Tetrahedron Letters,Vol.29,No.25,pp 3021-3024,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

# ORGANIC REACTIONS AT HIGH PRESSURE.
# INTERCONVERSION OF PREVITAMIN $D_3$ AND VITAMIN $D_3$.[1]

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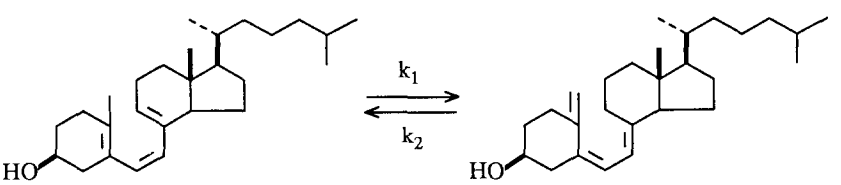
**Abstract:** The interconversion of previtamin $D_3$ and vitamin $D_3$ at 20 °C was effected at high pressure (15 kbar) in three solvent mixtures. The rate constants of $k_1$ and $k_2$ were determined to be 30 to 45 times larger than the corresponding 1 bar rate constants. The $\Delta V^*$ was calculated to be -5.14 $cm^3$/mol or lower, indicating a concerted [1,7] sigmatropic hydrogen shift.

Vitamin $D_3$ is formed *in vivo* and *in vitro* by the thermal interconversion of previtamin $D_3$.[2] This is a very important chemical transformation and thus has been extensively studied. It is believed to proceed *via* a concerted [1,7] sigmatropic hydrogen shift.[3] The position of equilibrium has been determined at various temperatures, and kinetic data are available in several solvents.[4] The interconversion at 1 bar is solvent independent and is not influenced by acid, base or radical chain inhibitors.[4b]




**Previtamin $D_3$** **Vitamin $D_3$**

High pressure has become a valuable tool in both organic synthesis and as a probe of reaction mechanism.[5] Upon examination of the literature, no study of a [1,7] sigmatropic shift under pressure conditions could be found. The closest analogies are [1,5] sigmatropic shifts which have been studied recently under pressure conditions.[6] These findings reveal a range of activation volumes ($\Delta V^*$) depending

upon the reaction mechanism.

The actual synthetic production of vitamin $D_3$ from previtamin $D_3$ is carried out at elevated temperature. This is done because the rate at room temperature is quite slow. Analogues of vitamin $D_3$ are frequently prepared by use of this [1,7] sigmatropic hydrogen shift. However, this hydrogen shift can proceed slowly with low yield even at elevated temperatures.[7] The application of synthetically useful high pressures could solve this problem if the $\Delta V^{\ddagger}$ is significantly negative. Synthetically useful high pressures generally begin at 5 kbar. At this pressure or above, rate enhancement can be quite substantial. Little kinetic data is available at these high pressures despite their synthetic usefulness. In this study, the rate of previtamin $D_3$ interconversion to vitamin $D_3$ was examined at 15 kbar.

Three dilute solutions of previtamin $D_3$ were made: solution bt (benzene/toluene, 3/8.25; $5.4\times10^{-6}$ mol/L), solution ae (absolute ethanol; $1.4\times10^{-4}$ mol/L), and solution ew (ethanol/water 9/1; $1.3\times10^{-4}$ mol/L). These solutions were pressurized to 15 kbar for various times, and the final amounts of previtamin $D_3$ and vitamin $D_3$ were determined by analytical HPLC with UV detection (Table 1).

Table 1
Percent vitamin $D_3$ after time t
at 15 kbar.

| t(min) | $A_{bt}$ | $A_{ae}$ | $A_{ew}$ |
|---|---|---|---|
| 0 | 5.0 | 3.2 | 3.3 |
| 30 | 20.2 | 13.1 | 12.3 |
| 60 | 16.5 | 15.3 | 17.7 |
| 90 | 27.9 | 25.0 | 25.6 |
| 120 | 32.4 | 29.4 | 30.1 |
| 240 | 45.2 | 35.2 | 36.2 |
| 690 | 82.0 | 84.0 | 76.7 |
| equil. | 91.9 | 90.9 | 90.6 |

A=percent vitamin $D_3$

A plot of $\ln[(A_o-A_{eq})/(A-A_{eq})]$ versus time for a unimolecular reaction should give a straight line with the slope equal to $k_1+k_2$. The slope was determined with a least squares fit. The correlation coefficient for each of the slopes was $\geq 0.985$.

The rate constants for this [1,7] hydrogen shift were increased by approximately 30 fold for the forward ($k_1$) and approximately 35 fold for the reverse ($k_2$) compared to the 1 bar rate constants (Table 2).

This rate increase does provide significantly more vitamin $D_3$ in the same amount of time at 20 °C (eg., 82% vitamin $D_3$ from previtamin $D_3$ in 11.5 h at 15 kbar, versus 80% in 13.3 d at 1 bar[4a]). There was quantitative recovery of material under high pressure conditions, determined by using an external standard.

