacetate was investigated in five solvents. The fraction of 1α -OH-vitamin D_3 diacetate was calculated from the HPLC peak areas (UV detection) of 1α -OH-previtamin D_3 diacetate and 1α -OH-vitamin D_3 diacetate. When 1α -OH-previtamin D_3 diacetate was dissolved in ethanol, benzene, toluene, isopropyl ether, or *n*-hexane, and heated at 60°C, the yield of 1α -OH-vitamin D_3 diacetate increased during the first 4 h, and reached an equilibrium level after 8.5 h. Differences in the ratio of 1α -OH-previtamin D_3 diacetate to 1α -OH-vitamin D_3 diacetate at thermal equilibrium, and in the rate of the thermal isomerization were observed among these five solvents. Molecular mechanics (MM) calculations were performed in order to estimate solvent effects on conformation for 1α -OH-previtamin D_3 diacetate and 1α -OH-vitamin D_3 diacetate. The solvent effect was treated by specifying a dielectric constant representative of each of the three solvents: ethanol (polar), *n*-hexane (nonpolar), and benzene (aromatic). The dielectric constants used were 24.3 for ethanol, 1.5 for *n*-hexane, and 2.3 for benzene. It is suggested that the confor-

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The following abbreviations are used: 1α -OH-vitamin D_3 , 1α -hydroxyvitamin D_3 (1α -hydroxycholecalciferol); 1α -OH-previtamin D_3 , 1α -hydroxyprevitamin D_3 (1α -hydroxy-precholecalciferol); $1\alpha,25$ -(OH)₂-vitamin D_3 , $1\alpha,25$ -dihydroxyvitamin D_3 ($1\alpha,25$ -dihydroxycholecalciferol); $1\alpha,25$ -(OH)₂-previtamin D_3 , $1\alpha,25$ -dihydroxyprevitamin D_3 ($1\alpha,25$ -dihydroxy-precholecalciferol); 1α -OH-7-DHC, cholesta-5,7-diene- $1\alpha,3\beta$ -diol; $1\alpha,25$ -(OH)₂-7-DHC, cholesta-5,7-diene- $1\alpha,3\beta,25$ -triol; HPLC, high-performance liquid chromatography; NMR, nuclear magnetic resonance; MM, molecular mechanics.

mation of 1 α -OH-vitamin D₃ diacetate is stabilized in polar solvent. However, the order of conformational stability when solvent effects are included in the calculations is: ethanol > benzene > *n*-hexane. This order does not follow the experimental results. The proton NMR chemical shifts of 1 α -OH-vitamin D₃ diacetate are different in deuterated *n*-hexane, ethanol, and benzene. The downfield shift of the C-6 vinyl proton of 1 α -OH-vitamin D₃ diacetate, when compared to the chemical shift in benzene, is 0.15 and 0.11 ppm relative to the chemical shift in *n*-hexane and ethanol, respectively, and that of the C-7 proton was 0.30 and 0.33 ppm, respectively. No significant proton shift of 1 α -OH-previtamin D₃ diacetate is recorded in these three solvents. To account for the increased ratio of 1 α -OH-vitamin D₃ diacetate to 1 α -OH-previtamin D₃ diacetate ratio in benzene, we suggest that 1 α -OH-vitamin D₃ diacetate may be stabilized *via* specific solute-solvent interactions in benzene.

Key Words 1 α -hydroxy-7-dehydrocholesterol diacetate, 1 α -hydroxy-vitamin D₃ diacetate, 1 α -hydroxyprevitamin D₃ diacetate, 1 α -hydroxy-cholecalciferol diacetate, 1 α -hydroxyprecholecalciferol diacetate, thermal conversion, thermal equilibrium, high-performance liquid chromatography, molecular mechanics, steric energy, nuclear magnetic resonance, solvent effect

We have reported the synthesis of 1 α -OH-vitamin D₃ and 1 α ,25-(OH)₂-vitamin D₃ from cholesterol and 25-hydroxycholesterol *via* the respective 7-dehydro intermediates which were hydroxylated at the 1 α position (1 α -OH-7-DHC, or 1 α ,25-(OH)₂-7-DHC) (1). We also investigated the photochemical conversion of cholesta-5,7-diene-1 α ,3 β -diol (1 α -OH-7-DHC) to 1 α -OH-previtamin D₃ by ultraviolet light (UV) and found that a wavelength of 295 nm was the most effective for the formation of 1 α -OH-previtamin D₃ (2). It was also reported that the conversion of previtamin D₃ to vitamin D₃ was a reversible isomerization reaction caused by heating, but not by light, catalyst, or solvent (3–6).

