Novel Oxidation of Vitamin D_2 by an Electrochemical Method

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Novel oxidation of vitamin D_2 was achieved by an electrochemical method. Under the conditions employing a metal salt-hematoporphyrin-O_2-cathodic reduction system, only the conjugated triene moiety of vitamin D_2 was affected, giving the cleavage products, while the double bond in the side chain remained intact.

Key words oxidation; vitamin D_2; electrolysis

The electrochemical method has proved to be useful for organic synthesis because it often promotes unique reactions that would otherwise be inaccessible.[2] We have shown that electrolysis using the metal salts-hematoporphyrin-O_2-cathodic reduction system selectively oxidizes terminal isopropyl groups to tertiary alcohols, yielding 25-hydroxycholesterol from cholesterol in a single step. In addition, steroidal 5,6-olefins are stereoselectively chlorinated, which was utilized for convenient synthesis of blattelastanoside B, an aggregation pheromone of the German cockroach.[3] During these studies, when vitamin D_2 (**1**) was subjected to similar conditions, three cleavage products **2**, **3** and **4** were obtained (Chart 1). This is a unique oxidation reaction, wherein only the conjugated triene moiety was affected, while the double bond in the side chain remained intact,[4] which may be useful for organic synthesis similar to ozonolysis. We therefore investigated this reaction in more detail, and report our findings here.[5,6]

The reactions were conducted under a constant current condition (C.C.E. at $-2.0\sim-2.4$ V *vs.* SCE, 25 mA/cm^2; 10 F/mol) in 80% aqueous MeCN (20 ml) containing vitamin D_2 (0.3 mmol), metal salts (0.06 mmol), hematoporphyrin (0.06 mmol), and $LiClO_4$ (1.8 mmol) with continuous bubbling of O_2 gas using platinum plates both as an anode and a cathode in an undivided cell.

First, we investigated the effects of various metal salts, and the results of which are summarized in Table 1. The use of $FeCl_3$ or $MnCl_2$ gave similar results, affording the ketone **2**[4] and the aldehyde **3**[7] in fair to good yield with a small amount of another aldehyde **4**,[8] resulting from the cleavage of 7,8-, 5,6-, and 6,7-bonds, respectively (Entries 1 and 2). The other metal salts $CrCl_3$, $CoCl_2$, $CuCl_2$, and $ZnCl_2$ were also effective but to a much lesser extent (Entries 3–6). Using $RuCl_3$, $CeCl_3$ and $HgCl_2$ resulted in a complex mixture with low recovery of the starting material (Entries 7–9). The reaction did not take place when KCl and $NiCl_2$ were used (Entries 10 and 11). $Tl(TFA)_3$ was most effective in view of the product yield (Entry 12). It is noteworthy that in this case not only were the yields increased, but also the product ratio was changed considerably. In contrast to case of $FeCl_3$, $Fe(acac)_3$ gave only low yield of the products, similar to Entries 3–6.

In all the above cases, no reaction took place when H_2O_2 instead of O_2 was used as an oxidant, which ruled out the possible involvement of electrochemically formed H_2O_2 from H_2O or O_2 under the conditions used. Similarly, the reactions did not proceed or resulted in a complex mixture without electrolysis or in the absence of one of the reagents (metal salt, O_2, or hematoporphyrin), implying that the metal salt-hematoporphyrin-O_2-cathodic reduction system as a whole is essential to promote the above reactions. In contrast, the same results were obtained under a constant potential condition (C.P.E. at -2.4 V *vs.* SCE; 15 F/mol). The experiments with a divided cell[9] gave the same results, demonstrating that this reaction proceeded at the cathode.

