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Selective Oxidation of Terminal Isopropyl Groups to Tertiary Alcohols by Electrochemical Methodology

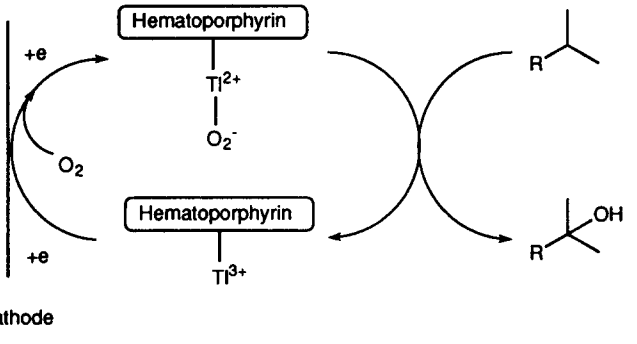
Shojiro Maki†, Katsuhiro Konno and Hiroaki Takayama*

Faculty of Pharmaceutical Sciences, Teikyo University,
Sagamiko, Kanagawa 199-01, Japan

Abstract: Selective oxidation of terminal isopropyl groups to the corresponding tertiary alcohols by an electrochemical method is described. Under the conditions using the $Tl(TFA)_3$-hematoporphyrin-O_2-cathodic reduction system, several substrates such as cholesterol (**1**) and Grundmann's alcohol (**3**) gave the corresponding tertiary alcohols **2** and **4**, respectively, in reasonable yield.

The oxidation of aliphatic saturated hydrocarbons (alkane hydroxylation) has been a subject of extensive studies in order to provide useful synthetic methods and to mimic biological oxygenation systems.[1] Among those, the oxidation of terminal isopropyl groups to the corresponding tertiary alcohols, for example 25-hydroxychoelsterol derivatives, is of particular interest in view of the biological significance. However, achieving such reactions has been difficult by conventional method, and only a few procedures have been reported.[2] The electrochemical methodology has proved to be useful for organic synthesis because it often promotes unique reactions otherwise inaccessible.[3] We, therefore, attempted the above oxidation by using an electrochemical method, and described herein are the successful results.

Scheme 1.



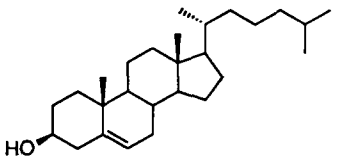
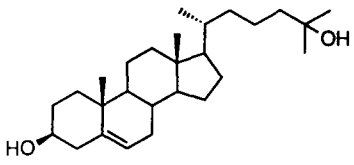
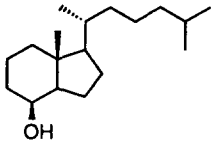
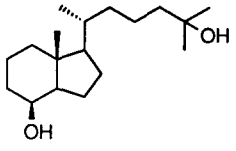
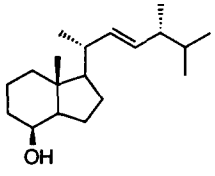
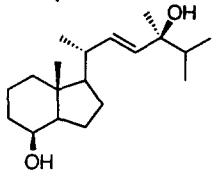
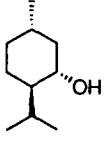
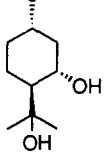
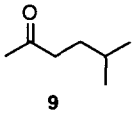
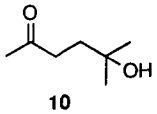
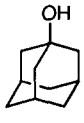
In analogy to the biological P-450 system, we assumed that using Tl^{3+}, which can bind oxygen more tightly than Fe^{3+}, hematoporphyrin and a cathodic electrochemical reduction instead of Fe^{3+}, cytochrome P-450 and $FADH_2$, respectively, could produce activated oxygen-like species as shown in Scheme 1.[4] Thus, the reactions were conducted under a constant current condition[5] (C.C.E. at -2.0 ~ 2.4 V *vs.* SCE, 25 mA/cm^2; 10 F/mol) in 80% aqueous MeCN (20 mL) containing a substrate (0.3 mmol), $Tl(TFA)_3$ (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.

The results are summarized in Table 1. When cholesterol (**1**) was subjected to the above conditions,[6] the terminal isopropyl group (C-25 position) was selectively oxidized to give 25-hydroxycholesterol (**2**) in 13% yield (25% conversion yield, Entry 1).[7] Although the yield was moderate, it is reasonable for this type of reaction.[8] Similarly, Grundmann's alcohol (**3**), an ozonolysis product of vitamin D_3, afforded the corresponding tertiary alcohol **4**, a key intermediate for synthesis of vitamin D derivatives,[9] in 13% yield (Entry 2). However, the compound **5**, the counterpart of **3** for vitamin D_2,[10] was exclusively hydroxylated at the allylic position to give the compound **6** in 27% yield (Entry 3). It is noteworthy that this oxidation is highly stereoselective,[11] and the metabolism of vitamin D_2 *in vivo* takes place in the same fashion.[12] Furthermore, oxidation of (+)-menthol (**7**) also proceeded regioselectively to give (-)-*trans*-*p*-menthane-3,8-diol (**8**) in 35% yield (Entry 4). In each of the above cases, the resultant ketone from the further oxidation of the secondary alcohol in the oxidation product was obtained as a by-product in a trace amount,[13] but the ketones derived from **1**, **3**, **5**, and **7** did not produce the corresponding tertiary alcohols. In contrast, isoamyl methyl ketone (**9**) afforded the corresponding tertiary alcohol **10**[14] in high yield (Entry 5). In this particular case, the presence of the methyl ketone is crucial; no reaction took place when the compounds bearing other functional groups (alcohol, carboxylic acid, and ester) instead of the methyl ketone were subjected to the reaction conditions, indicating that the methyl ketone is involved in the reaction pathway in some way.