In this paper, a study on the thermal isomerization of 1 α -OH-previtamin D₃ diacetate, **1**, in five solvents—ethanol, benzene, isopropyl ether, toluene, and *n*-hexane—is reported. The mechanism of the solvent effect is discussed on the basis of molecular mechanics (MM) calculations and nuclear magnetic resonance (NMR) spectral data.

EXPERIMENTAL

Instruments. All experiments were performed using a JASCO CRM-FA spectroirradiator with a xenon arc lamp light source, a Hitachi 303 automatic spectrophotometer, a JEOL JNM-GX 400 NMR spectrometer, and a high-

performance liquid chromatograph consisting of a Waters 510 pump, a JASCO UVIDEK-100V detector, a YMC-012 SIL column (6 $\times$ 150 mm) for analytical work and a YMC-024 SIL column (10 $\times$ 300 mm) for preparative work.

Chemicals and reagents. 1 α -Hydroxy-7-dehydrocholesterol diacetate (1 α -OH-7-DHC diacetate) was synthesized from cholesterol as described previously (1). Reagents used were of analytical grade.

Preparation of 1 α -OH-previtamin D₃ diacetate, 1. 1 α -OH-Previtamin D₃ diacetate, **1**, was prepared by the photochemical conversion of 1 α -OH-7-DHC diacetate followed by preparative HPLC. Four milliliters of a solution of 1 α -OH-7-DHC diacetate in ethanol (1.0 mg/ml) was placed in a quartz cell (10 $\times$ 10 $\times$ 50 mm) in a spectroirradiator, and was irradiated at a wavelength of 295 nm and quantum energy of 8.55×10^8 erg/cm². After the irradiation, the solvent was evaporated off under reduced pressure. The residue was dissolved in CH₂Cl₂/*n*-hexane (1:1) and was subjected to preparative HPLC under the following conditions: a YMC A-024 SIL column; CH₂Cl₂/*n*-hexane (1:1, v/v) mobile phase; 4 ml/min flow rate; UV absorption monitored at 254 nm; at ambient temperature. The 1 α -OH-previtamin D₃ diacetate, **1**, fraction was collected, and solvent was evaporated off under reduced pressure. UV $\lambda_{\text{max}}^{\text{ethanol}}$ 265.5 nm. NMR (in benzene-d₆) δ : 0.73 (3H, s, 18-H₃), 0.93 (6H, d, J =6.6 Hz, 26- & 27-H₃), 0.97 (3H, d, J =6.2 Hz, 21-H₃), 1.70 (3H, s, 19-H₃), 1.66 (3H, s, acetyl-CH₃), 1.69 (3H, s, acetyl-CH₃), 2.87 (1H, dd, J =4.4, 12.5 Hz, 4 α -H), 5.32 (1H, m, 3 α -H), 5.60 (1H, dd, J =3.6, 4.6 Hz, 1 β -H), 5.72 (1H, m, 9-H), 5.87 (1H, d, J =12.8 Hz, 7-H), 5.89 (1H, d, J =12.8 Hz, 6-H).

Preparation of 1 α -OH-vitamin D₃ diacetate, 2. 1 α -OH-Vitamin D₃ diacetate, **2**, was prepared by the thermal conversion of 1 α -OH-previtamin D₃ diacetate, **1**, (Fig. 1) followed by preparative HPLC. 1 α -OH-Previtamin D₃ diacetate, **1**, was dissolved in ethanol and heated at 60°C for 24 h. Solvent was evaporated under reduced pressure. The residue was dissolved in CH₂Cl₂/*n*-hexane (1:2), and subjected to preparative HPLC under the following conditions: a YMC A-024 SIL

Fig. 1. Structures of 1 α -OH-previtamin D₃ diacetate and 1 α -OH-vitamin D₃ diacetate.