Considering all the above results along with the reduction potential (*ca.* -450 mV) indicated from a cyclic voltammogram of a mixture of the $Tl(TFA)_3$-hematoporphyrin-O_2 system, it is likely that metal salt may form a complex with hematoporphyrin, then the metal coordinates with oxygen, followed by electron transfer between the complex and the electrodes to promote the oxidation. Therefore we next turned our attention to hematoporphyrin, *i.e.*, the effects of various porphyrins were investigated. As a result, we found that the combination of metal salt and porphyrin is important for this reaction. When combined with $FeCl_3$, most of the porphyrins other than hematoporphyrin and 5,10,15,20-tetra(2-nitrophenyl)porphyrin (TNP) resulted in a complex mixture. In marked contrast, in presence of $Tl(TFA)_3$, the oxidation proceeded smoothly with most of the porphyrins. The results are summarized in Table 2. Notably, TNP and 5,10,15,20-tetra(4-pyridyl)porphyrin (TPyP) gave results comparable to those with hematoporphyrin (Entries 5 and 6), and even bilirubin, a precursor and linear form of porphyrin, promoted the reaction (Entry 9). These results indicate that the structure and stability of the complex formed has an essential role in the reaction process.

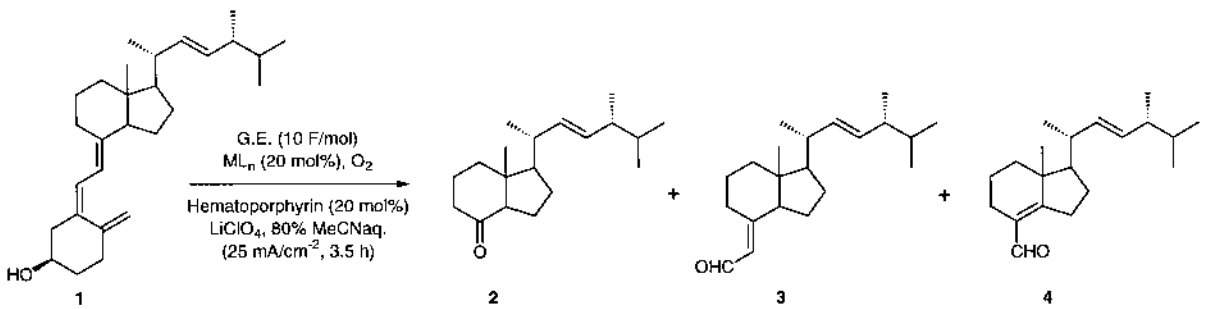

Chart 1

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Table 1. Oxidation of **1** Initiated by Cathodic Reduction of a Metal Salt

Entry	ML_n	Potential *vs*. SCE (V)	**2**, %	**3**, %	**4**, %	SM
1	$FeCl_3$	−2.0—−2.4	23 (63)	10 (29)	2 (6)	61
2	$MnCl_2$	−1.7—−1.8	22 (53)	9 (23)	2 (4)	51
3	$CrCl_3$	−1.8—−1.9	13 (30)	7 (16)	Trace	88
4	$CoCl_2$	−1.8—−1.9	10 (25)	3 (8)	2 (4)	62
5	$CuCl_2$	−1.6—−1.9	7 (15)	3 (6)	Trace	53
6	$ZnCl_2$	−2.0—−2.4	12 (32)	3 (7)	1 (4)	59
7	$RuCl_3$	−2.0—−2.2	Trace	Trace	—	37
8	$CeCl_3$	−2.1—−2.3	Trace	Trace	—	30
9	$HgCl_2$	−1.7—−1.8	—	—	—	38
10	KCl	−1.8—−2.0	—	—	—	88
11	$NiCl_2$	−2.0—−2.2	—	—	—	75
12	$Tl(TFA)_3$	−1.1—−1.8	36 (48)	33 (44)	4 (6)	26
13	$Fe(acac)_3$	−1.8—−2.0	12 (17)	5 (7)	3 (4)	30

* The conversion yield is shown in parentheses. ** SM; recovered starting material (%). *** The observation potential is noted during the C.C.E. reaction.