Table 2
Rate constants at 15 kbar.

| solution | $k_1 \times 10^3$ ($min^{-1}$) | $k_2 \times 10^4$ ($min^{-1}$) |
|---|---|---|
| bt | 2.8 | 2.5 |
| ae | 3.2 | 3.3 |
| ew | 2.3 | 2.4 |

at 1 bar in ae[4] $k_1=9.5\times10^{-5}$ $min^{-1}$
$k_2=7.3\times10^{-6}$ $min^{-1}$

Table 3
Activation volumes.

| solution | $\Delta V^*_1$ ($cm^3$/mol) | $\Delta V^*_2$ ($cm^3$/mol) |
|---|---|---|
| bt | -5.45 | -5.66 |
| ae | -5.70 | -6.11 |
| ew | -5.14 | -5.60 |

The activation volume ($\Delta V^*$) of previtamin $D_3$ interconversion to vitamin $D_3$ was determined with the rate at 15 kbar and the rate at 1 bar (Table 3). Having only two points to determine the slope is a limitation, because $\Delta V^*$ at high pressure tends to be pressure dependent. This non-ideal behavior at high pressure decreases the absolute magnitude of $\Delta V^*$ as the pressure increases. Therefore, the value of $\Delta V^*$ determined above provides a lower limit of the absolute magnitude of $\Delta V^*$.

The mechanism of previtamin $D_3$ interconversion to vitamin $D_3$ is formally a [1,7] sigmatropic hydrogen shift. The reaction rate is essentially solvent independent both at 1 bar and at 15 kbar. This result is not consistent with an ionic mechanism, leaving a non-ionic diradical or concerted mechanism. The range of $\Delta V^*$ for [1,5] shifts has been found to be +10 to -30 $cm^3$/mol, the stepwise diradical mechanism having a positive $\Delta V^*$ and the concerted mechanism having a negative $\Delta V^*$.[6] With a $\Delta V^*$ of -5.14 $cm^3$/mol, or lower, for previtamin $D_3$ interconversion to vitamin $D_3$, a stepwise diradical mechanism can be deemed unlikely. Typical values for concerted [1,5] sigmatropic shifts range from -4 to -30 $cm^3$/mol, the larger having some diradical character.[6] Therefore, this present interconversion appears to be a concerted [1,7] sigmatropic hydrogen shift.

The equilibrium concentration of vitamin $D_3$ and previtamin $D_3$ is essentially unchanged at 15 kbar (91 to 9) compared to 1 bar (93 to 7), therefore the $\Delta V$ of previtamin $D_3$ and vitamin $D_3$ is essentially zero.

In conclusion, the interconversion of previtamin $D_3$ to vitamin $D_3$ was accelerated at high

pressure (15 kbar). The significant rate increase and quantitative material recovery could be used beneficially in the production of vitamin $D_3$ analogues when the [1,7] hydrogen shift is slow or the compounds are thermally labile. The $\Delta V^*$ was determined to be -5.14 $cm^3$/mol or lower, indicating a concerted [1,7] sigmatropic hydrogen shift mechanism.

## References


1. This research was supported by National Science Foundation Grant No. 8618303 and National Institute of Diabetes and Digestive and Kidney Research Grant No. DK007009. D. J. H. F. was recipient of a Feodor-Lynen Fellowship of the Alexander von Humboldt-Stiftung 1986-87.
2. Norman, A. W. *Vitamin D The Calcium Homostatic Steroid Hormone*; Academic Press: New York, 1979.
3. (a) Schlatmann, J. C. M. A.; Pot, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1173. (b) Sheves, M.; Berman, E.; Mazur, Y.; Zaretskii, Z. *J. Am. Chem. Soc.* **1979**, *101*, 1882. (c) Akhtar, M.; Gibbons, C. J. *Tetrahedron Lett.* **1965**, 509.
4. (a) Hanewald, K. H.; Rappoldt, M. P.; Roborgh, J. R. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1003. (b) Cassis, E. G. Jr.; Weiss, R. G. *Photochemistry and Photobiology* **1982**, *35*, 439 and references cited therein.
5. For reviews see: (a) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1. (b) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999. (c) Isaacs, N. S. *Liquid Phase High Pressure*; Wiley-Interscience: Chichester, 1981.
6. (a) le Noble, W. J.; Daka, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 5961. (b) Schulman, E. M.; Merbach, A. E.; Turin, M.; Wedinger, R.; le Noble, W. J. *J. Am. Chem. Soc.* **1983**, *105*, 3988. (c) Sugiyama, S.; Takeshita, H. *Chemistry Letters* **1986**, 1203.
7. (a) Dauben, W. G.; Kohler, B.; Roesle, A. *J. Org. Chem.* **1985**, *50*, 2007. (b) Sialom, B.; Mazur, Y. *J. Org. Chem.* **1980**, *45*, 2201.


(Received in USA 23 March 1988)