column; CH₂Cl₂/*n*-hexane (1:2, v/v) mobile phase; 4 ml/min flow rate; UV absorption monitored at 254 nm; at ambient temperature. The 1 α -OH-vitamin D₃ diacetate, **2**, fraction was collected, and the solvent was evaporated off under reduced pressure. UV $\lambda_{\text{max}}^{\text{ethanol}}$ 265.5 nm. NMR (in benzene-d₆) δ : 0.60 (3H, s, 18-H₃), 0.927 & 0.930 (3H $\times$ 2, each d, J = 6.6 Hz, 26-H₃ & 27-H₃), 0.96 (3H, d, J = 6.6 Hz, 21-H₃), 1.63 (3H, s, acetyl-CH₃), 1.66 (3H, s, acetyl-CH₃), 2.42 (1H, dd, J = 8.1, 13.2 Hz, 4 β -H), 2.65 (1H, dd, J = 4.4, 13.2 Hz, 4 α -H), 2.76 (1H, br. d, J = 13.2 Hz, 9 β -H), 5.21 (1H, d, J = 1.8 Hz, 19Z-H), 5.34 (1H, tt, J = 4.0, 8.0 Hz, 3 α -H), 5.40 (1H, dd, J = 1.1, 1.8 Hz, 19E-H), 5.65 (1H, dd, J = 4.0, 6.6 Hz, 1 β -H), 6.29 (1H, d, J = 11.2 Hz, 7-H), 6.48 (1H, d, J = 11.2 Hz, 6-H). FAB/MS m/z : 484 (M⁺), 441 (M⁺ - CH₃CO), 424 (M⁺ - CH₃COOH), 382 (424 - CH₃CO), 365 (M⁺ - 2 $\times$ CH₃COOH + H).

HPLC determination of 1 α -OH-previtamin D₃ diacetate, **1, and 1 α -OH-vitamin D₃ diacetate, **2**.** In order to evaluate the ratio of the molar absorption coefficients of 1 α -OH-previtamin D₃ diacetate, **1**, and 1 α -OH-vitamin D₃ diacetate, **2**, which is required as a correction factor for the determination of the ratio of the two molecules by HPLC, a partially thermally isomerized sample that contained the two forms was analyzed by both HPLC and NMR. One milliliter of 1 α -OH-previtamin D₃ diacetate, **1**, in ethanol was placed in a 10 ml screwcap tube, flushed with nitrogen, and heated at 60°C for 4 h. After thermal conversion, the solvent was removed under a nitrogen stream. The residue was dissolved in 100 μ l of CH₂Cl₂/*n*-hexane (1:1) and subjected to HPLC under the following conditions: a YMC A-012 SIL column; CH₂Cl₂/*n*-hexane (1:1, v/v); 0.35 ml/min flow rate; UV absorption monitored at 254 nm; at ambient temperature. Under these conditions, the peak area ratio of 1 α -OH-previtamin D₃ diacetate, **1**, to 1 α -OH-vitamin D₃ diacetate, **2**, was determined. The thermally isomerized residue described above was dissolved in ethanol-d₆, and the proton NMR spectrum taken at 400 MHz.

As shown in Table 1, the molar ratio of 1 α -OH-previtamin D₃ diacetate, **1**, to 1 α -OH-vitamin D₃ diacetate, **2**, was determined from the integrated peak areas of the C-6 protons of the two molecules. The results indicate the molar absorption ratio of 1 α -OH-previtamin D₃ diacetate, **1**, to 1 α -OH-vitamin D₃ diacetate, **2**, is approximately 1.47.

For the analysis of thermally isomerized samples in the five solvents, the percentage of 1 α -OH-vitamin D₃ diacetate, **2**, was calculated from the HPLC peak

Table 1. Comparison of experimental values of **1** and **2** in the thermal isomerization mixture.

	Percent of the total mixture		
	2	1	2:1 ratio
HPLC	74.9	25.1	2.98
NMR	67	33	2.03
NMR/HPLC	0.9	1.3	1.47

areas of 1 α -OH-previtamin D₃ diacetate, **1**, and 1-OH-vitamin D₃ diacetate, **2**. A correction for the molar absorption ratio was used and is shown below:

$$\% \text{ of } \mathbf{2} = \frac{\text{peak area of } \mathbf{2}}{\text{peak area of } \mathbf{2} + (1.47 \times \text{peak area of } \mathbf{1})} \times 100.$$