Table 2. Oxidation of **1** Initiated by Cathodic Reduction of the $Tl(TFA)_3$/Porphyrin/O_2 System

Entry	Porphyrin	Potential *vs*. SCE (V)	**2**, %	**3**, %	**4**, %	SM
1	HP	−1.1—−1.8	36 (48)	33 (44)	4 (6)	26
2	TPP	−1.2—−1.3	23 (33)	20 (28)	10 (14)	30
3	TCPP	−2.2—−2.3	10 (12)	7 (8)	Trace	18
4	TAP	−1.2—−1.5	16 (24)	9 (14)	3 (4)	33
5	TNP	−1.2—−1.3	37 (47)	29 (37)	12 (15)	21
6	TPyP	−2.3—−2.4	30 (42)	17 (24)	4 (6)	29
7	TMPyP	−2.2—−2.3	—	—	—	43
8	PP	−2.6—−2.7	19 (31)	13 (29)	10 (16)	40
9	Bilirubin	−1.7—−2.1	26 (43)	15 (24)	11 (18)	37

* The conversion yield is shown in parentheses. ** SM; recovered starting material (%). *** Porphyrins: HP, hematoporphyrin; TPP, 5,10,15,20-tetra-phenylporphyrin; TCPP, 5,10,15,20-tetra(4-carboxyphenyl)-porphyrin; TAP, 5,10,15,20-tetra(4-dimethylaminophenyl)porphyrin; TNP, 5,10,15,20-tetra(2-nitropheny)porphyrin; TPyP, 5,10,15,20-tetra(4-pyridyl)porphyrin; TMPyP, 5,10,15,20-tetra(4-N-methyl-pyridyl)porphyrin; PP, protoporphyrin. **** The observation potential is noted during the C.C.E. reaction.

Finally, we applied this novel electrochemical oxidation to other closely related substrates. When vitamin D_3 (**5**) was subjected to conditions employing $Tl(TFA)_3$ and hematoporphyrin, the oxidation also took place, but in this case, only the ketone **6**, a cleavage product of the 7,8-bond, was obtained in 45% yield (79% conversion yield) as a mixture of C-14 epimers.[10] Ergosteryl acetate (**7**) afforded the peroxide **8**[11] in 75% yield under the same conditions. Again, only the conjugated double bond was oxidized, although not cleaved, while the olefin in the side chain remained intact (Chart 2).

Thus the reaction reported in this study is unique and would be useful for organic synthesis because it selectively oxidizes conjugated double bonds while isolated olefins remain intact, and the resulting cleavage products could be utilized for the synthesis of vitamin D analogues. Further elaboration of the mechanism and scope of this reaction is underway.