The mechanism in detail remains to be investigated, but some aspects related to the mechanism deserve comment. These oxidation reactions did not proceed at all or resulted in a complex mixture without electrolysis or under the conditions which omitted any one of the reagents [$Tl(TFA)_3$ or O_2 or hematoporphyrin]; in other words, the $Tl(TFA)_3$-hematoporphyrin-O_2-cathodic reduction system as a whole is essential to promote the above reactions. Indeed, cyclic voltammetry of a mixture of $Tl(TFA)_3$-hematoporphyrin-O_2 considerably differed from that of $Tl(TFA)_3$-hematoporphyrin or hematoporphyrin alone.[15] As for the metal salt, $FeCl_3$ was also effective but to a much lesser extent, giving the oxidation products only in poor yield. Using the porphyrins other than hematoporphyrin (tetraphenylporphyrin and its derivatives) resulted in a complex mixture. The use of H_2O_2 instead of O_2 as an oxidant resulted in a complex mixture again, which ruled out the possible involvement of electrochemically formed H_2O_2 from H_2O or O_2 under the conditions used. Furthermore, the experiments under a divided cell[16] showed that the oxidation proceeded only at the cathode, indicating that the electron transfer from the cathode triggered the reaction, and the oxidation took place in the electrical double layer[17] or at the electrode/solution interface, not in the medium. Moreover, the active species of this system was suggested to be a radical in nature, presumably a hydroxyl radical ($HO^{\cdot}$), since adamantane (**11**) almost exclusively afforded 1-adamantanol (**12**)[18] (Entry 6 in Table 1). Additionally, the regioselectivity observed might arise from some specific interaction or stacking of the metalloporphyrin-like complex with the substrate; that is, the substrate and the metalloporphyrin-like complex assemble in some sophisticated manner, which locates the terminal isopropyl group close to the active site. The stereoselectivity observed in the compound **6** could be rationalized in a similar way.

Thus, we demonstrated in this study that selective oxidation of terminal isopropyl groups to the corresponding tertiary alcohols is achieved by electrochemical methodology. This oxidation is very unique since it is otherwise inaccessible and, therefore, it would be highly useful for organic synthesis. Further elaboration of the mechanism and scope of this oxidation is underway.

Table 1.

Entry	Substrate	Product*	Yield (%)
1	 1	 2	13 (25)**
2	 3	 4	10 (13)
3	 5	 6	21 (27)
4	 7	 8	35
5	 9	 10	80
6	 11	 12	34

*All the spectral data of the products were in agreement with the assigned structure or the authentic specimen.
**The conversion yield was shown in parenthesis.

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† Present address: Department of Applied Physics and Chemistry, The University of Electro-Communications, Chofu, Tokyo 182, Japan.

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4. Similar electrocatalytic oxidation systems were reported: (a) Creager, S. E.; Raybuck, S. A.; Murray, R. W. *J. Am. Chem. Soc.*, **1986**, *108*, 4225-4227. (b) Balavoine, G.; Barton, D. H. R.; Boivin, J.; Gref, A.; Ozbalik, N.; Riviere, H. *Tetrahedron Lett.*, **1986**, *27*, 2849-2852.
5. The same results were obtained under a constant potential condition (C. P. E. at -2.4 V *vs.* SCE; 10 F/mol) .
6. In this particular case, CH_2Cl_2-MeCN-H_2O (2: 2: 1) and $^nBu_4NBF_4$ as solvent and supporting electrolyte, respectively, were used due to the solubility problem of the substrate.
7. The same oxidation using a metalloporphyrin model system of cytochrome P-450 was reported: Groves. J. T.; Neumann, R. J. *J. Org. Chem.*, **1988**, *53*, 3892-3893.
8. The turnover number (moles of product per mole of consumed Tl^{3+}) of each reaction: Entry 1, 1.3; Entry 2, 1.0; Entry 3, 2.1; Entry 4, 3.5; Entry 5, 8.0; Entry 6, 3.4.
9. (a) Kiegiel, J.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.*, **1991**, *32*, 6057-6060. (b) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc.*, **1992**, *114*, 9836-9845.
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11. The stereochemistry was tentatively assigned by comparison of the ^1H NMR spectrum with those of the closely related compounds: Koszewski, N. J.; Reinhardt, T. A.; Beitz, D. C.; Napoli, J. L.; Baggiolini, E. G.; Uskokovic, M. R.; Horst, R. L. *Anal. Chem.*, **1987**, *162*, 443-452.
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13. No other oxidation product was found in the crude product mixture.
14. This compound was characterized as its propane dithioacetal after treatment with propane dithiol and $BF_3 \cdot OEt_2$ due to the difficulty of the purification.
15. The cyclic voltammogram of a mixture of $Tl(TFA)_3$-hematoporphyrin-O_2 was irreversible, whereas those of $Tl(TFA)_3$-hematoporphyrin or hematoporphyrin alone were reversible. This dramatic difference suggested that the interaction of these three reagents plays a key role for the reaction, but the cyclic voltammogram was so complex that the analysis is still underway. We thank Professor Hiroshi Nishihara (The University of Tokyo) for helpful discussion about this subject.
16. The H-type cell (HX-108, Hokuto Denko Co. Ltd.) was used.
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