Molecular mechanics calculation. The total energy was obtained as a summation of valence geometry distortion, steric and coulombic energy terms using the MMFF option in CHEMLAB-II molecular modeling package (7); this is an enhanced version of Allinger's MM2 program (8) having extended parametrization and force field function generalizations. The reported conformational energy differences are based on the total conformational energy as computed using CHEMLAB-II. The initial coordinates of 1 α -OH-vitamin D₃ diacetate, **2**, were taken from the X-ray crystal structure obtained by Trinh-Toan *et al.* (9). After the CNDO/2 method (10) was employed to generate partial atomic charges, the initial molecular geometry was optimized using MM to ensure that the crystal geometry was not unduly influenced by crystal packing forces. The structure of 1 α -OH-previtamin D₃ diacetate, **1**, was taken from a Maruzen HGS molecular model, based on the structural model of Sheves *et al.* (11). Though there are different possible conformations of the A, C and D rings in 1 α -OH-vitamin D₃ diacetate, the (+)tZ(−)c form of 1 α -OH-vitamin D₃ diacetate model was used because, as discussed recently by Dauben and Funhoff (12), the (+)tZ(−)c form with a pseudoequatorial OH group is the global minimum in free-space energy. All hydrogen atoms and the acetyl group were initially assigned ideal valence geometries in 1 α -OH-previtamin D₃ diacetate model (A) and 1 α -OH-vitamin D₃ diacetate model (B). To make the calculation easier, the side chains in these molecules were removed. After the CNDO/2 method was employed to generate partial atomic charges, the molecular geometry was optimized using MMFF of CHEMLAB-II. The solvent effect was treated by specifying a dielectric constant for each of three representative solvents: ethanol (polar), *n*-hexane (nonpolar), and benzene (aromatic). The dielectric constants used were 24.3 for ethanol, 1.5 for *n*-hexane, and 2.3 for benzene (13).

NMR measurement. ¹H-NMR spectra were obtained in ethanol-d₆, benzene-d₆, and *n*-hexane-d₁₄ at 35°C on a JEOL JNM-GX 400 spectrometer operating at 400 MHz. In NMR study on 1 α -OH-vitamin D₃, a significant NOE (5%) was observed at the H-19 proton (δ 4.93) when the H-7 proton (δ 6.07) was irradiated. This signal at δ 4.93 was thus assigned to H-19Z proton. Consequently, the assignments of 1 α -OH-vitamin D₃ and 1 α -OH-vitamin D₃ diacetate should be revised (14).

RESULTS AND DISCUSSION

1. The thermal isomerization of 1 α -OH-previtamin D₃ diacetate, **1**, in five organic solvents

1 α -OH-Previtamin D₃ diacetate, **1**, was dissolved in 1 ml of each of five solvents, ethanol, benzene, toluene, isopropyl ether, or *n*-hexane (0.1 mg/ml). Each 1 ml of the solution was flushed with nitrogen and heated at 60°C for a desired time. The molar ratio of 1 α -OH-previtamin D₃ diacetate, **1**, to 1 α -OH-vitamin D₃ diacetate, **2**, was monitored by HPLC of samples taken at 0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 8.5, and 24 h (Table 2 and Fig. 2).

As shown in Fig. 2 and Table 2, the yield of 1 α -OH-vitamin D₃ diacetate, **2**, increased steadily during the first 4 h, but there were differences among the five solvents. The ratios of 1 α -OH-previtamin D₃ diacetate to 1 α -OH-vitamin D₃ diacetate in the five solutions reached thermal equilibrium at 8.5 h. Differences in the ratios at thermal equilibrium, and in the rates of the thermal isomerization were

Table 2. Thermal isomerization of **1** to **2** in organic solvents at 60°C.

	Proportion of 2 (%)								
	0	0.5	1.0	1.5	2.0	3.0	4.0	8.5	24
Ethanol	3.4	20.5	32.9	41.7	48.7	57.9	64.1	70.8	71.5
<i>n</i> -Hexane	3.3	18.4	30.6	39.3	46.4	54.4	59.2	66.4	67.6
Benzene	3.5	24.8	38.9	48.5	55.5	64.3	68.6	74.1	74.1
Toluene	3.8	25.3	38.8	48.4	54.6	64.0	68.2	72.9	72.9
IPE*	4.0	18.6	30.1	38.7	45.4	54.6	60.3	66.4	66.5

* Isopropyl ether.

Fig. 2. Time course of thermal isomerization of **1** to **2** in organic solvents at 60°C.

observed among these five solutions. For example, the ratio in benzene was 7.6% and 6.5% greater than those in isopropyl ether and *n*-hexane, respectively.