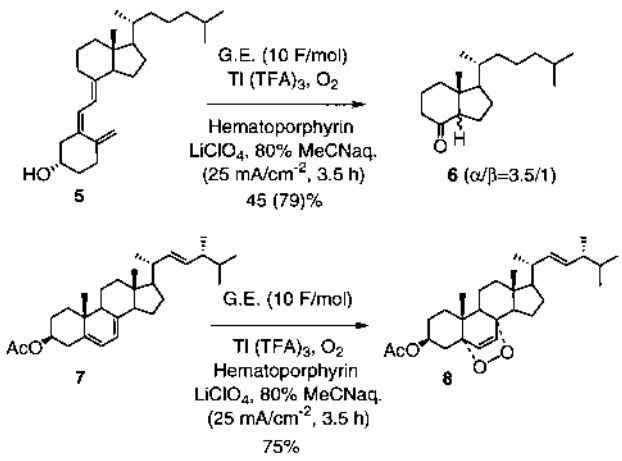

Chart 2

References and Notes

1) Present address: *Department of Applied Physics and Chemistry, The University of Electro-Communications, Chofu, Tokyo 182–8585, Japan*.
2) *a*) Maki S., Toyoda K., Kosemura S., Yamamura S., *Chem. Lett*., **1993**, 1059—1062; *b*) Maki S., Kosemura S., Yamamura S., Ohba S., *Tetrahedron Lett*., **34**, 6083—6086 (1993).
3) *a*) Maki S., Konno K., Takayama H., *Tetrahedron Lett*., **38**, 7067—7070 (1997); *b*) Maki S., Konno K., Takayama H., *Tetrahedron Lett*., **39**, 3541—3542 (1998).
4) *a*) Tabushi I, Morimitsu K, *Tetrahedron Lett.*, **27**, 51—54 (1986); *b*) Creager S. E., Raybuck S. A, Murray R. W., *J. Am. Chem. Soc*., **108**, 4225–4227 (1986); *c*) Karasevich E. I., Khenkin A. M., Shilov A. E., *Chem. Commun*., 731—732, (1987).
5) Similar results were obtained by two step conversion with $KMnO_4$–$Pb(OAc)_4$. *a*) Toh H. T., Okamura W. H., *J. Org. Chem*., **48**, 1414—1417 (1983); *b*) Mascarenas J. L., Mouriño A., Castedo L., *J. Org. Chem*., **51**, 1269—1272 (1986).
6) See also: Maki S., Konno K., Suzuki T., Takayama H., *Vitamin D: Chemistry Biology and Clinical Applications of the Steroid Hormone*, University of California, Riverside, 1997, p. 42. For biomimetic oxidation of vitamin D_2, see: Yamamoto K., Imae Y., Yamada S., *Tetrahedron Lett*., **31**, 4903—4906 (1990).
7) This compound was characterized after reduction with $NaBH_4$ to the corresponding alcohol: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.56 (3H, s), 0.82 (3H, d, J=6.7 Hz), 0.83 (3H, d, J=6.4 Hz), 0.92 (3H, d, J=6.8 Hz), 1.02 (3H, d, J=6.4 Hz), 2.62 (1H, dd, J=6.6, 13.2 Hz), 4.20 (2H, d, J=6.7 Hz), 5.17—5.23 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 12.09 (q), 17.60 (t), 19.64 (q), 19.94 (q), 21.11 (q), 22.15 (q), 23.49 (t), 27.76 (t), 28.70 (d), 29.69 (t), 33.09 (d), 40.25 (t), 40.36 (s), 42.83 (d), 55.72 (d), 56.46 (d), 77.65 (t), 119.20 (d), 132.03 (d), 135.56 (d), 155.08 (s); IR 3340 cm^{-1}; MS m/z 304 (M^+), 286 ($M-H_2O$), 261 ($M-{}^i$Pr); HR-MS m/z 304.2774 (M^+) calcd for $C_{21}H_{36}O$ 304.2766.
8) **4**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.83 (3H, d, J=6.7 Hz), 0.85 (3H, d, J=6.7 Hz), 0.93 (3H, d, J=6.7 Hz), 0.98 (3H, s), 1.07 (3H, d, J=6.7 Hz), 5.21 (1H, dd, J=7.4, 15.3 Hz), 5.28 (1H, dd, J=7.4, 15.3 Hz), 9.93 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 17.63 (t), 17.97 (t), 18.29 (q), 19.68 (q), 19.99 (q), 21.02 (t), 21.35 (q), 24.93 (t), 27.50 (t), 33.11 (d), 36.09 (t), 39.01 (d), 42.92 (d) 45.42 (s), 55.10 (d), 129.31 (s), 132.92 (d), 134.75 (d), 172.12 (s), 192.46 (d); IR 1672, 1460, 1372 cm^{-1}; MS m/z 288 (M^+), 273 (M−Me); HR-MS m/z 288.2454 (M^+) calcd for $C_{20}H_{32}O$ 288.2453.
9) The H-type cell (HX-108, Hokuto Denko Co. Ltd.) was used.
10) *a*) Peterson P. E., Breedlove Leffew R. L., Jensen B. L., *J. Org. Chem*., **51**, 1948—1954 (1986); *b*) Maestro M. A., Sardina F. J., Castedo L., Mouriño A., *J. Org. Chem.*, **56**, 3583—3587 (1991).
11) Barton D. H. R., Haynes R. K., Leclerc G., Magnus P. D., Menzies I. D., *J. Chem. Soc*., 2056 (1975). The spectral data of ergosteryl acetate peroxide (**8**) were identical to those of the authentic sample.