The results of these experiments appear to reflect a stabilization on 1 α -OH-vitamin D₃ diacetate, **2**, by formation of collision complex (a transient solute-solvent complex) with aromatic solvent such as benzene and toluene.

2. Analysis of solvent effects by molecular mechanics calculation

In order to clarify the mechanism of the solvent effect on the thermal isomerization of 1 α -OH-previtamin D₃ diacetate, **1**, the total energies of 1 α -OH-previtamin D₃ diacetate and 1 α -OH-vitamin D₃ diacetate model were calculated by molecular mechanics (MM). The solvent effect was treated by specifying a dielectric constant for each of three representative solvents: ethanol (polar), *n*-hexane (nonpolar), and benzene (aromatic). The dielectric constants used were 24.3 for ethanol, 1.5 for *n*-hexane, and 2.3 for benzene (13). The theoretical ratio at thermal equilibrium was based on the energy difference between 1 α -OH-previtamin D₃ diacetate model (A) and 1 α -OH-vitamin D₃ diacetate model (B). The initial coordinates of 1 α -OH-vitamin D₃ diacetate model (B) were taken from the crystal structure obtained by Trinh-Toan *et al.* (9). The structure of the 1 α -OH-previtamin D₃ diacetate model (A) was taken from a Maruzen HGS molecular model, based on Sheves' model (11). Figure 3 illustrates the MM optimized structures for 1 α -OH-previtamin D₃ diacetate model (A) and 1 α -OH-vitamin D₃ diacetate model (B). The MM optimized 1 α -OH-previtamin D₃ diacetate model (A) molecular structure was in accord with the minimum energy conformation of 1 α -OH-previtamin D₃ (12).

Table 3 shows the results of the MM calculation. The order of energy differences, when solvent effects were included in the molecular mechanics calculations, is: ethanol > benzene > *n*-hexane. 1 α -OH-Vitamin D₃ was stabilized in polar solvent (ethanol) by 2 kcal/mol compared with *n*-hexane. This order is not completely consistent with experimental results, namely benzene, toluene > ethanol > *n*-hexane, isopropyl ether. One possible explanation is that while the high dielectric constant of the solvent was used in the molecular mechanics calculations, the effective dielectric constant on a molecular scale may be substantially different and it seems to be a specific interaction between 1 α -OH-vitamin D₃ and solvent benzene molecules.

3. Analysis of solvent effect by means of NMR

The chemical shifts of 1 α -OH-vitamin D₃ diacetate, **2**, were different in deuterated *n*-hexane, ethanol, and benzene. The downfield shift of the C-6 vinyl proton of 1 α -OH-vitamin D₃ diacetate, **2**, in benzene, was 0.15 and 0.11 ppm, relative to the chemical shift in *n*-hexane and ethanol, respectively. The C-7 proton was shifted 0.30 and 0.33 ppm, respectively (see Table 4). The magnitude of downfield shift for 1 α -OH-vitamin D₃ diacetate, **2**, increased in the order: benzene > ethanol = *n*-hexane. No significant proton shift of 1 α -OH-previtamin D₃

Fig. 3. Molecular mechanics optimized structure for (A), 1 α -OH-previtamin D₃ diacetate model and (B), 1 α -OH-vitamin D₃ diacetate model.

Table 3. Total energies of (A) and (B) including solvent effects.

ϵ	Total energy (kcal/mol)		$-\Delta E((B)-(A))$
	(A)	(B)	
1.5 (<i>n</i> -Hexane)	31.3282	27.7385	3.5897
2.3 (Benzene)	39.6008	35.2739	4.3269
24.3 (Ethanol)	53.6160	48.0439	5.5721

diacetate, **1**, was observed in any of the three solvents. However, upfield shifts of the C-9 and C-4 protons were observed (shown in Table 5). Furthermore, it is likely that no conformational change occurred in any of the solvents because there was no change in the magnitude or pattern of the couplings in the spectra of these two molecules in the various solvents (14). As shown in Table 6, the same solvent shifts were observed on 1 α -OH-vitamin D₃. The acetyl group can possibly make a complex with benzene. However, we have observed changes in chemical shifts for

Table 4. Chemical shifts for **1** and **2** in NMR.

Solvent	Chemical shifts (ppm)					
	H6			H7		
	1	2	$\Delta\delta(2-1)$	1	2	$\Delta\delta(2-1)$
1 <i>n</i> -Hexane	5.87	6.33		5.78	5.99	
2 Ethanol	5.92	6.37		5.84	5.96	
3 Benzene	5.89	6.48		5.87	6.29	
$\Delta\delta(3-1)$	0.02	0.15	0.13	0.09	0.30	0.21
$\Delta\delta(3-2)$	-0.03	0.11	0.14	0.03	0.33	0.30

Table 5. Chemical shifts for 1 α -OH-vitamin D₃ (free) in the ¹H-NMR spectra.

	Solvent	Chemical shifts (ppm)								
		H6	H7	H19E*H19Z*	H1 β	H3 α	H9 β	H4 α	H4 β	
1	<i>n</i> -Hexane	6.32	6.07	5.26	4.93	4.30	4.10	2.84	2.52	2.21
2	Ethanol	6.29	6.10	5.30	4.89	4.37	4.15	2.84	2.50	2.29
3	Benzene	6.43	6.36	5.33	5.14	4.23	3.92	2.86	2.39	2.14
	$\Delta\delta(3-1)$	0.11	0.29	0.07	0.21	-0.07	-0.18	0.02	-0.13	-0.07
	$\Delta\delta(3-2)$	0.14	0.26	0.03	0.25	-0.14	-0.23	0.02	-0.11	-0.15

* Alternative assignments had been given by means of NOE experiments.

Table 6. Chemical shifts for 1 α -OH-vitamin D₃ diacetate in the ¹H-NMR spectra.

		Chemical shifts (ppm)										
Solvent		H6	H7	H19E*	H19Z*	H1 β	H3 α	H9 β	H4 α	H4 β	Ac	
1	<i>n</i> -Hexane	6.33	5.99	5.28	4.99	5.40	5.12	2.83	2.61	2.29	1.88	1.89
2	Ethanol	6.37	5.96	5.32	5.01	5.42	5.13	2.84	2.65	2.36	2.01	2.00
3	Benzene	6.48	6.29	5.40	5.21	5.64	5.34	2.77	2.65	2.42	1.66	1.63
	$\Delta\delta(3-1)$	0.15	0.30	0.12	0.22	0.24	0.22	-0.06	0.04	0.13	-0.23	-0.25
	$\Delta\delta(3-2)$	0.11	0.33	0.08	0.20	0.22	0.21	-0.07	0.00	0.06	-0.35	-0.37

* Alternative assignments had been given by means of NOE experiments.

both the diacetate and the free 1 α -OH-vitamin D₃ molecules which is not consistent with acetyl complexing.

The increase in the ratio of 1 α -OH-vitamin D₃ diacetate, **2**, to 1 α -OH-previtamin D₃ diacetate, **1**, in benzene (see Table 2), might be explained by the stabilization of 1 α -OH-vitamin D₃ diacetate, **2**, that may occur *via* a specific solute-solvent interaction (15-20). In our system it is possible that the solvent benzene molecule will be oriented in a nonplanar collision complex (a transient solute-solvent complex) with 5,7-diene moiety of 1 α -OH-vitamin D₃ diacetate, **2**, thus stabilizing the formation of 1 α -OH-vitamin D₃ diacetate, **2**, and hence increasing the ratio of 1 α -OH-vitamin D₃ diacetate, **2**, to 1 α -OH-previtamin D₃

diacetate, **1**, in the thermal reaction. However, 1α -OH-previtamin D_3 did not make a collision complex with benzene. A possible explanation is that the 1α -OH-previtamin D_3 molecule has more conformational flexibility close to the triene moiety than that of 1α -OH-vitamin D_3 . Thus, it makes a less stable complex with benzene. Fort (21,22) determined the values of the enthalpies of formation for complexes of a polar solute and an aromatic solvent. The enthalpies of formation were found to differ by only 0.5 to 2 kcal/mol. Furthermore, Ronayne and Williams (19) found the enthalpy for collision complex formation of an aromatic solute to differ by 0.59 to 0.74 kcal/mol. The solvent effect on the thermal isomerization of 1α -OH-previtamin D_3 diacetate, **1**, reported here is consistent with Fort's and Ronayne's values for the enthalpy of formation.

All vitamin D analogs should make complexes with benzene if the site of complexing is the triene moiety. However, the extent of complexing can be expected to be modulated by the substituents and/or chemical modifications of each analog. Solubility and steric accessibility of the triene will be dependent upon chemical modifications made to vitamin D.

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